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Review

Insect antifeedant activity of clerodane diterpenes and related model compounds

Edwin A. Klein Gebbinck[a], Ben J.M. Jansen[b], Aede de Groot[b,*]

[a]*SelAct B.V., Nijenborgh 4, 9747 AG Groningen, The Netherlands*
[b]*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*

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Abstract

A comprehensive compilation of all test results on the insect antifeedant activity of clerodane diterpenes and related model compounds is reported. To increase the compatibility of data from different sources, some of the results reported in the literature have been converted into a standardized form. The compounds were sorted into groups according to the different types of sidechain attached to C-9. Despite the wealth of information, collected in 15 tables, it remains difficult to assign importance to separate structural elements in relation to the observed antifeedant activity. A detailed analysis of the structure–activity relationships could not be presented, but some interesting trends can be distinguished based on the structures of the strongest antifeedants. The compilation covers the literature up to December 2001.

Keywords: *Neo*-clerodane diterpenes; Bioactive metabolites; Insect antifeedants; Crop protection

Contents

* Corresponding author. Tel.: +31-317-482361; fax: +31-317-484914.
E-mail address: aede.deGroot@wur.nl (A. de Groot).

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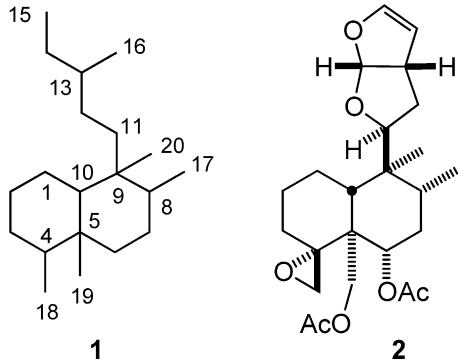
1. Introduction

Clerodane diterpenes have attracted considerable attention as a rich source of natural insect antifeedants. In general, insect antifeedants can offer properties that are highly desirable in environmentally friendly crop protection agents (van Beek and de Groot, 1986; Jermy, 1990). Significant activity is sometimes displayed at low concentrations and this may be directed specifically against a narrow group of insect pests, leaving benificial insects and other species unharmed. The possibility of insect species easily aquiring heritable resistance against antifeedants is considered unlikely (Schoonhoven, 1982; Jermy, 1990). Being compounds of natural origin, no problems with persistence in the environment are anticipated.

The use of insect-resistant plants has a long history. Leaves and fruits of the tropical Neem tree (*Azadirachta indica*) have been in use in India and Sri Lanka for centuries to protect books, clothes and stored foods from insect damage (Adhikari, 1980). Scientific interest in the application of antifeedants in insect control can be traced back to the late 1920s (Ruskin, 1992), but it was not until three decades later that the unique properties of antifeedants were truly recognized (Jermy, 1958) and renewed interest in their application arose. Since then thousands of plant species have been screened for the presence of antifeedant metabolites (Jacobsen, 1990; Simmonds and Blaney, 1992), yielding a bewildering array of natural insect antifeedants from diverse chemical classes (Chapman, 1974). Practical application of antifeedants is still limited and only few natural (mainly Neem extracts) or synthetic (Kristinsson, 1994; Fuog et al., 1998) insect antifeedants are commercially available.

In addition to the search for antifeedants from natural sources, preparation of insect antifeedants through (semi)synthetic routes has been considered. The total synthesis of natural antifeedants (de Groot and van Beek, 1987; Tokoroyama, 2000) usually is too complex and expensive for such approaches to be of much practical value. Simplified model compounds in some cases were shown to have retained considerable levels of activity (Ley et al., 1987; Bentley et al., 1990; Blaney et al., 1994a,b; Fernandez et al., 1998) and could constitute a more promising approach towards practical insect control agents. Alternatively, antifeedants of high structural complexity might be prepared (chemically or otherwise) from abundantly available natural products that are not or only weakly active.

Investigations into the structural elements that evoke insect antifeedant may contribute to such strategies to be successful. Diterpenoid insect antifeedants possessing a clerodane carbon skeleton **1** constitute an attractive starting point for such investigations, due to the extensive literature available and the structural diversity of the compounds reported active. To our knowledge, only a few papers reviewing parts of this literature have been published (Munakata, 1975; van Beek and de Groot, 1986; Camps and Coll, 1993). We therefore deemed it useful to establish a comprehensive compilation of all test results on insect antifeedant activity of clerodane diterpenes and related model compounds reported to date.



1 **2**

2. Structure, occurrence and bioactivity

The name, carbon skeleton and absolute stereochemistry of the natural insect antifeedant clerodin (**2**) form the basis for the classification of a large group of related *neo*-clerodane diterpenes. The prefix '*neo*' originates from a reversal of the initially assigned clerodane stereochemistry and indicates an absolute configuration similar to clerodin at all chiral centers of the carbon skeleton; clerodane diterpenes with the opposite absolute stereochemistry are to be called *ent-neo*-clerodanes (Rogers et al., 1979).

Clerodane-type secondary metabolites have been found in several hundreds of plant species from various families and in organisms from other taxonomic groups, such as fungi, bacteria and marine sponges (Merrit and Ley, 1992; Rodríguez-Hahn et al., 1994; Piozzi, 1994; Piozzi et al., 1998; Hanson, 1994–1999). Especially various genera from the plant families Labiatae and Verbenaceae have been identified as rich sources of antifeeding clerodanes, with species of the genus *Scutellaria* (Labiatae) producing some of the most potent clerodane antifeedants known so far (Anderson et al., 1989; Muñoz et al., 1997; Bruno et al., 1999a,b).

The physiological role of clerodane secondary metabolites in the plant species from which they are isolated is usually unknown and for many a direct function in the plants' physiology may not exist. Nevertheless, the ability to synthesise such metabolites can be of benefit to plants. Several plant species produce clerodane diterpenes that influence the growth of other plant species (Huneck and Schreiber, 1972; Rojas-Garciduenas

and Dominguez, 1976; Huneck et al., 1983; Siddiqui et al., 1992; Aoki et al., 1997; Vaccarini et al., 1999). Phytogrowth regulating activity may be one of the factors that determine the structure of plant communities (Vaccarini et al., 1999) and plant species able to exert such effects could thereby gain an advantage over competitors.

Clerodane secondary metabolites may also benefit a plant species by acting as a chemical defence mechanism against phytophagous animals or diseases. Apart from insect antifeedant properties, several clerodane diterpenes display other biological activity against insects. Insecticidal activity has been reported for the ajugarins I (**73**) (Kubo and Nakanishi, 1979) and IV (**98**) (Kubo et al., 1982). Ajugarin IV also displays insect growth regulating activity (Kubo et al., 1982), as do 3-*epi*-caryoptin (**167**) (Pereira and Gurudutt, 1990) and the 19-nor-clerodanes *cis*- and *trans*-dehydrocrotonin (Kubo et al., 1991). Fungicidal activity against plant pathogenic fungi has been reported for clerodin (**2**) and the related jodrellins A and B (**199**, **200**) (Cole et al., 1991).

3. Insect antifeedant activity

Clerodane diterpenes are best-known for their insect antifeeding properties, which is by far the most extensively studied bioactivity of these diterpenes. To date, over 300 natural and semi-synthetic clerodanes have been examined in laboratory assays, yielding several compounds with potent antifeedant activity against various insect species. To our knowledge, no experiments with clerodane antifeedants under actual field conditions have been reported.

An array of different bioassays have been used to study the antifeedant activity of the clerodanes. Because of the different formulas and units used to define and quantify essential parameters, such as the amount of compound applied and the degree of antifeedant activity found, the comparison of data for structure–activity relationships is often difficult. To increase the compatibility of data from different sources, we have attempted to convert some of the results reported in the literature into a standardized form.

3.1. Compounds

The review is resticted to diterpenes of natural or semi-synthetic origin with a clerodane carbon skeleton **1** and closely related derivatives thereof. Model compounds reflecting various substructures present in these diterpenes were also included. The compounds were sorted into groups according to the different types of sidechain attached to C-9 (Fig. 1). Unless otherwise indicated, the diterpenes possess the *neo*-clerodane absolute stereochemistry. The compilation covers the literature up to December 2001.

3.2. Insect species

The acceptance by a phytophagous insect of a plant species as a suitable host depends on the capability of

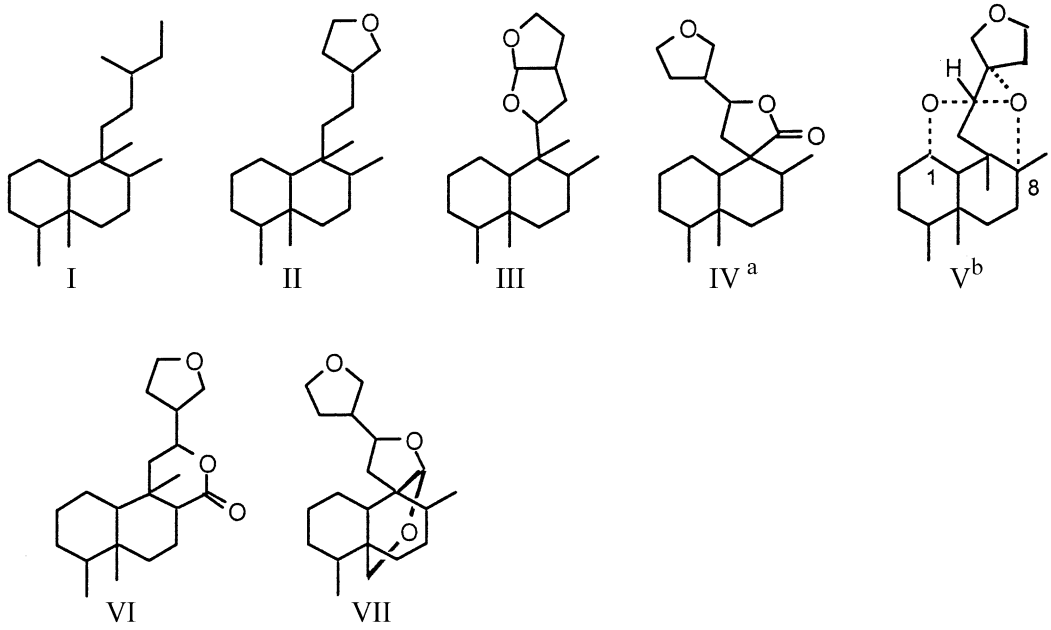


Fig. 1. Scheme of the different clerodane types in the compilation. [a]Including some 19-nor-clerodanes with a similar sidechain. [b]Dashed bonds in type V represent an ether linkage to C-1 or C-8.

the insect's chemosensory system to detect plant tissues with favourable levels of feeding stimulants and feeding deterrents (Schoonhoven, 1982; Bernays and Chapman, 1994, 2000). Since insect species usually differ in the range of plant species they accept as their hosts, a compound cannot a priori be expected to display similar antifeedant activity against different insect species. Also, structural changes in an antifeedant molecule may affect the activity in different manners for different species (Blaney et al., 1987, 1990). In the compilation, the data were therefore grouped according to the different test insect species used; species were sorted by insect order. When available, the developmental stage of the insect was included. Other potential differences among test populations have not been addressed due to lack of data.

3.3. Test substrate and protocol

Comparing data from different sources can be complicated by differences in the feeding bioassays used. Due to the sensitivity of insects to the chemical composition of their food, the activity of an antifeedant on a particular insect species may change when presented on a different feeding substrate. Bioassays in a dual-choice or a no-choice situation provide different types of information and may not always be directly compared. The effects of other variations in assay protocols (test duration, number of substrate discs and individual insects present in the test arena, well-fed insects or insects deprived of food, etc.) are not easy to evaluate but cannot be discarded a priori. When comparing data from different sources, one should therefore be mindful of effects due to differences other than the compounds tested. In Tables 1–15 the antifeedant activity was therefore combined with information on the corresponding bioassay. This information is provided in the form of a code, e.g. A1, referring to Table 16 in which details of the various assays are summarised. The capital 'A' signifies that an artificial substrate was used, while 'N' denotes natural substrates.

3.4. Test compound concentration

The concentration of the test solution *in ppm* was chosen to quantify the amount of test compound, as most literature data also use this quantity. A standard substrate surface area of 3.46 cm^2 and a standard test solution volume of 100 μl were chosen to correct for variations in the actual concentration of test compound that the insects encountered due to differences among test protocols. Literature data reported in quantities differing from this system were recalculated accordingly as far as possible.

It is important to realise that this system not always accurately reflects the potency of a test compound, since the molecular weight (and thus the number of molecules present) of the compound is not taken into account. Note also that in some test protocols the substrate is dipped into a test solution, instead of being treated with a specific volume. In such experiments the actual amount of compound present on the substrate is usually unknown.

3.5. Antifeedant activity

Different systems are in use to quantify insect antifeedant activity. In the compilation the reported activities were as much as possible converted to a standard index of antifeedant activity. For activities obtained from two-choice feeding assays, the dual-choice Antifeedant Index (AI_{dc}) according to Eq. (1) was chosen as the standard system. This system covers a major part of the published literature and can relatively easy be calculated from data reported in a different format. A similar no-choice Antifeedant Index (AI_{nc}), defined by Eq. (2), was used for antifeedant activity data determined in a no-choice situation.

$$\text{Dual-choice}: \quad AI_{dc} = [(C - T)/(C + T)] \tag{1}$$

$$\text{No-choice}: \quad AI_{nc} = [(C - T)/C] \tag{2}$$

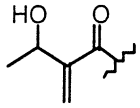
C and T are the amounts eaten from control and treatment substrates, respectively.

The antifeedant activity data in this review originate from assays that record the amount of substrate eaten over a period of time. Such experiments cannot easily discriminate between different mechanisms resulting in reduced feeding, such as sensory deterrency or toxicity, unless other assay designs (Ortgo et al., 1995) are used. The data also give no indication of which (types of) targets are involved in the antifeedant activity of a test compound. For most of the clerodane antifeedants, details on the mode of action and on the cellular or molecular targets are not available.

4. Compilation of clerodane insect antifeedants

Figs. 2–10 present a compilation of clerodane insect antifeedants. The clerodane diterpenes were ordered according to the scheme in Fig. 1. Underlined compound numbers refer to compounds of (semi)synthetic origin. Abbreviations used:

d: double bond
s: single bond
Fur: 3-furyl
$FurH_4$: 3-tetrahydrofuryl
Hmb: 2-hydroxy-3-methylene-butyryl (**3**)
Tig: tigloyl (**4**)
TigH2: dihydrotigloyl (**5**)
AcTig: 2-acetoxytigloyl (**6**)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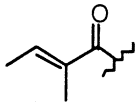
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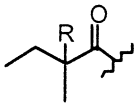
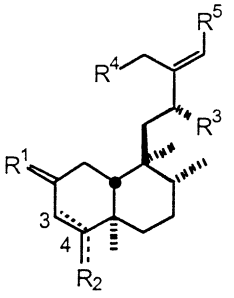
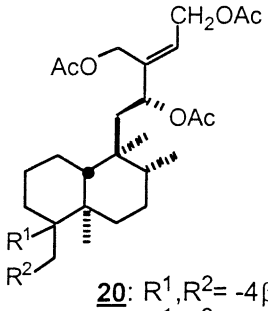
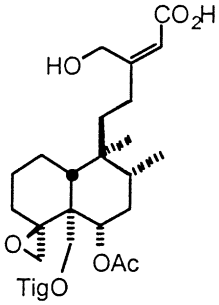

5: R=H
6: R=OAc



	R^1	C-3,4	R^2	R^3	R^4	R^5
7	H,H	d	Me	H	H	CH_2OH
8	H,H	d	Me	H	H	CO_2H
9	H,H	d	CHO	H	H	CO_2H
10	O	d	Me	H	H	CO_2H
11	H,H	s	CH_2	H	H	CO_2H
12	H,H	s	CH_2	OAc	OAc	CH_2OAc
13[a]	H,H	s	CH_2	OAc	OH/Ac	CH_2OAc/H
14	H,H	s	CH_2	OH	OAc	CH_2OAc
15	H,H	d	Me	OAc	OAc	CH_2OAc


20: R^1,R^2= -4β-O-
21: R^1,R^2= -4α,β-O-
22: R^1= α,β-OH, R^2=OH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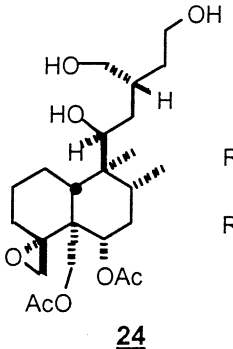
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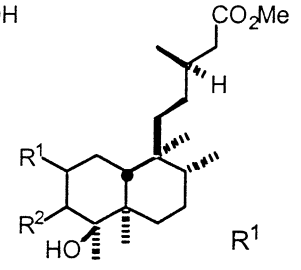
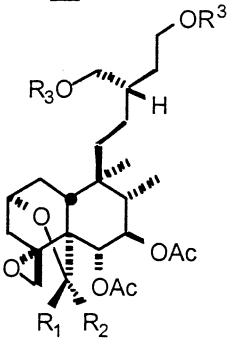
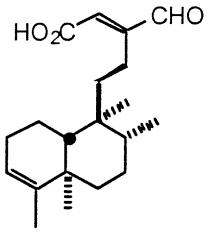


	R^1	R^2
25	α-OH	β-OH
26	α-OH	α-OH
27	β-OH	β-OH
28	β-OH	α-OH



	R^1	R^2	R^3
29	OTig	H	H
30	OTig	H	Ac
31	OH	H	Ac
32		O	Ac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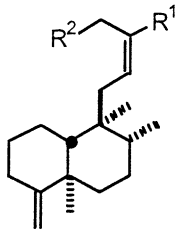
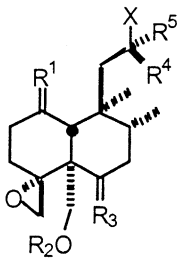
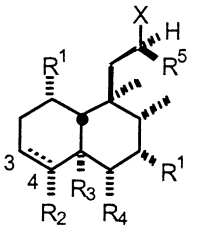


	R^1	R^2
17	CH_2OH	CH_2OH
18	CHO	CHO
19	C(O)Me	CHO

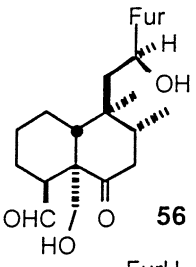
Fig. 2. Clerodane diterpenes of Type I with an acyclic sidechain at C-9. *Notes*: (a) Structure is identical to **12** in the original article; **13** is probably the mono-hydrolyzed form of **12** with C-15 OH or C-16 OH, as described in Gordaliza et al. (1994). Compound names: (**7**) kolavenol.



	R^1	R^2	R^3	R^4	R^5	X
33	H,H	Ac	α-OAc,H	OAc	H	Fur
34	H,H	Ac	α-OAc,H	OH	H	Fur
35	H,H	Ac	α-OAc,H	O		Fur
36	O	Ac	β-OH,H	H	H	Fur
37	O	Ac	β-OAc,H	H	H	Fur
38	O	Ac	O	H	H	Fur
39	α-OH,H	Ac	O	H	H	Fur
40	α-OH,H	Ac	α-OH,H	H	H	Fur
41	α-OH,H	H	α-OH,H	H	H	Fur
42	α-OH,H	Ac	α-OAc,H	H	H	Fur
43	α-OAc,H	Ac	α-OAc,H	H	H	Fur
44	α-OAc,H	Ac	O	H	H	Fur
45	α-OAc,H	H	α-OH,H	H	H	Fur
46	H,H	Ac	α-OAc,H	OAc	H	$FurH_4$
47	H,H	Ac	α-OAc,H	OH	H	$FurH_4$
48	α-OH,H	Ac	O	H	H	$FurH_4$



	R^1	C-3,4	R^2	R^3	R^4	R^5	X
49	H	d	Me	CO_2H	OH	H	Fur
50	H	d	Me	CO_2Me	OAc	H	Fur
51	H	d	CH_2OH	CH_2OH	H	H	Fur
52	H	d	-C(=O)-O-		H	H	Fur
53	OH	d	-C(=O)-O-		H	H	Fur
54	H	d	-C(=O)-O-		H	OAc	Fur
55	OH	s	-C(=O)-O-		H	H	$FurH_4$



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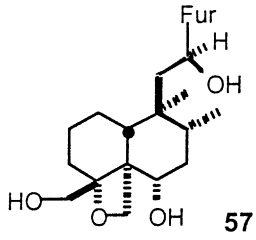

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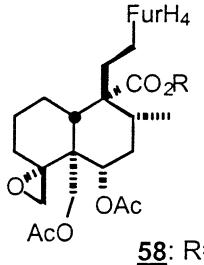
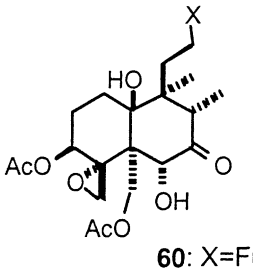
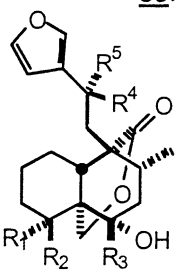


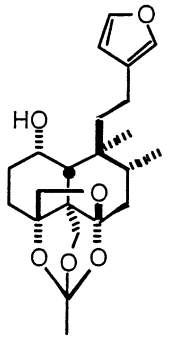
58: R=H
59: R=Me



60: X=Fur
61: X=$FurH_4$



	R^1	R^2	R^3	R^4	R^5
62	OH	CH_2OMe	H	OH	H
63	=CHCl		H	H	OH
64	OH	$-CH_2-O-$		O	



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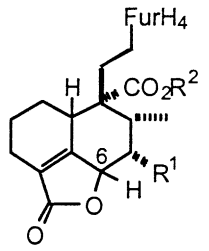
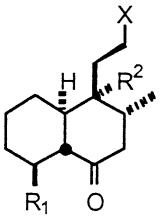
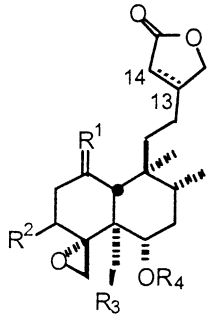


	H-6	R^1	H-10	R^2
66	β	OH	β	Me
67	α	H	α	H
68	α	H	α	Me

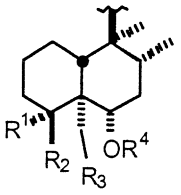


	R^1	R^2	X
69	CH_2OH	CH_2OH	Fur
70	CO_2Me	CO_2H	Fur
71	CO_2H	CO_2H	$FurH_4$
72	CO_2Me	CO_2Me	$FurH_4$

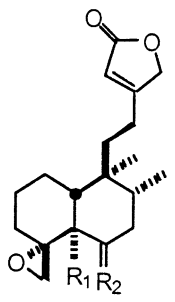
Fig. 3a. Clerodane diterpenes of Type IIa with a 2-ethylfuran-based sidechain at C-9. Compound names: (**33**) triacetylteumassilin; (**34**) 6,19-diacetylteumassilin; (**36**) isofruticolone; (**39**) fruticolone; (**49**) kerlinic acid; (**52**) hawtriwa lactone; (**53**) bacrispine; (**54**) tanabalin; (**55**) hexahydrobacrispine; (**56**) teumassilenin A; (**57**) teumassilenin C; (**60**) teucrolivin B; (**64**) 12-keto-teugnaphalodin.



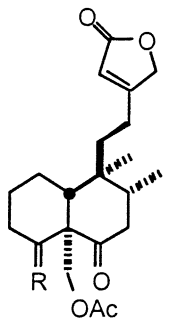
	R^1	R^2	R^3	R^4	C-13,14
73	H,H	H	OAc	Ac	d
74	H,H	H	OAc	H	d
75	H,H	H	OH	Ac	d
76	H,H	H	OH	H	d
77	H,H	H	H	Ac	d
78	H,H	H	OTig	Ac	d
79	H,H	H	OTig	H	d
80	H,H	H	OHmb	Ac	d
81	H,H	H	OHmb	C(O)Et	d
82	α-OAc,H	β-OAc	OTig	Ac	d
83	O	β-$OTigH_2$	OAc	Ac	d
84	H,H	H	OAc	Ac	s
85	H,H	H	OH	H	s
86	H,H	H	$OTigH_2$	Ac	s



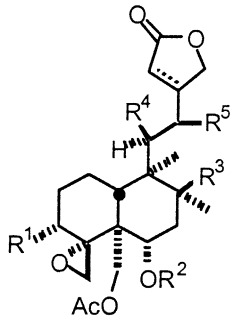
	R^1	R^2	R^3	R^4	C-13,14
87	OH	CH_2OH	OAc	Ac	d
88	OH	CH_2Br	OAc	Ac	d
89	OH	CH_2Cl	OTig	Ac	d
90	OH	CH_2Br	OTig	Ac	d
91	OH	CH_2I	OTig	Ac	d
92	OH	CH_2Br	OTig	H	d
93	CH_2Br	OH	OTig	H	d
94	α,β-CHO, H		OTig	Ac	d
95	α,β-CHO, H		OTig	H	d
96	CO_2H	H	H	H	d
97	CO_2H	H	H	Ac	d
98	CO_2Me	H	H	Ac	d
99	OH	Me	OH	H	s

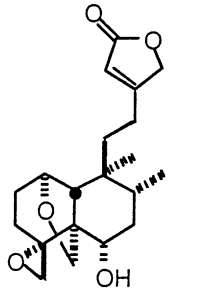


	R^1	R^2
100	CH_2OAc	O
101	CHO	α-OAc,H
102	CHO	α-OH,H



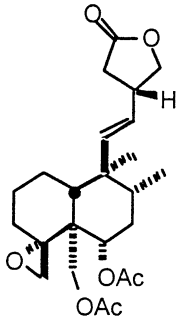
103: R=α-OH,CH_2Cl
104: R=O



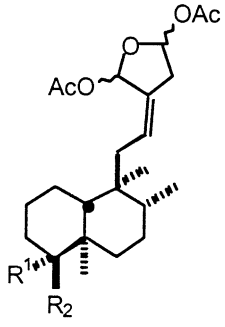


105

	R^1	R^2	R^3	R^4	R^5	C-13,14
106	H	Ac	H	OH	H	s (13R)
107	H	Tig	OH	OH	H	d
108	H	Tig	OH	OAc	H	d
109	OH	Ac	H	H	$OTigH_2$	d

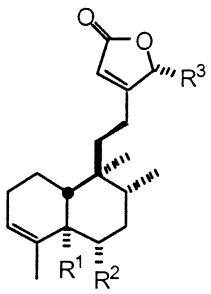


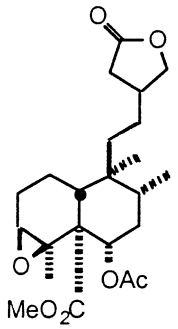
110



111: R^1,R^2= CH_2
112: R^1,R^2=-CH_2–O–

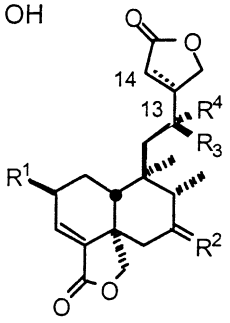
Fig. 3b. Clerodane diterpenes of Type IIb with a 3-ethylbut-2-enolide-based sidechain at C-9. Compound names: (**73**) ajugarin I; (**74**) ajugarin II; (**76**) deacetylajugarin II; (**77**) ajugarin V; (**78**) ajugacumbin A; (**79**) ajugacumbin B; (**80**) ajugacumbin G (Chen et al., 1995); (**82**) ajugacumbin C; (**83**) ajugareptansone A; (**87**) ajugarin III; (**98**) ajugarin IV; (**107**) scutalpin C; (**108**) scutalpin B; (**109**) 3a-hydroxyajugamarin F4; (**113**) melisodoric acid; (**120**) semiatrin; (**121**) kerlinolide.





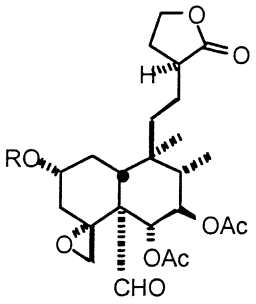
	R^1	R^2	R^3
113	CO_2H	OH	H
114	CO_2Me	OAc	H
115	Me	H	OH

116

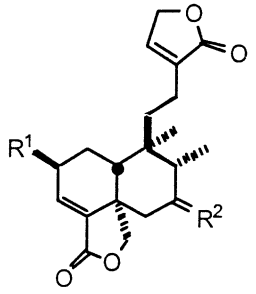


	R^1	R^2	R^3	R^4	C-13,14
117	H	H,H	H	H	s
118	H	α-OH,H	H	H	d
119	H	O	H	H	d
120	OH	H,H	OH	H	d
121	H	α-OAc,H	H	OH	d

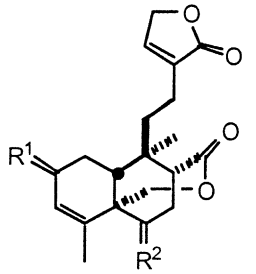
Fig. 3b. (contined)



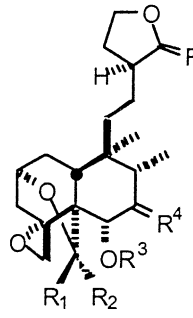
122: R=Ac
123: R=C(O)*i*-Pr



	R^1	R^2
124	H	α-OAc,H
125	OAc	H,H
126	OH	α-OH,H
127	OH	α-OAc,H
128	OAc	α-OH,H
129	OAc	O

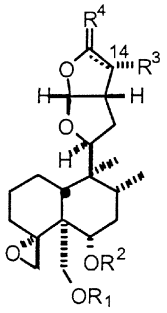


	R^1	R^2
130	H,H	α-OH,H
131	H,H	O
132	O	H,H

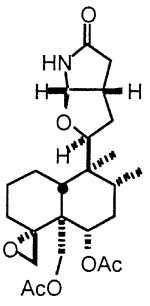


	R^1	R^2	R^3	R^4	R^5
133	OTig	H	Ac	β-OAc,H	O
134	OTig	H	Ac	β-OH,H	O
135	OTig	H	Ac	β-OH,H	α,β-OH,H
136	OTig	H	Ac	O	O
137	OTig	H	H	β-OAc,H	O
138	OC(O)*i*-Pr	H	H	β-OAc,H	O
139	OMe	H	Ac	β-OAc,H	O
140	OH	H	H	β-OAc,H	O
141	OH	H	Ac	β-OAc,H	O
142	O		Ac	O	O

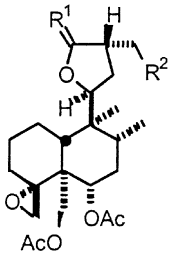
Fig. 3c. Clerodane diterpenes of Type IIc with a 2-ethylbut-2-enolide-based sidechain at C-9. Compound names: (**134**) salvimadrensin; (**135**) scutegalin B; (**136**) salvimadrensinone.



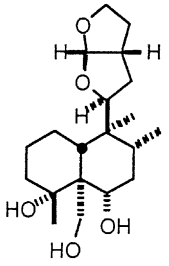
	R^1	R^2	R^3	R^4	C-14,15
2	Ac	Ac	H	H	d
143	Ac	Ac	H	H,H	s
144	Ac	Ac	H	O	s
145	Ac	Ac	H	α,β-OH,H	s
146	Ac	Ac	H	α,β-OEt,H	s
147	Ac	Ac	Br	O	s
148	Ac	Ac	Br	α,β-OH,H	s
149	Ac	Ac	Br	α,β-OAc,H	s
150	H	H	H	H,H	s
151	CMe_2		H	H,H	s



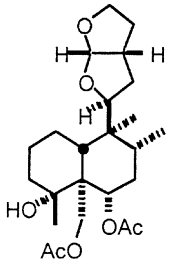
152



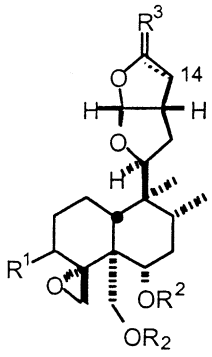
	R^1	R^2
153	O	CH_2OH
154	α,β-OH,H	$C(O)NH_2$



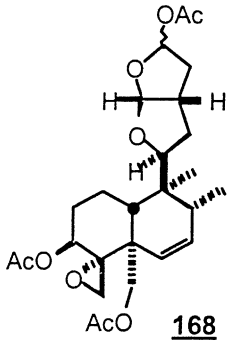
155



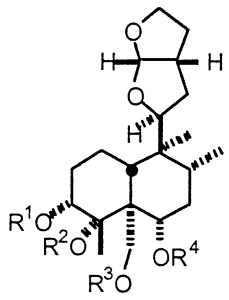
156



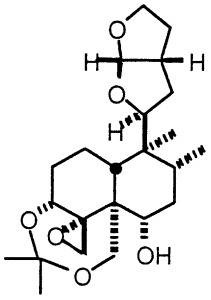
	R^1	R^2	R^3	C-14,15
157	α-OH	Ac	H	d
158	α-OH	Ac	H,H	s
159	α-OH	H	H,H	s
160	α-OAc	Ac	H	d
161	α-OAc	Ac	H,H	s
162	α-OAc	Ac	O	s
163	α-OAc	Ac	α,β-OH,H	s
164	α-OAc	Ac	α,β-OEt,H	s
165	β-OAc	Ac	H	d
166	β-OAc	Ac	H,H	s
167	β-OC(O)*i*-Pr	Ac	H,H	s



168

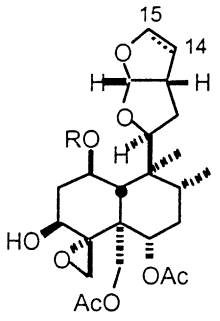


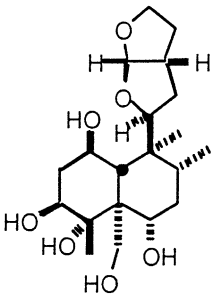
169: $R^1=R^2=R^3=R^4=H$
170: $R^1,R^2=R^3,R^4=CMe_2$



171

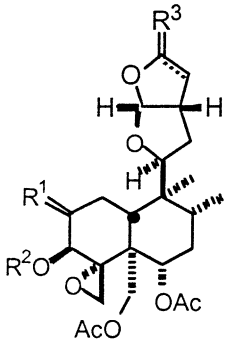
Fig. 4. Clerodane diterpenes of Type III with a furo[2,3b]furan-based sidechain at C-9. Compound names: (**2**) clerodin; (**143**) dihydroclerodin; (**145**) clerodin hemiacetal; (**157**) caryoptinol; (**158**) dihydrocaryoptinol; (**160**) caryoptin; (**161**) dihydrocaryoptin; (**163**) caryoptin hemiacetal; (**165**) 3-epi-caryoptin; (**167**) ivain II; (**172**) 14,15-dehydroajugareptansin; (**173**) 3β-hydroxyajugavensin B; (**174**) ajugareptansin; (**176**) ivain I; (**177**) hativene C; (**178**) ivain III; (**179**) ivain IV; (**180**) 2-acetylivain I; (**182**) ajugapitin; (**183**) 14,15-dihydro-ajugapitin; (**185**) 14-hydro-15-hydroxyajugapitin; (**186**) lupulin A; (**187**) 15-ethoxy-14-hydroajugapitin; (**188**) hativene A; (**189**) hativene B; (**190**) clerodendrin B; (**191**) clerodendrin A; (**199**) jodrellin A; (**200**) jodrellin B; (**201**) scutalbin A; (**202**) scutecyprol A; (**203**) scutalsin; (**204**) scutecyprol B; (**205**) scutalbin C; (**206**) 14,15-dihydrojodrellin T; (**207**) scutegalin A.



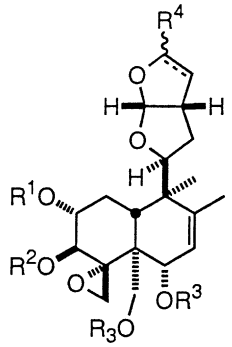


172: R=TigH_2, C-14,15=d
173: R=Tig, C-14,15=s
174: R=TigH_2, C-14,15=s

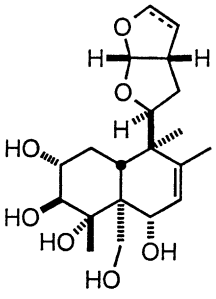
175



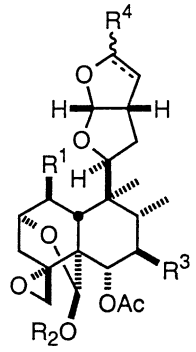
	R^1	R^2	R^3	C-14,15
176	β-OH,H	*i*-PrC(O)	H,H	s
177	β-OH,H	*i*-PrC(O)	α-OMe,H	s
178	β-OH,H	*i*-PrC(O)	α,β-OEt,H	s
179	β-OH,H	TigH_2	H,H	s
180	β-OAc,H	*i*-PrC(O)	H,H	s
181	O	TigH_2	O	s
182	α-OH,H	TigH_2	H	d
183	α-OH,H	TigH_2	H,H	s
184	α-OAc,H	TigH_2	H,H	s
185	α-OH,H	TigH_2	α,β-OH,H	s
186	α-OH,H	TigH_2	β-OMe,H	s
187	α-OH,H	TigH_2	α,β-OEt,H	s
188	α-OH,H	*i*-PrC(O)	β-OMe,H	s
189	α-OH,H	*i*-PrC(O)	α-OMe,H	s
190	α-OH,H	AcTig	H	d



	R^1	R^2	R^3	R^4	C-14,15
191	H	AcTig	Ac	H	d
192	Ac	AcTig	Ac	H	d
193	H	AcTig	Ac	H	s
194	H	AcTig	Ac	OMe	s
195	H	H	H	H	d
196	H	H	H	H	s

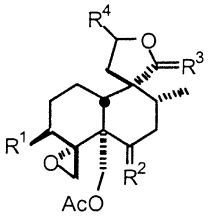


197: C-14,15=d
198: C-14,15=s

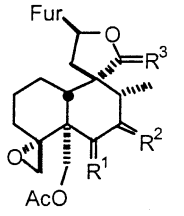


	R^1	R^2	R^3	R^4	C-14,15
199	H	Ac	H	H	d
200	H	*i*-PrC(O)	H	H	d
201	H	H	H	H	s
202	H	Ac	H	OH	s
203	H	*i*-PrC(O)	H	OH	s
204	H	Tig	H	OH	s
205	H	H	H	OH	s
206	OTig	Ac	H	H	s
207	H	Tig	OTig	H	s

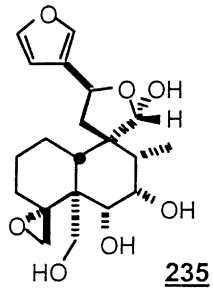
Fig. 4. (*continued on next page*)



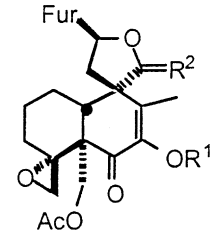
	R^1	R^2	R^3	R^4
208	H	α-OH,H	O	β-Fur
209	OAc	α-OH,H	O	β-Fur
210	OAc	α-OAc,H	O	β-Fur
211	H	α-OAc,H	O	β-Fur
212	H	β-OH,H	O	β-Fur
213	H	β-OAc,H	O	β-Fur
214	H	O	O	β-Fur
215	OAc	α-OAc,H	α-OAc,H	β-Fur
216	H	α-OAc,H	O	α-Fur
217	OAc	α-OAc,H	O	α-Fur
218	H	α-OAc,H	O	α-FurH_4



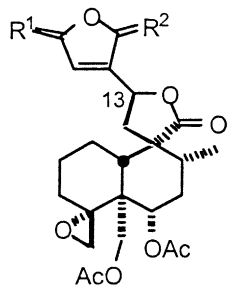
	R^1	R^2	R^3
219	O	α-OH,H	β-OAc,H
220	O	α-OAc,H	β-OAc,H
221	α-OH,H	O	β-OAc,H
222	α-OAc,H	α-OH,H	α-OH,H
223	α-OAc,H	α-OAc,H	α-OH,H
224	α-OH,H	α-OAc,H	α-OH,H
225	α-OAc,H	α-OAc,H	α-OAc,H
226	α-OH,H	α-OAc,H	β-OAc,H
227	O	α-OH,H	β-OH,H
228	O	α-OAc,H	α-OH,H
229	O	α-OAc,H	O
230	O	α-OAc,H	α-OMe,H
231	α-OH,H	O	α-OMe,H
232	α-OAc,H	O	α-OMe,H
233	α-OH,H	O	β-OMe,H
234	α-OH,H	α-OAc,H	O



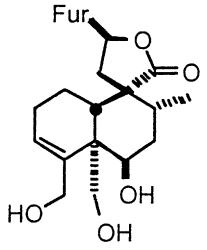
235



236: R^1=H, R^2=O
237: R^1=Ac, R^2=β-OAc,H



	R^1	R^2	H-13
238a	α,β-OH,H	O	β
238b	O	α,β-OH,H	β
239	α,β-OAc,H	O	β
240	α,β-OMe,H	α,β-OMe,H	α



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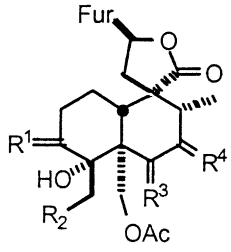
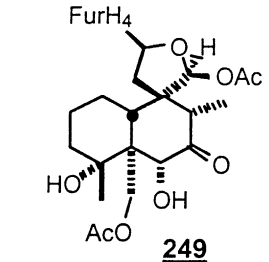


	R^1	R^2	R^3	R^4
242	H,H	Cl	α-OH,H	H,H
243	H,H	Cl	O	H,H
244	H,H	Cl	O	β-OAc,H
245	H,H	OH	α-OAc,H	H,H
246	H,H	OAc	α-OH,H	O
247	O	Cl	O	H,H
248	O	Cl	α-OAc,H	H,H

Fig. 5. Clerodane diterpenes of Type IV with an a-spiro-attached 4-(3-furyl)-g-butyrolactone-based sidechain at C-9. Notes: (‡) 19-nor-clerodane. (†) *ent-neo*-clerodane. Compound names: (**208**) teucjaponin B; (**209**) teumicropodin; (**210**) 12-epiteupyreinin; (**211**) 6-acetylteucjaponin B; (**212**) teucjaponin A; (**214**) 19-acetylgnaphalin; (**215**) teupyreinidin; (**216**) montanin C; (**217**) teupyreinin; (**219**) eriocephalin; (**220**) 7-*O*-acetyleriocephalin; (**221**) isoeriocephalin; (**227**) 20-deacetyleriocephalin; (**229**) capitatin; (**236**) picropolinone; (**241**) 19-deacetylteuscorodol; (**246**) picropolinol; (**247**) tafricanin A; (**248**) tafricanin B; (**256**) montanin D; (**257**) teucroxide; (**260**) teuflavoside; (**261**) dihydroteugin; (**262**) chamaedroxide; (**263**) 6b-hydroxyteuscordin; (**264**) teuscordinon; (**265**) teugin; (**266**) isoteuflidin; (**267**) teuscorolide; (**268**) teucvin; (**269**) teucrin A; (**272**) 12-epiteucvin; (**273**) teuflin; (**274**) teucvidin; (**275**) teuflidin; (**284**) bartemidiolide; (**285**) deoxybartemidiolide.



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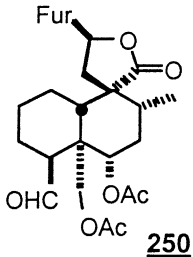

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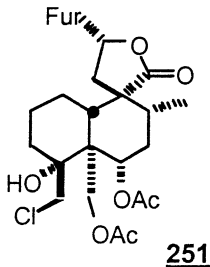

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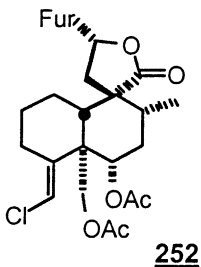

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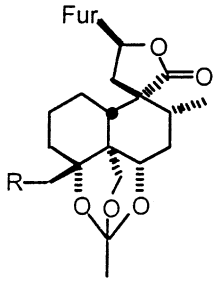
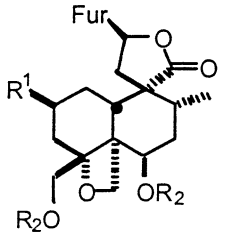
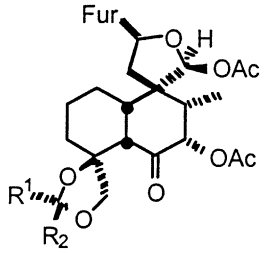


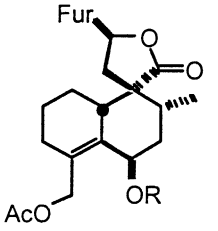
253: R=OAc
254: R=Cl



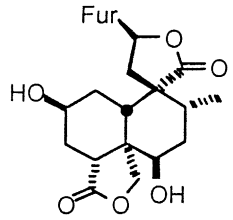
255: R^1=H, R^2=Ac
256: R^1=R^2=H
257: R^1=OH, R^2=H



258‡: R^1=H, R^2=Me
259‡: R^1=Me, R^2=H



260‡: R=2-acetyl-glucose



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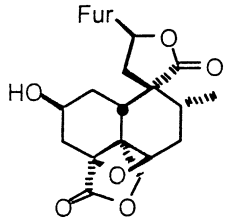

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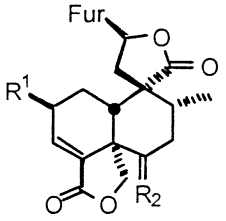
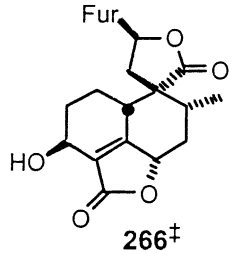
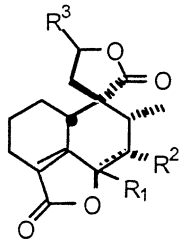


	R^1	R^2
263	H	β-OH,H
264	H	O
265	OH	β-OH,H

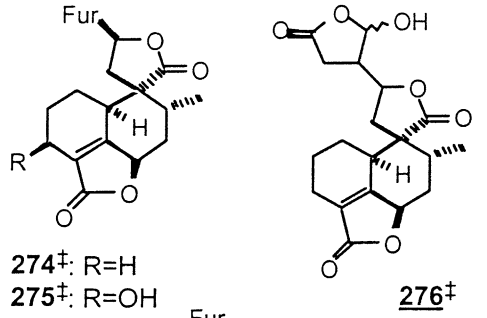


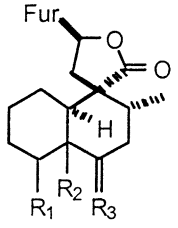
266‡



	R^1	R^2	C-6,7	R^3
267‡	-	H	d	β-Fur
268‡	β-H	H	s	β-Fur
269‡	β-H	OH	s	β-Fur
270‡	β-H	OAc	s	β-Fur
271‡	β-H	H	s	Fur
272‡	β-H	H	s	α-Fur
273‡	α-H	H	s	β-Fur

Fig. 5. (*continued*)





	R^1	R^2	R^3
277‡	β-CO_2H	α-H	O
278‡	α,β-CO_2Me	α-H	O
279‡	α,β-CO_2Me	α,β-H	O
280‡	α,β-CO_2Me	α,β-H	NOH
281‡	β-CO_2H	β-H	O
282‡	β-CO_2Me	β-H	O
283‡	β-$CONH_2$	β-H	O

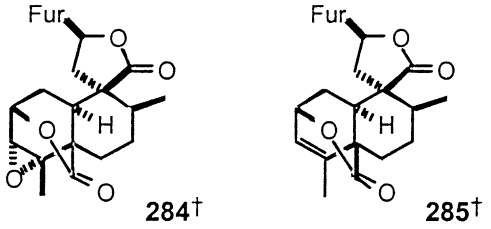


Fig. 5. (*continued*)

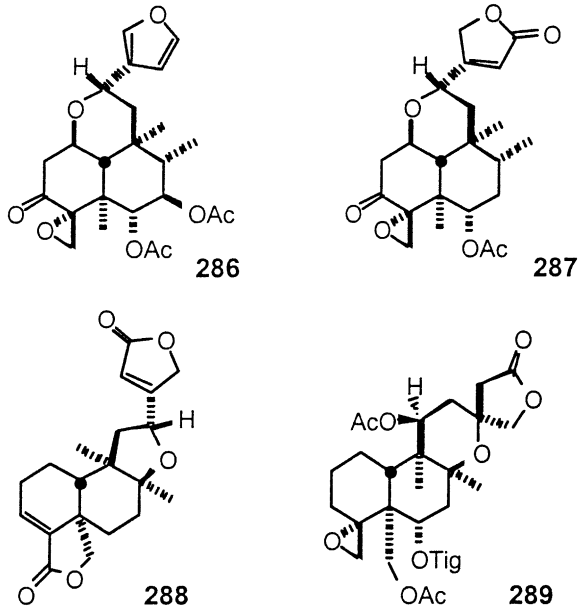
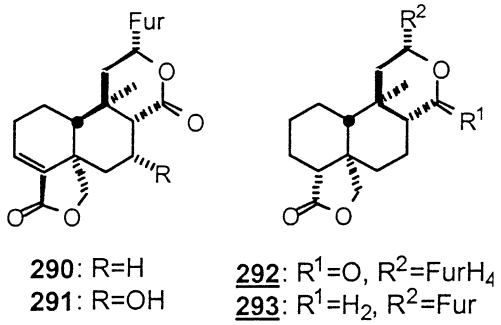
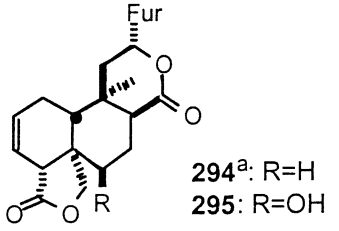


Fig. 6. Clerodane diterpenes of Type V with an 3-ethylfuran or 3-ethylbutenolide-based C-9 sidechain, containing a C-1,12, C-8,12 or C-8,13 ether-type linkage to the decalin fragment. Compound names: (**286**) cornutin A; (**287**) cornutin B; (**288**) kerlin; (**289**) scutalpin D.





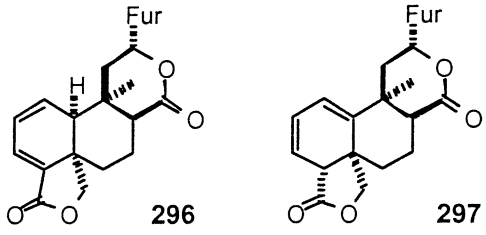
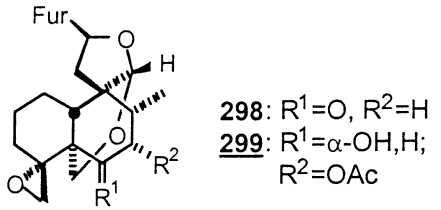
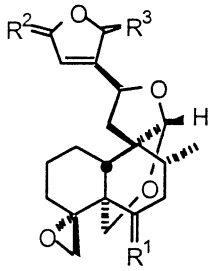
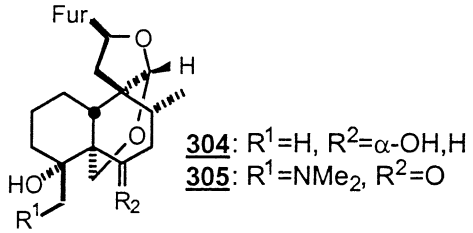


Fig. 7. Clerodane diterpenes of Type VI, incorporating a C-9 sidechain based on a 5-(3-furyl)-δ-valerolactone with its C-α,β-bond fused with the C-8,9-bond of the decalin fragment. Notes: (a) Tested clerodane **294** was salviarin and not the C-8 epimer depicted in the original articles (C.E. Tonn, pers. commun.). Compound names: (**290**) bacchotricuneatin A; (**291**) 7α-hydroxybacchotricuneatin A; (**294**) salviarin; (**295**) 6β-hydroxysalviarin; (**296**) linearolactone; (**297**) 1(10)-dehydrosalviarin.





	R1	R2	R3
300	O	O	O
301	O	α,β-OAc,H	O
302	α-OH,H	H,H	O
303	α-OH,H	O	H,H



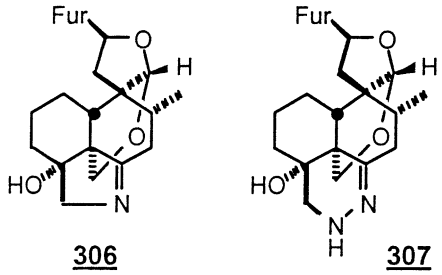


Fig. 8. Clerodane diterpenes of Type VII, incorporating a C-9 side-chain based on an α-spiro-attached 4-(3-furyl)-γ-butyrolactone moiety, connected to C-19 through a C-19,20 ether-linkage. Compound names: (**298**) teucrin P1.

	O-4	R1	R2	H-10
308	α	α-OAc	Me	β
309	β	α-OAc	Me	β
310	α	α-OAc	H	β
311	β	α-OAc	H	β
312	α	β-OAc	H	α

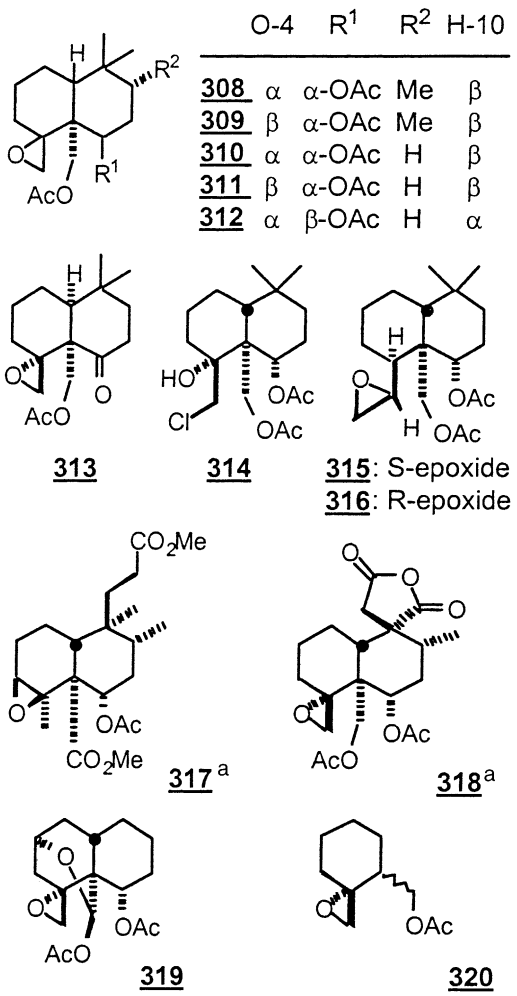
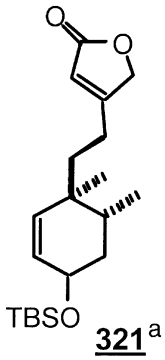
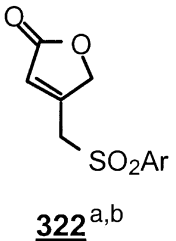


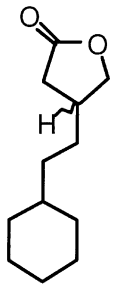
Fig. 9. Synthetic and semisynthetic analogs of the decalin-fragment of clerodane diterpenes. All compounds are racemic and were obtained via total synthesis, unless indicated otherwise. [a]Compound was obtained by derivatization of a natural compound and is therefore presumed to be homochiral.



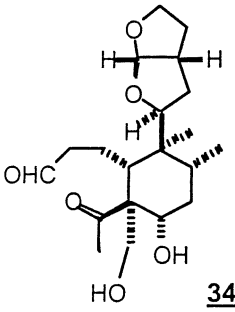
321[a]



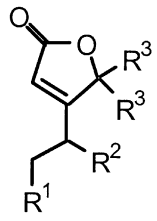
322[a,b]



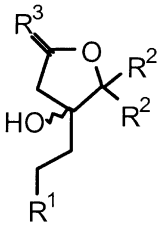
323



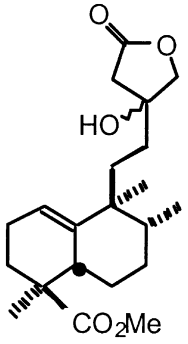
345[c]



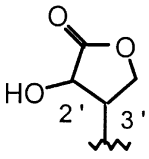
	R1	R2	R3
324	2-mesityl	H	H
325[a,b]	2-mesityl	SO_2Ar	H
326	Ph	H	H
327	Ph	H	Me
328	*c*-hexyl	H	H
329	*c*-hexyl	H	Me
330	*n*-Bu	H	Me



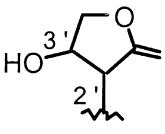
	R1	R2	R3
331	*c*-hexyl	H	O
332	*c*-hexyl	Me	O
333	*n*-Bu	Me	O
334	Ph	Me	O
335	Ph	Me	H,H
336	Ph	Me	OMe,H
337	Ph	Me	OH,H



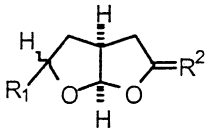
338[c]

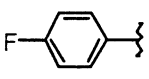


	3'-R	2'-OH
339a[c]	α	α
339b[c]	β	β
340a[c]	α	β
340b[c]	β	α

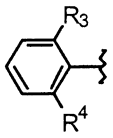


	2'-R	3'-OH
341[c]	α	α
342[c]	α	β
343[c]	β	β
344[c]	β	α



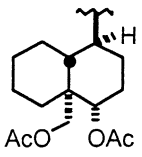


R^I



R^{II}: R^3=Me, R^4=H

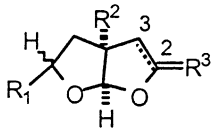
R^{III}: R^3=R^4=Me



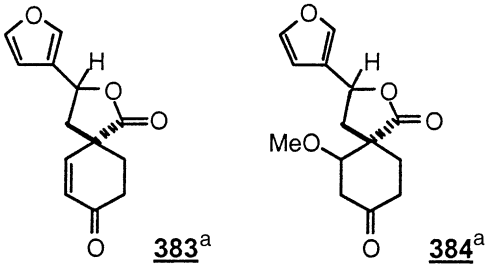
R^{IV}

	R1	R2
346	*t*-Bu	O
346a	α-*t*-Bu	O
347	*t*-Bu	OH,H
348	*t*-Bu	OAc,H
349	*t*-Bu	OMe,H
350	Ph	O
350a	α-Ph	O
351	Ph	OH,H
352	Ph	OAc,H
353	Ph	OMe,H
354[a]	β-R^I	H,H
355	R^{II}	O
356	R^{II}	OH,H
357	R^{II}	OAc,H
358	R^{II}	OMe,H
359	R^{III}	O
360	R^{III}	OH,H
361	R^{III}	OAc,H
362	R^{III}	OMe,H
363	R^{IV}	O
364	R^{IV}	OH,H
365	R^{IV}	OAc,H
366	R^{IV}	OMe,H
367	*c*-hexyl	O
367a	α-*c*-hexyl	O
367b	β-*c*-hexyl	O
368	*c*-hexyl	OH,H
369	*c*-hexyl	OAc,H
370	*c*-hexyl	OEt,H
371	*c*-hexyl	H,H
372	*n*-hexyl	O
373	*n*-decyl	O
373a	α-*n*-decyl	O

Fig. 10. Synthetic and semisynthetic analogs of the C-9 sidechain-fragment of clerodane diterpenes. Compounds are racemic and were obtained via total synthesis, unless indicated otherwise. [a]Synthesis not published. [b]Ar not specified. [c]Semisynthetic compound, presumably homochiral.



	R^1	R^2	R^3	C-2,3
374	*n*-hexyl	H	H	d
375	Ph	H	H	d
376	*c*-hexyl	H	H	d
377	α-*c*-hexyl	OH	H	d
378	α-*c*-hexyl	OH	O	s
379	α-*c*-hexyl	OH	OH,H	s
380	α-*c*-hexyl	OH	OAc,H	s
381	α-*c*-hexyl	OH	OMe,H	s
382	α-*c*-hexyl	OH	H,H	s



383[a] **384**[a]

Fig. 10. (*continued*)

In the tables' values printed in italics are derived or recalculated from the reported literature values. Abbreviations used:

Conc.: The concentration in ppm of a solution of the test compound, applied as a standard volume of 100 μl on a feeding substrate with a standard surface area of 3.46 cm^2. When necessary, literature values were recalculated to correspond to these standards. Values that deviate from these standards and could not be recalculated are placed in the tables inserted in brackets.

AI_{dc}: Mean dual-choice Antifeedant Index, $AI_{dc} = [(C-T)/(C+T)]$, in which C and T are the amounts consumed from the control and treatment substrates, respectively; s.e.m. = standard error of the mean. A positive sign denotes an antifeedant, while a negative value is associated with feeding stimulants.

AI_{nc}: Mean no-choice Antifeedant Index, $AI_{nc} = [(C-T)/C]$.

AI_{50}: The concentration required to give an estimated AI of 50%.

Assay: N = natural feeding substrate; A = artificial substrate. The code refers to a brief summary of the original assay conditions presented in Table 16; for full details see the cited literature. When necessary for inclusion in the tables, data from these original procedures was used to recalculate test concentrations or antifeedant activity to conform to the standards described above.

Ref. Literature references to the originally reported data. 1. Blaney et al., 1988; 2. Anderson et al., 1989; 3. Cole et al., 1990; 4. Gonzàlez-Coloma et al., 2000; 5. Urones et al., 1995; 6. Rodrìguez et al., 1999; 7. Simmonds et al., 1989; 8. Bruno et al., 1999b; 9. Simmonds et al., 1996; 10. Rodrìguez et al., 1994; 11. Malakov et al., 1994; 12. Kubo et al., 1976; 13. Belles et al., 1985; 14. Muñoz et al., 1997; 15. Bremner et al., 1998; 16. Rodrìguez et al., 1993; 17. Ben Jannet et al., 2000; 18. Bondi et al., 2000; 19. Blaney et al., 1994b; 20. Bruno et al., 2002b; 21. Bruno et al., 1999a; 22. de la Torre et al., 1994; 23. Bruno et al., 2002a; 24. Marcos et al., 2000; 25. Blaney et al., 1990; 26. Luteijn, 1982; 27. Geuskens et al., 1983; 28. Jackson and Ley, 1981; 29. Bruno et al., 2000; 30. Kubo and Nakanishi, 1979; 31. Kubo and Nakanishi, 1977; 32. Caballero et al., 2001; 33. Kato et al., 1972; 34. Hosozawa et al., 1974a; 35. Hosozawa et al., 1974b; 36. Munakata, 1977; 37. Miyase et al., 1981; 38. Kojima and Kato, 1981a; 39. Kojima and Kato, 1981b; 40. Messchendorp, 1998; 41. klein Gebbinck et al., 1999a; 42. klein Gebbinck et al., 1999b; 43. Xu et al., 1998; 44. Pickett et al., 1987; 45. Griffiths et al., 1988; 46. Min et al., 1989; 47. Kubo et al., 1996; 48. Chen et al., 1996; 49. Phadnis et al., 1988; 50. Enriz et al., 2000; 51. Sosa et al., 1994; 52. Enriz et al., 1994; 53. Luco et al., 1994; 54. Gallardo et al., 1996; 55. López-Olguín et al., 1999; 56. Ortego et al., 1995; 57. Govindachari et al., 1999; 58. Esquivel et al., 1995; 59. Ley et al., 1982; 60. Hanson et al., 1982; 61. Pereira and Gurudutt, 1990; 62. Hubert and Wiemer, 1985; 63. Howard et al., 1988; 64. Chen et al., 1992; 65. Lajide et al., 1995; 66. Kubo et al., 1983; 67. Kubo et al., 1982; 68. Esquivel et al., 1985; 69. Ladjel et al., 1994.

Table 1a
Insect antifeedant activity against larvae of the Egyptian cotton leafworm (Lepidoptera: *Spodoptera littoralis*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	AI_{50} (ppm)	Assay	Ref.
2	100	74.4 (8.4) *		A1	1–3
	50	59 (6.2) *		A1	3
	25	24 (9.8) *			2, 3
	1	14 (19.6)			2
12	*1730*	*11.4 (4.8)*[a]		N1	4
13	*1730*	*10.1 (3.1)*[a]		N1	4
14	*1730*	*27.0 (9.3)*[a]		N1	4
15	*1730*	*16.3 (6.6)*[a]		N1	4
18	*1730*	*13.2 (4.5)*[a]		N1	4
19	*1730*	*7.9 (3.7)*[a]		N1	4
21	*1730*	*9.8 (3.8)*[a]		N1	4
22	*1730*	*19.5 (12.3)*[a]		N1	4
24	100	21.4 (4.8)		A1	1
25	*37*	52.0 (6.8)		A1	5
	3.7	10 (3.6)			
26	*37*	−62 (16)		A1	5
	3.7	−54 (1.3)			
27	*37*	36 (9.7)		A1	5
	3.7	1 (14)			
28	*37*	33 (7.6)		A1	5
	3.7	−12 (28)			
29	100	18.8 (19.3)		A1	6
30	100	−0.4 (5.0)		A1	6
31	100	−38.8 (10.1)		A1	6
32	100	−27.4 (7.1)		A1	6
34	100	32.2 (22.2)		A1	1,7
	10	21.7 (15.9)			7
36	100	53 (12.6) *		A1	8
37	100	−27 (9.3)		A1	8
38	100	53 (5.3) *		A1	8
39	100	29 (7.4)		A1	8
40	100	49 (16.1)		A1	8
41	100	16 (13.8)		A1	8
42	100	60 (9.8) *		A1	8
43	100	14 (11.7)		A1	8
44	100	−5 (5.2)		A1	8
45	100	27 (8.5)		A1	8
49	100	−1 (12.8)	>100	A1	9
50	100	−8 (10.2)	>1000	A1	9
62	100	−51.2 (7.9) *		A1	10
63	100	−8.1 (0.5)		A1	11
	10	−23.0 (9.9)			
64	100	9.6 (11.4)		A1	7
	10	9.4 (10.6)			
65	100	12 (5.6)		A1	8
73[b]	(300)	*100*[c]		N2	12
	100	43.1 (7.3) *		A1	1, 3, 7, 1 1
	50	40 (11.3) *			3
	25	26 (14.8)			
	10	34.5 (7.0) *			7
		36.8 (8.5) *			11
76	100	29.6 (9.0) *		A1	7
	10	17.9 (9.7)			
83	*865*	*14.9*[d]		N3	13
	346	*-7.0*[d]			
106	100	48.8 (8.8)		A1	1
107	100	96.8 (1.2)		A1	14
108	100	26.9 (11.0)		A1	14
109	100	−32 (13.9)		A1	15
110	100	24.8 (5.8)		A1	1
111	*1730*	*5.9 (3.9)*		N1	4
112	*1730*	*58.6 (19.8)*		N1	4
114	100	−11 (9.8)	>1000	A1	9
116	100	73 (5.2) *		A1	9
118	100	32 (14.5) *	139	A1	9
119	100	26 (6.8) *	294	A1	9
120	100	57 (6.7) *	87	A1	9
121	100	70 (10.3) *	67	A1	9
122	100	17.2 (9.9)		A1	6
123	100	−10.0 (8.5)		A1	6
124	100	29 (5.3) *	192	A1	9
125	100	6 (2.5)	>1000	A1	9
126	100	34 (4.6) *	142	A1	9
127	100	54 (15.4) *	122	A1	9
128	100	83 (8.3) *	84	A1	9
129	100	−15 (11.1)	>1000	A1	9
130	100	27 (10.2) *	194	A1	9
131	100	20 (4.5)	254	A1	9
132	100	3 (7.1)	>100	A1	9
133	100	21 (13.9)		A1	16
134	100	29.3 (15.2)		A1	6
135	100	−27.0 (12.0)		A1	16
136	100	36.5 (9.9) *		A1	6
137	100	18.6 (7.9)		A1	6
138	100	37.5 (6.0) *		A1	6
139	100	−29.5 (7.8)		A1	6
140	100	67.0 (5.5) *		A1	6
141	100	34.0 (16.3)		A1	6
142	100	44.1 (10.4) *		A1	6
143	100	95.2 (16.6)		A1	1
144	100	49.2 (9.6)		A1	1
145	100	69.4 (13.3)		A1	1
147	100	69.7 (18.3)		A1	1
148	100	82.2 (12.1)		A1	1
149	100	39.1 (11.6)		A1	1
152	100	14.5 (6.1)		A1	1
153	100	24.8 (7.8)		A1	1
154	100	82.8 (13.7)		A1	1
156	100	35.0 (13.6)		A1	1
167	*35*	*75.4*[d]		N3	13
	3.5	*60.0*[d]			
	0.4	*19.8*[d]			
172	100	92 (5.5)*		A1	15
	25	60 (15.9)*			
173	100	0.3 (30.1)		A1	15
174	*346*	*66.7*[d]		N3	13
	100	−41 (19.6)		A1	15
	35	*25.0*[d]		N3	13
175	*865*[e]	*19.8*[d]		N3	13
176	*35*	*60.0*[d]		N3	13
	3.5	*14.9*[d]			
177	100	100 (2.7)		A1	17
	10	100 (8.1)			
	1	63.3 (9.2)			
	0.1	42.7 (8.3)			
178	*35*	*46.0*[d]		N3	13
	3.5	*17.0*[d]			
179	100	76 (4.4)**		A1	18
	35	*78.6*[d]		N3	13
	3.5	*17.6*[d]			

(*continued on next page*)

Table 1a. (*continued*)

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	AI_{50} (ppm)	Assay	Ref.
180	*35*	*78.6*[d]		N3	13
	3.5	*32.5*[d]			
181	*865*	*28.2*[d]		N3	13
	346	*35.0*[d]			
182	*35*	*92.3*[d]		N3	13
	3.5	*61.3*[d]			
	0.4	*41.8*[d]			
	0.04	*14.9*[d]			
183	100	100 (3.4)		A1	17
	100	48 (5.7)**		A1	18
	35	*80.2*[d]		N3	13
	10	100 (6.1)		A1	17
	3.5	*63.9*[d]		N3	13
	1	92.6 (16.2)		A1	17
	0.4	*51.5*[d]		N3	13
	0.1	65.9 (3.8)		A1	17
	0.04	*37.0*[d]		N3	13
184	*35*	*88.7*[d]		N3	13
	3.5	*31.6*[d]			
	0.4	*23.5*[d]			
185	*35*	*53.8*[d]		N3	13
	3.5	*46.0*[d]			
186	100	100 (11.5)		A1	17
	10	100 (12.1)			
	1	74.5 (14.5)			
	0.1	45.0 (5.1)			
187	*346*	*80.2*[d]		N3	13
	35	*43.9*[d]			
188	100	100 (7.2)		A1	17
	10	100 (8.5)			
	1	63.3 (10.2)			
	0.1	37.3 (6.2)			
189	100	100 (5.1)		A1	17
	10	100 (5.3)			
	1	69.0 (13.3)			
	0.1	41.2 (5.7)			
199	100	92 (7.6)*		A1	2, 3, 16, 19
		92 (3.2)*			20
	50	100 (0.0) *			3
	25	53 (13.3) *			2,3
	10	53 (13.3) *			19
	1	43 (15.9) *			2, 19
200	100	100 (0.0) *		A1	2, 3, 16, 20
	50	100 (0.0) *			3
	25	83 (10.3) *			2,3
	1	54 (14.4)			2
201	100	65 (8.6)*		A1	20
202	100	20 (6.4)		A1	20
203	100	15 (6.3)		A1	20
204	100	100 (0.0) *		A1	20, 21
205	100	32 (13.7)		A1	21
206	100	63 (7.8)*		A1	3, 16
	50	59 (4.2)*			3
	25	44 (4.5)*			
207	100	41 (18.6) *		A1	16
208	100	48.9 (5.98) *		A1	7, 10
	10	43.0 (7.64) *			
212	100	12.9 (7.67)		A1	7, 10
	10	7.5 (7.0)			
213	100	10.4 (13.2)		A1	7
	10	7.4 (10.4)			
214	100	23.7 (7.0)		A1	7, 10
		14.3 (9.2)			1
	10	21.9 (18.0)			7
216	100	6.5 (7.9)		A1	7
		9.4 (8.5)			11
	10	7.5 (10.0)			7
		10.1 (8.3)			11
217	100	14.8 (7.0)		A1	7
	10	12.6 (12.3)			
219	100	48.9 (6.0) *		A1	7
		5.5 (9.0)	> 1000		22
	10	40.9 (9.8) *			7
220	100	19.9 (12.9)		A1	7
	10	18.5 (10.6)			
221	100	38.9 (17.0)		A1	7
	10	33.1 (10.6)			
222	100	54.0 (9.7) *	39	A1	22
223	100	−14.3 (12.2)	> 1000	A1	22
224	100	5.4 (9.3)	> 1000	A1	22
225	100	26.7 (11.2)	> 1000	A1	22
226	100	−21.1 (13.9)	> 1000	A1	22
235	100	30.4 (14.0) *	300	A1	22
238e	100	−21.8 (10.4)		A1	11
	10	17.8 (12.5)			
239	100	23.7 (13.9)		A1	11
	10	12.5 (21.5)			
241	100	−54.5 (14.9)		A1	23
242	100	8.8 (11.0)		A1	10
243	100	21.0 (12.5) *		A1	10
246	100	2.3 (13.5) *		A1	10
251	100	−1.2 (5.0)		A1	11
	10	−12.1 (9.2)			
252	100	−21.5 (9.7)		A1	11
	10	−31.5 (12.9)			
253	100	−22.3 (9.0)		A1	10
254	100	−30.6 (9.8) *		A1	10
255	100	34.6 (12.7) *		A1	23
256	100	82.1 (7.3) **		A1	23
257	100	14.8 (7.0)		A1	7
	10	16.6 (7.4)			
258	100	34.1 (13.7) *	390	A1	22
259	100	−5.4 (12.0)	> 1000	A1	22
260	100	−9.8 (23.9)		A1	7
	10	−2.6 (16.9)			
261	100	−9.9 (13.9)		A1	7
		−1.2 (9.3)			23
	10	−18.6 (17.5)			7
262	100	31.8 (11.9)		A1	7
	10	25.6 (13.5)			
263	100	73.1 (15.6) **		A1	23
264	100	55.7 (18.5) *		A1	23
265	100	11.1 (15.9)		A1	23
266	100	11.0 (21.6)		A1	23
268	100	52.2 (15.7) *		A1	23
269	100	9.8 (11.9)		A1	7
	10	8.7 (15.9)			
272	100	49.9 (3.9) *		A1	7
	10	45.4 (9.6) *			
288	100	7 (21.2)	> 1000	A1	9

(*continued on next page*)

Table 1a. (*continued*)

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	AI_{50} (ppm)	Assay	Ref.
294	100	59 (5.2)*	81	A1	9
295	100	66 (8.3)*	24	A1	9
296	100	18 (8.9)	>1000	A1	9
297	100	66 (8.4)*	32	A1	9
298	100	−32.5 (7.5) *		A1	11
	10	−17.7 (14.2)			
300	100	−11.7 (18.4)		A1	11
	10	8.0 (11.6)			
301	100	6.8 (13.8)		A1	11
	10	−29.5 (17.3)			
302	100	67.9 (10.3) *		A1	11
	10	20.3 (7.2)			
303	100	−7.9 (11.9)		A1	11
	10	5.5 (27.6)			
304	100	−22.3 (11.9)		A1	11
	10	−34.3 (7.3)			
305	100	−45.0 (11.9)		A1	11
	10	−36.1 (13.7)			
306	100	−42.7 (7.4) *		A1	11
	10	6.8 (13.4)			
307	100	−43.2 (18.2)		A1	11
	10	1.9 (12.3)			
310	100	1.8 (0.9)		A1	1
312	100	−2.7 (7.9)		A1	1
314	100	7.2 (8.2)		A1	1
317	100	18 (4.8)	>1000	A1	9
318	100	−16.9 (7.7)		A1	11
	10	11.3 (4.3)			
319	1000	32 (8.8)*		A1	19
	100	24 (4.7)			
321	100	13.5 (5.3)		A1	1
322	*865*	*62.6*[d]		N3	13
	346	*16.3*[d]			
324	*1730*	*44.0*[d]		N3	13
	865	*17.6*[d]			
325	*1730*	*11.1*[d]		N3	13
	865	*−14.5*[d]			
326	*865*	*81.8*[d]		N3	13
	346	*13.0*[d]			
338	100	50	58	A1	24
339[f]	100	5	>5000	A1	24
340[f]	100	48	200	A1	24
341	100	−8	>5000	A1	24
342	100	−2	>5000	A1	24
343	100	20	>5000	A1	24
344	100	−44	>5000	A1	24
354	10	20 (21.2)		A1	25
383	100	9.4 (9.3)		A1	1
384	100	−5.3 (7.8)		A1	1

*Significant difference between control and treatment discs (Wilcoxon's matched pairs test, $P<0.05$); **$P<0.01$.

[a] Recalculated from the 'Percent Feeding Inhibition' (%FI).

[b] Insecticidal activity; $LD_{100}=0.001$ ppm (Kubo and Nakanishi, 1979).

[c] 'Minimum Inhibitory Concentration' (MIC), the limiting concentration to cause 100% feeding inhibition.

[d] Recalculated from the average FR_{50}.

[e] Lower test concentrations omitted.

[f] Tested as a mixture of the corresponding isomers **a** and **b**; ratio not known.

Table 1b
Insect antifeedant activity against larvae of the Egyptian cotton leafworm (Lepidoptera: *Spodoptera littoralis*) in no-choice feeding assays

	Conc. (ppm)	AI_{nc} (s.e.m.) (%)	AI_{50} (ppm)	Assay	Ref.
49	100	*14 (14.8)*[a,b]		A1	9
50	100	*0 (b)*[a]		A1	9
107			<1	A1	6, 14
108			>1000	A1	14
114	100	*6 (7.0)*[a]		A1	9
116	100	*71 (8.1)*[a]*		A1	9
118	100	*49 (19.1)*[a]		A1	9
119	100	*33 (8.0)*[a]		A1	9
120	100	*76 (6.3)*[a]*		A1	9
121	100	*86 (8.2)*[a]*		A1	9
124	100	*45 (19.1)*[a]		A1	9
125	100	*6 (7.4)*[a]		A1	9
126	100	*49 (18.9)*[a]		A1	9
127	100	*57 (20.0)*[a]		A1	9
128	100	*86 (6.2)*[a]*		A1	9
129	100	*0 (b)*[a]		A1	9
130	100	*41 (19.6)*[a]		A1	9
131	100	*47 (18.9)*[a]		A1	9
132	100	*12 (16.4)*[a]		A1	9
133			>1000	A1	16
134			>1000	A1	6
135			870	A1	6, 16
136			350	A1	6
137			>1000	A1	6
138			>1000	A1	6
140			51	A1	6
141			>1000	A1	6
142			>1000	A1	6
207			0.4	A1	16
288	100	*43 (18.3)*[a]		A1	9
294	100	*65 (6.5)*[a]*		A1	9
295	100	*86 (6.5)*[a]*		A1	9
296	100	*0 (b)*[a]		A1	9
297	100	*71 (5.7)*[a]*		A1	9
308	(1000)	*0–25*[c]		A2	26, 27
309	(1000)	*0–25*[c]		A2	26, 27
312	[d]	[e]		[f]	28
317	100	*43 (23.6)*[a]		A1	9

*Statistically significant difference between control and treatment discs (Mann–Whitney U-test); $P<0.05$.

[b] Calculated from the reported average amounts consumed from control (C) and treatment discs (T).

[b] Standard error could not be calculated.

[c] Originally reported as 'degree of antifeedant activity' with the same numerical value.

[d] Concentration not specified.

[e] Reported as 'no significant activity'.

[f] Assay on cotton (*Gosypium hirsatum*) leaves; no-choice test not explicitly stated; no further details were given.

Table 2
Insect antifeedant activity against larvae of the fall armyworm (Lepidoptera: *Spodoptera frugiperda*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Ref.
2	100	78.4 (3.8)	A1	1
24	100	19.2 (7.0)	A1	1
33	100	25 (6.4)	A1	29
34	100	94.2 (1.6)	A1	1
	100	24 (16.6)		29
37	100	47.1 (7.3)	A1	1, 29
39	100	32 (12.3) *	A1	29
46	100	12 (6.8)	A1	29
47	100	10 (12.4)	A1	29
48a[a]	100	10 (12.4)	A1	29
48b[a]	100	15 (4.6)	A1	29
58	100	48 (3.4)*	A1	29
59	100	48 (12.4) *	A1	29
60	100	36 (11.7) *	A1	29
61	100	14 (11.6)	A1	29
66	100	12 (7.2)	A1	29
74	100	25 (7.8)	A1	29
76	100	26 (8.4)	A1	29
84	100	25 (6.8)	A1	29
85	100	12 (6.4)	A1	29
99	100	25 (6.4)	A1	29
106	100	51.4 (5.6)	A1	1
110	100	10.4 (6.7)	A1	1
143	100	46.8 (9.1)	A1	1
144	100	43.1 (7.6)	A1	1
145	100	11.8 (14.1)	A1	1
147	100	21.6 (15.9)	A1	1
148	100	34.4 (13.3)	A1	1
149	100	11.3 (4.3)	A1	1
152	100	6.1 (8.4)	A1	1
153	100	19.4 (5.8)	A1	1
154	100	11.3 (9.5)	A1	1
156	100	14.3 (3.8)	A1	1
179	100	74 (11.4) **	A1	18
183	100	61 (4.1) **	A1	18
199	100	85 (8.4)*	A1	20
200	100	98 (0.9)*	A1	20
201	100	53 (11.2) *	A1	20
202	100	2 (16.4)	A1	20
203	100	10 (14.8)	A1	20
204	100	85 (3.8)*	A1	20, 21
205	100	32 (18.5)	A1	21
214	100	17.3 (7.1)	A1	1
216	100	6 (12.8)	A1	68
218	100	24 (8.4)	A1	29
221	100	29 (6.4)	A1	29
249	100	34 (6.5)	A1	29
269	100	4 (13.8)	A1	29
310	100	14.5 (5.9)	A1	1
312	100	13.9 (9.3)	A1	1
314	100	6.2 (7.6)	A1	1
321	100	11.8 (6.8)	A1	1
354	10	18 (6.4)	A1	25
383	100	14.0 (6.4)	A1	1
384	100	−3.3 (5.4)	A1	1

*Significant difference between control and treatment discs (Wilcoxon's matched pairs test, $P<0.05$); ** $P<0.01$.

[a] Tested as separate C-13 epimers; configuration not known.

Table 3
Insect antifeedant activity against larvae of the African armyworm (Lepidoptera: *Spodoptera exempta*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Ref.
2	100	75.8 (5.8)	A1	1
24	100	34.2 (7.9)	A1	1
34	100	38.0 (17.1)	A1	1
73	(100)	*100*[a]	N2	12, 30, 31
	100	73.1 (7.1)	A1	1
74	(100)	*100*[a]	N2	12, 30, 31
87	(100)	*100*[a]	N2	30, 31
106	100	59.4 (3.5)	A1	1
110	100	41.2 (5.0)	A1	1
143	100	94.4 (2.9)	A1	1
144	100	51.4 (6.8)	A1	1
145	100	84.2 (3.0)	A1	1
147	100	64.8 (2.5)	A1	1
148	100	63.6 (2.5)	A1	1
149	100	55.2 (2.4)	A1	1
152	100	26.6 (2.3)	A1	1
153	100	36.4 (4.9)	A1	1
154	100	75.0 (2.3)	A1	1
156	100	29.3 (3.1)	A1	1
214	100	44.4 (7.1)	A1	1
310	100	19.5 (5.4)	A1	1
312	100	14.9 (3.9)	A1	1
314	100	26.7 (1.8)	A1	1
321	100	34.2 (2.4)	A1	1
383	100	9.1 (3.9)	A1	1
384	100	13.3 (4.8)	A1	1

*Significant difference between control and treatment discs (Wilcoxon's matched pairs test); $P<0.05$.

** $P<0.01$.

[a] 'Minimum inhibitory concentration' (MIC), the limiting concentration to cause 100% feeding inhibition.

Table 4
Insect antifeedant activity against larvae of the beet armyworm (Lepidoptera: *Spodoptera exigua*) in dual-choice and no-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	AI_{nc} (s.e.m.) (%)	Assay	Ref.
56	*392*	10.5 (10.5)	−26.3 (9.6)	N4a	32
57	*392*	13.7 (9.1)	16.0 (7.3)	N4a	32
73	*392*	67.9 (17.2)	70.0 (6.8)	N4a	32
74	*392*	25.1 (9.8)	8.3 (9.8)	N4a	32
75	*392*	57.1 (9.1)	31.0 (9.2)	N4a	32
76	*392*	9.7 (6.6)	−22.4 (7.5)	N4a	32
100	*392*	25.8 (12.2)	34.3 (23.0)	N4a	32
101	*392*	39.5 (8.8)	14.9 (16.8)	N4a	32
102	*392*	38.5 (13.8)	24.5 (14.1)	N4a	32
103	*392*	91.4 (6.2)	30.0 (16.6)	N4a	32
104	*392*	72.9 (13.4)	9.9 (19.6)	N4a	32
105	*392*	26.1 (14.2)	−16.1 (19.2)	N4a	32
308	(1000)		*0–25*[a]	A2	26, 27

[a] Originally reported as 'degree of antifeeding activity'.

Table 5
Insect antifeedant activity against larvae of the tobacco cut leafworm (Lepidoptera: *Spodoptera litura*) in dual-choice feeding assays

	Conc.[a] (ppm)	AI_{dc} (%)	AI_{nc} (%)	Assay	Ref.
2	(80)[b]	*100*[c]		N5	33, 36
		82–100			34
	(50)	*100*[c]	*100*[d]		34–36
		82–100			34
	(25)	*54–82*			
	(12)	*54–82*			
143	(50)[b]	*100*[c]	*100*[d]	N5	34–36
		82—100			34
	(25)	*54–82*			
	(12)	*54–82*			
144	(50)[b]	*82–100*		N5	34
	(25)	*54–82*			
	(12)	*54–82*			
145	(50)[b]	*100*[c]	*100*[d]	N5	34–36
		82–100			34
	(25)	*54–82*			
	(12)	*33–54*			
146	(200)[b]	*82—100*		N5	34
	(100)	*54–82*			
	(80)	*54–82*			
	(50)	*0–33*			
150	(1000)[e]	*0–33*		N5	34
151	(1000)[e]	*0–33*		N5	34
155	(1000)[e]	*0–33*		N5	34
157	(200)	*100*[c]	*100*[d]	N5	35,36
158	(100)	*100*[c]	*100*[d]	N5	35,36
159	(1000)	*33–54*		N5	34
	(500)	*33–54*			
	(200)	*0–33*			
160	(200)[b]	*100*[c]	*100*[d]	N5	34–36
		82–100			34
	(100)	*0–33*			
161	(80)[b]	*100* c	*100*[d]	N5	34–36
		82–100			34
	(50)	*54–82*			
	(25)	*33–54*			
	(12)	*33–54*			
162	(500)[b]	*82–100*		N5	34
	(200)	*54–82*			
	(100)	*0–33*			
163	(200)[b]	*100*[c]	*100*[d]	N5	34–36
		82–100			34
	(100)	*54–82*			
	(80)	*54–82*			
	(50)	*54–82*			
	(25)	*33–54*			
	(12)	*33–54*			
164	(1000)	*54–82*		N5	34
	(500)	*33–54*			
	(200)[e]	*0–33*			
165	(200)	*100*[c]	*100*[d]	N5	35, 36
166	(100)	*100*[c]	*100*[d]	N5	35, 36
169	(1000)[e]	*0–33*		N5	34
170	(1000)[e]	*0–33*		N5	34
171	(1000)	*33–54*		N5	34
	(500)	*33–54*			
	(200)	*0–33*			
190	(400)		*100*[d]	N5	33
	(200)	*100*[c]			33, 36
191	(600)		*100*[d]	N5	33
	(300)	*100* c			33, 36
	(200)	*100*[c]	*100* d		35, 36
192	(>1000)	[f]		N5	33
193	(1000)		*100*[d]	N5	33
	(500)	*100*[c]			
194	(30)		*100* d	N5	33
	(15)	*100*[c]			
195	(>1000)	[f]		N5	33
196	(>1000)	[f]		N5	33
197	(>1000)	[f]		N5	33
198	(>1000)	[f]		N5	33
212	(400)	*67–100* [g]		[h]	37
345	(1000)[e]	*0–33.3*		N5	34
346	(1000)	*0–14.3*		N5	38, 39
347	(1000)	*0–14.3*		N5	38, 39
348	(1000)	*33.3–60.0*		N5	38
	(500)	*14.3–33.3*			
349	(1000)	*0–14.3*		N5	38
350	(1000)	*0–14.3*		N5	38, 39
	(500)	*14.3–33.3*			
351	(1000)	*0–14.3*		N5	38, 39
352	(1000)	*90.5–100*		N5	38
	(500)	*0–14.3*			
353	(1000)	*60.0–90.5*		N5	38
	(500)	*14.3–33.3*			
	(250)	*0–14.3*			
355	(1000)	*60.0–90.5*		N5	38, 39
	(500)	*33.3–60.0*			
	(250)	*14.3–33.3*			
356	(1000)	*60.0–90.5*		N5	38, 39
	(500)	*33.3–60.0*			
	(250)	*0–14.3*			
357	(1000)	*90.5–100*		N5	38
	(500)	*14.3–33.3*			
	(250)	*0–14.3*			
358	(1000)	*60.0–90.5*		N5	38
	(500)	*14.3–33.3*			
	(250)	*0–14.3*			
359	(1000)	*90.5–100*		N5	38,39
	(500)	*60.0–90.5*			
	(250)	*33.3–60.0*			
360	(1000)	*90.5–100*		N5	38,39
	(500)	*60.0–90.5*			
	(250)	*14.3–33.3*			
361	(1000)	*90.5–100*		N5	38
	(500)	*33.3–60.0*			
	(250)	*14.3–33.3*			
362	(1000)	*60.0–90.5*		N5	38
	(500)	*33.3–60.0*			
	(250)	*0–14.3*			
363	(1000)	*90.5–100*		N5	38, 39
	(500)	*60.0–90.5*			
	(250)	*33.3–60.0*			
364	(1000)	*90.5–100*		N5	38, 39
	(500)	*60.0–90.5*			
	(250)	*0–14.3*			
365	(1000)	*90.5–100*		N5	38
	(500)	*60.0–90.5*			
	(250)	*14.3–33.3*			
366	(1000)	*90.5–100*		N5	38
	(500)	*60.0–90.5*			
	(250)	*14.3–33.3*			

[a] For all tests in this table, the substrate was dipped into a solution of the test compound at the indicated concentration; the actual amount of compound present on the substrate is unknown.

[b] Higher concentrations omitted.

[c] 'Minimum inhibitory concentration (MIC)'.

[d] 'Absolute antifeedant' (Munakata, 1977; Kato et al., 1972; Hosozawa et al., 1974): treatment discs were not bitten by the larvae even when the assay duration was extended to 24 h (control discs were >90% consumed after 2 h) and the larvae eventually starved to death.

[e] Lower concentrations omitted.

[f] No 100% antifeedant activity found at 1000 ppm.

[g] 'Threshold concentration', the lowest concentration to give >20% reduction in feeding, relative to control discs.

[h] Assay as N5 but on cabbage leaf discs of only 15 mm diam.; assay duration 5 h.

Table 6
Insect antifeedant activity against larvae of the cotton bollworm (Lepidoptera: *Helicoverpa armigera*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Ref.		Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Ref.
33	100	41 (11.2) *	A1	29	**212**	100	3.9 (15.0)	A1	7
34	100	63.2 (5.4) *	A1	1, 7		10	3.4 (14.7)		
		63 (12.4) *		29	**213**	100	4.6 (10.2)	A1	7
	10	16.9 (7.8)		7		10	3.0 (18.4)		
39	100	20 (11.2)	A1	29	**214**	100	11.7 (14.9)	A1	7
46	100	2 (14.6)	A1	29			10.4 (4.2)		1
47	100	10 (18.4)	A1	29		10	19.5 (7.1)		7
48a[a]	100	15 (6.1)	A1	29	**216**	100	4 (12.9)	A1	29
48b[a]	100	15 (12.4)	A1	29	**217**	100	8.8 (8.8)	A1	7
58	100	43 (6.7) *	A1	29		10	6.8 (3.7)		
59	100	45 (9.9) *	A1	29	**218**	100	16 (6.8)	A1	29
60	100	25 (12.3)	A1	29	**219**	100	23.9 (14.6)	A1	7
61	100	8 (11.6)	A1	29		10	24.0 (7.2)		
64	100	8.6 (10.4)	A1	7	**220**	100	16.9 (13.0)	A1	7
	10	2.4 (3.8)				10	11.5 (5.7)		
66	100	16 (11.4)	A1	29	**221**	100	24 (11.6)	A1	29
73	100	39.6 (9.7) *	A1	7			24.8 (17.0)		7
		39 (9.6) *		29		10	20.9 (8.0)		
	10	23.9 (9.9)		7	249	100	43 (8.6) *	A1	29
74	100	48 (7.4) *	A1	29	**257**	100	9.8 (15.6)	A1	7
76	100	23.9 (9.6)	A1	7		10	19.6 (6.5)		
		23 (9.6)		29	**260**	100	2.8 (12.0)	A1	7
	10	2.9 (5.7)		7		10	−2.9 (7.0)		
84	100	20 (11.2)	A1	29	**261**	100	−0.9 (11.9)	A1	7
85	100	15 (11.4)	A1	29		10	−5.8 (5.0)		
99	100	8 (14.4)	A1	29	**262**	100	18.9 (7.7)	A1	7
106	100	50.2 (1.3)	A1	1		10	16.7 (13.7)		
143	100	37.4 (6.4)	A1	1	**269**	100	11.9 (6.0)	A1	7
148	100	24.5 (6.7)	A1	1			11 (5.9)		29
199	100	84 (4.2) *	A1	20		10	15.6 (6.5)		7
200	100	90 (2.4) *	A1	20	**272**	100	29.6 (8.9)	A1	7
201	100	58 (11.8) *	A1	20		10	29.2 (8.6)		
202	100	12 (13.6)	A1	20	**310**	100	17.4 (4.7)	A1	1
203	100	9 (12.4)	A1	20	**312**	100	9.4 (4.1)	A1	1
204	100	65 (8.4) *	A1	20, 21	**314**	100	1.7 (7.4)	A1	1
205	100	14 (13.8)	A1	21	**321**	100	21.4 (5.4)	A1	1
208	100	29.8 (15.0)	A1	7	**354**	10	8 (11.3)	A1	25
	10	23.2 (6.6)			**383**	100	14.3 (6.0)	A1	1
211	100	4.9 (13.0)	A1	7	**384**	100	6.2 (7.2)	A1	1
	10	8.9 (16.0)							

*Statistically significant difference between control and treatment discs (Wilcoxon's ranked pairs test); $P < 0.05$.
[a] Tested as separate C-13 epimers; configuration not known.

Table 7
Insect antifeedant activity against larvae of the tobacco budworm (Lepidoptera: *Heliothis virescens*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Ref.
34	100	91.8 (5.1)	A1	1
106	100	48.6 (1.6)	A1	1
214	100	12.7 (9.2)	A1	1
310	100	14.7 (7.2)	A1	1
312	100	9.1 (4.8)	A1	1
	[a]	[b]	[c]	28
314	100	2.6 (1.7)	A1	1
321	100	24.6 (1.3)	A1	1
354	10	10 (3.4)	A1	25
383	100	15.9 (5.4)	A1	1
384	100	9.5 (7.9)	A1	1

[a] Test concentration not specified.
[b] Reported to have 'no significant activity'.
[c] Assay on cotton (*Gosypium hirsatum*) leaf; no details given.

Table 8a
Insect antifeedant activity against larvae of the large cabbage white butterfly (Lepidoptera: *Pieris brassicae*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Ref.
199	100	91 (1.4)	N6	20
200	100	96 (0.9) *	N6	20
201	100	54 (6.4)	N6	20
202	100	10 (21.4)	N6	20
203	100	8 (11.6)	N6	20
204	100	75 (8.9) *	N6	20, 21
205	100	12 (14.6)	N6	21
323	*89*	−9.2 (12)	N7	40, 42
327	*99*	33 (10) **	N7	40, 42
328	*88*	35 (8) **	N7	40, 42
329	*101*	26 (6) **	N7	40, 42
330	*84*	9 (9)	N7	40, 42
331	*97*	−4 (10)	N7	40, 42
332	*109*	15 (8)	N7	40, 42
333	*91*	11 (9)	N7	40, 42
334	*93*	36 (7) **	N7	40, 42
335	*100*	28 (10) **	N7	40, 42
336	*114*	23 (8) **	N7	40, 42
337	*107*	5 (8)	N7	40, 42
346a	*84*	28 (11) *	N7	40
350a	*88*	18 (9) *	N7	40, 41
367	*97*	*10 (6)*[a]	N7	40, 41
367a	*97*	*9 (3)*[a]	N7	40, 41
367b	*97*	24 (8) *	N7	40, 41
368	*97*	10 (9)	N7	40, 41
369	*116*	16 (9)	N7	40, 41
370	*109*	20 (9)	N7	40, 41
371	*89*	26 (7) **	N7	40, 41
372	*97*	−11 (8)	N7	40, 41
373	*122*	41 (11) **	N7	40, 41
373a	*122*	10 (6)	N7	40, 41
374	*89*	11 (9)	N7	40, 41
375	*86*	*11 (14)*[a]	N7	40, 41
376	*88*	−2.5 (7)	N7	40, 41
377	*97*	54 (12) **	N7	40, 41
378	*95*	*9 (4)*[b]	N7	40, 41
379	*105*	16 (6) **	N7	40, 41
380	*124*	9 (7)	N7	40, 41
381	*112*	18 (10)	N7	40, 41
382	*98*	24 (9) *	N7	40, 41

**Statistically significant difference between control and treatment discs (Wilcoxon's matched pairs test); $P<0.01$; (*) $P<0.05$.

[a] Average value from two experiments performed on different days.

[b] Average value from three experiments.

Table 8b
Insect antifeedant activitiy against larvae of the large cabbage white butterfly (Lepidoptera: *Pieris brassicae*) in no-choice feeding assays

	Conc. (ppm)	Period[a]	AI_{nc} (s.e.m.) (%)	Assay	Ref.
308	(100)[b]		*95—100*[c]	A2	26, 27
	(50)		*75–95*[c]		
	(25)		*50–75*[c]		
309	(1000)		*95–100*[c]	A2	26, 27
	(500)		*75–95*[c]		
320	(1000)		*0–25*[c]	A2	26, 27
367	*96*	I	*22.4 (5.0)* **	N7	40, 41
		II	*13.9 (4.3)* **		
368	*97*	I	*18.6 (7.6)* *	N7	40, 41
		II	*15.9 (7.0)* *		
369	*116*	I	*16.7 (5.4)**	N7	40, 41
		II	*3.0 (3.8)*		
370	*109*	I	*18.3 (8.5)*	N7	40, 41
		II	*9.5 (5.8)*		
371	*88*	I	*−9.3 (5.2)*	N7	40, 41
		II	*−12.3 (4.3)*		
374	*89*	I	*20.3 (5.3)* **	N7	40, 41
		II	*10.6 (4.6)* *		
375	*86*	I	*−1.7 (6.2)*	N7	40, 41
		II	*−2.6 (3.0)*		
376	*90*	I	*6.7 (6.8)*	N7	40, 41
		II	*5.4 (6.9)*		

**Statistically significant difference between control and treatment discs (Mann–Whitney U-test); $P<0.01$; (*) $P<0.05$.

[a] Assay N7 was performed in two consecutive periods of 1.5 h each; leaf discs were renewed between periods.

[b] Higher concentrations were omitted.

[c] Originally reported as 'degree of antifeeding activity'.

Table 9a
Insect antifeedant activitiy against larvae of the Asian corn borer (Lepidoptera: *Ostrinia furnacalis*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.)[a] (%)	Assay	Ref.
23	(250)	3.7	N8	43
67	(250)	31.1 (2.9)	N8	43
68	(250)	15.5	N8	43
69	(250)	1.1	N8	43
70	(250)	7.5 (6.9)	N8	43
71	(250)	25.3	N8	43
72	(250)	25.1	N8	43
78	(250)	41.3[b]	N8	43
80	(250)	11.5	N8	43
81	(250)	19.0 (8.0)	N8	43
86	(250)	15.0 (0.4)	N8	43
88	(250)	7.8	N8	43
89	(250)	57.9	N8	43
90	(250)	26.3	N8	43
91	(250)	12.3 (0.8)	N8	43
92	(250)	36.2 (6.3)	N8	43
93	(250)	34.6	N8	43
94	(250)	39.7 (5.2)	N8	43
95	(250)	6.0	N8	43
271	(250)	5.3	N8	43
274	(250)	26.4	N8	43
276	(250)	2.3	N8	43
278	(250)	26.5	N8	43
279	(250)	26.9 (7.6)	N8	43
280	(250)	33.9	N8	43

[a] Average Antifeedant Index; s.e. = standard error.

[b] Average value from two experiments.

Table 9b
Insect antifeedant activity against larvae of the Asian corn borer (Lepidoptera: *Ostrinia furnacalis*) in no-choice feeding assays

	Conc. (ppm)	AI_{nc} (s.e.)[a] (%)	Assay	Ref.
23	(500)	−2.9 (3.1)	N8	43
67	(500)	21.7 (5.5)	N8	43
68	(500)	9.8	N8	43
70	(500)	0.8	N8	43
71	(500)	12.7	N8	43
72	(500)	16.4	N8	43
78	(500)	34.6 (4.9)[b]	N8	43
80	(500)	−4.4 (0.8)	N8	43
81	(500)	15.4 (3.4)	N8	43
86	(500)	28.0 (6.8)	N8	43
88	(500)	5.2	N8	43
89	(500)	43.2 (2.3)	N8	43
90	(500)	15.1	N8	43
91	(500)	26.0 (7.8)	N8	43
92	(500)	16.3 (0.7)	N8	43
93	(500)	20.1	N8	43
94	(500)	29.3	N8	43
271	(500)	5.4	N8	43
274	(500)	36.4	N8	43
276	(500)	−5.2	N8	43
278	(500)	2.8	N8	43
279	(500)	43.1 (6.4)	N8	43
280	(500)	30.2 (4.7)	N8	43

[a] Average Antifeedant Index; s.e. = standard error.
[b] Average value from three experiments.

Table 10
Insect antifeedant activity against various other species from the order of Lepidoptera in dual-choice assays[d]

			Conc. (ppm)	AI (s.e.m.) (%)	Assay[a]	Ref.
Diamondback moth	**73**	*(2500)*[b]	*86.6****[c]	dc	N9	44
(*Plutella xylostella*)		*(250)*[b]	*85.6****[c]	dc	N9	45
			*68.5**[c]	dc	N9	44
		(25)[b]	*27.1***[c]	dc	N9	45
			5.2[c]	dc	N9	44
		(2.5)[b]	*10.9*[c]	dc	N9	45
	74	*(250)*[b]	*46.5***[c]	dc	N9	45
		(25)[b]	*41.2*[c]			
European corn borer	**190**	(5000)	100	dc	N5	36
(*Ostrinia mubilalis*)	**191**	(5000)	100	dc	N5	36
Oriental tussock moth	**190**	(1000)	*100*[e]	dc	N5	36
(*Euproctis subflava*)	**191**	(1000)	*100*[e]	dc	N5	36
Cabbage moth	**199**	100	90 (2.4)*	dc	N6	20
(*Mamestra brassicae*)	**200**	100	95 (1.2)*	dc	N6	20
	201	100	45 (8.4)*	dc	N6	20
	202	100	8 (18.5)	dc	N6	20
	203	100	12 (12.8)	dc	N6	20
	204	100	86 (3.5)*	dc	N6	20, 21
	205	100	41 (22.8)	dc	N6	21
Yellow coaster butterfly	**78**	(50)	*67–100*[f]	dc	[g]	46
(*Pareba vesta*)	**79**	(200)	*67–100*[f]	dc	[g]	46
	82	(200)	*67–100*[f]	dc	[g]	46
Magpie moth	**190**	(5000)	*100*[h]	dc	N5	36

Table 10 (*continued*)

			Conc. (ppm)	AI (s.e.m.) (%)	Assay[a]	Ref.
(*Abraxas miranda*)	**191**	(5000)	*100*[h]	dc	N5	36
Pink bollworm (*Pectinophara gossypiella*)[i]	**54**	*3460*	*82*[j]	dc	N5	47
Paddy armyworm	**78**	(1000)	*84.9*[k]	nc	N10	48
(*Leucania separata*)	**274**	(1000)	*68.9*[k]	nc	N10	48
	277	(1000)	*48.0*[k]	nc	N10	48
	281	(1000)	*100.0*[k]	nc	N10	48
	282	(1000)	*59.3*[k]	nc	N10	48
	283	(1000)	*27.3*[k]	nc	N10	48
Castor looper	**16**	[l]	[m]		[l]	49
(*Achaea janata*)	**115**	[l]	[m]		[l]	49

***Statistically significant difference between control and treatment discs, $P<0.001$; ** $P<0.01$; * $P<0.05$.
[a] dc = dual-choice; nc = no-choice.
[b] From the reported concentration in % (0.1% = ca. 250 ppm; Pickett et al., 1987).
[c] Calculated from the amounts eaten of the control and treatment discs.
[d] Originally reported as 'degree of antifeeding activity'.
[e] Reported as 'feeding was prevented'.
[f] 'Lowest effective concentration', presumably the lowest concentration to cause strong feeding inhibitory activity (i.e. >20% reduction in feeding, relative to control; Wada and Munakata, 1968).
[g] 'Host plant leaf disc method' with *Boehmeria nivea* leaves, probably two-choice assay; no further details supplied.
[h] Reported as 'no inhibition of feeding below' specified concentration.
[i] Ajugarin IV (**98**) displays insect growth regulatory activity; ED_{50} = 500 ppm (Kubo et al., 1982).
[j] Calculated from PC_{50}, the concentration at which less than 5% of the treatment discs are consumed in the time that over 50% of the control discs are eaten (van Beek and de Groot, 1986).
[k] Recalculated from the AI_{dc} reported for this no-choice assay.
[l] Not specified.
[m] Reported as 'exhibited antifeedant activity'.

Table 11
Insect antifeedant activity against larvae of the yellow mealworm (Coleoptera: *Tenebrio molitor*) in dual-choice and no-choice feeding assays

	Conc. (ppm)	Dual-choice AI_{dc}[a] (%)	No-choice AI_{nc} (s.d.)[a] (%)	Assay	Ref.
17	*71*		*−34.2*	N11	50
20	*71*		*−7.9*	N11	50
33	*71*	*84.0*	*54.1 (6.9)*	N11	50–54
34	*71*	*7.8*	*−66.7 (23.8)*	N11	51, 53
35	*71*	*4.0*	*−37.9 (28.3)*	N11	50–53
51	*71*	*18.0*	*5.0 (22.0)*	N11	50–52
52	*71*	*88.0*	*55.2 (10.0)*	N11	50–53
53	*71*	*84.0*	*54.5 (8.8)*	N11	50–53
55	*71*	*25.9*	*6.4 (24.8)*	N11	50–53
117	*71*	*18.0*	*−67.8 (27.7)*	N11	50–53
210	*71*		*55.6 (10.9)*	N11	50, 54
211	*71*	*84.0*	*66.6 (6.6)*	N11	50, 51, 53
240	*71*		*10.2 (14.0)*	N11	50, 54
245	*71*		*18.2 (15.9)*	N11	50, 54
250	*71*		*30.5 (13.2)*	N11	50, 54
284	*71*	*−18.3*	*−37.4 (21.5)*	N11	50, 51, 53
285	*71*	*7.8*	*−68.4 (46.2)*	N11	50, 51, 53
290	*71*	*86.0*	*70.8 (7.8)*	N11	50–53
291	*71*		*70.8 (7.7)*	N11	50, 54
292	*71*	*32.0*	*2.4 (11.0)*	N11	50–53
293	*71*		*14.8 (14.4)*	N11	50, 54
294	*71*	*6.1*	*10.2 (16.9)*	N11	50–52

[a] Average Antifeedant Index, recalculated from the reported average Percentage of Feeding Inhibition (PFI); s.d. = standard deviation.

Table 12a
Insect antifeedant activity against larvae of the Colorado potato beetle (Coleoptera: *Leptinotarsa decemlineata*) in dual-choice feeding assays

	Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Internal toxicity	Ref.
12	*1730*	*39.8 (5.5)*[a]	N1	−[b]	4
13	*1730*	*23.8 (7.8)*[a]	N1	+[b]	4
14	*1730*	*44.3 (8.5)*[a]	N1	−[b]	4
15	*1730*	*18.6 (6.1)*[a]	N1	−[b]	4
18	*1730*	*82.0 (10.4)*[a]	N1	−[b]	4
19	*1730*	*81.7 (8.6)*[a]	N1	−[b]	4
21	*1730*	*93.4 (3.7)*[a]	N1	+[b]	4
22	*1730*	*94.4 (2.4)*[a]	N1	+[b]	4
56	*392*	88.2 (6.4)	N4a		32
57	*392*	73.7 (19.7)	N4a		32
73	*392*	26.8 (8.6)	N4a		32
74	*392*	31.4 (17.7)	N4a		32
75	*392*	26.8 (5.4)	N4a		32
76	*392*	13.7 (11.8)	N4a		32
100	*392*	39.9 (7.1)	N4a		32
101	*392*	8.6 (11.6)	N4a		32
102	*392*	46.1 (8.0)	N4a		32
103	*392*	33.1 (16.3)	N4a		32
104	*392*	36.4 (16.0)	N4a		32
105	*392*	28.5 (12.6)	N4a		32
111	*1730*	*20.3 (6.4)*[a]	N1	−[b]	4
112	*1730*	*83.8 (5.9)*[a]	N1	+[b]	4
214	*235*	9.4 (20.2)	N4b		55
219	*235*	−1.2 (18.5)	N4b		55
	196	23.8 (5.0)*	N4c	−[c]	56
	59	6.2 (6.9)		−[c]	
	20	−7.8 (5.4)		−[c]	
227	*235*	9.5 (8.2)	N4b		55
228	*235*	28.5 (8.7)	N4b		55
229	*235*	−10.1 (14.8)	N4b		55
230	*235*	10.7 (10.1)	N4b		55
231	*235*	49.0 (7.6)	N4b		55
232	*235*	61.7 (7.2)	N4b		55
233	*235*	38.0 (3.8)	N4b		55
234	*235*	0.7 (18.7)	N4b		55
236	*235*	20.1 (17.0)	N4b		55
237	*235*	31.8 (13.4)	N4b		55
244	*235*	22.8 (14.9)	N4b		55
267	*235*	53.4 (7.1)	N4b		55
	196	32.9 (6.2)*	N4c	−[c]	56
	59	25.2 (4.8)*		−[c]	
	20	14.0 (8.4)		−[c]	
268	*235*	46.2 (9.8)	N4b		55
	196	25.1 (5.8)*	N4c	+[c]	56
	59	8.1 (4.6)		+[c]	
	20	5.5 (7.2)		−[c]	
269	*235*	26.8 (20.2)	N4b		55
	196	34.0 (7.6)*	N4c	+[c]	56
	59	8.4 (3.6)		+[c]	
	20	11.6 (4.6)		−[c]	
270	*235*	57.6 (15.4)	N4b		55
273	*235*	44.1 (19.4)	N4b		55
275	*235*	57.5 (12.6)	N4b		55
299	*235*	54.5 (8.6)	N4b		55

*Significant difference between control and treatment discs (Wilcoxon's signed rank test); $P<0.05$.

[a] Recalculated from the 'Percent Feeding Inhibition' (% FI). The associated EC_{50} corresponds to $AI_{50}=33.3\%$ and was therefore not included in this table.

[b] Mortality after injection of 10 μg of the test compound; + indicates a significant difference from the control after 72 h (Fisher's exact test); $P<0.05$.

[c] Postingestive toxic effect indicated in 'choice vs. no-choice' feeding assays (Ortego et al., 1995); + indicates a significant difference between treatment and control discs (Dunnet two-tailed test); $P\leqslant 0.05$.

5. Structure–activity relationships

Despite the substantial efforts invested in the testing of clerodane diterpenes for insect antifeedant activity, no all-embracing structure–activity relationships have yet been identified. In the absence of detailed information on the modes of action of clerodane antifeedants and the biological targets involved, such relationships can only attempt to correlate structural elements from antifeedant molecules with the overall effect on insect feeding. Unfortunately the mechanisms governing insect feeding behaviour are highly complex and it is possible that structurally similar antifeedants affect insect feeding through different pathways involving unrelated biological targets.

In the early 1980s, several authors proposed either a furo[2,3b]furan moiety (Kojima and Kato, 1981a,b) or a decalin ring system with an epoxy–diacetate combination of functional groups (Jackson and Ley, 1981; Luteijn and de Groot, 1981; Geuskens et al., 1983) to be key structural elements responsible for antifeedant activity. Model compounds representing these substructures indeed elicited antifeedant activity, albeit only for some insect species and with less potency than the parent clerodane diterpenes from which they were derived. These results suggested that a synergistic action of both the epoxy–diacetate moiety and the furo[2,3b]furan system present in one molecule might account for the observed antifeedant activity, possibly with other types of sidechain instead of the furofuran (Geuskens et al., 1983; Belles et al., 1985).

Since then many new clerodane antifeedants have been identified, including diterpenes with structures not covered by this early model. Despite this wealth of new information (Tables 1–15) it remains difficult to assign importance to individual functional groups in relation to the observed antifeedant activity. Especially when moderately and weakly active clerodane antifeedants are included in the analyses a confusing picture emerges in which specific changes of a functional group often have a different and unpredictable outcome on the activity of different types of clerodanes. Although a detailed analysis of the structure–activity relationships cannot be presented, some interesting trends can be distinguished when only the 10–20% of the most active clerodanes per insect species are considered. Many of these trends have been mentioned before by other researchers in this field.

i. Active clerodanes in general possess the *trans*-decalin skeleton of the *neo*-clerodanes. *cis*-Decalin (19-nor)-clerodanes with antifeedant activity are limited to a few cases (**275** against *L. decemlineata*, **278** against *O. furnacalis*). In the majority of the *trans*-decalin clerodanes an epoxy-diester combination of functional groups is present at C-4, C-6 and C-18. Di-acetates are most common, but sometimes one of the acetates is replaced by another ester function, or the acetate

Table 12b
Insect antifeedant activitiy against larvae of the Colorado potato beetle (Coleoptera: *Leptinotarsa decemlineata*) in no-choice feeding assays

	Conc. (ppm)	AI_{nc} (s.e.m.) (%)	AI_{50} (ppm)	Assay	Ref.
12	*1730*	*11.6 (7.9)*	*>1730*	N1	4
13	*1730*	*22.2 (9.0)*	*>1730*	N1	4
14	*1730*	*22.6 (9.1)*	*>1730*	N1	4
15	*1730*	*35.5 (16.6)*	*>1730*	N1	4
18	*1730*	*90.7 (5.7)*	*294*	N1	4
19	*1730*	*98.9 (0.7)*	*266*	N1	4
21	*1730*	*40.7 (8.5)*	*>1730*	N1	4
22	*1730*	*86.5 (6.3)*		N1	4
56	*392*	75.6 (8.6)		N4a	32
57	*392*	67.6 (12.3)		N4a	32
73	*392*	5.3 (6.3)		N4a	32
74	*392*	−12.7 (9.0)		N4a	32
75	*392*	5.3 (5.6)		N4a	32
76	*392*	11.3 (8.4)		N4a	32
100	*392*	−9.2 (7.3)		N4a	32
101	*392*	16.1 (5.5)		N4a	32
102	*392*	9.0 (17.6)		N4a	32
103	*392*	29.4 (11.7)		N4a	32
104	*392*	−13.8 (6.3)		N4a	32
105	*392*	5.5 (12.9)		N4a	32
111	*1730*	*28.8 (7.8)*	*>1730*	N1	4
112	*1730*	*73.3 (4.7)*		N1	4
214	*235*	86.6 (2.7)	*24*[a]	N4b	55
219	*235*	86.1 (1.5)	*67*[a]	N4b	55
	196	60.1 (3.2)*		N4c	56
	59	33.4 (6.3)*			
	20	−7.7 (11.1)			
227	*235*	40.5 (4.2)		N4b	55
228	*235*	53.5 (4.3)		N4b	55
229	*235*	89.3 (2.8)	*49*[a]	N4b	55
230	*235*	51.7 (2.9)		N4b	55
231	*235*	64.7 (2.9)		N4b	55
232	*235*	58.3 (4.1)		N4b	55
233	*235*	77.4 (1.6)	*>70*[a]	N4b	55
234	*235*	89.9 (2.3)	*22*[a]	N4b	55
236	*235*	89.2 (2.0)	*25*	N4b	55
237	*235*	62.6 (2.9)		N4b	55
244	*235*	46.4 (2.6)		N4b	55
267	*235*	70.4 (2.7)	*92*[a]	N4b	55
	196	39.0 (5.2)*		N4c	56
	59	7.3 (5.3)*			
	20	−10.1 (6.7)			
268	*235*	85.9 (2.5)	*22*[a]	N4b	55
	196	77.8 (5.3)*		N4c	56
	59	59.4 (2.6)*			
	20	45.6 (7.7)*			
269	*235*	87.4 (3.0)	*17*[a]	N4b	55
	196	75.0 (5.9)*		N4c	56
	59	51.0 (7.8)*			
	20	35.6 (9.3)*			
270	*235*	91.0 (1.4)	*20*[a]	N4b	55
273	*235*	89.3 (1.1)	*21*[a]	N4b	55
275	*235*	92.9 (1.6)	*12*[a]	N4b	55
299	*235*	30.9 (2.8)		N4b	55
367	*160*	I: *−6.3 (9.3)*[b]		N7	40
		II: *−4.8 (5.7)*			
368	*162*	I: *−13.5 (6.1)*[b]		N7	40
		II: *3.8 (4.7)*			
369	*194*	I: *−21.3 (5.2)*[b]		N7	40
		II: *6.3 (4.9)*			
370	*183*	I: *−4.8 (9.2)*[b]		N7	40
		II: *3.0 (9.1)*			
371	*149*	I: *−20.2 (11.7)*[b]		N7	40
		II: *0.8 (6.3)*			
374	*149*	I: *−1.7 (8.0)*[b]		N7	40
		II: *1.0 (5.9)*			
375	*143*	I: *8.7 (8.5)*[b]		N7	40,41
		II: *15.9 (5.5)*‡			
376	*147*	I: *−7.1 (8.1)*[b]		N7	40
		II: *−17.4 (6.0)*			

*Significant difference between control and treatment discs (Dunnet two-tailed test); $P=0.05$; †Significant difference between C and T (Mann–Whitney U test); $P<0.01$.

[a] The associated 95% confidence interval was omitted from the table.

[b] Assay N7 was conducted in two consecutive periods of 1.5 h each; leaf discs were renewed between periods.

Ring opening or removal of the epoxide generally result in significant loss of activity, except for chlorohydrin **89** which displays moderate activity against *O. furnacalis*.

In a second group of active compounds the epoxy–diester combination is replaced by an α,β-unsaturated lactone at C-3- C-5. For *Tenebrio molitor* significant loss of activity is observed upon reduction of the lactone ring to a diol (**52** vs. **51**) or after simultaneous hydrogenation of the C-3 double bond and the furan-based C-9 sidechain (**53** vs. **55**, **290** vs. **292**). A related α,β-unsaturated lactone moiety is found at C-4- C-6 of various 19-nor clerodanes (**267**, **270**, **275**) active against *L. decemlineata*.

For the Homopteran insect species *M. persicae* antifeedant activity is elicited by structural features differing from those described above. From the limited data available it seems that at C-4,18 an exocyclic methylene is highly preferred over an epoxide (**14**, **18**, **19**, **111** vs. **21**, **73**, **74**). On the whole, however, the activity of the clerodanes tested on these aphids was rather low, compared to Lepidopteran and Coleopteran species.

Table 13
Insect antifeedant activity against other insect species from the order of Coleoptera

		Conc. (ppm)	AI_{dc} (s.e.m.) (%)	Assay	Ref.
Mustard beetle (*Phaedon cochleariae*)	**73**	(*250*)[a]	*100***[b]	N9	45
		(*25*)[a]	*100****[b]		
		(*2.5*)[a]	*97.5****[b]		
		(*0.25*)a	*46.5**[b]		
		(*0.025*)a	*17.9**[b]		
	74	(*25*)[a]	*56.7****[b]	N9	45
		(*2.5*)[a]	*7.7**[b]		
		(*0.25*)a	*−5.0*[b]		
Potato beetle			Nymphs	Adults	
(*Henosepilachna vigintioctopunctata*)	**160**	*353*	*13.4 (1.3)*	*19.0 (0.9)*	N12 57
		35	*4.9 (0.7)*	*22.7 (0.9)*	
		3.5	*8.8 (0.5)*	*18.4 (0.5)*	
	161	*353*	*24.4 (0.7)*	*24.5 (0.8)*	N12 57
		35	*11.4 (0.7)*	*4.4 (0.4)*	
		3.5	*11.8 (0.6)*	*5.4 (0.6)*	
	165	*353*	*28.6 (0.7)*	*73.8 (1.1)*	N12 57
		35	*56.9 (0.5)*	*−4.8 (0.5)*	
		3.5	*20.8 (0.9)*	*−2.6 (0.7)*	
	168	*353*	*0.6 (0.7)*	*13.3 (0.3)*	N12 57
		35	*−0.7 (0.7)*	*12.7 (0.5)*	
		3.5	*−8.6 (0.7)*	*-9.2 (0.7)*	
Western corn rootworm beetle (*Diabrotica virgifera vir.*)	**297**	ED_{50} = 1.1 nmol/disc		[c]	58

***Significant difference between treatment and control discs ($P<0.001$); **$P<0.01$; *$P<0.05$.

[a] From the reported concentration in % (0.1% = ca. 250 ppm; Pickett et al., 1987).

[b] Calculated from the amounts eaten from control and treatment discs.

[c] No details of the bioassay were specified.

Table 14
Deterrent activity on the settling behaviour of the green peach aphid (Homoptera: *Myzus persicae*) in dual-choice bioassays

	Conc. (ppm)	DI (s.e.m.)[a] (%)	Assay	Ref.
12	*1730*	*18.0 (5.0)*[b]	N13	4
13	*1730*	*10.9 (3.5)*[b]	N13	4
14	*1730*	*31.8 (4.8)*[b]	N13	4
15	*1730*	*20.1 (4.7)*[b]	N13	4
18	*1730*	*28.5 (5.7)*[b] *	N13	4
19	*1730*	*29.5 (4.6)*[b] *	N13	4
21	*1730*	*15.1 (3.3)*[b]	N13	4
73	(*2500*)[c]	*12.5*[d]	N9	58
74	(*250*)[c]	*−6.7*[d]	N9	58
111	*1730*	*27.5 (5.6)*[b] *	N13	4
346a	*121*	5 (21)	A3	40
350a	*121*	−41 (16)[‡]	A3	40
367	*121*	20 (19)	A3	40
367a	*121*	29 (14)	A3	40
368	*121*	31 (20)	A3	40
369	*121*	10 (19)	A3	40
370	*121*	−10 (17)	A3	40
371	*121*	*1 (12)*[e]	A3	40
372	*121*	*0 (9)*[f]	A3	40
373a	*121*	−19 (18)	A3	40
374	*121*	*4 (12)*[e]	A3	40
375	*121*	*−5 (12)*[e]	A3	40
376	*121*	29 (19)	A3	40
378	*121*	−18 (18)	A3	40

*Statistically significant difference between control and treatment areas (Mann–Whitney W-test); $P<0.05$; ‡Wilcoxon's matched pairs test; $P<0.05$.

[a] Mean Deterrency Index DI = $[(C-T)/(C+T)]$; s.e.m. = standard error of the mean. C and T are the numbers of aphids settled on control and treatment areas, respectively.

[b] Recalculated from the reported Settling Inhibition (SI).

[c] Recalculated from the reported concentration in % (0.1% = ca. 250 ppm; Pickett et al., 1987).

[d] Calculated from the reported number of aphids on control and treatment areas. The difference between C and T was reported to be 'not significant'.

[e] Average value from two experiments performed on different days.

[f] Average value from three experiments.

ii. In all of the most active clerodanes the sidechain-fragment at C-9 contains an oxygenated ring-system. With many Lepidopteran insect species, a furofuran-based structure appears to be most favourable for strong activity, either in its dide-hydro or hemiacetal form, or completely saturated. Furans and butenolides are also frequently found among the most active clerodanes; hydrogenation of the unsaturation in these moieties usually results in diminished activity.

iii. For high activity, structural elements from (i) and (ii) must be present simultaneously in one molecule. Partial fragments as **308**–**384** usually show markedly diminished activity in the tests. However, a number of exceptions to this general observation are known. For *L. migratoria* the decalin fragment **310** with an 4β-O epoxide showed equal antifeedant activity under no-choice contitions as the clerodin derivative **145**, contrary to model compound **311** incorporating the more common 4α-O epoxide which was inactive. Also with *P. brassicae* and *M. persicae* some synthetic compounds modelled upon the decalin fragment e.g. **308**, **309**) or the C-9 sidechain moiety (e.g. **367a**, **376**, **377**) displayed appreciable levels of activity in comparison to the few clerodane diterpenes that were tested against these species.

iv. In addition to being present in one molecule, it appears that for high activity the key structural elements from (i) and (ii) must be able to adopt a distinct spatial orientation. Molecular modeling experiments with clerodanes active against

Table 15
Insect antifeedant activities against species from other orders

			Conc. (ppm)	AI (%)	Assay[a]		Ref.
Order: ***Orthoptera***							
Migratory locust (*Locusta migratoria*)		**145**	(100)	*70*[b]	nc	A4	59
		247	(1000)	*38*[b]	nc	A4	60
		248	(100)	*70*[b]	nc	A4	60
		310	(100)	*70*[b]	nc	A4	59
		311	(1000)	[c]	nc	A4	59
		312	(1000)	*72*[b]	nc	A4	28
		313	(1000)	*<36*[b]	nc	A4	28
		315	[d]	[c]	nc	A4	59
		316	[d]	[c]	nc	A4	59
Desert locust (*Schistocerca gregaria*)		**73**	*(0.06)*	*100*[e]	dc	[f]	30
Vagrant grasshopper (*Schistocerca vaga*)		**73**	*(1000)*	*100*[e]	nc	[g]	30
Order: ***Diptera***							
Housefly (*Musca domestica*)	•First instar larvae	**165**	(4.5–8.6)	[h,i]	nc	N14	61
	•Third instar larvae		(14.3–28.6)	[h,j]			
Order: ***Hymenoptera***							
Umbrella ant (*Atta cephalotes*)		**7**	*(0.11 μg)*[k,l]	*47.4***	dc	N15	62, 63
Leafcutting ant (*Acromyrmex octospinosus*)		**96**	(0.50 mg/g)[m]	*22.4*	dc	N15	64
		97	(0.50 mg/g)[m]	*5,2*	dc	N15	64
		286	(0.33 mg/g)[m]	*51.2****	dc	N15	64
		287	(0.33 mg/g)[m]	*39.5**	dc	N15	64
Order: ***Isoptera***							
Subterranean termite (*Reticulitermes speratus*)		**8**	*2768*	*100*[‡]	dc	N16	65
		9	*2768*	*100*[‡]	dc	N16	65
		10	*2768*	*94.0*[‡]	dc	N16	65
		11	*2768*	*100*[‡]	dc	N16	65
Insect species ***unspecified***							
Not specified		**77**		[n]			66
Not specified		**98**		[n,o]			66, 67
Not specified		**113**		[p]			68
Not specified		**209**		[q]			69
Not specified		**215**		[q]			69

***Statistically significant difference between control and treatment flakes; $P<0.001$; ** $P<0.005$; *$P<0.01$; ‡Significant difference between control and treatment discs (Mann–Whitney U-test); $P<0.05$.

[a] dc = dual-choice; nc = no-choice.

[b] From the 'percentage of feeding inhibition'.

[c] Activity 'negligible' or 'not significant'.

[d] Not specified.

[e] 'Minimum Inhibitory Concentration' (MIC), the limiting concentration needed to cause 100% feeding inhibition.

[f] Assay on glass-fibre discs with 0.1 M sucrose; no details given.

[g] Assay on corn seedling leaf; no details given.

[h] Decreased weight gain of the larvae after 144 h, relative to controls.

[i] Dose-dependent *delayed* pupariation, decreased weight of puparia and increased mortality during moult, relative to controls.

[j] *Accelerated* pupariation, decreased weight of puparia and increased mortality during moult.

[k] Recalculated to μg of compound per rye flake.

[l] No toxicity to ants or growth inhibition of the mutualistic ant fungus detected (Howard et al., 1988).

[m] Represents mg of compound per g of rye flakes.

[n] 'No antifeeding activity'; probably tested against *S. exempta* and *Bombyx mori*, but insect species not explicitly stated.

[o] Insecticidal activity against *B. mori*; $LD_{95} = 500$ ppm (Kubo et al., 1982).

[p] Reported to 'show antifeedant activity'.

[q] Compound 'appeared to be devoid of such [antifeedant] activities'.

Table 16
Summary of the feeding bioassay conditions

Assays using artificial substrates

A1: Final instar larvae of *S. littoralis*, *S. frugiperda*, *S. exempta*, *H. virescens* or *H. armigera* were tested on glass-fibre discs (diam. 2.1 cm), made palatable with sucrose. Treatment discs were treated with 100 μl of a solution of the test compound. The assay was terminated after 50% of either disc was eaten or after 12, 18 or 24 h. The discs were weighed to determine the mass eaten of control (*C*) and treatment discs (*T*), from which the standard Antifeedant Indexes AI_{dc} and AI_{nc} were calculated.

A2: Tested on styropor lamellae (6 ∞ 3 cm), dipped into an ethanol-water mixture containing sucrose and the test compound (treatment substrate). The amount of feeding was determined after 24 h by weighing the remaining feeding substrate. The degree of antifeeding activity, [1-(*T*/*C*)], was reported in five activity classes (e.g. + + + + = 100–95%).

A3: The substrate consisted of a parafilm layer, stretched over a plastic ring (2.7 cm diameter). One half of the lower surface was painted with 10 μl of a solution of the test compound in ethanol at the indicated concentration, while the other half was painted with ethanol only. A parafilm sachet containing two compartments filled with artificial diet was stretched over the upper surface. *M. persicae* nymphs were placed on the painted lower side of this test set-up (diet sachet on top). After 24 h, the numbers of aphids present on the treatment and control halves of the diet were counted and a Deterrency Index was calculateded; DI = [(*C*−*T*)/(*C* + *T*)].

A4: This assay is poorly described in the cited literature. The substrate consisted of glassfibre GF/A discs, coated with glucose solution. Probably a no-choice set-up was used, although this was only explicitly stated inHanson et al. (1982). The antifeedant activity was reported as the percentage of feeding inhibition,%FI = [1−(*T*/*C*)].

N—Assays using natural substrates

N1: *S. littoralis* larvae (fifth instar) or *L. decemlineata* adults were tested on sweet potato (*Ipomoea batatas*) leaf discs (1 cm^2 surface area), coated with 10 μl of test compound solution in acetone (treatment discs) to a final amount of 50 mg compound/cm^2 leaf area. After 16–20 h the assay was terminated and the uneaten leaf disc surfaces were measured. From the consumption from treatment and control discs the antifeedant activity was determined and reported as the percentage of feeding inhibition,%FI = [1−(*T*/*C*)].

N2: Leaf disc assay (see N5); maize (*Zea mays*) leaves for tests with *S. littoralis* (instar unknown); *Ricinis communis* leaves with third instar larvae of *S. exempta*. The activity was reported as Minimal Inhibitory Concentration (MIC), which is the minimum required concentration to completely inhibit the insects from feeding on the treatment discs.

N3: Assay with fifth instar larvae of *S. littoralis* on lettuce (*Lactuca sativa*) leaf discs (area 1 cm^2) treated with 10 μl of test compound solution in acetone (treatment discs). The consumed areas of treated discs (CTD) and control discs (CCD) were simultaneously measured every 30 min during the entire assay duration (4–5 h). The antifeedant activity was expressed as Feeding Ratio, FR = [CTD/CCD]. For comparative purposes the authors recommended the use of FR50, which is the Feeding Ratio when CTD = 50% (FR75 was also given). CTD_{50} and CCD_{50} were obtained for each separate test by extrapolation of the nearest empirical values.

N4: Tested with *S. exigua* larvae (fifth instar) or *L. decemlineatae* larvae (fourth instar) on leaf discs (1.77 cm^2) of sugar beet or potato (*Solanum tuberosum*), respectively. Treatment discs were coated on the upper surface with 20 μl (N4a), 12 μl (N4b) or 10 μl (N4c) of test compound solution in acetone and were fitted in holes in an agar layer. The assays were terminated either after consumption of 50% of all discs (dual-choice assay; maximum duration 24 h) or after 75% of the control discs had been consumed (dual-choice assay). The remaining discs were weighed and the amount eaten of control and treatment discs determined. Antifeedant activity was reported as the average standard Antifeedant Index AI_{dc} or AI_{nc}.

N5: Several insect species were tested using this 'leaf disc method'; except for *S. litura* (third instar) the larval stage of the insects was not specified. The feeding substrate consisted of sweet potato (*Ipomoea batatas*) leaf discs (20 mm diam), which were dipped into an acetone solution containing the test compound (treatment discs). The assay was terminated when about 50% of the leaf area of the control discs was consumed. The consumed areas of control and treatment discs were measured. The degree of antifeeding activity, [1-(*T*/*C*)], was reported as belonging to one of four (or five) activity classes, (i.e. + + + = −90–100%).

N6: A binary choice feeding bioassay using glass-fibre disks was used to evaluate the activity at 100 ppm of the neo-clerodane diterpenoids against the final stadium larvae of *Spodoptera litoralis* (Boisd.) (Lepidoptera). All disks were made palatable by the addition of 100 μl of a sucrose solution (50 mM), control disks carried only sucrose. The disks were dried and weighed before use. For the bioassay, larvae were placed individually in a Petri dish with a control disk and a treatment disk. The bioassay terminated after the larvae had eaten approximately 50% of one of the disks or after 12 h. The larvae were then removed and the disks were dried and reweighed. The antifeedant index [(*C*−*T*)/(*C* + *T*)]% was calculated, where *C* and *T* represent the amount eaten of the control and treatment disks, respectively.

N7: *P. brassicae* larvae (fifth instar) were tested on cabbage leaf discs (*Brassica oleracea* var. *gemmifera*, cv. Titurel or cv. Cyrus; surface area 3.80 cm^2). Potato leaf discs (*Solanum tuberosum* L., cv. Surprise; surface area 2.27 cm^2) were used for *L. decemlineata* larvae (fourth instar). Treatment discs were painted on the upper surface with 10 μl of test compound solution in water containing 2% of ethanol and 2% of Tween-80 (treatment discs). After 3 h the remaining leaf disc areas were measured and the amount of feeding from treatment and control discs was determined (dual-choice assay). The no-choice assay was performed in a similar manner over two consequtive 1.5 h periods; the leaf discs were renewed between periods. The antifeedant activity was reported as the standard Antifeedant Index AIdc (dual-choice assay) or as the Inhibition Percentage, IP = [(*C*−*T*)/*C*] (no-choice assay).

(*continued on next page*)

Table 16 (*continued*)

N8:	Larvae of *O. furnacalis* (fifth instar) were tested on a feeding substrate prepared by mixing a warm paste of corn powder, soybean powder, agar and water with a solution (no volume given) of the test compound in ethanol (treatment substrate). After cooling the substrate was divided into short columns (diam. 0.6 cm, 1.0 cm length). After 4 h the assay was terminated and the remaining substrates were weighed. The consumed amounts from the treatment and control substrates were determined and the standard Antifeedant Indexes AI_{dc} and AI_{nc} were calculated.
N9:	Tested on Chinese cabbage leaves, painted on one half (T) with a solution of the test compound (leaf area and volume of test compound solution not specified). For *P. xylostella* larvae and *P. cochleariae* adults the antifeedant activity was indicated as the area or weight of leaf consumed. For *M. persicae* the average number of aphids settled on *C* and *T* were given.
N10:	*No-choice* assay at 1000 ppm concentration on maize (*Zea mays*) leaf discs; no further details supplied. The activity was given as a (*dual-choice*) Antifeedant Index $AI=[(C-T)/(C+T)]$.
N11:	Assay with third instar larvae of *T. molitor* on carrot slices (2.5 cm diam.), which were coated with 100 μl of test compound emulsion (treatment slices) in a mixture of water/methanol/acetone (90:5:5) and Triton CS-7 (0.1% v/v). Assay duration 24 h (dual-choice assay) or 10 days (no-choice assay); slices were renewed every 24 h. Percentages consumed from treatment and control slices were determined by weighing and the antifeedant activity was calculated as the average Percentage of Feeding Inhibition $PFI=[T/(C+T)]$.
N12:	*H. vigintioctopunctata* beetles (fourth instar nymphs or adults) were tested on *Solanum nigrum* leaf discs (diam. 30 mm), coated with test compound solution in acetone (treatment discs) to a final amount of 5, 0.5 or 0.05 μg compound/cm^2 leaf area. After 4 h the uneaten surface areas were measured and the amounts eaten from control and treatment discs calculated. The antifeedant activity was determined as $[1-(T/C)]$.
N13:	Tested with *M. persicae* (apterous adults) on bell pepper (*Capsicum annuum*) leaf discs (2 cm^2 surface area). One half of each disc was treated with 10 μl of test compound solution to a final amount of 50 μg compound/cm^2 leaf area (treatment half). After 24 h the numbers of aphids on the control and treatment areas were counted and the Settling Inhibition Index was calculated according to $\%SI=[1-(T/C)]$ in which *T* is the percentage of aphids on the treament surface.
N14:	Housefly (*M. domestica*; third instar larvae) feeding and development was assessed on a diet of 6 g of flocked filter paper treated sequentially with 8 ml of a test compound solution in acetone (treatment substrate) and a solution of milk powder (2.7 g), corn starch (2.7 g) and dried yeast (0.6 g) in 26 ml of water. The test compound concentration was calculated, based on the total weight of the dry components of the diet. The weight of the larvae, the number of larvae pupariating and the mortality rate were determined at regular intervals over a 6-day period.
N15:	Ant feeding deterrency assay with colonies of *A. cephalotes* or *A. octospinosus*, using pressed rye flakes soaked in a solution containing the test compound (treatment flakes). For the assay 60 control and 60 treatment flakes were randomly arranged in a grid-like fashion. After 50% of the control flakes had been taken by the ants, the assay was terminated and the numbers of control and treatment flakes harvested by the ants were counted.
N16:	The test arena consisted of a Petri dish, coated on the bottom with a layer of agar which was covered with sand. Filter paper discs (Whatman No. 1, 2.0 cm diam.), treated with a 1% solution (25 μl) of the test compound (1% solution = 80 mg/cm^2, which results from the use of a 10,000 ppm solution; Lajide et al., 1995) and placed on aluminum foil, were used as the treated substrate. Termites (*R. speratus* workers, older than third instar) were allowed to feed on the discs for 14 days before the remaining areas of treatment and control discs were measured. The antifeeding activity was reported as $AI=[T/(C+T)]$.

T. molitor showed the lowest energy conformations of **52**, **211** and **290** to share a common geometry in which the C-4,18 moiety (i.e. the C-18 carbonyl from the unsaturated lactone or the C-4,18 oxirane ring) and the furan ring in the different molecules can be superimposed upon each other (Enriz et al., 1994, 2000). Maps of the molecular electrostatic potential (MEP) for these compounds revealed similar electronic properties in the vicinity of these groups. It was hypothesized that these moieties might act as essential binding sites to a common receptor, with a required distance of 9.8–10.8 Å between the active centers.

In view of the general importance of these key structural elements as described in (i)–(iii) it can be speculated that these groups may act as binding sites in a similar fashion with other insect species, though a different geometry may be required. Salviarin **294** differs from **290** both in the spatial orientation of the lactone and the furan ring and in the position of the unsaturation. For *T. molitor* **294** is inactive, but with *S. littoralis* **294** and related clerodanes display moderate antifeedant activity, suggesting that different geometry requirements may exist for *T. molitor* and *S. littoralis*. Interestingly, the furan ring in **294** appears to protrude into the same region of space that is occupied by the furofuran moiety in many active clerodanes, such as **143** (Fig. 11).

v. Both rings in the decalin fragment regularly are substituted with additional hydroxyl or ester groups, but these do not seem to be essential for antifeedant activity, since the non-substituted

analogues often show comparable activities. In combination with a furofuran sidechain at C-9 however, the presence of a hydroxyl group at C-2 and an ester at C-3 markedly increases the activity against a number of Lepidopteran insect species.

Additional substituents may also affect antifeedant activity by changing the conformation of the molecule. The low activity of **83** and **174** on *S. littoralis* compared to related clerodane diterpenes has been attributed (Belles et al., 1985) to the presence of a substituent at C-1 forcing ring A into a skew boat conformation and possibly also limiting the rotational freedom of the C-9 sidechain; more recent data (Bremner et al., 1998) suggest that for **174** the loss of unsaturation in the furofuran moiety is a more likely reason for the observed inactivity (**174** vs. **172** and **173**). A rigid ring A boat-conformation enforced by an C-2,19 ether bridge is reported to favour high antifeedant activity for several Lepidoptan insects when present in diterpenes with a C-9 furofuran sidechain (e.g. **199**, **200**, **204**) (Anderson et al., 1989; Blaney et al., 1994a,b; Bruno et al., 1999a,b).

The general observations under (i)–(v) represent a reasonable summary of the structural features involved in the overall antifeedant activity of clerodane diterpenes. However, it must be stressed that the underlying mechanisms of insect antifeedant activity are more complex than this simplified picture suggests. For clerodanes active against *L. decemlineata* for instance, some compounds display strong activity in either dual-choice or no-choice tests only, while others are active in both types of assays (Fig. 8, Table 11). These effects may be attributed to the mixture of (sensory) antifeedant activity and toxic effects that have been shown to occur with clerodanes for this insect species (Ortego et al., 1995; López-Olguin et al., 1999; Gonzàlez-Coloma et al., 2000).

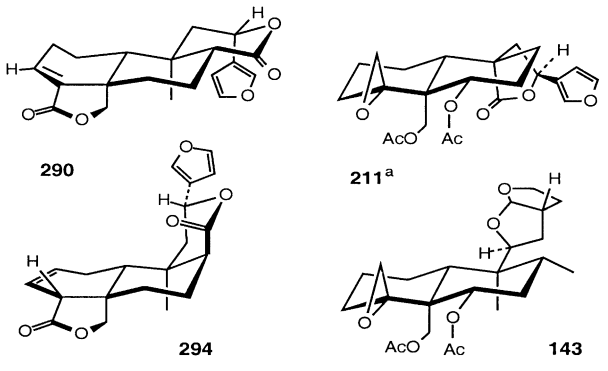


Fig. 11. [a]The 8α-CH_3 substituent in **211** was omitted for clarity.

Continued investigations into the biological mechanisms involved in insect antifeedant activity may provide the means to differentiate among different types of antifeedants and give better defined sets of clerodanes with a distinct mode of action from which more detailed structure-activity relationships can be deduced. Electrophysiological techniques have been widely used to study the action of insect antifeedants at the cellular level (Schoonhoven, 1982; Schoonhoven et al., 1992) and may prove useful in this respect. Similar comments can be made regarding the biomolecular targets the clerodanes interact with and from which little is known at present (Norris, 1986; Simmonds et al., 1990; Mullin et al., 1994).

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