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Short communication

Essential oils-oriented chiral esters as potential pesticides: Asymmetric syntheses, characterization and bio-evaluation

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ABSTRACT

In an attempt to find potential pesticides derived from natural products, a novel series of essential oils-oriented chiral esters have been designed and synthesized based on the scaffold of natural pyrethrin. The newly synthesized compounds were screened for their potential insecticidal activity against *Plutella xylostella*, and the preliminary results revealed that about half of the target compounds' activities have been significantly improved comparing with the essential oil molecules, and some compounds exhibited better insecticidal activity in contrast to the commercialized specie of D-*trans*-Phenothrin at the concentration of 3.7 mg/L.

1. Introduction

Essential oils are an important class of secondary metabolites of aromatic plants, which can usually be obtained by steam distillation method. Most essential oils are consisting of a lot of chemical components, and mainly include some terpenes, phenolics and alcohols. In recent years, essential oils have attracted much attention owning to their diverse biological activities (Isman, 2006; Kordali et al., 2008; Bakkali et al., 2008; Regnault-Roger et al., 2012) such as insecticidal (Kumar et al., 2011; Machial et al., 2010; Maciel et al., 2010; Liu et al., 2010), repellent (Gu et al., 2009; Zhang et al., 2011; Mann et al., 2012; Ukeh and Umoetok, 2011), lure (Dev et al., 2010; Kendra et al., 2014), antifeedant (Kumar et al., 2009; Baskar and Ignacimuthu, 2012) activities and growth-reducing effect on a variety of insects (Regnault-Roger and Hamraoui, 1994; Ketoh et al., 2005), as well as excellent antimicrobial activity (Smith-Palmer et al., 1998; Seow et al., 2014; Dhara and Tripathi, 2013). However, most of essential oils are volatile, unstable to light and heat, easy to decompose, et c, and so which are mainly used together with chemical pesticide to reduce the dosage of chemical pesticide nowadays (Abbassy et al., 2009; Wen et al., 2013; Tong and Bloomquist, 2013). On the other hand, growing concern about the biological activity difference between the enantiomers *via* chiral synthesis has becoming an active field in drug design. Among them, camphorsultam and its derivatives have been widely used in the asymmetric synthesis as chiral auxiliary agents (Cao and Liu, 2011). It provides us a new approach to obtain chiral carboxylic acid through high regioselectivity and high diastereoselectivity conjugate addition reaction, which has been introduced by chiral auxiliary in the Grignard reagent and unsaturated carbonyl compounds reaction system. Meanwhile, during the past two decades, the excessive use of pyrethriods led to the rapid development of resistance (Wang et al., 2012; Wolansky and Harrill, 2008). Therefore, an effort is urgent needed to find new insecticidal chemical structures as alternatives to the existing ones.

Thus, based on the aforementioned results, we decided to combine the essential oil molecules to the newly prepared chiral building blocks such as 2-(4-chlorophenyl)-3-methylbutanoic acid analogues. We think that the hybridization of these two moieties could result in functional synergy that leads to target molecules with interesting biological properties. Setting pyrethroid molecules as the structure model (Fig. 1), we selected some alcohols and phenols from essential oils to splice with the chiral carboxylic acid moieties which can be obtained *via* the asymmetric synthesis. Accordingly, a series of novel essential oils oriented chiral pyrethroid analogues have been synthesized by asymmetric synthesis method, and all newly synthesized chiral compounds have been screened for their potential insecticidal activity against *Plutella xylostella*. About half of the target compounds' activities have an obvious improvement comparing with the essential oil molecules.

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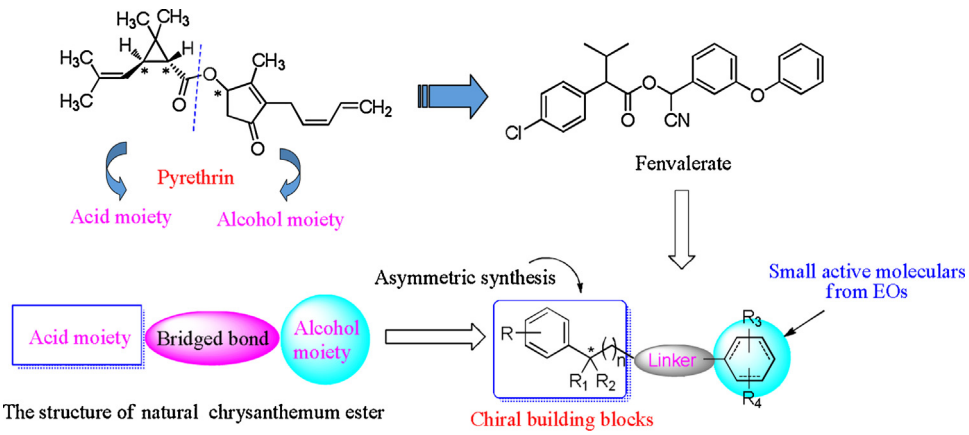

Fig. 1. Design strategy of essential oils oriented chiral pyrethroid analogues.

2. Materials and methods

2.1. Instrumentation and chemicals

Melting points (m.p.) were determined on a RY-2 apparatus and are uncorrected. Optical rotations were measured with a Jasco P-1010 polarimeter at 25 °C. ^{1}H NMR spectra were recorded on a Brucker spectrometer with $CDCl_3$ as solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Coupling constants ^nJ are reported in Hz. Mass spectra were performed on a MicroMass Quattro micro™ API instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates, and spots were visualized with ultraviolet light. Column chromatography was carried out on silica gel (200–300 mesh, Qingdao Haiyang Chemical). Anhydrous solvents such as tetrahydrofuran (THF) were dried according to standard methods. All other solvents and reagents were analytical reagent and used directly without purification.

2.2. General synthetic procedure for chiral carboxylic acid **2**

A solution of **1** (8 mmol) in THF/H_2O (40 mL THF, 10 mL H_2O) was cooled to 0 °C, to which lithium hydroxide (9.6 mmol) and hydrogen peroxide (19.2 mmol) was added in. After 12 h reaction, a small amount of sodium sulfite was added in to remove the excess hydrogen peroxide. Then 2 N HCl was added dropwise to adjust the pH value to 2–3. The reaction mixture was extracted with ether (2 × 30 mL). The combined organic layers were washed with brine (50 mL), concentrated under vacuum, and purified by silica gel chromatography to get pure acids **2** and auxiliary sultam.

2.3. General synthetic procedure for target compounds **3**

A solution of acid **2** (2 mmol) and alcohol (phenol) of essential oil (2 mmol) in CH_3CN (10 mL) was stirred under room temperature, to which a catalytic amount of DMAP (0.1 g) and dicyclohexylcarbodiimide (2.4 mmol) was added after the solid in the solution has absolutely dissolved. And then the mixture was stirred for another 10 h. The precipitate of DCU was removed by filtration through a Buchner funnel, and the filtrate was washed with two 20 mL portions of saturated sodium carbonate solution and three 20 mL portions of saturated sodium chloride solution. The organic solution was dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. Column chromatography separating of the concentrate gave the desired products **3**, and all the characterization data for the target molecules were included in the Supplementary data.

2.4. Biological assay

Plutella xylostella cultivated from our laboratory were used as general tested species. The standard assay was performed by placing artificial diets (300 μL) in a 24-well or 96-well microtiter plates, which were covered with the solution of different tested concentration compounds in ethanol (20 μL). Ethanol alone was used as a control. When the ethanol was completely evaporated leaving the effective compounds as a coat on the surface of the artificial diets, the tested species were introduced and the culture plates was closed with a plastic cover. Mortality in the assay was recorded at 96 h, and each treatment was replicated three times.

3. Results and discussion

3.1. Synthesis

The important chiral intermediates **1** were obtained by highly diastereoselectivity conjugate addition of Grignard reagents to *N*-enoylsultams (Vandewalle et al., 1986) according to the modified methods (Cao et al., 2008, 2009). Hydrolysis of adducts **1** under mild conditions provided the chiral acids **2**. The mixture of **2** and auxiliary sultam were separated by silica gel column chromatography to get pure acids **2** and auxiliary sultam, and the chiral auxiliary can also be recycling and reusing. The following convenient esterification reaction of chiral acids **2** with various alcohols (phenol) of essential oils gave the target chiral esters **3**.

The general methods for the preparation of chiral pyrethroid analogues **3** are outlined in Scheme 1, and the target molecules were obtained in good to excellent yields as summarized in Table 1. All compounds **3-A1-R – 3-E1-S** were characterized by NMR spectroscopy, MS data, [α] 25D, and gave satisfactory chemical analyses, and the chemical structures of the synthesized compounds were also described in Table 1.

3.2. Spectroscopy

The analytical data for all target compounds gave satisfactory chemical analyses, which including optical rotation, ^{1}H NMR and ESI–MS. The ^{1}H NMR spectra of compounds **3** indicated distinctive signals of protons for substituted aryl moieties, which presented several groups of peaks in the range 6.4-7.5 ppm. The general signals at higher fields in their ^{1}H NMR spectra were assigned to the alkyl protons attached to the chiral units and the aromatic ring respectively as shown in the representative spectra (Fig. 2). Mass spectra, in particular, also showed the molecular ion peaks at the appropriate *m*/*z* values. Especially, the optical rotations for all *R*