JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

ARTICLE

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Design, Synthesis, Structure, and Acaricidal/Insecticidal Activity of Novel Spirocyclic Tetronic Acid Derivatives Containing an Oxalyl Moiety

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Supporting Information

ABSTRACT: A series of novel spirocyclic tetronic acid derivatives containing an oxalyl moiety was designed and synthesized via the key intermediate 3-(2,4,6-trimethyl)-2-oxo-1-oxaspiro[4.4]-decyl-3-en-4-ol. The target compounds were identified by ^{1}H NMR and elemental analysis or high-resolution mass spectrum (HRMS). The results of bioassays indicated that most of the target compounds possessed excellent acaricidal activities against carmine spider mite larvae and eggs. Especially, diisopropylamino oxalyl compound **7g** and piperidine oxalyl compound **7h** were 1.4- and 2.3-fold as high as the activities of commercial Spiromesifen, respectively, against spider mite eggs. Moreover, most of the target compounds exhibited insecticidal activities against Lepidoptera pest. Interestingly, compounds containing alkylamino-substituted oxalyl moiety showed obvious selectivity between spider mite larvae and eggs because the activities against spider mite eggs of **7g** and **7h** were 25-fold those against spider mite larvae, whereas Spiromesifen had no significant differences in these activities. This meant that the introduction of an oxalyl moiety to spirocyclic tetronic acid might lead to novel biological activity characteristics.

KEYWORDS: spirocyclic tetronic acid, oxalyl moiety, acetyl coenzyme A carboxylase (ACCase), acaricidal activity, insecticidal activity

INTRODUCTION

Phytophagous mite is one of the most important pest species; it is responsible for significant yield losses in many important agricultural and horticultural cropping systems worldwide, such as tomato, pepper, watermelon, bean, onion, and amaranth.[1] It includes the two-spotted spider mite (*Tetranychus urticae* Koch), the carmine spider mite (*Tetranychus cinnabarinus*), and the European red mite (*Panonychus ulmi*), etc. Their extremely short life cycle and high reproductive potential coupled with frequent applications of acaricides facilitate their resistance development to many important acaricides, resulting in control failure,[2−4] so finding acaricidal compounds with new modes of action becomes an important way to overcome this problem.[5]

Spirocyclic tetronic acid derivatives are novel pesticides developed by Bayer Cropscience AG. Spirodiclofen (BAJ2740) and Spiromesifen (BSN2060) are two representative commercial varieties,[1,6,7] both of which are broad-spectrum acaricides with excellent efficacy against all relevant phytophagous mite species such as *Panonychus*, *Tetranychus*, *Phyllocoptruta*, *Brevipalpus*, and *Aculus*.[8,9] Research has shown that they could inhibit lipid synthesis, and further analysis of enzymes suggested they have a selective and potent inhibition on acetyl coenzyme A carboxylase.[10] This meant they had novel modes of action compared to other acaricides, thus avoiding cross-resistance with them.

The discovery process of Spirodiclofen and Spiromesifen had been reported and is drawn in Figure 1.[7] Compound **A** was first studied as a herbicide, whereas the central nitrogen atom was replaced by a carbon atom, leading to structures **B1** and **B2**, and **B2** showed acaricidal activity. Further research gave compounds **C1** and **C2** with good acaricidal activity but low plant compatibility. Finally, compound **D** was found, which showed both good acaricidal activity and good plant compatibility in all relevant crops. Using **D** as lead compound, a series of spirocyclic tetronic acid derivatives were synthesized and found to have high acaricidal activity, of which Spirodiclofen and Spiromesifen were selected to commercialize. From the discovery process we noted two important things. One was that different enols (**B1**, **C1**, and **D**) had different biological activities and selectivities, which indicated that the enol moiety was crucial to activity. Another phenomenon we found was that activities were sensitive to the acyl group. A slight modification at this location resulted in great change of activity (Figure 2).[11] In our opinion, introducing a tertiary butyl, isopropyl, or neopentyl at this location had no significant variation on the physical and chemical properties of these compounds. This meant that the change in activity could not be well explained by the changes in physical and chemical properties. Therefore, we speculated that the acyl group attached to the enol hydroxy group may be a key to the acaricidal activity of the spirocyclic tetronic acids.

Recent patent works on spirocyclic tetronic acid derivatives mainly focused on changing substituents on the benzene ring,[12] replacing the benzene ring with a heterocyclic ring,[13] changing the furanone ring,[14] and modifying the spirocycle.[15] From the

Received: September 13, 2011
Revised: November 1, 2011
Accepted: November 1, 2011
Published: November 01, 2011

dx.doi.org/10.1021/jf203722z | J. Agric. Food Chem. 2011, 59, 12543–12549

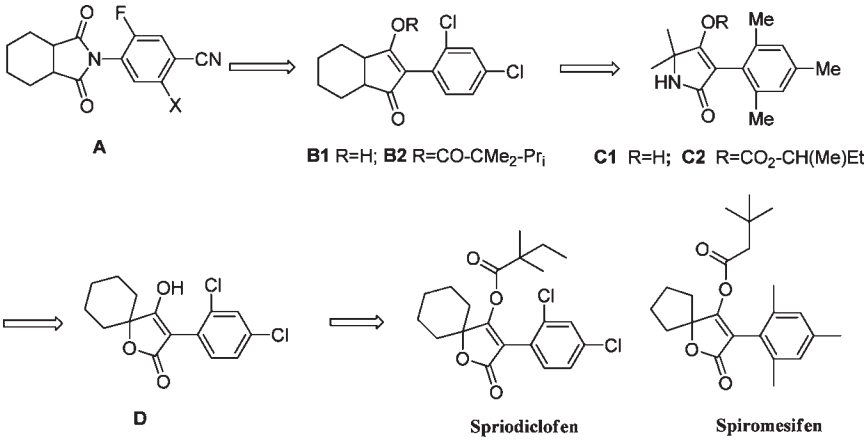
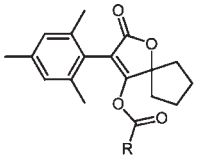


Figure 1. Discovery of Spirodiclofen and Spiromesifen.



R	0.0008% Kill in % after 14 days[b]
t-Bu	0
i-Pr	0
neo-pentyl[a]	95

[a] Spiromesifen. [b] Against plant-damaging insects Bemisia tabaci

Figure 2. Effect of variation in acyl group in Spiromesifen on insecticidal activity.

literature we can see there was no special research on the effect of variation in acyl group in these compounds.

In our previous work on 2-arylpyrrole and Tebufenozide derivatives we found that the oxalyl moiety displayed different physical properties compared to other substituent groups, which might lead to compounds with better biological activity and characteristics.[16,17] Also, we believed that the conformation of products might change a lot when using an oxalyl moiety in place of a neo-pentylcarbonyl group in Spiromesifen, and the changes would definitely affect the acaricide/insecticide activity. Herein, we report the synthesis and biological activity of different oxalyl-substituted 3-(2,4,6-trimethyl)-2-oxo-1-oxa-spiro[4.4]-decyl-3-en-4-ols (**7a**−**7n**).

MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were obtained at 400 MHz using a Bruker AC-P 400 spectrometer in $CDCl_3$ or DMSO solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in parts per million. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. HRMS data were obtained on an FTICR-MS instrument (Ionspec 7.0T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized.

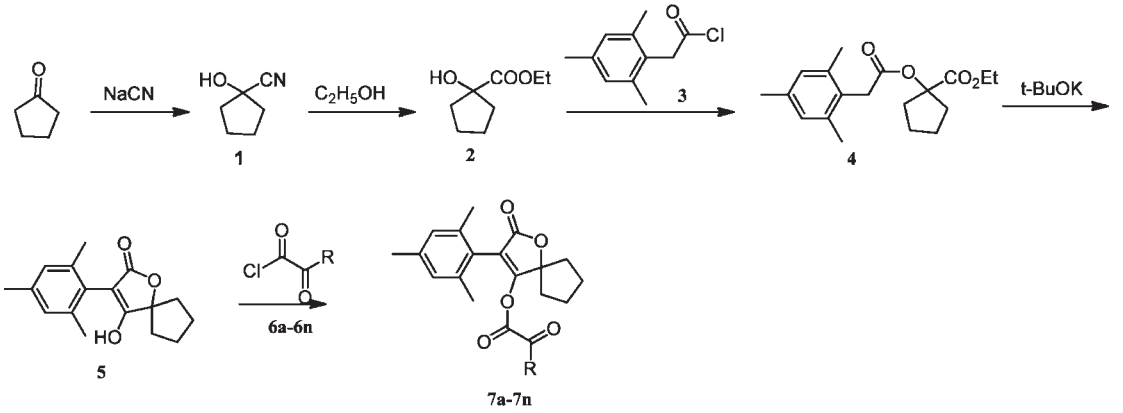
Ethyl 1-hydroxycyclopentanecarboxylate (**2**) was prepared according to the methods in the literature[18,19] using cyclopentanone as initial material. The key intermediate, 3-(2,4,6-trimethyl)-2-oxo-1-oxa-spiro-[4.4]-decyl-3-en-4-ol (**5**), was prepared according to the methods described in the reported patent.[20]

General Procedure for the Synthesis of 6a and 6b. To oxalyl chloride (200 mmol) was added dropwise appropriate alcohol (100 mmol) over 20 min at 0 °C. When the addition was completed, the mixture was allowed to warm to room temperature for an hour. Excess oxalyl chloride was removed by vacuum distillation. Further distillation afforded alkyloxy oxalyl chlorides **6a** and **6b**.

General Procedure for the Synthesis of 6c−6e and 6j−6n. The mixture of phenol (0.02 mol) or arylamine hydrochloride (0.02 mol) and oxalyl chloride (20 mL) was refluxed for 8 h. Excess oxalyl chloride was removed in vacuo, and to the residue oil was added toluene (30 mL). The resulting yellow solution was filtered to remove diaryl oxalate or remaining arylamines hydrochloride, and then the filtrate was concentrated in vacuo. The remaining oil solidified upon cooling. Recrystallization from toluene gave the product as white crystal.

General Procedure for the Synthesis of 6f−6i. To a mixture of 20% K_2CO_3 aqueous solution (35 mL) and toluene (40 mL) was added alkylamine (0.05 mol). The mixture was cooled to 0 °C, and then a solution of ethyl oxalyl monochloride (0.06 mol) in toluene (15 mL) was added dropwise within 30 min. After 1 h of stirring at room temperature, the two layers were separated. To the organic layer was added 1 mol/L NaOH (60 mL), and the mixture was heated to 40 °C for 3 h. After cooling, the aqueous layer was separated and acidified with 2 mol/L HC1 to pH 2, and water was removed in vacuo. To the remaining white solid was added ethyl acetate (60 mL), and the mixture was filtered. Then the filtrate was dried over magnesium sulfate and concentrated in vacuo. The corresponding acid was obtained as a white solid with 80−90% yield. To the resulting acid was added $SOCl_2$ (20 mL) followed by 6 h of refluxing. Excess $SOCl_2$ was removed by vacuum distillation, and then **6f**−**6i** were obtained through reduced pressure distillation.

Scheme 1. General Synthetic Route for the Target Compounds 7a−7n



General Procedure for the Synthesis of Target Compounds 7a−7n. To a solution of **5** (2 mmol) in toluene (30 mL) was added DMAP (0.2 mmol), and the mixture was stirred at room temperature for 5 min. Acyl chloride (2.4 mmol) in toluene (10 mL) was added dropwise in 30 min, and then the mixture was refluxed and monitored by TLC. As soon as **5** disappeared, the solution was cooled and then successively washed with water (20 mL), saturated $NaHCO_3$ (2 × 20 mL), and saturated salt solution (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo, and the crude product was purified by recrystallization or column chromatography. The physical data in detail can be found in the Supporting Information.

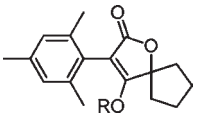
X-ray Diffraction. The crystal structure of compounds **7h** and **7i** were determined, and X-ray intensity data were recorded on a Bruker SMART 1000 CCD diffraction meter using graphite monochromated Mo K radiation (λ = 0.71073 Å). All calculations were refined anisotropically. All hydrogen atoms were located from a difference Fourier map and were placed at calculated positions and were included in the refinements in the riding mode with isotropic thermal parameters.

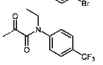
Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.[21] Evaluations were based on a percentage scale of 0−100, where 0 equals no activity and 100 equals total kill. Error of the experiments was 5%. For comparative purpose, Spiromesifen was tested under the same conditions.

Acaricidal Activity against Eggs of Spider Mite (*Tetranychus cinnabarinus*). The acaricidal activities of the target compounds **7a−7n** and the contrast compound Spiromesifen against eggs of spider mite were evaluated using the reported procedure.[16] Sieva bean plants (*Phaseolus vulgaris* L.) with two primary leaves expanded to 10 cm were selected and cut back to one plant per pot. The female mites were taken from the main colony and placed on leaves of the test plants using a fine brush; each leaf had seven mites. About 24 h later, the adult mites were removed, obtaining about 60−100 eggs per plant. The leaves were kept for no more than 24 h before treatment. The mite-egg-infested leaves were dipped into the test solution for 3 s with agitation, excess liquid was removed by shaking, and then the leaves were placed in a tube (10 cm inner diameter) lined with a piece of filter paper. Percentage mortalities were evaluated 4 days after treatment, and three replicates were carried out.

Acaricidal Activity against Larvae of Spider Mite (*Tetranychus cinnabarinus*). The acaricidal activities of the target compounds **7a−7n** and the contrast compound Spiromesifen against larvae of spider mite were evaluated using a reported procedure.[16] The mite-egg-infested leaves (eggs that were laid on the same day) were kept at 25 °C for 4 days. Then they were placed on leaves of tested plant as above. After 1 day, the larvae were hatched and moved to the fresh leaves. Each leaf was about 60−100 mites. The leaf was cut and dipped into the test solution for 3 s, the excess liquid was removed, and then the leaf was placed in a tube (10 cm inner diameter) lined with a piece of filter paper. Percentage mortalities were evaluated 4 days after treatment, and three replicates were carried out.

Table 1. Structures of Target Compounds

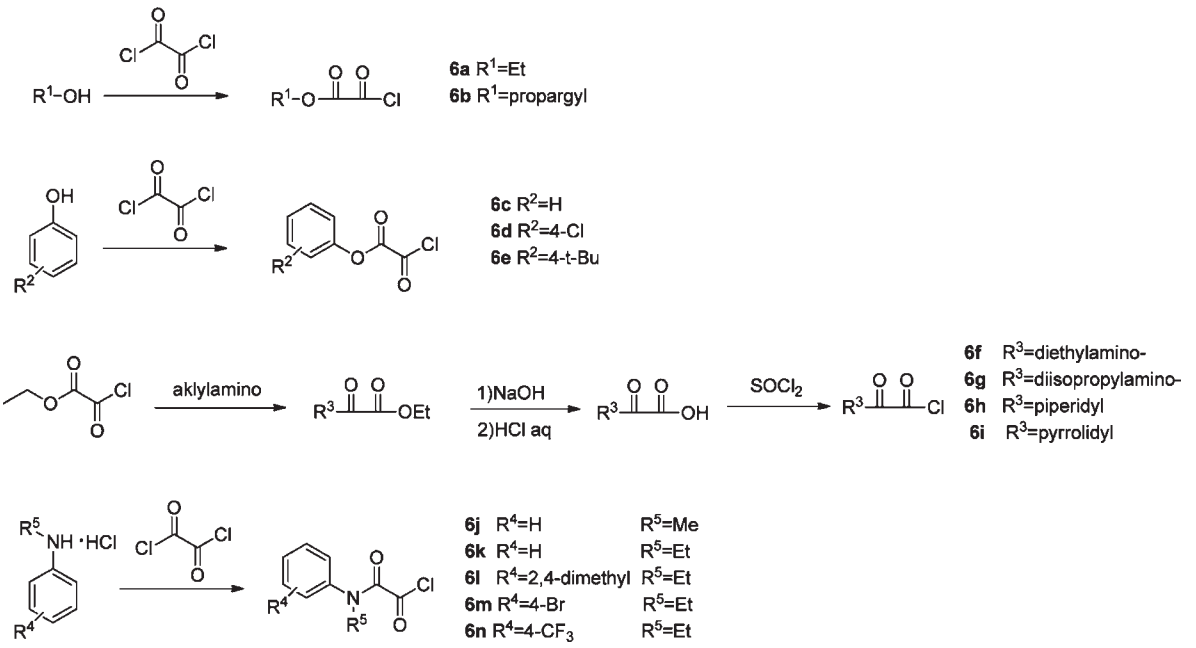


compd	R	compd	R	compd	R
7a		**7f**		**7k**	
7b		**7g**		**7l**	
7c		**7h**		**7m**	
7d		**7i**		**7n**	
7e		**7j**		Spriomesifen	

Stomach Toxicity against Oriental Armyworm (*Mythimna separata*). The insecticidal activities of the target compounds **7a−7n** and the contrast compound Spiromesifen against oriental armyworm were evaluated by foliar application using the reported procedure.[22,23] Individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed three times.

Stomach Toxicity against Diamondback Moth (*Plutella xylostella*). The stomach toxicities of the target compounds **7a−7n** and the contrast compound Spiromesifen against diamondback moth were tested by the leaf dip method using the reported procedure.[22,23] Leaf disks (6 cm × 2 cm) were cut from fresh cabbage leaves and then dipped into the test solution for 3 s. After air-drying, the treated leaf disks were placed individually into glass tubes. Each dried treated leaf disk was infested with seven third-instar diamondback moth larvae. Percentage mortalities were evaluated 4 days after treatment. Leaves treated with

Scheme 2. Acyl Chloride Synthesis



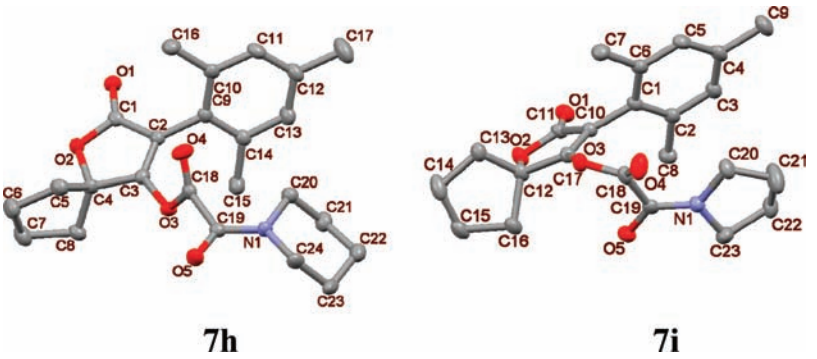


Figure 3. Single-crystal structures of **7h** and **7i**.

water and dimethylformamide were provided as controls. Each treatment was performed three times.

Stomach Toxicity against Corn Borer (*Ostrinia nubilalis*). The stomach toxicities of the target compounds **7a**−**7n** and the contrast compound Spiromesifen against corn borer were tested by the leaf-dip method using the reported procedure.[22,23] Leaf disks (about 5 cm) were cut from fresh corn leaves and then dipped into the test solution for 3−5 s. After air-drying, the treated leaf disks were placed individually into a glass surface vessel (7 cm). Each dried treated leaf disk was infested with 10 third-instar corn borer larvae. Percentage mortalities were evaluated 4 days after treatment. Leaves treated with acetone were provided as controls.

Stomach Toxicities against Cotton Bollworm (*Helicoverpa armigera*). The stomach toxicities of the title compounds **7a**−**7n** and the contrast Spiromesifen against cotton bollworm were tested by the leaf-dip method using the reported procedure.[22,23] Corn leaves were dipped into the test solution. After air-drying, the treated leaf disks were placed individually into boxes that had 24 holes. Each dried treated leaf disk was infested with 10 third-instar cotton bollworm larvae. Percentage mortalities were evaluated 4 days after treatment.

RESULTS AND DISCUSSION

Chemistry. The target compounds **7a**−**7n** were prepared from 3-(2,4,6-trimethyl)-2-oxo-1-oxaspiro[4.4]-decyl-3-en-4-ol (**5**) with different substituted oxalyl chlorides (Scheme 1). **7a**, **7b**, and **7f**−**7i** were obtained successfully using DAMP as catalyst, but the synthesis of **7c**−**7e** and **7j**−**7n** needed equivalent DMAP due to the low activities of corresponding oxalyl chloride. The structures of the target compounds are listed in Table 1.

Oxalyl chlorides **6a**−**6n** were synthesized using different methods according to Scheme 2. **6a** and **6b** were synthesized easily by dropping the corresponding alcohol in excess oxalyl chloride. Aryl chloroformylformates were reported[17,24,25] to use phenol or phenolate reacting with oxalyl chloride in the presence of a base at room temperature. However, when these methods were applied to our substrates, either the reactions failed or the conversion was poor. Inceasing the reaction temperature only made the reaction mixture complex and hard to purify. Because diaryl oxalate was separated as the main byproduct, we then let

phenol reflux in excess oxalyl chloride. The reaction was found to work well and gave only a little diaryl oxalate, which could be removed by filtration after distilling excess oxalyl chloride. By using the above purification method, pure aryl chloroformylformates **6c**−**6e** were obtained. In the synthesis of aryl chloroformylformides **6j**−**6n**, a similar problem was encountered when using the reported procedure.[26−28] The reaction was hard to control when using arylamine as starting material and a large amount of diaryloxalamide formed. Our procedure for preparing **6c**−**6e** could not give the desired product either. Using arylamine hydrochloride to reflux in excess oxalyl chloride successfully solved the problem,[29] by which pure **6j**−**6n** were obtained as white crystals. To obtain alkyl chloroformylformides **6f**−**6i**, the same procedure was tried, but the alkylamine hydrochloride was so active that a large amount of dialkyloxalamide formed and the target product was hard to purify. Therefore, the procedure described in Scheme 2 was used. Alkylamine was first reacted with ethyl chloroformylformate, and the ester conducted hydrolysis to get the corresponding acid, then the acid was treated with $SOCl_2$ to get the corresponding acyl chloride.[16] At first, when we repeated the procedure described in the literature the corresponding acids were obtained at very low yields (<40%). We found these acids had good solubility in water and were hard to extract completely from the water layer. We then altered the workup procedure. After hydrolysis and acidification of the water layer, water was removed in vacuo. To the remaining solid was added ethyl acetate, the inorganic salt was filtered, and then the filtrate was concentrated to give acid in 80−90% yield. Alkyl chloroformylformides **6f**−**6i** were then synthesized by refluxing the corresponding acid in $SOCl_2$.

Crystal Structure Analysis. Compound **7h** was recrystallized from ethyl acetate/petroleum ether (60−90 °C) to give colorless crystals (0.2 mm × 0.18 mm × 0.12 mm) suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a = 8.905 (2) Å, b = 11.210 (3) Å, c = 11.742 (3) Å, α = 86.40 (1)°, β = 73.81 (2)°, γ = 74.92 (3)°, μ = 0.09 mm^{-1}, V = 1086.80 Å^3, Z = 2, Dx = 1.257 mg m^{-3}, $F(000)$ = 440.0, T = 113 (2) K, 1.81° < θ < 27.89°, final R factor = 3.71%. Compound **7i** was recrystallized from dichloromethane/petroleum ether to gave colorless crystals (0.2 mm × 0.18 mm × 0.10 mm) suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a = 8.256 (4) Å, b = 10.973 (4) Å, c = 12.469 (4) Å, α = 65.90 (2)°, β = 78.69 (3)°, γ = 76.39 (2)°, μ = 0.09 mm^{-1}, V = 995.83 Å^3, Z = 2, Dx = 1.326 mg m^{-3}, $F(000)$ = 424.0, T = 113 (2) K, 1.80° < θ < 27.90°, final R factor = 4.39%. Their structures are shown in Figure 3. The dihedral angels of **7h** and **7i** are shown in Table 2.

Bioassays. *Acaricidal Activities against Spider Mite (T. cinnabarinus Boisduval) Larvae.* Table 3 shows the acaricidal activities of the target compounds **7a**−**7n** and contrast compound Spiromesifen against spider mite (*T. cinnabarinus* Boisduval) larvae and eggs. All of the target compounds possess moderate to excellent activities against *T. cinnabarinus* larvae. Most of the compounds showed 100% activity at 10 mg kg^{-1} except compounds **7a**, **7b**, **7i**, and **7j**, which showed 50, 30, 40, and 80% activities, respectively. Upon comparison of the activity of alkoxy (**7a**, **7b**) with aryloxy (**7c**, **7d**, **7e**) derivatives, we found that the aryloxy derivatives showed a 10-fold higher activity. For example, the activities of alkoxy oxalyl substituted derivatives **7a** and **7b** were 50 and 30% at 10 mg kg^{-1}, whereas aryloxy oxalyl substituted derivatives **7c**, **7d**, and **7e** were 50, 60, and 60%, respectively, even at 1 mg kg^{-1}. Also, the alkylamino and arylamino oxalyl derivatives showed the same rule, but the substituents on the aromatic ring showed no significant effect on the activity. For example, the activities of different substituted

Table 2. Dihedral Angles of 7h and 7i

			angle (deg)	
no.	plane 1	plane 2	**7h**	**7i**
I	benzene ring	furanone ring	67.95	61.24
II	benzene ring	cyclopentane	24.00	26.20
III	furanone ring	cyclopentane	88.12	87.54
IV	nitrogen heterocycle	furanone ring	46.91	60.53
V	nitrogen heterocycle	cyclopentane	87.24	27.12
VI	nitrogen heterocycle	benzene ring	69.99	4.15

Table 3. Acaricidal Activities of the Target Compounds against Spider Mite

	acaricidal activity (%) against spider mite larvae at concn of					acaricidal activity (%) against spider mite eggs at concn of						
compd	10 mg kg^{-1}	5 mg kg^{-1}	2.5 mg kg^{-1}	1 mg kg^{-1}	0.5 mg kg^{-1}	5 mg kg^{-1}	2.5 mg kg^{-1}	1 mg kg^{-1}	0.5 mg kg^{-1}	0.25 mg kg^{-1}	0.1 mg kg^{-1}	0.05 mg kg^{-1}
7a	50	0				20						
7b	30	0				30						
7c	100	90	80	50	20	100	100	70	50			
7d	100	90	70	60	0	100	100	90	80	60		
7e	100	90	90	60	40	90	70	50				
7f	100	100	90	70		100	100	60	0			
7g	100	80	40			100	100	100	100	80	40	10
7h	100	90	70			100	100	100	100	100	60	30
7i	40	0				70	30					
7j	80	70	40	0		100	100	100	100	50		
7k	100	100	90	80	60	100	100	90	50	30		
7l	100	100	90	60	20	100	90	70	30			
7m	100	100	100	90	50	100	100	90	60	40		
7n	100	100	80	50	40	100	90	90	80	60		
Spiromesifen	100	100	100	90	90	100	100	90	90	60	20	0

Table 4. LC_{50} Values of 7g and 7h and Spiromesifen against Spider Mite Eggs

compd	$y = a + bx$	LC_{50} (mg kg^{-1})	toxic ratio
7g	$y = 0.7159 + 0.2296x$	0.1147	1.4
7h	$y = 0.7271 + 0.1939x$	0.0675	2.3
Spiromesifen	$y = 0.6614 + 0.2006x$	0.1567	1

phenol derivatives **7c**, **7d**, and **7e** were of the same level, and different substituted aniline derivatives **7k**, **7l**, **7m**, and **7n** had similar activities at 0.5 mg kg^{-1}. However, considering another substituent on the nitrogen atom of aniline, ethyl was a little better than methyl, which could be deduced from the activity of **7j** and **7k**. Among aklylamino derivatives **7f**—**7i**, when the substituent became bigger, the activity became a little lower. For example, diethylamino derivative **7f** showed 90% mortality at 2.5 mg kg^{-1}, whereas diisopropylamino derivative **7g** and piperidine derivative **7h** showed 40 and 70% mortality, respectively, at the same concentration. When it was changed to pyrrolidine **7i**, the mortality was only 40% even at 10 mg kg^{-1}.

Acaricidal Activities against Spider Mite (T. cinnabarinus Boisduval) Eggs. The results of acaricidal activities given in Table 3 indicated that all of the target compounds possessed moderate to excellent activities against *T. cinnabarinus* eggs. Compounds **7d**, **7g**, **7h**, **7j**, **7k**, **7m**, and **7n** showed >90% mortality at 1 mg kg^{-1}. Especially, **7g** and **7h** showed higher activities than Spiromesifen at lower concentration. The LC_{50} values in Table 4 showed that the activities of **7g** and **7h** were 1.4- and 2.3-fold as high as Spiromesifen, respectively.

Alkoxy and aryloxy derivatives **7a**—**7e** had the same structure—activity relationship as activities against spider mite larvae, with the aryloxy moieties better. However, the *p*-tertiary butyl compound **7e** had the best activities against spider mite larvae, whereas the *p*-chlorinephenol compound was the best against eggs.

Turning to the amino derivatives, it was hard to say whether the arylamino groups or aklylamino groups were better. For the arylamino derivatives, the introduction of a substituent group in the benzene ring had no significant effect on activity. It could be seen from the phenomenon that **7k**, **7l**, **7m**, and **7n** caused 50, 30, 60, and 80% mortality, respectively, at 0.5 mg kg^{-1}, but it was observed that when the alkyl group at the nitrogen atom became bigger, their activity became lower, which was adverse to the activities against spider mite larvae. For example, *N*-methyl-*N*-phenylamino compound **7j** caused 100% mortality at 0.5 mg kg^{-1}, but *N*-ethyl-*N*-phenylamino compound **7k** was only 50%. For the alkylamino derivatives, the larger the groups on the nitrogen atom, the better the activities were. For example, diisopropylamino derivative **7g** and the piperidine derivative **7h** were much more effective than diethylamino derivative **7f**. Both **7g** and **7h** could cause 100% mortality at 0.5 mg kg^{-1}, whereas **7f** caused no detectable mortality at this concentration. Similarly, to the activities against spider mite larvae, when the pyrrolidine was introduced, the activity reduced greatly. Why did **7h** and **7i** have similar structures, but show very different activities? This question was answered by determining their X-ray crystal structures. Although the two molecules had only one atom change, their structures changed a lot, which could be clearly seen from their single-crystal structures (Figure 3). The nitrogen heterocycles had totally different positions corresponding to benzene ring. In **7h** piperidine ring has a 69.99° dihedral angel with benzene ring, whereas in **7i** the two planes were almost parallel (Table 2). We supposed that it was the differences in structural conformation that led to the large differences in the overall activity.

Table 5. Insecticidal Activities of the Target Compounds against Lepidoptera Pest (Mortality, Percent)

compd	cotton bollworm (600 mg kg^{-1})	corn borer (600 mg kg^{-1})	oriental armyworm (600 mg kg^{-1})	diamondback moth (200 mg kg^{-1})
7a	10	20	80	70
7b	20	70	50	*c*
7c	20	60	100[a]/0[b]	60
7d	30	50	70	*c*
7e	10	10	80	*c*
7f	20	30	100[a]/40[b]	85
7g	40	80	50	*c*
7h	30	40	40	*c*
7i	30	30	40	*c*
7j	50	30	80	70
7k	40	40	40	*c*
7l	20	20	30	*c*
7m	30	40	80	*c*
7n	10	30	50	*c*
Spiromesifen	50	60	100[a]/60[b]	70

[a] Activities at 100 mg kg^{-1}. [b] Activities at 50 mg kg^{-1}. [c] Untested.

Insecticidal Activities against Lepidoptera Pests. The insecticidal activities of the target compounds **7a**—**7n** against oriental armyworm (*M. separata*), diamondback moth (*P. xylostella*), corn borer (*O. nubilalis*), and cotton bollworm (*H. armigera*) are listed in Table 5. It could be seen that most of the target compounds showed insecticidal activities against Lepidoptera pest, and their activities were at the same level. Interestingly, compounds **7c** and **7f** had remarkable insecticidal activities against oriental armyworm. For example, they showed 100% mortality even at 100 mg kg^{-1}, whereas other compounds showed <100% mortality at 600 mg kg^{-1}. However, at 50 mg kg^{-1}, the activities of **7c** and **7f** reduced to 0 and 40%, respectively, whereas the mortality of Spiromesifen maintained at 60%.

In summary, a series of spirocyclic tetronic acid derivatives containing an oxalyl moiety were designed and synthesized via the key intermediate 3-(2,4,6-trimethyl)-2-oxo-1-oxaspiro[4.4]-decyl-3-en-4-ol. The results of bioassays indicated that most of the target compounds possessed excellent acaricidal activities against spider mite larvae and eggs and exhibited insecticidal activities against Lepidoptera pest. In particular, diisopropylamino oxalyl compound **7g** and piperidine oxalyl compound **7h** showed 1.4- and 2.3-fold higher activities than Spiromesifen, respectively, against spider mite eggs. Single-crystal structure analysis of piperidine oxalyl compound **7h** and pyrrolidine oxalyl compound **7i** indicated that the conformation of oxalyl group led to a great change of activity, which confirmed our ideas. Furthermore, the activities of alkylamino-containing compounds showed structure—activity relationships against spider mite larvae and eggs different from that of Spiromesifen. It could be seen from the table that the activities against spider mite egg of **7g** and **7h** were 25-fold those against spider mite larvae, whereas Spiromesifen had no significant differences in these activities. This means that the introduction of an oxalyl moiety to spirocyclic tetronic acid might lead to novel biological activity characteristics.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization of target compounds and boiling points of **6a**, **6b**, **6f**, **6g**, **6 h**, and **6i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding Sources

This work was supported by the National Key Project for Basic Research (2010CB126106), the National Natural Science Foundation of China (21072109), and the National Key Technologies R&D Program(2011BAE06B05).

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