Chimia 57 (2003) 697–701

ISSN 0009–4293

Spirodiclofen and Spiromesifen – Novel Acaricidal and Insecticidal Tetronic Acid Derivatives with a New Mode of Action

Thomas Bretschneider[a]*, Jordi Benet-Buchholz[b], Reiner Fischer[a], and Ralf Nauen[a]

Abstract: The broad spectrum acaricides spirodiclofen (BAJ2740, trade name: Envidor®) and spiromesifen (BSN2060, trade name: Oberon®) with an additional excellent activity against whiteflies, both belong to the new chemical class of tetronic acid derivatives discovered at Bayer CropScience during the 1990s. The discovery process starting from herbicidal PPO (protoporphyrinogen oxidase) chemistry, the synthetic routes leading to the products, and some insight into process development of central intermediates is given. Spirodiclofen and spiromesifen have a new mode of action (interference with lipid biosynthesis), show no cross-resistance to any resistant mite or whitefly field population and are therefore valuable tools for resistance management.

Keywords: Acaricide · Insecticide · Spirodiclofen · Spiromesifen · Tetronic acid

Introduction

Spider mites (*e.g. Tetranychus spec.*) and whiteflies (*e.g. Bemisa* and *Trialeurodes*) belong to the most serious sucking pests and cause severe damage in many different agricultural and horticultural cropping systems world-wide (Fig. 1).

The broad spectrum acaricides spirodiclofen (BAJ2740, trade name: Envidor®) and spiromesifen (BSN2060, trade name: Oberon®) with high activity against whiteflies and mites, both belong to the new group of tetronic acid derivatives discovered at Bayer CropScience during the 1990s [1][2].

In the first part the discovery process of spirodiclofen and spiromesifen is presented. The synthetic routes leading to both products together with some remarks re-

Fig 1. Spidermite *Tetranychus urticae*

Whitefly *Bemisia tabaci*

*Correspondence: Dr. T. Bretschneider[a]
Tel.: +49 21 73 38 38 38
Fax: +49 21 73 38 41 07
E-Mail: thomas.bretschneider@bayercropscience.com
[a]Bayer CropScience AG
Research
Alfred Nobel Str.50
D-40789 Monheim
[b]Bayer Business Services
D-51368 Leverkusen

garding process chemistry follows. The last part deals with the new mode of action of these compounds and their great value to farmers resulting from the high activity against resistant mites and whiteflies worldwide.

Discovery

In the course of a synthesis program in the area of bicyclic N-aryl PPO herbicides of type **1** with activity against broad-leaved weeds the central nitrogen atom was replaced by a carbon atom leading to the corresponding C-aryl compounds (Fig. 2).

Interestingly the herbicidal activity of the 2,4-dichloro derivative **2** switched from the original broad activity of compound **1** to activity against grassy weeds. Biochemical work showed that we had a new class of herbicides acting on the acetyl CoA carboxylase (ACCase) in our hands, a target well known from the commercial cyclohexanedions (DIM) and aryloxyphenoxypropionate (FOP) herbicides [3].

Even more surprisingly the acylated derivative **2A** showed an acaricidal activity against *Tetranychus urticae*. To improve this activity many different aromatic substitution patterns were screened. The 2,4,6-trimethyl-phenyl ('mesityl') compounds **3** and their acylated derivatives **3A** showed an improved acaricidal activity against *Tetranychus urticae*, but were not satisfactory regarding another important mite species, *Panonychus ulmi*.

To improve this *Panonychus* activity a broad screening of the substitution on the 'left side' of the lead structures was performed. The monocyclic dimethyl-derivatives of type **4** and **4A** showed good activity against both relevant mite species, but caused phytotoxic effects in some crops.

To overcome this drawback the core structures of the molecules were modified. The synthesis of the tetronic acid analogues **5** and especially the acylated analogues like *e.g.* the pivaloyl derivative **5A** showed a high acaricidal potential together with an improved plant compatibility [4].

In some sensitive crops however, like stone fruits or grapes, we still observed phytotoxic effects under special conditions. Therefore, in a 'back to the roots' approach, we changed the mesityl substitution pattern back to the dichloro-type examined earlier in the program. This led to the enol **6** as a template that combined good acaricidal activity against both mite species and a good plant compatibility in all relevant crops. The 'fine tuning' of these properties was achieved by scanning a large set of different acylating reagents – the optimum was the 2,2-dimethyl-butyric acid derivative **7**, which was selected for development under the common name spirodiclofen (BAJ2740, trade name: Envidor®) [1].

During the acaricidal optimisation process it was noticed that several compounds, especially acylated 3-mesityl tetronic acids with a spiro cyclopentyl ring in position 5, showed additional excellent activity against white flies (*Bemisia tabaci*). The fine-tuning process regarding activity, spectrum and plant compatibility finally led to the 3,3-dimethyl-butyric acid derivative spiromesifen (**8**) (BSN2060, trade name: Oberon®) [2].

Some physicochemical properties of the new products are given in Fig. 2. Both have a relatively high partition coefficient logP (octanol/water) in the range of 4.5 to 5.8 and a low solubility in water of approximately 0.1 mg/l . Therefore after application on plants they mainly stay on the leaf and in the wax cuticle and are not systemic.

The X-ray structure analysis shows that both compounds crystallise in a monoclinic cell, Spirodiclofen (**7**) with the space group $P2_1/n$ and spiromesifen (**8**) $P2_1/c$ (Fig. 3). The torsion angles between the tetronic acid ring and the 3-phenylring are in the range of 50–60°, mainly due to steric

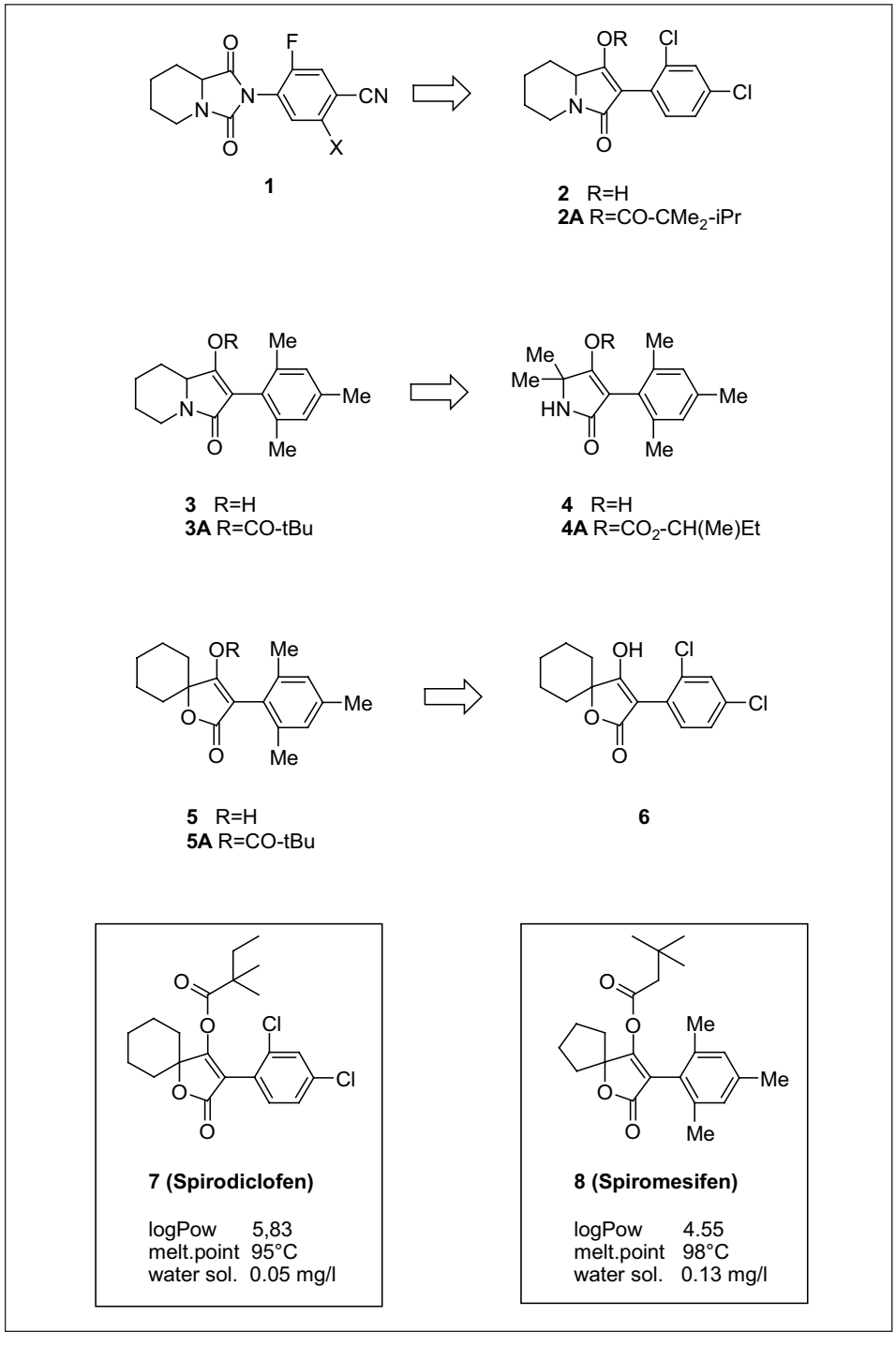


Fig. 2. Discovery of spirodiclofen (**7**) and spiromesifen (**8**)

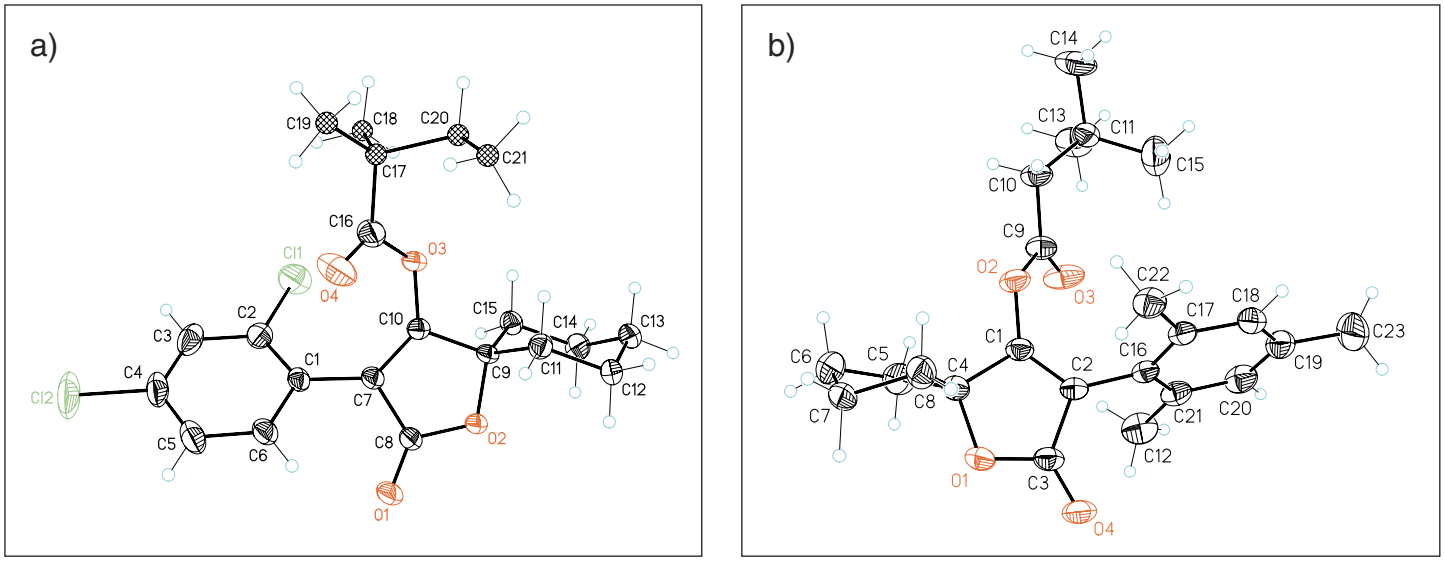
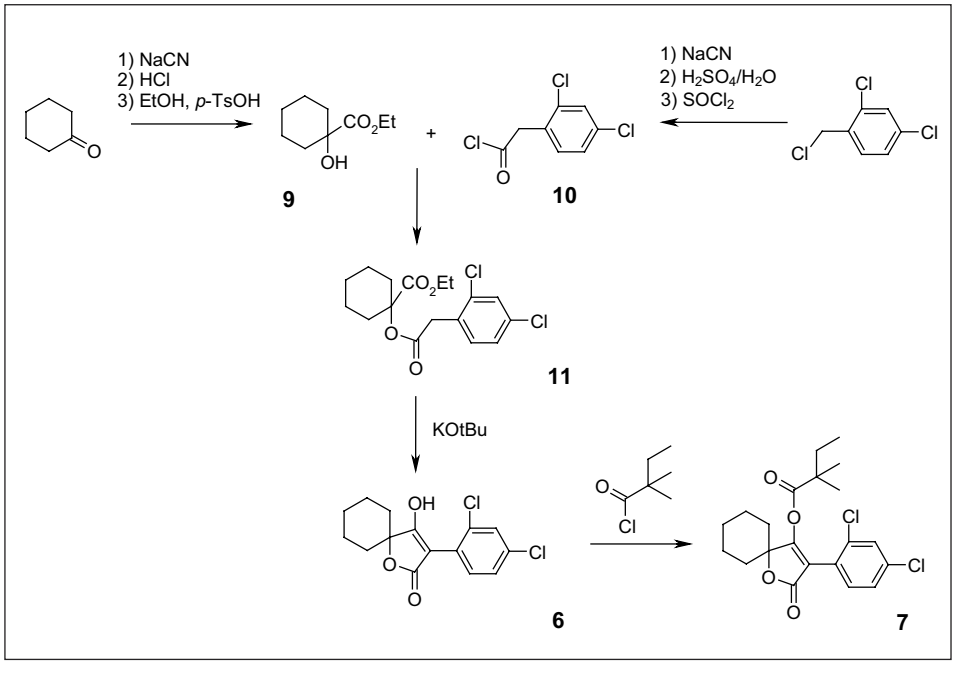


Fig. 3. X-ray structures of spirodiclofen (**7**) and spiromesifen (**8**). a) Structure of spirodiclofen (monoclinic cell, space group P21/n, phenyl ring–tetronic acid ring angle 49.7°). b) Structure of spiromesifen (monoclinic cell, space group P21/c, phenyl ring–tetronic acid ring angle 62.3°).



Scheme 1. Synthesis of spirodiclofen (**7**)

repulsions of the *ortho* substituents with the substituents in position 2 and 4 of the tetronic acid ring system.

Synthesis

The first central intermediate of the spirodiclofen (**7**) synthesis is ethyl 1-hydroxy-cyclohexanecarboxylate (**9**), which is synthesised from cyclohexanone by HCN addition to the cyanhydrine, followed by saponification and esterification. The second central intermediate is 2,4-dichlorophenylacetyl acid chloride (**10**), which is synthesised from 2,4-dichlorobenzyl chloride by cyanide exchange, saponification and acid chloride preparation.

The combination of these two building blocks leads in a convergent way to the 'diester' **11**, which is treated with a base, *e.g.* KOtBu, to form the tetronic acid **6**. The final acylation with 2,2-dimethyl-butyryl chloride leads to spirodiclofen (**7**) (Scheme 1).

Several possibilities for a large-scale synthesis of mesitylacetic acid **12**, a central building block in the synthesis of spiromesifen (**8**), were examined (Scheme 2). Using the classical standard route, mesitylene (**13**) is transferred into mesityl acetonitrile (**14**) *via* chloromethylation and cyanide exchange, which is then saponified to the aryl acetic acid. Another route examined was the Friedel-Crafts alkylation of mesitylene (**13**) with 1,3-dichloro-propene to the adduct **15**, which is ozonolysed to the corresponding aldehyde in form of its dimethyl acetal and than further oxidised with hydrogen peroxide under acidic conditions to mesityl acetic acid [5]. A straightforward route is the $AlCl_3$ mediated Friedel-Crafts alkylation of mesitylene with the C2-building block butyl methoxysulfonyl-oxyacetate yielding **16**, which is than saponified to the free acid [6].

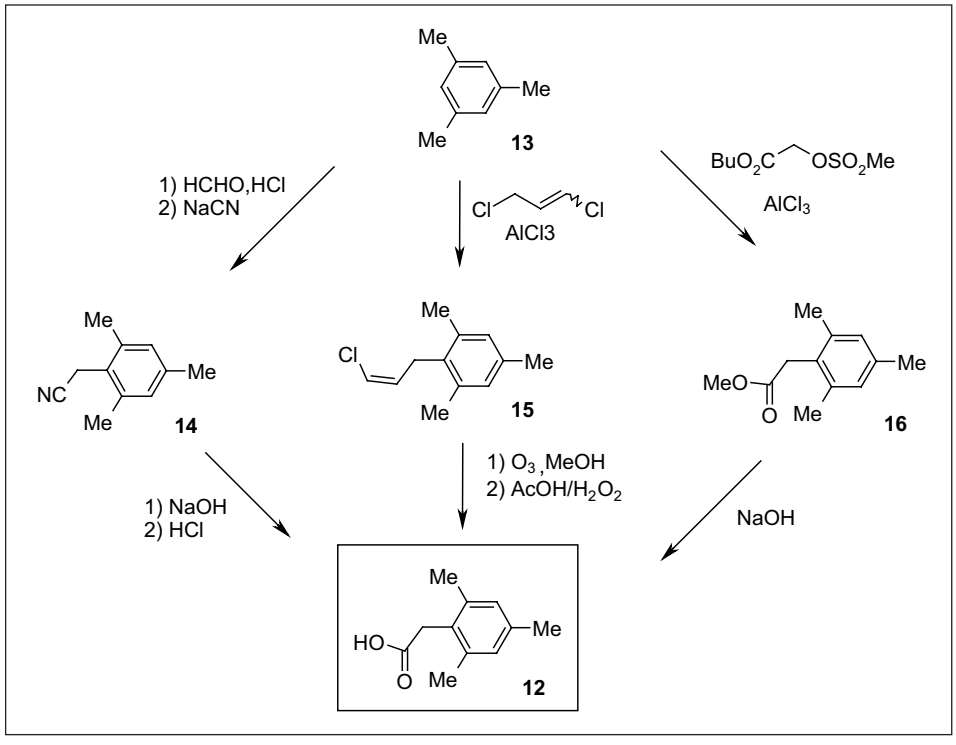
The further route to spiromesifen (**8**) is similar to the above shown spirodiclofen synthesis (Scheme 3). Acylation of the cyclopentyl hydroxyester **17** (synthesised from cyclopentanone *via* the classical cyanhydrine route in three steps) with mesitylacetyl chloride (**18**) leads to the intermediate **19**, which is cyclised to the tetronic acid **20** using *e.g.* potassium *tert*-butylate in DMF.

Several synthesis routes for the 3,3-dimethylbutyric acid (**23**), used as the acyl side chain in spiromesifen (**8**), were investigated. One interesting route starts from trimethylpyruvic acid (**21**), which is transferred to the corresponding hydrazone **22** using hydrazine hydrate (optionally in a solvent, *e.g.* triethylene glycol) followed by a reductive cleavage with a base, *e.g.* potassium hydroxide, at elevated temperatures. This whole process may also be conveniently done in a single step/one pot procedure [7].

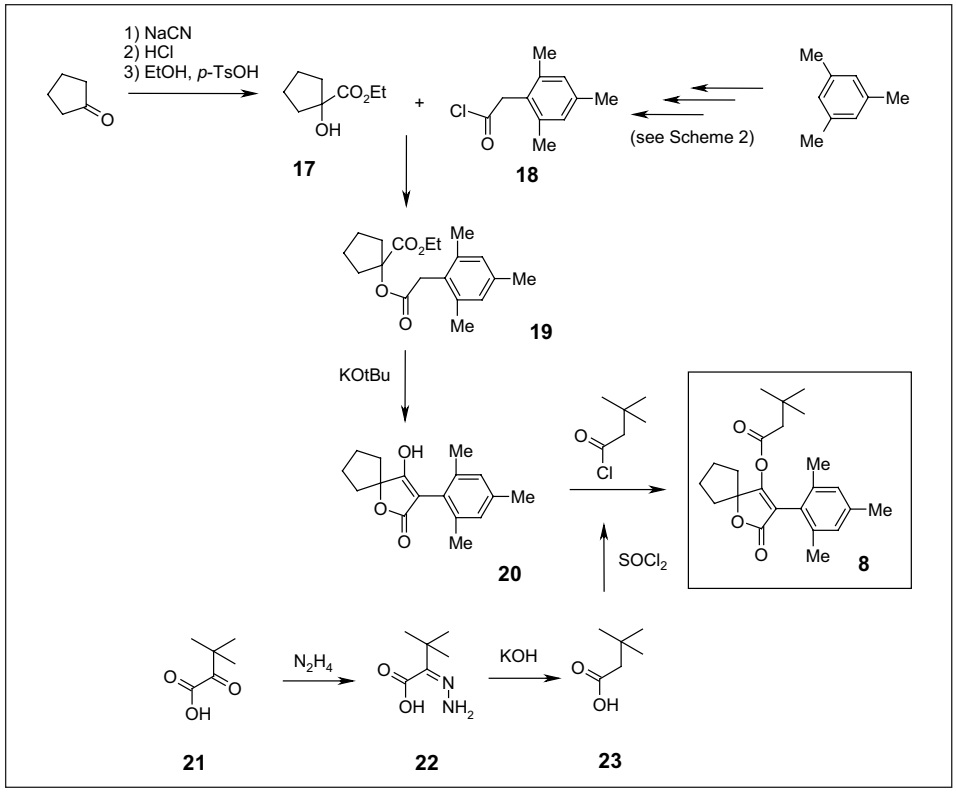
The final acylation of the enol **20** with 3,3-dimethylbutyryl chloride leads to spiromesifen (**8**).

Biology and Mode of Action

Whiteflies (*e.g. Bemisia tabaci*) and spider mites (*e.g. Tetranychus urticae*) belong to the most serious sucking pests in



Scheme 2. Synthesis of mesityl acetic acid (**12**)



Scheme 3. Synthesis of spiromesifen (**8**)

many cropping systems. They have developed a high degree of resistance to many chemical classes of insecticides and acaricides commercially available ([8–10] and references cited therein). Therefore new active ingredients with novel modes of action are needed to participate in resistance management programmes to control these pests efficiently.

The symptomology of poisoning observed with the new tetronic acid derivatives indicated a new biochemical mode of action not yet observed with any commercially available acaricide or insecticide. They show no signs of neurotoxic activity, but act on mite and whitefly development. Spirodiclofen (**7**) exhibited activity against all developmental stages of the mites, including the eggs. Additionally it reduces the fecundity of the female adults with the result that the number of eggs laid is strongly decreased. The eggs of females exposed to sublethal doses are not fertile. It was observed that the lipid content in treated female adults of *Tetranychus urticae* was significantly decreased, suggesting an interference with lipid biosynthesis (Fig. 4). This is in line with the slightly delayed onset of activity of the compounds. On the other hand they show an excellent long-lasting effect and good plant compatibility under field conditions. The biological profile of spirodiclofen (**7**) has recently been reviewed by Wachendorff *et al.* [11]. Spirodiclofen (**7**) and spiromesifen (**8**) were extensively tested on several strains of *Tetranychus urticae* collected worldwide and showing a high level of resistance to established commercial acaricides. Both were shown to perform outstandingly [2][8][12].

Similarly to spirodiclofen (**7**), the second compound in this class, Spiromesifen (**8**), is also particularly active against juvenile stages. However, it also strongly affects fecundity of mite and whitefly adults in a dose-dependent manner by transovariole effects. It shows ovicidal effects in mites, whereas egg hatch in whiteflies was markedly reduced through transovariole effects upon pre-exposure of female adults. Spiromesifen (**8**) was extremely effective against whiteflies resistant to pyrethroids, organophosphates, carbamates, cyclodienes, and neonicotinoids (Table) [2]. Furthermore, field simulator studies revealed that spiromesifen (**8**) is also a valuable tool to control pyriproxyfen resistant whiteflies (Fig. 5). In particular, the combination with neonicotinoid (chloronicotinyl) insecticides such as imidacloprid renders spiromesifen (**8**) a new valuable tool in resistance management strategies for whitefly control [2].

Conclusion

The discovery process of spirodiclofen (**7**) and spiromesifen (**8**) started with an 'indication shift', meaning a shift from (in our case) herbicidal to acaricidal activity in an closely related chemical structure often associated with a change in the mode of action (in our case from protoporphyrinogen oxidase inhibition to lipid biosynthesis).

The careful follow-up of the only weak acaricidal activities of the first hits and a tailor-made acaricidal test in the biological research delivering fast results played a vital role in the first part of the optimisation process.

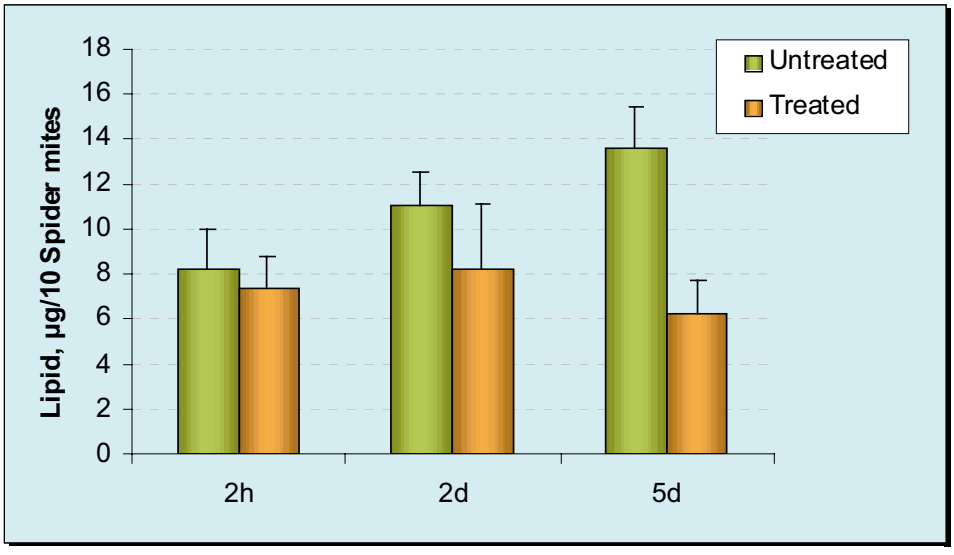


Fig. 4. Lipid decrease in spiromesifen-treated spider mites

Process chemistry was an important piece in the later part of the optimisation process with the goal to find the most economic routes for a commercial large-scale production of the products. Many different synthesis routes for the central intermediates had to be examined as shown in the case of mesitylacetic acid.

Physiological, biological, and biochemical work revealed a new mode of action for spirodiclofen (**7**) and spiromesifen (**8**) (inference with lipid biosynthesis) and as a consequence both compounds showed high activity against mite and whitefly populations resistant to conventional chemistry. Especially this attribute of the new tetronic acid derivatives, combined with their excellent long-lasting efficacy and the favourable environmental profile will make them a valuable tool for farmers worldwide.

Received: September 16, 2003

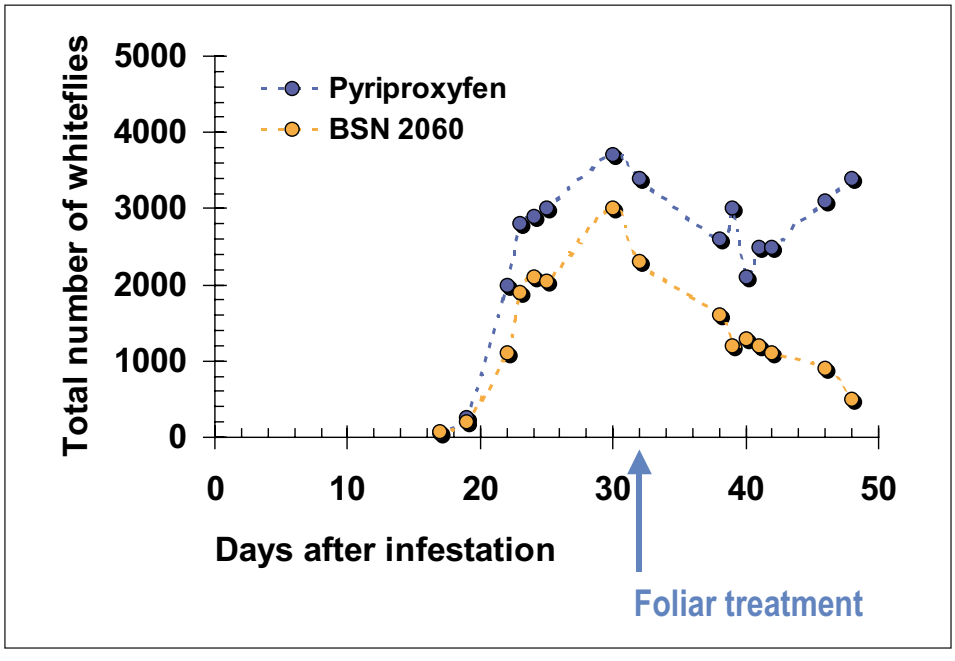


Fig. 5. Comparative effects of pyriproxyfen and BSN 2060 (spiromesifen (**8**)) on large whitefly populations (pyriproxyfen-resistant Q-type) of mixed life stages in 'field simulators' on cotton plants

Table. Resistance factors of several *Tetranychus* strains against commercial acaricides and spiromesifen (**8**)

	NL-00	AKITA	UK-99	Au
Abamectin	54	3	–	2
Pyridaben	22	2000	860	13
Fenpyroximate	–	1400	74	5
Hexythiazox	–	4	–	1100
Clofentenzine	–	4	–	>770
Spiromesifen	**4**	**1**	**1**	**3**

[1] U. Wachendorff, E. Brück, A. Elbert, R. Fischer, R. Nauen, N. Stumpf, R. Tiemann, *Proceed. Brighton Crop Protect. Conf.* **2000**, *1* (2A-6), 53.
[2] R. Nauen, T. Bretschneider, E. Brück, A. Elbert, U. Reckmann, U. Wachendorff, R. Tiemann, *Proceed. Brighton Crop Protect. Conf.* **2002**, *1* (2A-3), 39.
[3] P. Babczinski, R. Fischer, *Pestic. Sci.* **1991**, *33*(4), 455.
[4] J. Bachmann, T. Bretschneider, C. Erdelen, R. Fischer, B. Krüger, K. Lürssen, H. Santel, R.R. Schmidt, U. Wachendorff (Bayer AG), Patent EP 528156, **1993**.
[5] R. Lantzsch, R. Fuchs (Bayer AG), Patent EP 676388, **1995.**
[6] U. Stelzer (Bayer AG), Patent EP 665212, **1995**.
[7] U. Stelzer (Bayer AG), Patent EP 884299, **1998**.
[8] R. Nauen, N. Stumpf, A. Elbert, *Proceed. Brighton Crop Protect. Conf.* **2000**, *1* (4D-9), 453.
[9] R. Nauen, N. Stumpf, A. Elbert, C.P.W. Zebitz, W. Kraus, *Pest Management Science* **2001**, *57*, 253.
[10] I. Denholm, G. Devine, S. Foster, K. Gorman, R. Nauen, *Proceed. Brighton Crop Protect. Conf.* **2002**, *1*, 161.
[11] U. Wachendorff, R. Nauen, H.J. Schnorbach, N. Rauch, A. Elbert, *Pflanzenschutz-Nachrichten Bayer* **2002**, *55*, 149.
[12] N. Rauch, R. Nauen, *Pesticide Biochemistry and Physiology* **2003**, *74*, 91.