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Asymmetric syntheses and bio-evaluation of novel chiral esters derived from substituted tetrafluorobenzyl alcohol

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ABSTRACT

A series of novel chiral esters derived from tetrafluorobenzyl alcohol were designed and prepared via asymmetric synthesis. The target molecules have been identified on the basis of analytical spectra data. All newly synthesized compounds have been screened their potential insecticidal activity against *Plutella xylostella* compared with those of fenvalerate and D-*trans*-phenothrin by standard method, and the respective pairs of enantiomers (**3-B1-R/S**, **3-C1-R/S**, **3-D1-R/S**) indicated significantly different activities.

During the last two decades, the use of pyrethroids has continuous increased.[1] The expansion of pyrethroid use has accompanied with pyrethroid resistance in pest insect populations, which have made the vector control more and more difficult.[2–4] Therefore, there is an urgent need to develop new insecticidal structures in order to combat resistance.[5] In the typical commercial pyrethroids, many structures have a substituted benzyl alcohol moiety such as Transfluthrin, Dimefluthrin, Meperfluthrin etc.[6] Many studies have also shown that the introduction of fluorine atoms in many compounds could remarkably gain their biological activity.[7,8] According to literatures, *Musca domestica L.* and other insects showed very low resistance factors against fenfluthrin and other polyfluorobenzyl pyrethroid in contrast to the *meta* phenoxybenzyl pyrethroids.[9] Furthermore, the polyfluorobenzyl pyrethroid could be used repeatedly to give satisfactory control without causing resistance as their lack of extended residual activity.[10] Thus, the less persistent polyfluorobenzyl pyrethroid could become an interesting material in insect resistance management practices.

On the other hand, many pyrethroids analogues have one or more chiral centers, and the enantiomers always exhibited different bioactivities. So the questions concerning the synthetic method to obtain pure active enantiomers, and the influence of stereochemistry upon biological activity for novel chiral compounds are therefore of two particular interests in this study. Based on the aforementioned results, as part of our agrochemistry program aimed at searching for active chiral esters derivatives, we would like to report herein our effort to design, distereoselectively synthesize, and investigate the bioactivities of novel chiral esters derived from tetrafluorobenzyl alcohol (Fig. 1).

In the present study, a series of novel chiral esters derivatives **3** were constructed by reacting functionalized chial building blocks **2** with substituted tetrafluorobenzyl alcohol. General procedure for the preparation of target compounds **3** is outlined in Scheme 1.

The key intermediates *N*-alkanoylcamphorsultams **1** were obtained by using a chiral auxiliary as a controlling reagent following the literature methods,[11–13] which can be conveniently transformed into various chiral acids **2** via a nucleophilic cleavage reaction of corresponding *N*-alkanoylcamphorsultams in the presence of lithium peroxide. The auxiliary sultam recovered here can also be reused. And then, the dehydration condensation of chiral acids **2** and tetrafluorobenzyl alcohol gave our desired products **3**. All target compounds gave satisfactory chemical analyses, and the chemical structures of the synthesized compounds are summarized in Table 1. The ^{1}H NMR spectra of compounds **3** indicated distinctive signals of protons for substituted tetrafluorobenzyl moiety, which presented a singlet peak in the range 5.50–3.00 ppm. The general signals at lower and higher fields respectively in their ^{1}H NMR spectra were assigned to the aromatic and alkyl protons in the chiral acid units. Their ^{13}C NMR spectra presented obvious signals of different alkyl carbon (70–5 ppm), and the signals that appeared at about 170 ppm were attributed to the C=O carbon. The other signals at about 160–100 ppm in the ^{13}C NMR spectra were assigned to the aromatic carbon as shown in the

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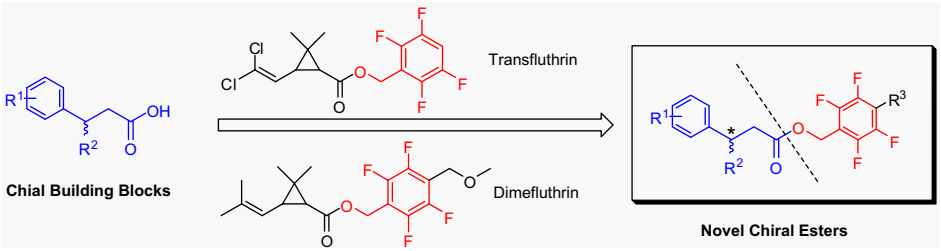
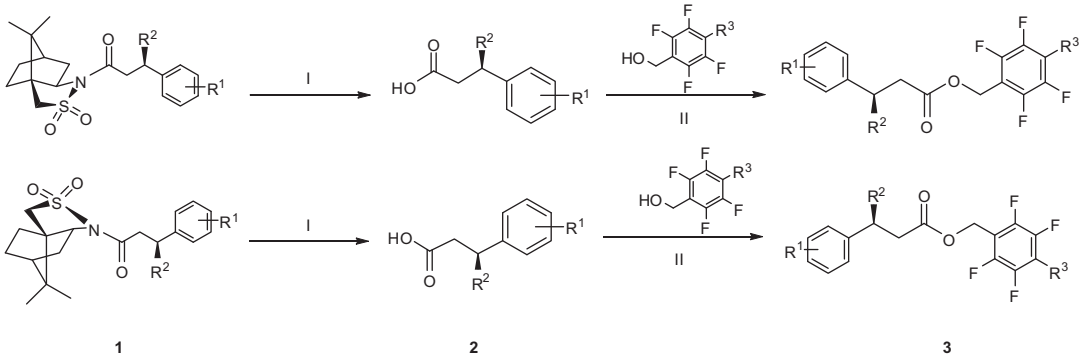


Figure 1. Design strategy of novel chiral esters derived from tetrafluorobenzyl alcohol.



Scheme 1. Synthetic route for novel chiral esters **3.** Reagent and conditions: (I) LiOH, H_2O_2, THF–H_2O (4:1), 0 °C, 12 h; (II) DCC, DMAP, CH_3CN, rt, 10 h.

Table 1
Chemical structures, physical properties of compounds synthesized and their insecticidal activity against *Plutella xylostella*

Entry	Compd no.	R^1	R^2	R^3	Appearance	Insecticidal activity[a] (mg/L)			
						167	100	33.3	11.1
1	**3-A1-R**	H	Bn	CH_2OMe	White solid	0	0	0	0
2	**3-A1-S**	H	Bn	CH_2OMe	White solid	0	0	0	0
3	**3-B1-R**	H	*i*Pr	CH_2OMe	White solid	9	9	9	5
4	**3-B1-S**	H	*i*Pr	CH_2OMe	White solid	5	0	0	0
5	**3-B2-R**	H	*i*Pr	Me	White solid	9	9	9	7
6	**3-B2-S**	H	*i*Pr	Me	White solid	9	9	9	7
7	**3-C1-R**	4-MeO	4-Me-Bn	Me	White solid	9	9	7	5
8	**3-C1-S**	4-MeO	4-Me-Bn	Me	White solid	0	0	0	0
9	**3-D1-R**	4-Cl	*n*Bu	CH_2OMe	White solid	9	9	5	0
10	**3-D1-S**	4-Cl	*n*Bu	CH_2OMe	White solid	0	0	0	0
11	Fenvalerate	—	—	—	—	9	9	9	9
12	D-*trans*-Phenothrin	—	—	—	—	9	9	9	9
13	Blank control	—	—	—	—	0	0	0	0

[a] Hierarchical levels of insecticidal activity:9 (>90% mortality), 7 (70–90% mortality), 5 (50–69% mortality), 3 (30–49% mortality), 1 (10–29% mortality), 0 (0–9% mortality).

representative spectra. Mass spectra, in particular, also showed the molecular ion peaks at the appropriate *m*/*z* values.

The insecticidal activities in vivo were evaluated according to the reported method.[14] The results of compounds **3-A1-R** ~ **3-D1-S** against *Plutella xylostella* are also listed in Table 1.

Generally speaking, as shown in Table 1, some of the synthesized compounds exhibited good insecticidal activities against *Plutella xylostella* at 11.1 mg/L, such as **3-B1-R**, **3-B2-R**/**S**, **3-C1-R**, which present >50% mortality at the lower concentration. Meanwhile, most of the compounds with an *R* configuration indicated obviously better activity in contrast with the compounds of *S* configuration. Changing the group size of R^2, we were surprised to find that most of the compounds with an isopropyl in R^2 provided higher activity than the others (entries 3–6). In addition, some electron-withdrawing groups and electron-donating substituents were introduced into the molecules in R^1 to explore the influence of structural changes on activities, the result showed that the influence was little.

Interestingly, the results described in Table 1 indicated the enantiomers always presented different biological activities. Specifically speaking, the (*R*)-enantiomers of **3-B1** (entry 3) still displayed good activity against *Plutella xylostella* at the concentration of 11.1 mg/L, whereas the corresponding (*S*)-enantiomer (entry 4) was almost lost activity at the same level. Especially in the cases of compounds **3-C1** and **3-D1**, the (*S*)-enantiomers (entries 8 and 10) exhibit no activity at highest concentrations (167 mg/L). However, the enantiomers of compounds **3-B2** (entries 5 and 6) display little difference in terms of their activities against *Plutella xylostella*, implying that this enantiomers need further investigation for their structure–activity relationships.

In conclusion, a series of new chiral esters **3-A1-R** ~ **3-D1-S** were distereoselectively synthesized and their potential activities have been evaluated. The preliminary bioassay results indicated that some of these derivatives have good insecticidal activity against *Plutella xylostella*. From the experimental results, it could also be concluded that the absolute configuration for target

molecules can affect their activities, and the respective pairs of enantiomers (**3-B1-R/S**, **3-C1-R/S**, **3-D1-R/S**) showed significantly different activities. To our best knowledge, this is the first report on the distereoselective syntheses and insecticidal activity of novel chiral esters derived from tetrafluorobenzyl alcohol, which are promising lead compounds for further developing novel agrochemicals containing fluorine. Further structural optimization and activity profiles about the designed novel chiral ester derivatives are well ongoing in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.04.055.

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