Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 1174–1181
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Synthetic studies of fluorine-containing compounds for household insecticides

Tatsuya Mori [a,*], Kazuya Ujihara [a], Osamu Matsumoto [a], Kazunori Yanagi [b], Noritada Matsuo [a]

[a] *Agricultural Chemicals Research Laboratory, Sumitomo Chemical Co. Ltd., 4-2-1 Takatsukasa, Takarazuka, Hyogo 665-8555, Japan*
[b] *Genomic Science Laboratory, Dainippon Sumitomo Pharma Co. Ltd., 3-1-98 Kasugadenaka, Konohana, Osaka 554-0022, Japan*

Received 12 July 2007; received in revised form 23 July 2007; accepted 30 July 2007
Available online 17 August 2007

Abstract

The discovery stories of three fluorine-containing insecticides in our laboratory are described, i.e. amidoflumet, a new trifluoromethanesulfonanilide with high miticidal activity against various house dust mites, Metofluthrin, a potent new fluorinated pyrethroid with extremely high knockdown activity against various mosquitoes, and a new α-pyrone compound, 3-[1*R*-*trans*-(2-trifluoromethyl)cyclopropanecarbonyl]-4-hydroxy-6-methyl-2-pyrone with outstanding insecticidal activity against *Blattella germanica*.

Keywords: Fluorine; Pesticide; Insecticide; Amidoflumet; House dust mite; Metofluthrin; Mosquitoe; Pyrone; Cockroach

1. Introduction

It is well recognized that the ratio of fluorine-containing pesticides is increasing along with the progress of fluorine chemistry. In recent years, one third of new pesticides contains fluorine atom(s). New synthetic methods and novel fluorinating reagents have been developed that facilitate introduction of fluorine or fluorine-containing units into many kinds of compounds, and in many cases, they have remarkable biological activity as well as physicochemical properties by introduction of fluorine atom(s). In this paper, our recent studies of fluorine-containing compounds for household insecticides in our laboratory are described.

2. Results and discussion

2.1. Amidoflumet, a new trifluoromethanesulfonanilide with high miticidal activity against various house dust mites

House dust mites and their products are known to be major household allergens to children and the elderly to cause asthma and atopic dermatitis [1]. In order to avoid these illnesses, it is essential to remove these allergens. Phenyl salicylate and benzyl benzoate have long been used to control house dust mites. However their miticidal efficacy is insufficient against predatory cheyletid mites which often cause biting damage to humans. There is therefore an urgent need for the development of a new effective miticide not only to remove allergens but avoid a biting damage by cheyletid mites in houses. We had previously found some trifluoromethanesulfonanilide compounds having high insecticidal activity against houseflies and cockroaches [2]. Further exploratory work in our laboratory resulted in the discovery of trifluoromethanesulfonanilide derivatives 1–11 as shown in Fig. 1 with high activity against house dust mites including cheyletid mites [3].

The miticidal activity of compounds **1–11** against two species of a house dust mite and one species of a cheyletid mite was determined by a filter paper contact method. As shown in Table 1, introduction of a halogen atom at the 4-position of the benzene ring substantially increased the activity against house dust mites. Introduction of other groups such as a nitro and a trifluoromethyl group increased the activity against *Tyrophagus putrescentiae* (Tp), but decreased the activity against *Dermatophagoides farinae* (Dp). An electron-donating methyl and a methoxy group at the 4-position of the benzene ring slightly decreased the miticidal activity.

* Corresponding author. Tel.: +81 797 74 2035; fax: +81 797 74 2043.
E-mail address: morit7@sc.sumitomo-chem.co.jp (T. Mori).

0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2007.07.016

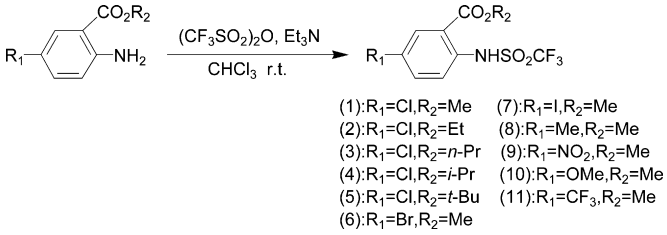
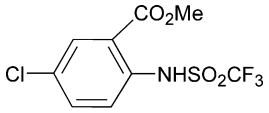


Fig. 1. Synthetic method of 2-alkoxycarbonyltrifluoromethanesulfonanilides.



amidoflumet

Fig. 2. Structure of amidoflumet.

With respect to the 2-position of the benzene ring, an lower alkyl ester showed strong activity against *Chelacarops moorei* (Cm). Compounds **1**–**7** completely controlled *Dermatophagoides farinae* (Df) and *Tyrophagus putrescentiae* (Tp), as well as *Chelacarops moorei* (Cm).

Judging from these findings and the availability of the starting materials, compound **1** (methyl 5-chloro-2-[(trifluoromethyl)sulfonyl]aminobenzoate) was selected and has been developed as a new miticide (amidoflumet) for house dust mites (Fig. 2) [4].

It is conceivable that the trifluoromethanesulfonyl group plays an important role in the high miticidal activity and chemical stability in this compound.

2.2. Metofluthrin, a potent new fluorinated pyrethroid with extremely high knockdown activity against various mosquitoes

Much attention has recently been directed to the development of non-heated formulations such as fan vaporizers because of their increased safety and ease of use, especially during outdoor activities. However, the insecticidal activity and/or the vapor action of the existing pyrethroids were unsatisfactory to be used in non-heated formulations. Therefore, we started our research to find a new pyrethroid with higher vapor action as well as high activity against mosquitoes.

Table 1
Miticidal activity of 2-alkoxycarbonyltrifluoromethanesulfonanilides against *Dermatophagoides farinae* (Df) and *Tyrophagus putrescentiae* (Tp)

No.	Compound		Dosage (g/m^2)–activity (%)	
	R_1	R_2	d.f. 0.008 (g/m^2)	Tp 0.08 (g/m^2)
1	Cl	Me	+++	+++
2	Cl	Et	+++	+++
3	Cl	nPr	+++	+++
4	Cl	iPr	+++	+++
5	Cl	tBu	+++	+++
6	Br	Me	+++	+++
7	I	Me	+++	+++
8	Me	Me	+++*	–
9	NO_2	Me	–	+++
10	OMe	Me	+*	–
11	CF_3	Me	–	+++

+++: 100% mortality, +: >90% mortality, +: 70–90% mortality, –: almost the same as untreated sample *: 0.08 (g/m^2).

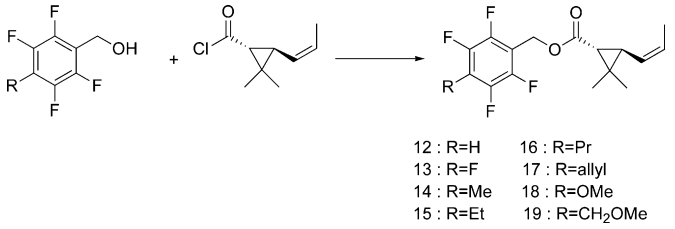


Fig. 3. Synthetic method of 4-substituted 2,3,5,6-tetrafluorobenzyl norchrysanthemates.

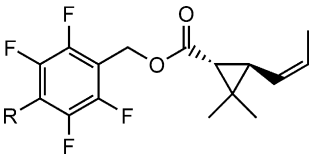
Ohno [5] and Elliott [6] independently reported insecticidal norchrysanthemates in the 1970s. According to their reports, these norchrysanthemates showed comparable insecticidal activity to that of the corresponding chrysanthemates.

We directed our attention to the norchrysanthemates because they had a higher vapor pressure and showed comparable insecticidal activity to that of correspondong chrysanthemates. We synthesized various 4-substituted 2,3,5,6-tetrafluorobenzyl norchrysanthemates as shown in Fig. 3 and screened them by the standard topical application method [7].

As a result of the screening, all analogs had much higher activity against mosquitoes than compound **12** as shown in Table 2. The relative toxicity reached the maximum with between two and three carbon atoms 15 and 16 at the 4-position. Unsaturation and incorporation of an oxygen atom also showed substantial activity, *inter alia*, the 4-methoxymethyl derivative 19 exhibited the highest lethal potency, being over twenty five times as active as *d*-allethrin against *Culex pipiens pallens*.

From these compounds, we selected compounds **14**, **18** and **19**, considering to their molecular weight, basic efficacy, ease of synthesis and other physical and chemical properties, and

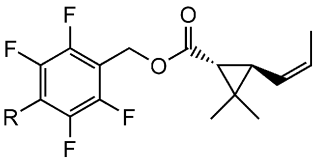
Table 2
Insecticidal activity of 4-substituted-2,3,5,6-tetrafluorobenzyl norchrysanthemates against *Culex pipiens pallens*



Compound	R	R.E.[a]
12	H	30
13	F	100
14	Me	200
15	Et	490
16	nPr	250
17	allyl	500
18	OMe	360
19	CH_2OMe	2500
d-allethrin		100

[a] Relative efficacy against *Culexpipiens pallens* based on LD_{50} by the topical application method.

Table 3
Insecticidal activity of 4-substituted-2,3,5,6-tetrafluorobenzyl norchrysanthemates in the non-heated formulation against *Culex pipiens pallens*



Compound	R	KT_{50} [min][a]	KD%[b]
12	H	55	60
14	Me	38	94
18	OMe	52	70
19	CH_2OMe	27	100

[a] Time for 50% knockdown calculated by the probit method.
[b] The average of knockdown mosquitoes after 60 min.

evaluated their vapor activities in a non-heated formulation. Above all, the 4-methoxymethyl derivative 19 clearly showed a significantly faster action in comparison with other compounds in the non-heated formulation (Table 3).

As a result, [(2,3,5,6-tetrafluoro-4-methoxymethylphenyl)-methyl (1*R*, 3*R*)-2,2-dimethyl-3-(1-propenyl)] cyclopropane-carboxylate was selected as a new synthetic pyrethroid (Metofluthrin) with high vapor activity against mosquitoes (Fig. 4) [8].

It is conceivable that the four fluorine atoms on the benzene ring play an important role in the high insecticidal activity and a vapor action against mosquitoes in this compound.

2.3. A new α-pyrone compound, 3-[1R-trans-(2-trifluoromethyl)cyclopropane carbonyl]-4-hydroxy-6-methyl-2-pyrone with outstanding insecticidal activity against Blattella germanica

Many kinds of biologically active compounds containing an α-pyrone skeleton such as 7,8-dihydro-5,6-dehydrokawain [9], Yangonin [10] and Podoblastin B [11] were isolated from medicinal plants (Fig. 5).

As a part of our research for a new pesticide, we directed our next attention to α-pyrone compounds with expectation to find a new insecticidal compound. We synthesized various 3-substituted α-pyrones as shown in Fig. 6 and tested their insecticidal activity by the standard topical application method against *Blattella germanica*.

With respect to the length of the acyl group, the compound **22** having a butanoyl group showed the strongest activity against *Blattella germanica* among alkanoyl groups as shown in Fig. 7.

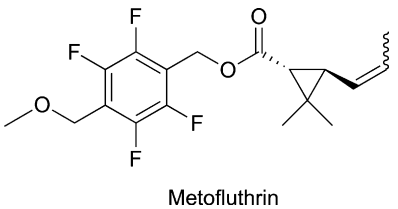


Fig. 4. Structure of Metofluthrin.

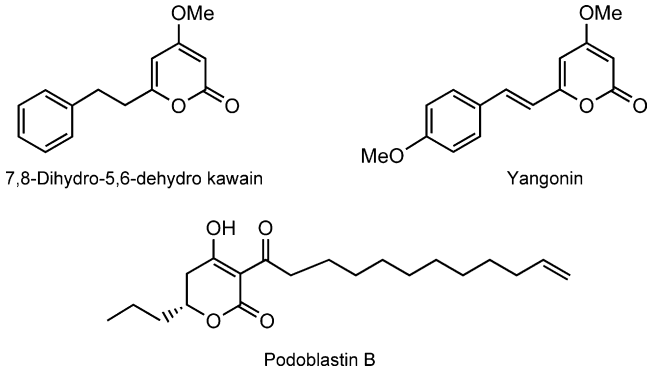


Fig. 5. Some natural products containing an α-pyrone skeleton isolated from medicinal plants.

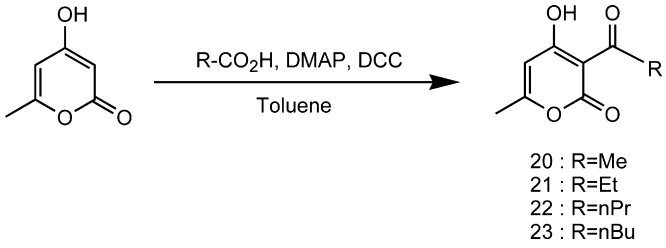


Fig. 6. Synthetic method of 3-substitued α-pyrones.

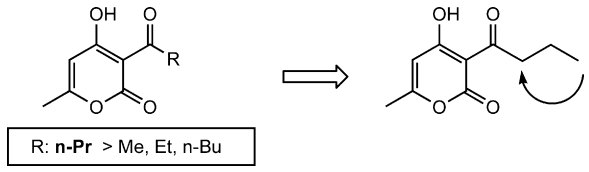


Fig. 7. Insecticidal activity of 3-substituted α-pyrones.

Therefore, We synthesized various 3-[(*trans*-2-substituted)-cyclopropyl]-carbonyl-4-hydroxy-6-methyl-2-pyrones as shown in Fig. 8 in order to fix the conformation of a butanoyl group and tested their insecticidal activity.

The results are shown in Fig. 9. Introduction of one carbon atom at the 2-position of the cyclopropane ring resulted in high

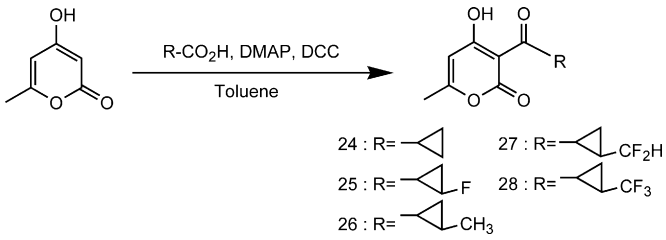


Fig. 8. Synthetic method of 3-[(*trans*-2-substituted)-cycropropyl]-carbonyl-4-hydroxy-6-methyl-2-pyrones.

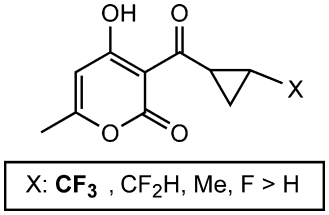


Fig. 9. Insecticidal activity of 3-[(*trans*-2-substituted)-cyclopropyl]-carbonyl-4-hydroxy-6-methyl-2-pyrones.

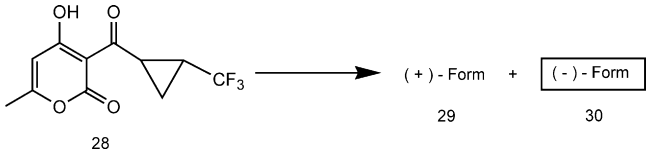


Fig. 10. Separation of compound **28** into each optical isomers (+)-Form **29** and (−)-Form **30**.

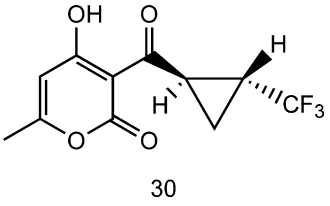


Fig. 12. Structure of (−)-Form **30**.

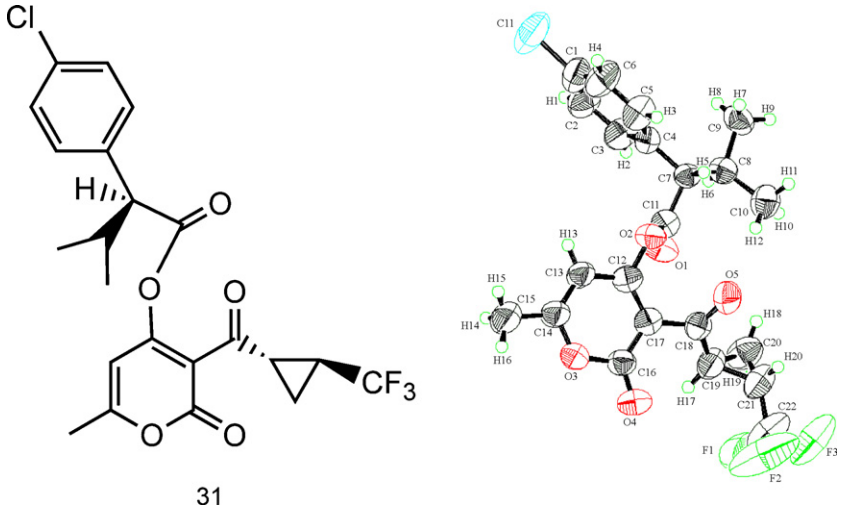


Fig. 11. Absolute structure and ORTEP drawing of the crystalline compound **31**.

insecticidal activity and the relative toxicity reached the maximum with a trifluoromethyl derivative 28.

Optical resolution of the compound **28** into each optical isomer **29** and **30** by HPLC method was accomplished using the chiral column (CHIRALPAK AD) as shown in Fig. 10, and their insecticidal activity against *Blattella germanica* was obtained.

As a result, the more insecticidal isomer was found to be (−)-Form **30** and showed outstanding insecticidal activity over five times as active as *permethrin,* which is one of widely used synthetic pyrethroids for the control of various cockroaches. We could decide the absolute configuration of the (+)-Form **29** as shown in Fig. 11 by X-ray crystallographic analysis of the ester **31** derived from (+)-Form **29**.

Accordingly, we could decide the absolute structure of the more insecticidal stereoisomer, (−)-Form **30** as having a 1*R*, 2*R* configuration (Fig. 12).

Although the mode of action of these α-pyrone compounds is still unknown, we believe to find a more active compound considering preferred comformation of the (−)-Form.

It is conceivable that the trifluoromethyl group on the cyclopropane ring plays an important role in the high insecticidal activity, lipophilicity and chemical stability in this compound.

3. Conclusion

In our discovery research of new insecticides in our laboratory, the important effects of the fluorine atom(s) were described. Further studies are necessary to clarify a role of fluorine atom, and these should provide greater insight into the essential requirements for the position and the number of fluorine in order to enhance biological activities.

A steady increase in the number of fluorinated new pesticides and pharmaceutical drugs has been observed, and the influence of fluorine on compounds in development in both areas is also increasing. Further development of novel methods of incorporating fluorine into organic molecules as well as commercial availability of novel fluorine-containing building blocks will continue to increase this number.

4. Experimental

Melting point (mp) data were determined with Yanagimoto micro melting point apparatus and are uncorrected. Refractive indexes (n_D) were determined with Atago refractive index apparatus. NMR spectra were measured with a Hitachi R-24B spectrometer (60 MHz), JEOL EX-300 spectrometer (300 MHz) or JEOL AL400 spectrometer (400 MHz).

*4.1. Methyl 5-chloro-2-[(trifluoromethyl)sulfonyl]aminobenzoate **1***

To a stirred solution of methyl 2-amino-5-chlorobenzoate (3.8 g) and triethylamine (3.2 g) in dry chloroform (50 ml) was added dropwise trifluoromethanesulfonic anhydride (8.7 g) below 5 °C. After stirring at room temperature for 8 h, the resulting mixture was poured into ice-cooled water and extracted twice with chloroform. The organic layers were combined, washed with water and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was chromatographed on silica gel with chloroform as the

eluent to give 1, 3.8 g, 58%; mp 80.7 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ3.99 (3H, s), 7.53 (1H, dd, J = 2.4, 9.1 Hz), 7.73 (1H, d, J = 9.1 Hz), 8.05 (1H, d, J = 2.4 Hz), 11.2 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.6 (s, 3F); HRMS: calcd. for $C_9H_7O_4NClF_3S$, 316.9736; found, 316.9737.

Compounds **2**–**11** were prepared in a similar manner.

4.2. Ethyl 5-chloro-2-[(trifluoromethyl)sulfonyl]aminobenzoate **2**

58%; mp 65.7 °C; ^{1}H NMR (60 MHz, $CDCl_3$): δ1.42 (3H, t, J = 7.2 Hz), 4.42 (2H, q, J = 7.2 Hz), 7.42 (1H, dd, J = 2.2, 8.6 Hz), 7.73 (1H, d, J = 8.6 Hz), 7.96 (1H, d, J = 2.2 Hz), 11.2 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.6 (s, 3F).

4.3. n-Propyl 5-chloro-2-[(trifluoromethyl)sulfonyl]aminobenzoate **3**

62%; n_D (25.5), 1.4898; ^{1}H NMR (250 MHz, $CDCl_3$): δ1.05(3H, m), 1.84 (2H, m), 4.35 (2H, m), 7.55 (1H, d, J = 9.0 Hz), 7.72 (1H, dd, J = 2.0, 9.0 Hz), 8.03 (1H, d, J = 2.0 Hz), 11.3 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.6 (s, 3F); HRMS: calcd. for $C_{11}H_{11}O_4NClF_3S$, 345.0049; found, 345.0047.

4.4. Isopropyl 5-chloro-2-[(trifluoromethyl)sulfonyl]aminobenzoate **4**

20%; mp 41.9 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ1.42 (3H, d,J = 6.2 Hz), 5.30 (1H, m), 7.52 (1H, dd, J = 2.5, 9.2 Hz), 7.73 (1H, d, J = 9.2 Hz), 8.02 (1H, d, J = 2.5 Hz), 11.2 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.6 (s, 3F).

4.5. t-Butyl 5-chloro-2-[(trifluoromethyl)sulfonyl]aminobenzoate **5**

14%; mp 87.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ1.63 (9H, s), 7.51 (1H, dd, J = 2.7, 9.0 Hz), 7.72 (1H, d, J = 9.0 Hz), 7.94 (1H, d, J = 2.7 Hz), 11.4 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.7 (s, 3F); HRMS: calcd. for $C_{12}H_{13}O_4NClF_3S$, 316.0206; found, 359.0220.

4.6. Methyl 5-bromo-2-[(trifluoromethyl)sulfonyl]aminobenzoate **6**

41%; mp 73.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ4.01 (3H, s), 7.68 (2H, s), 8.20 (1H, s), 11.2 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.6 (s, 3F); HRMS: calcd. for $C_9H_7O_4NBrF_3S$, 360.9231; found, 360.9258.

4.7. Methyl 5-iodo-2-[(trifluoromethyl)sulfonyl]aminobenzoate **7**

34%; mp 61.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ4.05 (3H, s), 7.52 (1H, m), 7.84 (1H, m), 8.37 (1H, d, J = 2.2 Hz), 11.2 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.6 (s, 3F); HRMS: calcd. for $C_9H_7O_4NF_3SI$, 408.9093; found, 408.9115.

4.8. Methyl 5-methyl-2-[(trifluoromethyl)sulfonyl]aminobenzoate **8**

33%; mp 57.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ2.42 (3H, s), 4.02 (3H, s), 7.39 (1H, d, J = 8.8 Hz), 7.67 (1H, d, J = 8.8 Hz), 7.87 (1H,s), 11.1 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.7 (s, 3F); HRMS: calcd. for $C_{10}H_{10}O_4NClF_3S$, 297.0282; found, 297.0291.

4.9. Methyl 5-nitro-2-[(trifluoromethyl)sulfonyl]aminobenzoate **9**

20%; mp 89.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ4.07 (3H,s), 7.97 (1H, d, J = 9.3 Hz), 8.44 (1H, d, J = 9.3 Hz), 8.98 (1H, s), 11.7 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.5 (s, 3F).

4.10. Methyl 5-methoxy-2-[(trifluoromethyl)sulfonyl]aminobenzoate **10**

32%; n_D (26.0), 1.4921; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.85 (3H, s), 4.01 (3H, s), 7.15 (1H, dd, J = 2.9, 9.2 Hz), 7.54 (1H, d, J = 2.9 Hz), 7.68 (1H, d, J = 9.2 Hz), 10.8 (1H, broad s). ^{19}F NMR (376 MHz, C_6F_6): δ85.9 (s, 3F); HRMS: calcd. for $C_{10}H_{10}O_5NF_3S$, 313.0232; found, 313.0244.

4.11. Methyl 5-trifluoromethyl-2-[(trifluoromethyl)sulfonyl]aminobenzoate **11**

32%; n_D (26.0), 1.4632; ^{1}H NMR (400 MHz, $CDCl_3$): δ4.03 (3H, s), 7.83 (1H, d, J = 9.0 Hz), 7.95 (1H, d, J = 9.0 Hz), 8.35 (1H, s), 11.6 (1H, broad s); HRMS: calcd. for $C_{10}H_7O_4NF_6S$, 350.9999; found, 350.9994.

4.12. Evaluation method of the miticidal activity of the test compounds

The miticidal activity against *Dermatophagoides Farinae* (Df), *Tyrophagus putrescentiae* (Tp) and *Chelacaropsis moorei* (Cm) was tested by the filter paper contact method. A test solution (0.2 ml) diluted in acetone was applied to a filter paper 3.8 cm in diameter. The filter paper was placed in an aluminum dish 4.0 cm in diameter. Sticky material was applied to the rim of the dish to prevent the escape of the test mites. Twenty to thirty mites were released on to the filter paper. The mites in the dish were kept at 25 °C and 70 ± 10% relative humidity, and the number of dead mites was counted 24 h after the treatment. Mortality (%) was calculated as follows:

$$\text{Mortality}(\%) = \frac{\text{No. of dead mites}}{\text{Total no. of mites on the filter paper}} \times 100$$

4.13. (2,3,5,6-Tetrafluorophenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate **12**

Diisopropyl azodicarboxylate (a 40% in toluene, 2.0 ml) was added to a mixed solution of (1*R*, 3*R*)-2,2-dimethyl-3-[(Z)-

1-propenyl] cyclopropanecarboxylic acid (0.42 g), (2,3,5,6-tetrafluorophenyl)methanol (0.49 g), triphenylphosphine (0.93 g) and tetrahydrofuran (20 ml). After 16 h, the reaction solution was concentrated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography with hexane-ethyl acetate (20:1 by volume) as an eluant to give 12 (0.80 g, 93%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ1.15 (3H, s), 1.29 (3H, s), 1.47 (1H, d, J = 5.3Hz), 1.70 (3H, dd, J = 6.9, 1.6 Hz), 2.19 (1H, br dd, J = 8.1, 5.3 Hz), 5.12 (1H, ddd, J = 10.6, 8.1, 1.6 Hz), 5.24 (1H, t, J = 1.6 Hz), 5.25 (1H, t, J = 1.6 Hz), 5.60 (1H, dqd, J = 10.6, 6.9, 1.1 Hz), 7.10 (1H, tt, J = 9.7, 7.4 Hz). ^{19}F NMR (376 MHz, C_6F_6): δ22.9 (m, 2F), 19.1 (m, 2F).

Compounds **13**–**18** were prepared in a similar manner.

4.14. (2,3,4,5,6-Pentafluorophenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate ***13***

^{1}H NMR (400 MHz, $CDCl_3$): δ1.15 (3H, s), 1.28 (3H, s), 1.45 (1H, d, J = 5.4Hz), 1.70 (3H, dd, J = 6.8, 1.7 Hz), 2.18 (1H, br dd, J = 8.4, 5.4 Hz), 5.11 (1H, ddq, J = 10.6, 8.4, 1.7 Hz), 5.21 (1H, brs), 5.60 (1H, dqd, J = 10.6, 7.0, 1.2 Hz).

4.15. (2,3,5,6-Tetrafluoro-4-methylphenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate ***14***

^{1}H NMR (400 MHz, $CDCl_3$): δ1.14 (3H, s), 1.28 (3H, s), 1.45 (1H, d, J = 5.3 Hz), 1.70 (3H, dd, J = 7.0, 1.7 Hz), 2.17 (1H, br dd, J = 8.4, 5.3 Hz), 2.28 (2H, t, J = 2.1 Hz), 5.11 (1H, ddq, J = 10.7, 8.4, 1.7 Hz), 5.20 (1H, t, J = 1.5 Hz), 5.21 (1H, t, J = 1.5 Hz), 5.59 (1H, dqd, J = 10.7, 7.0, 1.3 Hz). ^{19}F NMR (376 MHz, C_6F_6): δ18.0 (dd, 2F, J = 22.1, 13.0 Hz), 17.3 (dd, 2F, J = 22.1, 13.0 Hz).

4.16. (4-Ethyl-2,3,5,6-tetrafluorophenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate ***15***

^{1}H NMR (400 MHz, $CDCl_3$): δ1.14 (3H, s), 1.23 (3H, t, J = 7.6 Hz), 1.28 (3H, s), 1.46 (1H, d, J = 5.4 Hz), 1.70 (3H, dd, J = 6.8, 1.7 Hz), 2.18 (1H, br dd, J = 8.4, 5.4 Hz), 2.77 (2H, q, J = 7.6 Hz), 5.10 (1H, ddq, J = 10.7, 8.4, 1.7 Hz), 5.21 (1H, t, J = 1.3 Hz), 5.22 (1H, t, J = 1.3 Hz), 5.59 (1H, dqd, J = 10.7, 6.8, 1.3 Hz). ^{19}F NMR (376 MHz, C_6F_6): δ17.6 (dd, 2F, J = 21.9, 12.8 Hz), 16.0 (dd, 2F, J = 21.9, 12.8 Hz).

4.17. (2,3,5,6-Tetrafluoro-4-propylphenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate ***16***

^{1}H NMR (400 MHz, $CDCl_3$): δ0.97 (3H, t, J = 7.5 Hz), 1.13 (3H, s), 1.28 (3H, s), 1.46 (1H, d, J = 5.4 Hz), 1.64 (2H, sext, J = 7.5 Hz), 1.70 (3H, dd, J = 6.8, 1.7 Hz), 2.18 (1H, dd, J = 8.4, 5.4 Hz), 2.72 (2H, t, J = 7.5 Hz), 5.11 (1H, ddq, J = 10.7, 8.4, 1.7 Hz), 5.21 (1H, t, J = 1.3 Hz), 5.22 (1H, t, J = 1.3 Hz), 5.59 (1H, dqd, J = 10.7, 6.8, 1.3 Hz). ^{19}F NMR (376 MHz, C_6F_6): δ17.5 (dd, 2F, J = 21.9, 12.8 Hz), 16.9 (dd, 2F, J = 21.9, 12.8 Hz).

4.18. (4-Allyl-2,3,5,6-tetrafluorophenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate ***17***

^{1}H NMR (400 MHz, $CDCl_3$): δ1.13 (3H, s), 1.24 (3H, s), 1.48 (1H, d, J = 5.4 Hz), 1.68 (3H, dd, J = 6.6, 1.4 Hz), 2.03 (1H, br dd, J = 8.2, 5.4 Hz), 3.48 (2H, dt, J = 6.3, 1.3 Hz), 5.07-5.24 (5H, m), 5.62 (1H, dq, J = 15.1, 6.5 Hz), 5.89 (1H, ddt, J = 16.7, 10.3, 6.3 Hz).

4.19. (2,3,5,6-Tetrafluoro-4-methoxylphenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate ***18***

^{1}H NMR (400 MHz, $CDCl_3$): δ1.14 (3H, s), 1.28 (3H, s), 1.45 (1H, d, J = 5.4 Hz), 1.70 (3H, dd, J = 6.9, 1.7 Hz), 2.18 (1H, br dd, J = 8.4, 5.4 Hz), 4.10 (3H, t, J = 1.4 Hz), 5.11 (1H, ddq, J = 10.5, 8.4, 1.7 Hz), 5.18 (1H, t, J = 1.6 Hz), 5.19 (1H, t, J = 1.6 Hz), 5.60 (1H, dqd, J = 10.5, 7.1, 1.4 Hz). ^{19}F NMR (376 MHz, C_6F_6): δ17.8 (dd, 2F, J = 20.2, 8.0 Hz), 3.7 (dd, 2F, J = 20.2, 8.0 Hz).

4.20. (2,3,5,6-Tetrafluoro-4-methoxymethylphenyl)methyl (1R, 3R)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarboxylate ***19***

(1*R*, 3*R*)-2,2-dimethyl-3-[(Z)-1-propenyl] cyclopropanecarbonyl chloride (1.82 g) was added to a solution of (2,3,5,6-tetrafluoro-4-methoxymethylphenyl)methanol (2.24 g) and pyridine (0.87 g) in tetrahydrofuran (20 ml) under ice-cooling, and the mixture was stirred for 8 h at room temperature. The reaction mixture was poured into 100 ml of ice-cooled water and extracted twice with 100 ml each of ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was subjected to silica gel column chromatography with hexane-ethyl acetate (20:1 by volume) as an eluant to give 19 (3.17 g, 88%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ1.15 (3H, s), 1.28 (3H, s), 1.46 (1H, d), 1.70 (3H, dd), 2.18 (1H, dd), 3.41 (3H, s), 4.59 (2H, s), 5.08–5.12 (1H, m), 5.24 (2H, s), 5.58–5.62 (1H, m). ^{19}F NMR(376 MHz, C_6F_6): δ18.8 (dd, 2F, J = 22.1, 13.7 Hz), 18.2 (dd, 2F, J = 22.1, 13.7 Hz).

4.21. Evaluation method of the insecticidal activity of the test compounds in non-heated formulations

A test compound (100 mg) was dissolved in 20 ml of acetone and applied onto a sheet of filter paper (20 cm × 50 cm), the acetone then being removed by air-drying. In the center of a 28 m^3 test chamber (4.3 m × 2.65 m × 2.45 m height), the filter paper was hung from the ceiling with the upper end of the filter paper 1.7 m in height from the floor. Four nylon-net cages (cylindrical, 30 cm in diameter and 20 cm in height) each

containing 20 female common house mosquitoes (*Culex 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 paper. The number of knocked down mosquitoes was counted at designed intervals for 60 min. In order to circulate air in the chamber, a fan was positioned under the treated filter paper, and a board was placed between the fan and the filter paper to prevent direct air flow between the two.

Compounds **20–27** were prepared in a similar manner as compound **28**.

- *3-Methylcarbonyl-4-hydroxy-6-methyl-2-pyrone 20*: ^{1}H NMR (400 MHz, $CDCl_3$): δ2.28 (3H, s), 2.67 (3H, s), 5.94 (1H, s).
- *3-Ethylcarbonyl-4-hydroxy-6-methyl-2-pyrone 21*: ^{1}H NMR (400 MHz, $CDCl_3$): δ16 (3H, t, J = 8.0 Hz), 2.28 (3H, s), 3.12 (2H, q, J = 8.0 Hz), 5.94 (1H, s).
- *3-n-Propylcarbonyl-4-hydroxy-6-methyl-2-pyrone 22*: ^{1}H NMR (400 MHz, $CDCl_3$): δ0.98 (3H, t, J = 8.0 Hz), 1.67 (2H, m), 2.25(3H, s), 3.10 (2H, m), 5.92 (1H, s).
- *3-n-Butylcarbonyl-4-hydroxy-6-methyl-2-pyrone 23*: ^{1}H NMR (400 MHz, $CDCl_3$): δ0.95 (3H, t, J = 8.0 Hz), 1.42 (2H, m), 1.62 (2H, m), 2.27 (3H, s), 3.08 (2H, m), 5.93 (1H, s).
- *3-Cyclopropylcarbonyl-4-hydroxy-6-methyl-2-pyrone 24*: ^{1}H NMR (400 MHz, $CDCl_3$): δ1.18 (2H, m), 1.32 (2H, m), 2.27 (3H, s), 3.58 (1H, m), 5.92 (1H, s).
- *3-(Trans-2-fluorocyclopropylcarbonyl)-4-hydroxy-6-methyl-2-pyrone 25*: ^{1}H NMR (400 MHz, $CDCl_3$): δ1.56–1.65 (1H, m), 1.66–1.78 (1H, m), 2.29 (3H, s), 4.04–4.16 (1H, m), 4.81-5.03 (1H, m), 5.94 (1H, s). ^{19}F NMR (376 MHz, C_6F_6): δ226.3 (m, 1F).
- *3-(Trans-2-methylcyclopropylcarbonyl)-4-hydroxy-6-methyl-2-pyrone 26*: ^{1}H NMR (400 MHz, $CDCl_3$): δ0.99–1.06 (1H, m), 1.22 (3H, d, J = 5.9 Hz), 1.49–1.56 (1H, m), 1.63–1.75 (1H, m), 2.26 (3H, s), 3.32–3.38 (1H, m), 5.90 (1H, s).
- *3-(Trans-2-difluoromethylcyclopropylcarbonyl)-4-hydroxy-6-methyl-2-pyrone 27*: ^{1}H NMR (400 MHz, $CDCl_3$): δ1.38 (1H, m), 1.46 (1H, m), 2.19 (1H, m), 2.23 (3H, s), 3.83 (1H, m), 5.72 (1H, t, J = 42 Hz), 5.95 (1H, s). ^{19}F NMR (376 MHz, C_6F_6): δ46.4 (ddd, 1F, J = 284.6, 56.8, 10.3 Hz), 45.1 (ddd, 1F, J = 284.6, 56.8, 10.3 Hz).

4.22. 3-(Trans-2-trifluoromethylcyclopropylcarbonyl)-4-hydroxy-6-methyl-2-pyrone *28*

Dicyclohexylcarbodiimide (1.23 g) was added to a solution of 4-hydroxy-6-methyl-2-pyrone (0.75 g), trans-2-trifluoromethylcyclopropanecarboxylic acid (0.92 g) and 4-dimethylaminopyridine (0.15 g) in toluene (12 ml), and the mixture was stirred for 3 h at room temperature and further stirred for 5 h at 100 °C. After cooling to room temperature, the reaction mixture was subjected to filtration. The filtrate was washed twice with toluene (10 ml × 2). The combined toluene solution was concentrated under reduced pressure to give a crude product, which was subjected to silica gel column chromatography with hexane–ethyl acetate (10:1 by volume) as an eluant to give 28 (0.18 g, 12%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ1.48 (2H, m), 2.30 (3H, s), 2.42 (1H, m), 4.00 (1H, m), 5.96 (1H, s). ^{19}F NMR (376 MHz, C_6F_6): δ94.9 (d, 3F, J = 6.1 Hz).

4.23. Separation of 3-(trans-2-trifluoromethyl-cyclopropyl carbonyl)-4-hydroxy-6-methyl-2-pyrone *28* into each optical isomer *29* and *30*

0.15 g of compound **28** was separated into each optical isomer **29** {51 mg, $[\alpha]_D^{24.0}$ = + 35.2 (C = 0.52,$CHCl_3$)} and **30** {54 mg, $[\alpha]_D^{24.0}$ = −34.0 (C = 0.52, $CHCl_3$)} by HPLC method using the chiral column (CHIRALPAK AD) with *n*-hexane/ethanol/trifluoroacetic acid (90:10:0.1) as the moving phase.

4.24. 3-(1S-trans-2-trifluoromethylcyclopropyl carbonyl)-4-2S-(4-chlorophenyl)-3-methylbutyloxy-6-methyl-2-pyrone *31*

2S-(4-chlorophenyl)-3-methylbutyloyl chloride (0.043 g) was added to a solution of 3-(1S-*trans*-2-trifluoromethyl)cyclopropylcarbonyl-4-hydroxy-6-methyl-2-pyrone 29 (0.04 g) and 1,8-diazabicyclo [5,4,0] undec-7-ene (0.028 g) in toluene (4 ml) under ice-cooling, and the mixture was stirred for 4 h at room temperature. The reaction mixture was poured into 10 ml of 1% hydrochloric acid and extracted twice with 50 ml each of ethyl acetate. The combined ethyl acetate extracts were washed with saturated sodium bicarbonate, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was subjected to silica gel column chromatography with hexane-ethyl acetate (20:1 by volume) as an eluant to give **31** (0.039 g, 56%) as a colorless crystal. Single crystal of compound **31** was obtained by slow recrystallization from hexane–ether. Crystal data of compound **31** were as follows; $C_{22}H_{20}O_5F_3Cl_3$, Mr = 456.84, monoclinic space group $P2_1$(#4), a = 11.906(5) Å; b = 5.427(3) Å; c = 17.817(8) Å; β = 97.02(3)°; V = 1142.5(9) Å^3; D_{calc} = 1.328 g/cm^3; Z_{value} = 2; crystal size = 0.15 mm × 0.15 mm × 0.20 mm. A total 12381 reflections with $2\theta \leqq 136°$ were collected on a Rigaku RAXIS-RAPID automated four-circle diffractometer using graphite monochromated Cu Kα radiation (1.54187 Å). Structure was solved by direct methods (SIR92) using 2218 unique reflections and refined by Full-matrix least-squares on F program. Non-H atoms were assigned with anisotropic thermal parameters. All H atoms were located in a difference Fourier map and refined with the equivalent isotopic thermal parameters to those for the bonded atoms. The final unweighted R factor was 0.049 after minimized.

Acknowledgement

We thank Drs. M. Hatakoshi, Y. Shono, Y. Takada and Mr. T. Iwasaki, Mrs. M. Sugano and Mr. H. Okamoto for their contribution to the biological evaluations.

References

[1] P. Maienfisch, R.G. Hall, Chimia 58 (2004) 93.
[2] G.W. Wharton, J. Med. Entomol. 12 (1976) 577.
[3] M. Hatakoshi, H. Konishi, T. Yano, M. Hirano, JP Patent 57,156,407 (1982).
[4] T. Mori, Y. Takada, M. Hatakoshi, N. Matsuo, Biosci. Biotechnol. Biochem. 68 (2) (2004) 425.
[5] Y. Okuno, N. Itaya, T. Mizutani, N. Ohno, T. Matsuo, S. Kitamura, JP Patent 4,743,333 (1972).
[6] M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, D.A. Pulman, Pestic. Sci. 7 (1976) 499.
[7] T. Yamaguchi, G. Shinjo, S. Tsuda, K. Yoshida, E. Inaba, Y. Okuno, Jap. J. Sanit. Zool. 32 (1981) 59.
[8] K. Ujihara, T. Mori, T. Iwasaki, M. Sugano, Y. Shono, N. Matsuo, Biosci. Biotechnol. Biochem. 68 (1) (2004) 170.
[9] P. Tuchinda, V. Reutrakul, P. Claeson, U. Pongprayoon, T. Sematong, T. Santisuk, W.C. Taylor, Phytochemistry 59 (2002) 169.
[10] J. Weiss, A. Sauer, A. Frank, M. Unger, Drug Metab. Disposit. 33 (2005) 1580.
[11] M. Miyakado, S. Inoue, Y. Tanabe, K. Watanabe, N. Ohno, H. Yoshioka, Chem. Lett. 10 (1982) 1539.