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FORM 1

SPRUSON & FERGUSON

PATENT OFFICE ONE HUNDRED DOLLARS

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

Ciba-Geigy AG, incorporated in Switzerland, of Klybeckstrasse 141, 4002 Basle, SWITZERLAND, hereby apply for the grant of a standard patent for an invention entitled:

Composition for Controlling Parasites in Productive Livestock

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Appl'c. No:	Country:	Application Date:
1117/87-3	SWITZERLAND	24 March 1987
4878/87-0	SWITZERLAND	15 December 1987

The address for service is:-

FEE STAMP TO VALUE OF $ 610 ATTACHED
MAIL OFFICER

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

DATED this TWENTY FIRST day of MARCH 1988

Ciba-Geigy AG

By: M.J. Anderson

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 52985
S&F CODE: 52760

5845/2

~~AU Case 5-16389/1+2/+~~ FORM 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952 - 1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made by CIBA-GEIGY AG for a patent for an invention entitled:

Composition for controlling parasites in productive livestock

We, Arnold Seiler and Ernst Altherr } of CIBA-GEIGY AG, Klybeckstrasse 141, 4002 Basle, Switzerland

do solemnly and sincerely declare as follows:

1. We are authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act ~~was~~ (were) made in Switzerland
on March 24, 1987 and December 15, 1987

both by CIBA-GEIGY AG, 4002 Basle, Switzerland.

3. Peter Maienfisch, Traugott Meyer-Strasse 5, 4147 Aesch, Switzerland

is (~~are~~) the actual inventor(~~s~~) of the invention and the facts upon which the applicant is entitled to make the application are as follows: The said applicant is the assignee of the actual inventor(~~s~~).

4. The basic application(s) referred to in paragraph 2 of this Declaration ~~was~~ (were) the first application(s) made in a Convention country in respect of the inventionsthe subject of the application.

DECLARED at Basle, Switzerland on March 4, 1988

CIBA-GEIGY AG

pp

To: The Commissioner of Patents

12.87 521

(12) PATENT ABRIDGMENT (11) Document No. AU-B-13502/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 614509

(54) Title
MILBEMYCIN DERIVATIVES

International Patent Classification(s)
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4878/87	15.12.87	CH SWITZERLAND

(43) Publication Date : 22.09.88

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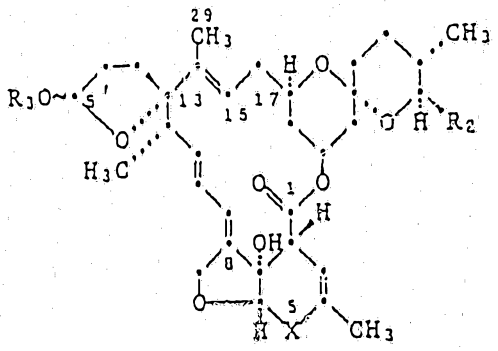
(71) Applicant(s)
CIBA-GEIGY AG

(72) Inventor(s)
PETER MAIENFISCH

(74) Attorney or Agent
SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001

(57) Claim

1. A compound of formula I



(I)

in which

X represents one of the groups $-CH(OR_1)-$, $-C(=O)-$ or $-C(=N-OH)-$;

R_1 represents hydrogen or a OH-protecting group;

R_2 represents methyl, ethyl, isopropyl or sec.-butyl or the group $-C(CH_3)=CH-A$ in which A represents methyl, ethyl or isopropyl; and

R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxy-alkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, C_1-C_3-alkyl-substituted C_3-C_7-cycloalkyl, hydroxy, benzyloxy, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen, and C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before, it being possible for each of the above-mentioned radicals representing or containing an alkoxy

.../2

group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen, and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; 1-adamantylmethyl; menthyl; carveyl; phenyl, benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

23. A 13-spiro-2'-[tetrahydrofuran]-milbemycin derivative, substantially as hereinbefore described with reference to any one of Examples H1 to H23, 1.1 to 1.149, 2.1 to 2.149, 3.1 to 3.149, 4.1 to 4.149, 5.1 to 5.149, 6.1 to 6.149, 7.1 to 7.149 or 8.1 to 8.149.

28. A method of controlling parasites in animals or of controlling insect pests wherein an parasiticidally or insecticidally effective amount of a compound as defined in claim 23 or a composition as defined in claim 24 or claim 25 is applied to the parasite, the insect pest or to the locus thereof.

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S & F Ref: 52985

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name and Address of Applicant: Ciba-Geigy AG
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Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

Composition for Controlling Parasites in Productive Livestock

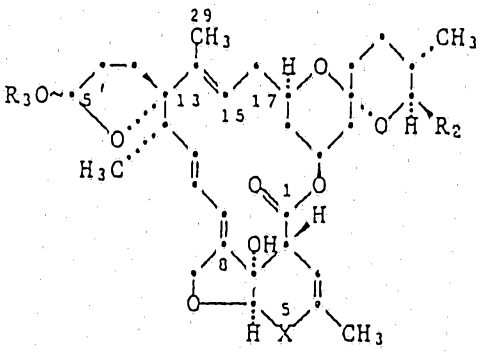
The following statement is a full description of this invention, including the best method of performing it known to me/us

5845/3

Composition for controlling parasites in productive livestock

The present invention relates to novel 13-spiro-2'-[tetrahydrofuran]-milbemycin derivatives of the formula I below, to their preparation, to compositions that contain at least one of these substances as active ingredient, and to their use for controlling ecto- and endo-parasites in productive livestock.

According to a broad form of the present invention there is provided a compound of formula I



(I)

in which

X represents one of the groups $-CH(OR_1)-$, $-C(=O)-$ or $-C(=N-OH)-$;

R_1 represents hydrogen or a OH-protecting group;

R_2 represents methyl, ethyl, isopropyl or sec.-butyl or the group $-C(CH_3)=CH-A$ in which A represents methyl, ethyl or isopropyl; and

R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxy-alkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, C_1-C_3-alkyl-substituted C_3-C_7-cycloalkyl, hydroxy, benzyloxy, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen, and C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen, or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and

C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; 1-adamantylmethyl; menthyl; carveyl; phenyl, benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

Menthyl groups that come into consideration are those menthyl groups which are derived from o-, m- and p-menthane and can be linked to the oxygen atom located at the C_5' atom via one of the unsubstituted ring carbon atoms. 2-methyl-6-isopropylcyclohexyl should be mentioned as a preferred menthyl group. Carveyl is preferably 2-methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl.

The compounds of formula I can be in the form of a mixture of epimers in respect of the C_5' carbon atom in the tetrahydrofuran ring. The pure epimers are obtained by means of customary physical separation methods. Hereinafter the two epimers are identified by the letters A and B.

Here and hereinafter, OH-protecting groups for substituent R_1 should be understood as meaning the protective functions customary in organic chemistry. These are especially acyl and silyl groups. Suitable acyl groups are, for example, radicals R_4-C(O)- in which R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl that is unsubstituted or is substituted by at least

one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro and is preferably C_1-C_6-alkyl, C_1-C_6-haloalkyl or phenyl that is unsubstituted or is substituted by halogen, C_1-C_3-alkyl, CF_3 or by nitro. A suitable silyl group for R_1 is the radical $-Si(R_5)(R_6)(R_7)$ in which R_5, R_6 and R_7 preferably independently of one another, represent C_1-C_6-alkyl, benzyl or phenyl and, together with the silicon atom, form, for example, one of the groups trimethylsilyl, thexyldimethylsilyl (thexyl = 1,1,2-trimethyl-1-propyl: $(CH_3)_2CH-C(CH_3)_2-$), diphenyl-tert.-butylsilyl, bis-(isopropyl)methylsilyl, triphenylsilyl and especially tert.-butyldimethylsilyl. The 5-OH group can also be etherified in benzyl ether or methoxyethoxymethyl ether form or, in accordance with European A-specification No. 195 623, can be bonded to a carbohydrate radical, hereinafter referred to as a sugar radical for the sake of simplicity.

Suitable structural elements that are substituted "by at least one substituent" selected from a specified group of substituents are those which can be derived from compounds that can be prepared according to customary chemical methods. The said structural elements are preferably substituted by from 1 to 3 substituents, there generally being no more than one nitro or cyano group present.

Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents a protecting group can be converted into the highly active free 5-hydroxy derivatives ($X = -CH(OR_1)-$, $R_1 = H$) by simple, for example hydrolytic, removal of the protective function and therefore also have the character of intermediates.

Preferred substituents of phenyl groups are from 1 to 3 halogen atoms, C_1-C_2-alkyl, C_1-C_2-alkoxy, C_1-C_2-alkylthio, C_1-C_2-haloalkyl or nitro and cyano. Of all the substituents of phenyl groups that contain an alkyl group, those having 1 carbon atom are especially preferred. Where there is more than one substituent, these substituents can be present independently of one another. An α-methylbenzyl group is also to be regarded as an alkyl-substituted benzyl group.

The term "alkyl" on its own or as part of another substituent, depending upon the number of carbon atoms indicated, is to be understood as including, for example, the following radicals: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl, and also the isomers, such as, for example, isopropyl, isobutyl, tert.-butyl and isopentyl. Haloalkyl represents a mono- to per-halogenated alkyl substituent, such as, for example, $CHCl_2$, CHF_2, CH_2Cl, CCl_3, CF_3, CH_2F, CH_2CH_2Cl and $CHBr_2$, preferably CF_3. Halogen should be understood here and hereinafter as being fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine. Alkenyl represents an aliphatic hydrocarbon radical characterised by at least one C=C double bond, such as, for example, vinyl, propen-1-yl, allyl, buten-1-yl, buten-2-yl and buten-3-yl.

C_2-C_6-alkoxyalkoxy represents an alkoxy radical of which the carbon chain consists of up to 6 carbon atoms and is interrupted by an oxygen atom, for example OCH_2OCH_3, $OCH_2CH_2OCH_3$, $OCH_2OC_2H_5$, $OCH_2CH_2CH_2OC_3H_7$ or $OC(CH_3)_2OC_2H_5$. C_3-C_9-alkoxyalkoxyalkoxy consists of an alkoxy radical of which the carbon chain consists of from 3 to 9 carbon atoms and is interrupted in two places by an oxygen atom, for example $OCH_2OCH_2OCH_3$, $OC_2H_4OC_2H_4OC_2H_5$ or $OCH_2CH_2OCH_2CH_2OCH_2CH_2CH_3$. Alkynyl represents, for example, ethynyl, propyn-1-yl, propargyl or butyn-1-yl. Cycloalkyl represents, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Of the alkyl groups substituted by benzyloxy, those are preferred which contain from 1 to 3 carbon atoms in the alkyl moiety and are monosubstituted by benzyloxy, especially 2-benzyloxyethyl. Acyl as R_3 or as part of R_3 preferably represents the alkanoyl radical derived from a straight-chain or branched alkanoic acid, for example CH_3CO, C_2H_5CO, i-C_3H_7CO, n-C_3H_7CO, n-C_4H_9-CO or tert.-butylCO, in which the alkyl radicals may also be halogenated, such as, for example, as indicated above for haloalkyl. Cycloalkenyl represents one of the above cycloalkyl radicals but contains at least one double bond and does not have aromatic character.

Of the four-membered heterocyclic rings, special preference is given to those which contain a hetero atom from the group consisting of oxygen, sulphur and nitrogen and are saturated. Typical examples are:

 ,  ,  ,

Typical five-membered heterocyclic rings are: furan, thiophene, pyrrole, isoxazole, isothiazole, furazan, imidazole, 1,2,4-triazole, 1,2,3-triazole, pyrazole, pyrroline, oxazole, thiazole, thiadiazoles, pyrazoline, thiazoline, pyrazolidine, pyrrolidine, oxazolidine, thiazolidine, oxadiazole, imidazoline, imidazolidine, pyrazolidine, tetrahydrofuran; and typical six-membered heterocyclic rings are pyridine, pyridazine, pyrimidine, pyrazine, thiazine, thiadiazines, pyrans, piperidine, piperazine, morpholine, perhydrothiazine, dioxan and their partially hydrogenated or partially saturated homologues. The heterocyclic radical is generally bonded via a carbon atom, preferably the carbon atom adjacent to a hetero atom, to the rest of the molecule.

Compounds of formula I in which X represents $-CH(OR_1)-$ or $-C(=N-OH)-$ in which R_1 represents hydrogen or a OH-protecting group, are preferred, especially those compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen. Acyl and silyl groups as R_1 are generally to be understood as protecting groups.

Compounds of formula I in which R_2 represents methyl, ethyl, isopropyl or sec.-butyl, especially ethyl or methyl, preferably ethyl, are preferred.

Compounds in which R_2 represents sec.-butyl shall here and hereinafter also be considered as milbemycin derivatives although according to conventional classification they are derived from avermectin derivatives. Avermectin-aglycones (with an OH group in the 13α-position) can, however, be converted in accordance with US-PS 4 173 571 into milbemycin homologues.

In naturally occurring milbemycins (R_1 = H; R_2 = CH_3, C_2H_5 or iso-C_3H_7) the 13-position is always occupied only by hydrogen. In avermectins, however, the 13-position is occupied by an α-L-oleandrosyl-α-L-oleandrose radical which is linked via oxygen in the α-configuration to the macrolide molecule. Avermectins also differ structurally from milbemycins by a 23-OH group or $\Delta^{22,23}$ double bond and generally by a substituent R_2 = sec.C_4H_9. By hydrolysing the sugar radical of avermectins it is readily

possible to obtain the corresponding avermectin- aglycones that have an allylic 13α-hydroxy group. The avermectin-aglycones can be converted into the milbemycin homologues as indicated above. In the milbemycin derivatives of the present application, the $\Delta^{22,23}$ double bond is always in hydrogenated form.

The following sub-groups of compounds of formula I are especially preferred because of their pronounced parasiticidal and insecticidal action:

Group Ia: Compounds of formula I in which
X represents $-CH(OR_1)-$ or $-C(=N-OH)-$, preferably $-CH(OR_1)-$;
R_1 represents hydrogen or a OH-protecting group;
R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and
R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; an ethyl group substituted by benzyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy,

C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

Group Ib: Compounds of formula I in which
X represents $-CH(OR_1)-$;
R_1 represents hydrogen or a OH-protecting group;
R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and
R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

Group Ic: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, R_4-C(O)- or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is sub-

stituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_6-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents hydrogen, C_1-C_5-alkyl; C_1-C_5-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_3-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine and methyl; C_2-C_6-alkenyl; C_2-C_6-alkynyl; a radical selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl, which radical is substituted by fluorine, chlorine, bromine, C_1-C_3-alkoxy or by C_1-C_6-acyloxy; phenyl; benzyl; α-naphthyl; β-naphthyl; a radical selected from the group consisting of phenyl, benzyl, α-naphthyl and β-naphthyl, which radical is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, methoxy, CF_3, CF_3O, CH_3S, nitro and cyano; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, ethyl, CF_3, CH_3O, CF_3O, CH_3S, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

Group Id: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, R_4-C(O)- or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, iso-

propyl or sec.-butyl; and R_3 represents C_1-C_5-alkyl, or C_1-C_5-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_3-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy.

Group Ie: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, R_4-C(O)- or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine and methyl; C_2-C_6-alkenyl; C_2-C_6-alkynyl; a radical selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl, which radical is substituted by fluorine, chlorine, bromine, C_1-C_3-alkoxy or by C_1-C_6-acyloxy; phenyl; benzyl; α-naphthyl; β-naphthyl; a radical selected from the group consisting of phenyl, benzyl, α-naphthyl and β-naphthyl, which radical is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, methoxy, CF_3, CF_3O, CH_3S, nitro and cyano; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, ethyl, CF_3, CH_3O, CF_3O, CH_3S, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

Group If: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, $R_4-C(O)-$ or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents phenyl, benzyl, α-naphthyl, β-naphthyl or a radical selected from the group consisting of phenyl, benzyl, α-naphthyl and β-naphthyl, which radical is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, methoxy, CF_3, CF_3O, CH_3S, nitro and cyano.

Group Ig: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, $R_4-C(O)-$ or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents C_2-C_6-alkenyl, C_2-C_6-alkynyl, or a radical selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl, which radical is substituted by fluorine, chlorine, bromine, C_1-C_3-alkoxy or by C_1-C_6-acyloxy.

Group Ih: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, $R_4-C(O)-$ or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the

group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, ethyl, CF_3, CH_3O, CF_3O, CH_3S, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

Group Ii: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, R_4-C(O)- or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents an unsaturated or preferably saturated four-membered heterocyclic radical having a hetero atom selected from the group consisting of oxygen, nitrogen and sulphur, or represents furan, thiophene, pyrrole, isoxazole, isothiazole, furazan, imidazole, 1,2,4-triazole, 1,2,3-triazole, pyrazole, pyrroline, oxazole, thiazole, thiadiazoles, pyrazoline, thiazoline, pyrazolidine, pyrrolidine, oxazolidine, thiazolidine, oxadiazole, imidazoline, imidazolidine, pyrazolidine, tetrahydrofuran, pyridine, pyridazine, pyrimidine, pyrazine, thiazine, thiadiazines, pyrans, piperidine, piperazine, morpholine, perhydrothiazine or dioxan, it being possible for the said heterocyclic radical also to be bonded via a C1-C4-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

Group Ik: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen or $-Si(R_5)(R_6)(R_7)$; wherein R_5, R_6 and R_7, independently of one another, represent C_1-C_6-alkyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of C1-C4-alkoxy, C_1-C_3-alkylthio, C_1-C_6-alkanoyloxy, benzyloxy and C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl; phenyl; benzyl; or a radical selected from the group consisting of phenyl and benzyl, which radical is

substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy and C_1-C_3-alkylthio.

Group Il: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen or $-Si(R_5)(R_6)(R_7)$; wherein R_5, R_6 and R_7, independently of one another, represent C_1-C_6-alkyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-alkanoyloxy, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; or a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano.

Group Im: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, trimethylsilyl, tert.-butyldimethylsilyl or thexyldimethylsilyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-alkanoyloxy, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from

the group consisting of halogen and C_1-C_3-alkyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; 1-adamantylmethyl; menthyl; carveyl; phenyl, benzyl; naphthyl; or a radical selected from the group consisting of phenyl and benzyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano.

Group In: Compounds of formula I in which X represents $-CH(OR_1)-$ in which R_1 represents hydrogen or tert.-butyldimethylsilyl, or $-C(=N-OH)-$; R_2 represents methyl or preferably ethyl; and R_3 represents

- hydrogen,
- C_1-C_8-alkyl,
- C_1-C_5-alkyl that is substituted by from 1 to 3 halogen atoms, preferably chlorine or bromine atoms, or is monosubstituted by
- C_1-C_3-alkoxy,
- C_2-C_6-alkoxy that is interrupted by an oxygen atom and is unsubstituted or is terminally monosubstituted at the terminal alkoxy group by hydroxy or by halogenated, preferably chlorinated, C_1-C_3-alkanoyloxy,
- C_1-C_3-alkylthio,
- C_3-C_7-cycloalkyl or
- hydroxy,
- C_2-C_4-alkyl that is monosubstituted by unsubstituted or halogenated, preferably chlorinated, C_1-C_3-alkanoyl- oxy or by benzyloxy,
- C_3-C_7-cycloalkyl that is unsubstituted or mono- or di- substituted by C_1-C_3-alkyl,
- 1-adamantylmethyl,
- phenyl,
- benzyl that is unsubstituted, monosubstituted by phenoxy or substituted by from 1 to 3 C_1-C_3-alkoxy groups,
- α-methylbenzyl, or a
- heterocyclic radical selected from the group consisting of oxetanyl and furyl that is bonded via C_1-C_3-alkyl and is unsubstituted or is substituted by methyl.

Group Io: Compounds of formula I in which X represents $-CH(OR_1)$ and R_1 represents hydrogen or tert.-butyldimethylsilyl; R_2 represents ethyl; and R_3 represents

- hydrogen,
- C_1-C_8-alkyl,
- C_1-C_5-alkyl that is substituted by from 1 to 3 halogen atoms, preferably chlorine or bromine atoms, or is monosubstituted by
- C_1-C_3-alkoxy,
- C_2-C_6-alkoxy that is interrupted by an oxygen atom and is unsubstituted or is terminally monosubstituted at the terminal alkoxy group by hydroxy or by halogenated, preferably chlorinated, C_1-C_3-alkanoyloxy,
- C_1-C_3-alkylthio,
- C_3-C_7-cycloalkyl, or
- hydroxy,
- ethyl that is monosubstituted by acetoxy, chloro- acetoxy or by benzyloxy,
- C_3-C_7-cycloalkyl that is unsubstituted or is mono- or di-substituted by C_1-C_3-alkyl,
- 1-adamantylmethyl,
- phenyl,
- benzyl that is unsubstituted, monosubstituted by phenoxy or substituted by from 1 to 3 C_1-C_3-alkoxy groups,
- α-methylbenzyl, or a
- heterocyclic radical selected from the group consisting of oxetanyl and furyl that is bonded via C_1-C_3-alkyl and is unsubstituted or substituted by methyl.

Group Ip: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen or tert.-butyldimethylsilyl; R_2 represents ethyl; and R_3 represents hydrogen, C_1-C_8-alkyl, 2,2,2-tribromoethyl, 2,2-bis(chloromethyl)-propyl, 3-chloro-2,2-dimethylpropyl, 2-ethoxyethyl, 2-(2-methoxyethoxy)-ethyl, 2-[2-(2-hydroxyethoxy)-ethoxy]-ethyl, 2-{2-[(2-chloroacetoxy)-ethoxy]-ethoxy}-ethyl, 2-methylthioethyl, cyclobutylmethyl, cyclohexylmethyl, 2-hydroxyethyl, benzyloxyethyl, 2-acetoxyethyl, 2-(chloroacetoxy)-ethyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-methyl-6-isopropylcyclohexyl, 1-adamantylmethyl, phenyl, benzyl, 3-phenoxybenzyl, 3,4-dimethoxybenzyl, α-methylbenzyl, (3-methyloxetan-3-yl)-methyl or furfuryl.

Group Iq: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen or tert.-butyldimethylsilyl; R_2 represents ethyl; and R_3 represents

- C_1-C_5-alkyl,
- C_2-C_4-alkyl that is substituted by from 1 to 3 halogen atoms, especially bromine atoms, or is monosubstituted by
- C_1-C_3-alkoxy,
- C_2-C_6-alkoxy that is interrupted by an oxygen atom and is unsubstituted or is terminally monosubstituted at the terminal alkoxy group by hydroxy or by halogenated, especially chlorinated, C_1-C_3-alkanoyl,
- C_1-C_3-alkylthio, or
- hydroxy,
- 2-acetoxyethyl,
- cyclohexyl that is unsubstituted or mono- or di- substituted by C_1-C_3-alkyl,
- 1-adamantylmethyl,
- benzyl, or a
- heterocyclic radical selected from the group consisting of oxetanyl and furyl that is bonded via C_1-C_3-alkyl and is unsubstituted or substituted by methyl.

Group Ir: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen or tert.-butyldimethylsilyl; R_2 represents ethyl; and R_3 represents C_1-C_5-alkyl, 2,2,2-tribromoethyl, 2-ethoxyethyl, 2-(2-methoxyethoxy)-ethyl, 2-[2-(2-hydroxyethoxy)-ethoxy]-ethyl, 2-{2-[(2-chloroacetoxy)-ethoxy]-ethoxy}-ethyl, 2-methylthioethyl, 2-hydroxyethyl, 2-acetoxyethyl, cyclohexyl, 2-methyl-6-isopropylcyclohexyl, 1-adamantylmethyl, benzyl, (3-methyloxetan-3-yl)-methyl or furfuryl.

Group Is: Compounds of formula I in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen; R_2 represents ethyl; and R_3 represents C_4-C_5-alkyl, C_4-C_6-cycloalkyl, C_4-C_6-cycloalkyl bonded via methyl, or phenyl, benzyl or α-methylbenzyl. Representatives of this group that are of special interest are: milbemycin A_4-13-spiro-2'-[5'-(2"-methylbutoxy)-tetrahydrofuran] and milbemycin A_4-13-spiro-2'-[5'-(1"-methylpropoxy)-tetrahydrofuran.

Group It: Compounds of formula I in which X represents -C(=N-OH)-; R_2 represents methyl or preferably ethyl; and R_3 represents C_1-C_5-alkyl, C_1-C_3-alkyl that is substituted by C_1-C_3-alkoxy, or C_3-C_7-cycloalkyl.

Within groups Ia to Im, those representatives of formula I in which R_2 represents methyl or ethyl, especially ethyl, are preferred.

Preferred individual substances of formula I are, for example:

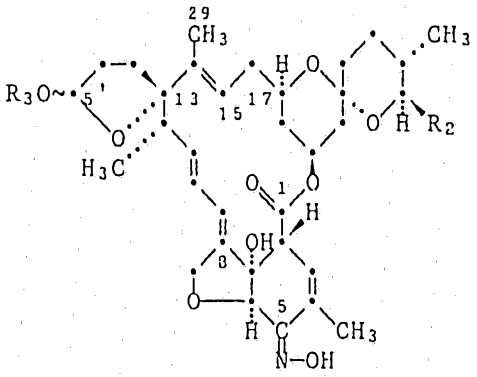
milbemycin A_4-13-spiro-2'-[5'-(2"-ethoxyethoxy)-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethylpropoxy)-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-cyclohexyloxytetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-benzyloxytetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-{2"-(2"'-methoxyethoxy)-ethoxy}-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-{2"-(2"'-(hydroxymethoxy)-ethoxy)-ethoxy}-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-{2"-(2"'-(2""-(chloroacetoxy)-ethoxy)-ethoxy)-ethoxy}-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-methoxytetrahydrofuran], and
milbemycin A_4-13-spiro-2'-[5'-(2"-hydroxyethoxy)-tetrahydrofuran].

Other individual substances that are worthy of mention are:
milbemycin A_4-13-spiro-2'-[5'-(2"-methoxybutoxy)-tetrahydrofuran], and
milbemycin A_4-13-spiro-2'-[5'-(1"-methylpropoxy)-tetrahydrofuran].

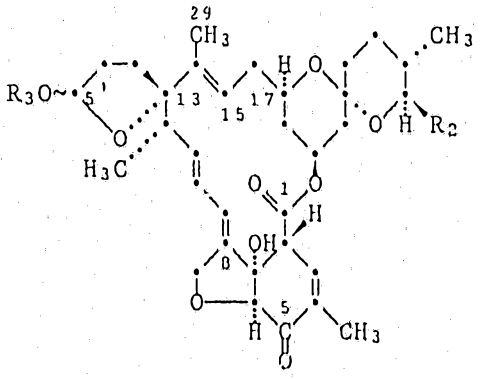
Likewise, the analogous representatives of formula I that are protected in the 5-position by a 5-O-tert.-butyldimethylsilyl group are also preferred.

The present invention relates also to processes that enable an additional, spiro-linked tetrahydrofuran ring to be introduced specifically into the 13-position of derivatives of milbemycin, 13-deoxy-22,23-dihydro-avermectin-aglycone or 23-deoxy-antibiotics S541 in order thus to obtain highly active novel parasiticides of formula I. The invention relates also to intermediates obtainable according to the processes.

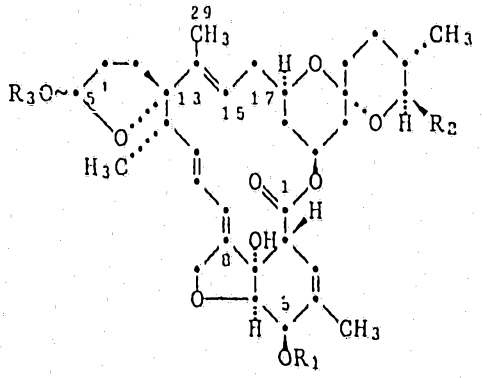
Formula I includes the compounds of the formulae Ia, Ib and Ic:



(Ia)



(Ib)



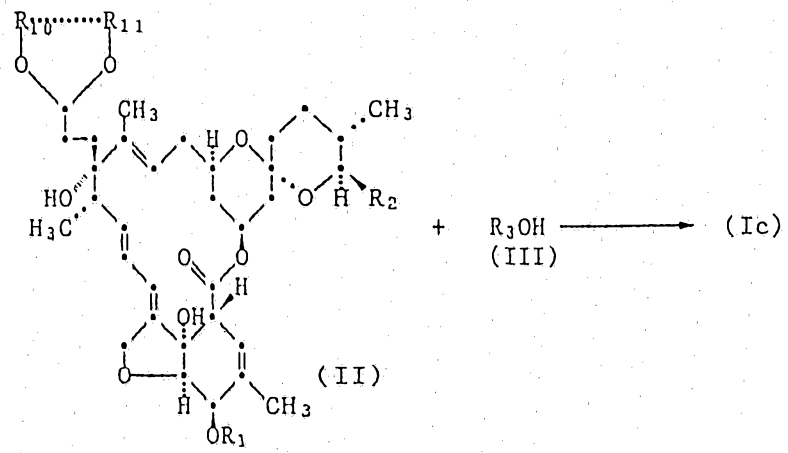
(Ic)

in which R_1, R_2 and R_3 have the meanings given for formula I and which can be prepared according to the methods described below.

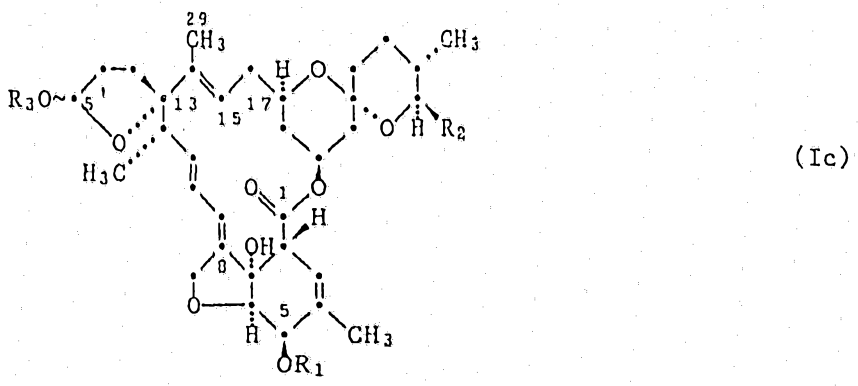
The preparation of the oximes [X = -C(=N-OH)-] within the scope of formula I, and therefore of the compounds of formula Ia, is effected by reacting a derivative of formula Ib with hydroxylamine or a salt thereof, preferably a mineral acid salt thereof, especially the hydrochloride. The reaction is advantageously carried out in a suitable solvent, for example a lower alkanol, such as methanol, ethanol, propanol; an ethereal compound, such as tetrahydrofuran or dioxan; an aliphatic carboxylic acid, such as acetic acid or propionic acid; in water or in mixtures of these solvents with one another or with other customary inert solvents. The reaction temperatures may vary within wide ranges. The reaction is advantageously carried out, for example, within a range of from +0°C to +100°C. If hydroxylamine is used in the form of one of its salts, for example in hydrochloride form, it is advantageous if, to bind the acid (for example HCl), one of the bases customary for such purposes is added and the operation is optionally carried out in the presence of a water binder, for example a molecular sieve. Suitable bases are organic and inorganic bases, for example tertiary amines such as trialkylamines (trimethylamine, triethylamine, tripropylamine etc.), pyridine and pyridine bases (4-dimethylaminopyridine, 4-pyrrolidylaminopyridine etc.), oxides, hydrides and hydroxides, carbonates and hydrogen carbonates of alkali metals and alkaline earth metals (CaO, BaO, NaOH, KOH, NaH, $Ca(OH)_2$, $KHCO_3$, $NaHCO_3$, $Ca(HCO_3)_2$, K_2CO_3, Na_2CO_3), and also alkali metal acetates, such as CH_3COONa or CH_3COOK. Furthermore, alkali metal alcoholates, such as C_2H_5ONa, n-C_3H_7ONa etc., are also suitable. Triethylamine is preferred. The oximation is most advantageously carried out with hydroxylamine hydrochloride in pyridine.

The derivatives of formula Ib can be prepared from the corresponding free 5-hydroxy derivatives of formula Ic by mild oxidation, for example with brownstone (MnO_2), CrO_3/pyridine or by Oppenauer oxidation. The reaction can be carried out in a solvent, such as, for example, a representative of the ethereal compounds or of the halogenated hydrocarbons or in mixtures of these compounds with one another, but especially advantageously in dichloromethane.

To prepare compounds of formula Ic, the process according to the invention is as follows: a compound of formula II is reacted in the presence of an acid catalyst in an inert solvent with a compound of formula III:

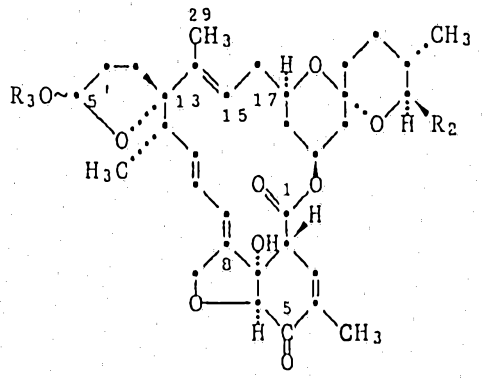


in which the substituents R_1, R_2 and R_3 have the meanings given under formula I and R_{10} and R11, independently of one another, represent C_1-C_6-alkyl or form a C_2-C_{10}-alkylene bridge, and, if desired, the resulting compound of formula Ic



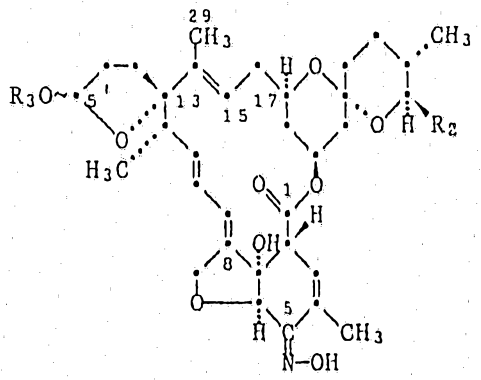
(Ic)

in which R_1, R_2 and R_3 have the meanings given for formula I, is converted by mild oxidation into a corresp ing compound of formula Ib



(Ib)

in which R_2 and R_3 have the meanings given for formula Ic, and, if desired, the compound of formula Ib is converted by reaction with hydroxylamine or a salt thereof into the corresponding compound of formula Ia



(Ia)

in which R_2 and R_3 have the meanings given for formula Ib.

The compounds of formula II are novel and have the character of intermediates. Their structure makes them especially suitable for the preparation of active ingredients of formula I. The compounds of formula II therefore form part of the present invention. For the preparation of process products according to the invention it is preferable to use those starting materials of formula II which result in the compounds, especially the individual compounds of the formula I, described above as being especially preferred.

The reaction for the preparation of compounds of formula Ic is generally carried out at temperatures of from -30°C to +70°C, preferably from -10°C to +50°C. The reaction is advantageously carried out in the presence of

an inert solvent or solvent mixture. Suitable solvents for this purpose are, for example, aliphatic and aromatic hydrocarbons such as benzene, toluene, xylenes, petroleum ether, hexane; halogenated hydrocarbons such as chlorobenzene, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, tetrachloroethylene; ether and ethereal compounds such as dialkyl ethers (diethyl ether, diisopropyl ether, tert.-butyl-methyl ether etc.), anisole, dioxan, tetrahydrofuran; and mixtures of such solvents with one another.

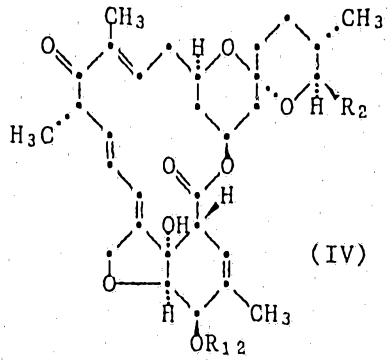
The compound of formula III is generally used in excess. The compounds of formula III are known or can be prepared analogously to known processes.

Suitable acid catalysts are, for example, carboxylic acids such as oxalic acid and especially sulphonic acids such as methanesulphonic acid, p-toluenesulphonic acid, camphor-10-sulphonic acid and salts thereof with tert.-amines, such as, for example, pyridinium p-toluenesulphonate.

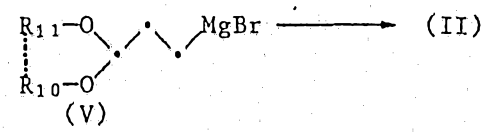
Compounds of formula Ic are obtained in the form of mixtures of epimers in respect of C5'. The pure epimers can be obtained therefrom by means of a physical separation operation. Suitable physical separation operations are, for example, column chromatography, flash chromatography, thick-layer chromatography, HPLC and fractional crystallisation.

Compounds of formula Ic can, however, also be prepared from other compounds of formula Ic by suitable reactions

The preparation of compounds of formula II likewise forms part of the present invention and is effected by reacting a compound of formula IV in an inert solvent with a Grignard reagent of formula V:



(IV)



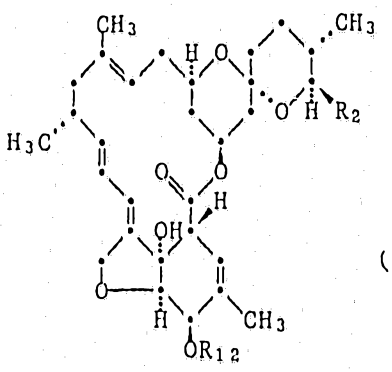
(V)

in which R_2 has the definition given under formula I, R_{10} and R_{11}, independently of one another, represent C_1-C_6-alkyl or together form a C_2-C_{10}-alkylene bridge, and R_{12} represents hydrogen or a silyl group as indicated, for example, under formula I.

The reaction is generally carried out at temperatures of from -80° to +70°C, preferably from -50° to +50°C. The reaction is advantageously carried out in the presence of an inert solvent or solvent mixture. Suitable solvents for this purpose are, for example, aliphatic and aromatic hydrocarbons such as benzene, toluene, xylenes, petroleum ether, hexane; ether and ethereal compounds such as dialkyl ethers (diethyl ether, diisopropyl ether, tert.-butylmethyl ether etc.), anisole, dioxan, tetrahydrofuran; and mixtures of such solvents with one another.

The Grignard reagents of formula V can be obtained in solution by reaction of the corresponding bromides with magnesium in one of the above-mentioned solvents and can be used further directly without it being necessary to isolate and purify them beforehand.

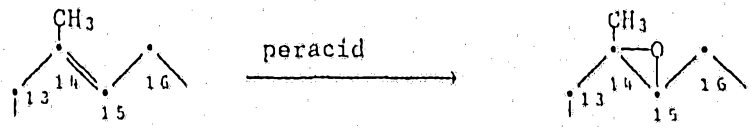
The compounds of formula IV are known or can be prepared analogously to known methods. For example, compounds of formula IV can be prepared according to the process described in EP 180 539 and EP 184 989, or analogously thereto, as follows: in a first step, compounds of formula VI



(VI)

in which R_2 has the definition given for formula I and R_{12} has the definition given for formula IV, are converted with peracids into the 14,15-epoxides of formula VII:

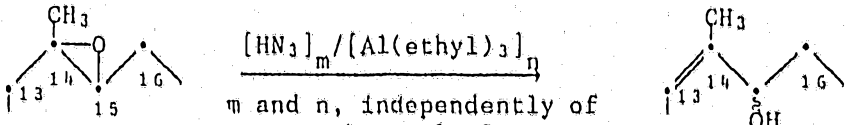
Step 1



(VI) (VII)

and the 14,15-epoxides of formula VII are then reacted with the aid of a special complex reagent to form 15-hydroxy compounds of formula VIII:

Step 2



(VII)

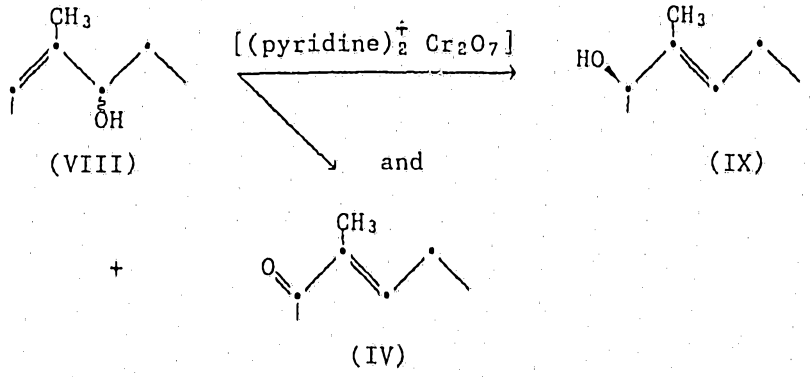
$[HN_3]_m/[Al(ethyl)_3]_n$

m and n, independently of one another = 1, 2 or between 1 and 2

(VIII)

In a further step, the 15-hydroxy compounds of formula VIII are then reacted with chromate, halochromate or dichromate ions, especially with pyridinium dichromate, the starting compound of formula VIII preferably being a compound in which the 5-OH group is protected and can be, for example, in the form of a 5-silyloxy group:

Step 3



(VIII) (IX) (IV)

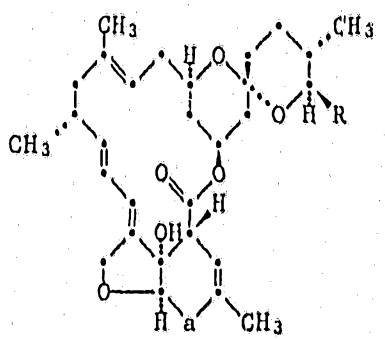
there also being formed, in addition to the desired 13-hydroxymilbemycins of formula IX, 13-oxo compounds which can be separated from one another by known methods.

The majority of the described reactions are advantageously carried out under a protective gas, such as, for example, nitrogen or argon.

The compounds of formula VI are known or can be prepared from the known compounds analogously to known processes.

The 13-oxo derivatives of formula IV can be obtained from the 13β-hydroxy derivatives of formula IX by oxidation with dimethyl sulphoxide (DMSO)/ oxalyl chloride. The reaction is preferably carried out at temperatures of from -60°C to room temperature. Suitable solvents are DMSO itself and also aromatic hydrocarbons such as benzene, toluene, xylenes and chlorinated hydrocarbons, such as, for example, dichloromethane. The operation is preferably carried out with the addition of a base, such as, for example, triethylamine.

The known compounds include milbemycins of formula M:



(M)

R = CH_3, a = $-\underset{OH}{CH}-$ = milbemycin A_3 from US-PS 3,950,360

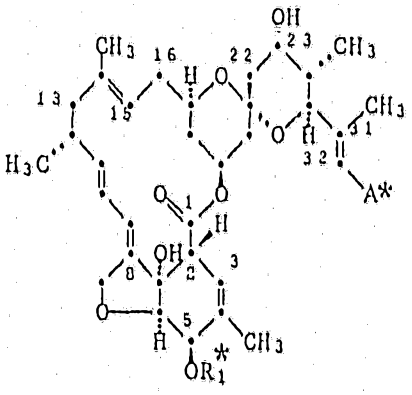
R = C_2H_5, a = $-\underset{OH}{CH}-$ = milbemycin A_4 from US-PS 3,950,360

R = $isoC_3H_7$, a = $-\underset{OH}{CH}-$ = milbemycin D from US-PS 4,346,171

R = $sek.C_4H_9$, a = $-\underset{OH}{CH}-$ = 13-deoxy-22,23-dihydro-C-076-Bla-aglycone from US-PS 4,173,571.

Compounds in which R represents sec.-butyl shall here and hereinafter also be considered as milbemycin derivatives although according to conventional classification they are derived from avermectin derivatives. Avermectin-aglycones (with an OH group in the 13-position) can, however, be converted into milbemycin homologues in accordance with US-PS 4 173 571.

The constitution of natural antibiotics S541 is known from DE-OS 35 32 794 and is as follows:



(antibiotics S541)

Factor A	A*=$isoC_3H_7$	R_1^*=H
Factor B	A*=CH_3	R_1^*=CH_3
Factor C	A*=CH_3	R_1^*=H
Factor D	A*=C_2H_5	R_1^*=H
Factor E	A*=C_2H_5	R_1^*=CH_3
Factor F	A*=$isoC_3H_7$	R_1^*=CH_3

In order to simplify the nomenclature, hereinafter the derivatives of antibiotic S541 are classified according to these factors as derivatives of S541A, S541B, S541C, S541D, S541E and S541F.

Compounds of formula VI in which R_2 represents the group $-C(CH_3)=CH-A$ and A has the meaning given for formula VI, which can be used as starting materials in the process according to the invention, can be produced in a manner known per se from the natural antibiotics S541.

The hydroxy group in the 23-position in antibiotics S541 can be removed analogously to the method described in US-PS 4 328 335, and the antibiotics S541 can thus be converted into the corresponding 23-deoxy derivatives. Those compounds having a free 5-OH group (R_1^*=H) must first be protected selectively by reaction with one of the silylation reagents $Y-Si(R_5)(R_6)(R_7)$ indicated hereinafter or with tert.-butyldimethylsilyloxyacetyl chloride. The reaction of those protected compounds in which R_1^* has been replaced by $Si(R_5)(R_6)(R_7)$ or $C(=O)CH_2OSi(CH_3)_2t\text{-}C_4H_9$ and the 23-C atom has been substituted by OH, with p-methylphenyl-chlorothionoformate yields derivatives of antibiotics S541 that are substituted at the 23-position by $p\text{-}CH_3\text{-}C_6H_4\text{-}O\text{-}C(=S)\text{-}O$. These 23-O-(4-methylphenoxy)-thiocarbonyl derivatives of antibiotics S541 are then reduced with tributyltin hydride in toluene in the presence of azobisisobutyronitrile at from 80°C to 120°C to form the corresponding 23-deoxy derivatives (position 23 unsubstituted).

Silylation or acylation of the 5-OH group is used to produce all those derivatives of formulae I, II and IV in which R_1 has a meaning other than hydrogen (R_1 = OH-protecting group). For silylation it is advantageous to use a silane of the formula $Y-Si(R_5)(R_6)(R_7)$ in which R_5, R_6 and R_7, preferably independently of one another, represent C_1-C_6-alkyl, benzyl or phenyl and, together with the silicon atom, form, for example, one of the groups trimethylsilyl, tris(tert.-butyl)silyl, thexyldimethylsilyl, diphenyl-tert.-butylsilyl, bis(isopropyl)methylsilyl, triphenylsilyl and especially tert.-butyldimethylsilyl. Y represents a silyl-leaving group which includes, for example, bromine, chlorine, cyano, azido, acetamide, trifluoroacetoxy and trifluoromethane- sulphonyloxy. This list does not constitute a limitation; the person skilled in the art will know of other typical silyl-leaving groups. The 5-OH group can also be in benzyl ether or methoxyethoxymethyl ether form.

The introduction of the acyl group is customarily effected using the corresponding acyl halides or acyl anhydrides and is preferably used to introduce the R_4-C(O) group defined at the beginning. Of the acyl halides, the chlorides and bromides are preferred.

5-O-silylations and 5-O-acylations are carried out in an anhydrous medium, preferably in inert solvents and more especially in aprotic solvents. The reaction is advantageously carried out in a temperature range of from 0°C to +80°C, preferably from +10° to +40°C. Preferably, an organic base is added. Suitable bases are, for example, tertiary amines, such as triethylamine, triethylenediamine, triazole and preferably pyridine, imidazole or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The removal of these silyl radicals R_1 in the 5-position is effected by selective mild hydrolysis (→ R_1=H) with, for example, arylsulphonic acid in alcoholic solution, HF in acetonitrile, HFx.pyridine in tetrahydrofuran or according to another method known to the person skilled in the art.

All the steps included in the described process for the preparation of compounds of formula I form part of the present invention.

The compounds of formula I are excellently suitable for controlling pests of animals and plants, including ectoparasites of animals. These last-mentioned pests comprise those of the order Acarina, in particular pests of the families Ixodidae, Dermanyssidae, Sarcoptidae, Psoroptidae; of the orders Mallophaga, Siphonaptera, Anoplura (e.g. family of the Haemotopinidae); and of the order Diptera, in particular pests of the families Muscidae, Calliphoridae, Oestridae, Tabanidae, Hippoboscidae and Gastrophilidae.

The compounds of formula I can also be used to combat hygiene pests, especially of the order Diptera (families Sarcophagidae, Anophilidae and Culicidae); of the order Orthoptera, of the order Dictyoptera (e.g. family of the Blattidae), and of the order Hymenoptera (e.g. family of the Formicidae).

The compounds of formula I also have a lasting action against mites and insects that are parasites of plants. When used to control spider mites of the order Acarina, they are effective against eggs, nymphs and adults of Tetranychidae (Tetranychus spp. and Panonychus spp.).

They also have excellent activity against sucking insects of the order Homoptera, in particular against pests of the families Aphididae, Delphacidae, Cicadellidae, Psyllidae, Coccidae, Diaspididae and Eriophydidae (e.g. the rust mite on citrus fruit); of the orders Hemiptera, Heteroptera and Thysanoptera; and against plant-feeding insects of the orders Lepidoptera, Coleoptera, Diptera and Orthoptera.

They are also suitable as soil insecticides against soil pests.

The compounds of formula I are therefore effective against all developmental stages of sucking and feeding insects in crops of useful plants, such as cereals, cotton, rice, maize, soybeans, potatoes, vegetables, fruits, tobacco, hops, citrus fruit, avocados and others.

The compounds of formula I are also effective against plant nematodes of the species Meloidogyne, deterodera, Pratylenchus, Ditylenchus, Radopholus, Rhizoglyphus and others.

The compounds are also effective against helminths in all developmental stages, and among these the endoparasitic nematodes which can be the cause of severe diseases in mammals and fowl, for example in sheep, pigs, goats, cattle, horses, donkeys, dogs, cats, guinea pigs and cage-birds. Typical nematodes having this indication are: Haemonchus, Trichostrongylus, Ostertagia, Nematodirus, Cooperia, Ascaris, Bunostomum, Oesophagostomum, Chabertia, Trichuris, Strongylus, Trichonema, Dictyocaulus, Capillaria, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancylostoma, Uncinaria, Toxascaris and Parascaris. The particular advantage of the compounds of formula I is their activity against those parasites which are resistant to benzimidazole-base[illegible]asiticides.

Certain species of the genera Nematodirus, Cooperia and Oesophagostomum attack the intestinal tract of the host animal, whereas others of the species Haemonchus and Ostertagia parasiticise the stomach, and those of the species Dictyocaulus parasiticise the lung tissue. Parasites of the families Filariidae and Setariidae are found in the internal cell tissue and organs, e.g. in the heart, blood vessels, lymph vessels and in subcutaneous tissue. In this connection, particular mention is to be made of the dog heartworm, Dirofilaria immitis. The compounds of formula I are highly effective against these parasites.

The compounds of formula I are also suitable for controlling pathogenic parasites in humans, among which parasites there may be mentioned as typical representatives occurring in the alimentary tract those of the species Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Trichuris and Enterobius. The compounds of this invention are also effective against parasites of the species Wuchereria, Brugia, Onchocerca and Loa of the family of the Filariidae, which occur in the blood, in tissue and various organs, and, in addition, against Dracunculus and parasites of the species Strongyloides and Trichinella which infest in particular the gastro-intestinal tract.

The compounds of formula I are used in unmodified form, or preferably together with the adjuvants conventionally employed in the art of formulation, and can therefore be formulated in known manner, for example to emulsifiable concentrates, directly sprayable or dilutable solutions, dilute emulsions, wettable powders, soluble powders, dusts, granulates, and also encapsulations in, for example, polymer substances. As with the compositions, the methods of application, such as spraying, atomising, dusting, scattering or pouring, are chosen in accordance with the intended objectives and the prevailing circumstances.

The compounds of formula I are administered to warm-blooded animals in doses of from 0.01 to 10 mg/kg body weight. In the case of enclosed areas they are advantageously applied at rates of from 10 g to 1000 g per hectare. They are also used in stables, pens, stalls or other areas.

The formulations, i.e. the compositions, preparations or mixtures containing the active ingredient of formula I are prepared in known manner, for example by homogeneously mixing and/or grinding the active ingredients with extenders, for example solvents, solid carriers and, in some cases, surface-active compounds (surfactants).

Suitable solvents are: aromatic hydrocarbons, preferably the fractions containing 8 to 12 carbon atoms, for example xylene mixtures or substituted naphthalenes, phthalates such as dibutyl phthalate or dioctyl phthalate, aliphatic hydrocarbons such as cyclohexane or paraffins, alcohols, and glycols and their ethers and esters, such as ethanol, ethylene glycol, ethylene glycol monomethyl or monoethyl ether, ketones such as cyclohexanone, strongly polar solvents such as N-methyl-2-pyrrolidone, dimethyl sulphoxide or dimethylformamide, as well as vegetable oils or epoxidised vegetable oils such as epoxidised coconut oil or soybean oil; or water.

The solid carriers used, for example for dusts and dispersible powders, are normally natural mineral fillers such as calcite, talcum, kaolin, montmorillonite or attapulgite. In order to improve the physical properties it is also possible to add highly dispersed silicic acids or highly dispersed absorbent polymers. Suitable granulated adsorptive carriers are porous types, for example pumice, broken brick, sepiolite or bentonite; and suitable nonsorbent carriers are materials such as calcite or sand. In addition a great number of granulated materials of inorganic or organic nature can be used, for example especially dolomite or pulverised plant residues.

Depending upon the nature of the active ingredient to be formulated, suitable surface-active compounds are non-ionic, cationic and/or anionic surfactants having good emulsifying, dispersing and wetting properties. The term "surfactants" will also be understood as comprising mixtures of surfactants.

Suitable anionic surfactants can be both so-called water-soluble soaps and water-soluble synthetic surface-active compounds.

Suitable soaps are the alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts of higher fatty acids (C_{10}-C_{22}), for example the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures which can be obtained, for example, from coconut oil or tallow oil. Further suitable surfactants are also the fatty acid methyl taurin salts.

More frequently, however, so-called synthetic surfactants are used, especially fatty sulphonates, fatty sulphates, sulphonated benzimidazole derivatives or alkylarylsulphonates.

The fatty sulphonates or sulphates are usually in the form of alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts and generally contain a C_8-C_{22}-alkyl radical which also includes the alkyl moiety of acyl radicals, for example the sodium or calcium salt of lignosulphonic acid, of dodecylsulphate, or of a mixture of fatty alcohol sulphates obtained from natural fatty acids. These compounds also comprise the salts of sulphated and sulphonated fatty alcohol/ethylene oxide adducts. The sulphonated benzimidazole derivatives preferably contain 2 sulphonic acid groups and one fatty acid radical containing 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or triethanolamine salts of dodecylbenzenesulphonic acid, dibutylnaphthalenesulphonic acid, or of a condensate of naphthalenesulphonic acid and formaldehyde.

Also suitable are corresponding phosphates, for example salts of the phosphoric acid ester of an adduct of p-nonylphenol with 4 to 14 moles of ethylene oxide, or phospholipids.

Non-ionic surfactants are preferably polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, or saturated or unsaturated fatty acids and alkylphenols, said derivatives containing 3 to 30 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenols.

Further suitable non-ionic surfactants are the water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol and alkylpolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethylene glycol ether groups and 10 to 100 propylene glycol ether groups. These compounds usually contain 1 to 5 ethylene glycol units per propylene glycol unit.

Examples of non-ionic surfactants are nonylphenolpolyethoxyethanols, castor oil polyglycol ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethylene glycol and octylphenoxypolyethoxyethanol.

Fatty acid esters of polyoxyethylene sorbitan, for example polyoxyethylene sorbitan trioleate, are also suitable non-ionic surfactants.

Cationic surfactants are preferably quaternary ammonium salts which contain, as N-substituent, at least one C_8-C_{22}alkyl radical and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl or hydroxy-lower alkyl radicals. The salts are preferably in the form of halides, methylsulphates or ethylsulphates, for example stearyltrimethylammonium chloride or benzyldi(2-chloroethyl)ethylammonium bromide.

The surfactants customarily employed in the art of formulation are described, inter alia, in the following publication:

"1986 International McCutcheon's Emulsifiers and Detergents", The Manufacturing Confectioner Publishing Co., Glen Rock, New Jersey, USA.

The pesticidal compositions usually contain 0.01 to 95 %, preferably 0.1 to 80 %, of active ingredient of formula I, 5 to 99.99 % of a solid or liquid adjuvant, and 0 to 25 %, preferably 0.1 to 25 %, of a surfactant.

Whereas commercial products are preferably formulated as concentrates, the end user will normally employ diluted formulations containing from 1 to 10,000 ppm of active ingredient.

The present invention therefore relates also to pesticidal compositions that contain in addition to customary carriers and/or dispersion agents at least one compound of formula I as active ingredient.

The compositions may also contain further ingredients, such as stabilisers, antifoams, viscosity regulators, binders and tackifiers, as well as fertilisers or other active ingredients in order to obtain special effects.

Preparation examples

Preparation of intermediates

A1. Preparation of 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_4

A solution of 2.40 ml of 2-(2-bromoethyl)-1,3-dioxolan in 10 ml of THF were added within a period of 2 1/2 hours at 40°C to a suspension of 650 mg of magnesium chips in 20 ml of tetrahydrofuran (THF). In order to initiate the formation of the Grignard reagent, a few crystals of iodine were added at the beginning of the reaction. The reaction mixture was then stirred for a further 30 minutes at 40°C under an argon atmosphere and then decanted. There was thus obtained a 0.2M solution of 2-(1,3-dioxolan-2-yl)-ethylmagnesium bromide in THF.

A solution of 1.006 g of 5-O-tert.-butyldimethylsilyl-13-oxo-milbemycin A_4 in 8 ml of THF was cooled to -15°C and then 17.0 ml of the 0.2M solution of 2-(1,3-dioxolan-2-yl)-ethylmagnesium bromide in THF were added within a period of 30 minutes. After stirring for 30 minutes at -15°C, 5 ml of saturated NH_4Cl solution were carefully added and then the reaction mixture was poured onto 100 ml of saturated $NaHCO_3$ solution and extracted three times with 150 ml of ether. The organic phases were washed with 100 ml of saturated NaCl solution, dried with $MgSO_4$ and concentrated by evaporation. Chromatography of the crude product on silica gel with hexane/dimethoxyethane 6:1 yielded, in addition to 87 mg (8 %) of the C(13)-epimer, 969 mg (84 %) of product.

Mass spectrum (MS): m/e: 772 (M^+, $C_{43}H_{68}O_{10}Si$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.05 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

4.42 ppm (bs, $w_{\frac{1}{2}}$ = 11) (C_5H)

4.85 ppm (t, J = 3) ($OC\underline{H}(CH_2)O$)

A2. Preparation of 13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_4

A solution of 40 mg of 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_4 in 1 ml of a HF_x·pyridine/THF solution (prepared from 6.5 ml of HF_x·pyridine, 15.7 ml of pyridine and 50 ml of THF) was stirred at room temperature for 18 hours. The reaction mixture was then poured onto 50 ml of saturated $NaHCO_3$ solution and extracted with 100 ml of diethyl ether. The organic phase was washed with 50 ml of saturated NaCl solution, dried with $MgSO_4$ and concentrated by evaporation. After chromatography of the crude product on silica gel with hexane/ethyl acetate 1:1, 27 mg (79 %) of product were obtained.

MS: (m/e): 658 (M^+, $C_{37}H_{54}O_{10}$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

4.28 ppm (t, J = 7) (C_5H)

4.85 ppm (t, J = 4) ($OC\underline{H}(CH_2)O$)

A3. Preparation of 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_3

In a manner analogous to that described in Example A1 the title compound is obtained from 420 mg of 5-O-tert.-butyldimethylsilyl-13-oxo-milbemycin A_3 and 7.0 ml of a 0.2M solution of 2-(1,3-dioxolan-2-yl)-ethylmagnesium bromide.

Mass spectrum (MS): (m/e): 758 (M^+, $C_{42}H_{66}O_{10}Si$)

A4. Preparation of 13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_3

The title compound can be prepared analogously to Example A2 from 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3- dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_3.

Mass spectrum (MS): (m/e): 644 (M^+, $C_{36}H_{52}O_{10}$)

Preparation of compounds of formula I

H1. Preparation of milbemycin A_4-13-spiro-2'-[5'-methoxytetrahydro-furan]

A solution of 50 mg of 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_4 in 1 ml of a 1 % solution of p-toluenesulphonic acid in methanol was stirred for 90 minutes at room temperature. The reaction mixture was then poured onto 50 ml of saturated $NaHCO_3$ solution and extracted with 100 ml of diethyl ether. The organic phase was washed with 50 ml of saturated NaCl solution, dried with $MgSO_4$ and concentrated by evaporation. After chromatography of the crude product on silica gel with hexane/ethyl acetate 2:1, it was possible to isolate 35 mg (86 %) of product in the form of a mixture of epimers at C5' (isomer A:isomer B approximately 3:1).

MS: (m/e): 628 (M^+, $C_{36}H_{52}O_9$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.09 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.40* and 3.45 ppm (2s) (CH_3O)

4.03 and 4.12* ppm (2s) (OH)

4.29 ppm (6s, $w\frac{1}{2}$ = 15) (C_5H)

4.99* ppm (d, J = 4) and 5.10 ppm (dd, J = 4, J' = 2) ($OC\underline{H}(CH_2)O$).

H2. Preparation of 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2''-ethoxyethoxy)-tetrahydrofuran]

24 mg of (±)-camphor-10-sulphonic acid were added to a solution of 80 mg of 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_4 and 200 µl of ethylene glycol monoethyl ether in 2 ml of methylene chloride. After stirring for 2 hours at room temperature, the reaction mixture was poured onto 50 ml of saturated $NaHCO_3$ solution and extracted with 100 ml of diethyl ether. The organic phase was washed with 50 ml of saturated NaCl solution, dried with $MgSO_4$ and concentrated by evaporation. Chromatography of the crude product on silica gel with hexane/ethyl acetate 6:1 yielded 62 mg (50 %) of isomer A product and 32 mg (26 %) of isomer B product.

Isomer A:

MS: (m/e): 800 (M^+, $C_{45}H_{72}O_{10}Si$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.08 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

4.09 ppm (s) (OH)

4.42 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)

5.13 ppm (bs, $w_{\frac{1}{2}}$ = 6) ($OC\underline{H}(CH_2)O$)

Isomer B:

MS: (m/e): 800 (M^+, $C_{45}H_{72}O_{10}Si$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.07 ppm (dt, J_d = 2.5, Jt = 9) ($C_{25}H$)

4.03 ppm (s) (OH)

4.42 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)

5.23 ppm (bd, J = 3) ($OC\underline{H}(CH_2)O$)

5.51 ppm (dd, J = 11, J' = 6) ($C_{15}H$)

H3. Preparation of milbemycin A_4-13-spiro-2'-[5'-(2"-ethoxyethoxy)-tetrahydrofuran]

a) Isomer A

A solution of 58 mg of 5-O-tert.-butyldimethylsilyl-13-spiro-2'-[5'-(2"-ethoxyethoxy)-tetrahydrofuran] (isomer A) in 1 ml of HF_x·pyridine/THF solution (see above) was stirred for 16 hours at room temperature. The reaction mixture was then poured onto 50 ml of saturated $NaHCO_3$ solution and extracted with 100 ml of diethyl ether. The organic phase was washed with 50 ml of saturated NaCl solution, dried with $MgSO_4$ and concentrated by evaporation. Chromatography of the crude product on silica gel with hexane/ethyl acetate 2:1 yielded 47 mg (94 %) of product.

MS: (m/e): 686 (M^+, $C_{39}H_{58}O_{10}$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.08 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

4.10 ppm (s) (OH)

4.28 ppm (t, J = 7) (C_5H)

5.13 ppm (bd, J = 4) ($OC\underline{H}(CH_2)O$)

b) Isomer B

22 mg (88 %) of product were obtained from 29.5 mg of 5-O-tert.-butyldimethylsilyl-13-spiro-2'-[5'-(2"-ethoxyethoxy)-tetrahydrofuran] (isomer B) analogously to procedure H3.a.

MS: (m/e): 686 (M^+, $C_{39}H_{58}O_{10}$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.06 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

4.03 ppm (s) (OH)

4.28 ppm (t, J = 7) (C_5H)

5.22 ppm (bd, J = 4) ($OCH(CH_2)O$)

5.50 ppm (dd, J = 11, J' = 5) ($C_{15}H$)

H4. Preparation of 5-O-tert.-butyldimethylsilylmilbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethylpropoxy)-tetrahydrofuran]

36 mg of (±)-camphor-10-sulphonic acid were added to a solution of 120 mg of 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_4 and 274 mg of neopentyl alcohol in 2 ml of methylene chloride. After stirring for 2 hours at room temperature, the reaction mixture was worked up as described under Preparation Example H2. After chromatography of the crude product on silica gel with hexane/diethyl ether 5:1, it was possible to isolate 64 mg (52 %) of isomer A product and 35 mg (28 %) of isomer B product.

Isomer A:

MS: (m/e): 798 (M^+, $C_{46}H_{74}O_9Si$)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.88 ppm (s) ($C(CH_3)_3$)

2.96 ppm (d, J = 9) ($OC\underline{H}HC(CH_3)_3$)

3.08 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.50 ppm (d, J = 9) ($OCH\underline{H}C(CH_3)_3$)

4.09 ppm (s) (OH)

4.42 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)

4.07 ppm (bd, J = 3) ($OC\underline{H}(CH_2)O$)

Isomer B:

MS: (m/e): 798 (M^+, $C_{46}H_{74}O_9Si$)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.88 ppm (s) ($C(CH_3)_3$)

3.02 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.06 ppm (d, J = 9) ($OC\underline{H}HC(CH_3)_3$)

3.51 ppm (d, J = 9) ($OCH\underline{H}C(CH_3)_3$)

4 11 ppm (s) (OH)

4.42 ppm (bs, $w_{\frac{1}{2}}$ ≈ 10) (C_5H)

5.14 ppm (dd, J = 5, J' = 2.5) ($OC\underline{H}(CH_2)O$)

5.56 ppm (t, J = 7.5) ($C_{15}H$)

H5. Preparation of milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethylpropoxy)-tetrahydrofuran]

a) Isomer A

47 mg (90 %) of product were obtained from 61 mg of 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethylpropoxy)-tetrahydrofuran] (isomer A) analogously to Preparation Example H3.

MS: (m/e): 684 (M^+, $C_{40}H_{60}O_9$)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.87 ppm (s) ($C(CH_3)_3$)

2.95 ppm (d, J = 9) ($OC\underline{H}HC(CH_3)_3$)

3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.40 ppm (d, J = 9) ($OCH\underline{H}C(CH_3)_3$)

4.11 ppm (s) (OH)

4.28 ppm (t, J = 7) (C_5H)

5.06 ppm (bs, $w_{\frac{1}{2}}$ = 6) ($OC\underline{H}(CH_2)O$)

b) Isomer B

22 mg (85 %) of product were obtained from 29 mg of 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethylpropoxy)-tetrahydrofuran] (isomer B) analogously to Preparation Example H3.

MS: (m/e): 684 (M^+, $C_{40}H_{60}O_9$)

^{1}H-NMR (300 MHz, $CDCl_3$):

0.88 ppm (s) ($C(CH_3)_3$)

3.01 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.05 ppm (d, J = 9) ($OC\underline{H}HC(CH_3)_3$)

3.50 ppm (d, J = 9) ($OCH\underline{H}C(CH_3)_3$)

4.09 ppm (s) (OH)

4.28 ppm (t, J = 7) (C_5H)

5.15 ppm (dd, J = 5,m J' = 2.5) ($OC\underline{H}(CH_2)O$)

5.55 ppm (t, J = 8) ($C_{15}H$)

H6. Preparation of 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-(2""-hydroxyethoxy)-ethoxy)-ethoxy)-tetrahydrofuran]

36 mg of (±)-camphor-10-sulphonic acid were added to a solution of 120 mg of 5-O-tert.-butyldimethylsilyl-13β-[2-(1,3-dioxolan-2-yl)-ethyl]-13α-hydroxy-milbemycin A_4 and 828 µl of triethylene glycol in 2 ml of methylene chloride. After stirring for 2 hours at room temperature, the reaction mixture was worked up as described under Preparation Example H2. Chromatography of the crude product on silica gel with hexane/ethyl acetate 1:1 yielded 96 mg (72 %) of product in the form of a mixture of epimers at C5' (isomer A:isomer B approximately 3:1).

MS: (m/e): 860 (M^+, $C_{47}H_{76}O_{12}Si$)
^{1}H-NMR (300 MHz, $CDCl_3$):
3.08 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
4.02 ppm and 4.10* ppm (2s) (OH)
4.42 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)
5.12* ppm (bs, $w_{\frac{1}{2}}$ = 5) and 5.16 ppm
(dd, J = 5, J' = 2) ($OC\underline{H}(CH_2)O$)

H7. Preparation of milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-(2""-hydroxyethoxy)-ethoxy)-ethoxy)-tetrahydrofuran]

39 mg (90 %) of product, in the form of a mixture of epimers at C5' (isomer A:isomer B approximately 2.5:1), were obtained from 50 mg of 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-(2""-hydroxyethoxy)-ethoxy)-ethoxy)-tetrahydrofuran] analogously to Preparation Example H3.

MS: (m/e): 746 (M^+, $C_{41}H_{62}O_{12}$)
^{1}H-NMR (300 MHz, $CDCl_3$):
3.07 ppm (bt, J = 9) ($C_{25}H$)
4.00 ppm and 4.10* ppm (2s) (OH)
4.27 ppm (t, J = 7) (C_5H)
5.11* ppm (bt, J = 2) and 5.22 ppm
(dd, J = 5, J' = 2) ($OC\underline{H}(CH_2)O$)

H8. Preparation of 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-(2""-(chloroacetoxy)-ethoxy)-ethoxy)-ethoxy)-tetrahydrofuran]

At 0°C, 1 µl of chloroacetyl chloride was added to a solution of 42 mg of 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-(2""-hydroxyethoxy)-ethoxy)-ethoxy)-tetrahydrofuran] [mixture of epimers at C5' (isomer A:isomer B approximately 3:1)] and 39 µl of pyridine in 2 ml of methylene chloride. After stirring for 6 hours at 0°C, the reaction mixture was poured onto 50 ml of 1N HCl solution and extracted with 100 ml of diethyl ether. The organic phase was washed with 50 ml of saturated $NaHCO_3$ solution and 50 ml of saturated NaCl solution, dried with $MgSO_4$ and concentrated. Chromatography of the crude product on silica gel with hexane/ethyl acetate 3:1 yielded 42 mg (92 %) of product in the form of a mixture of epimers at C5' (isomer A:isomer B approximately 3:1).

MS: (m/e): 936 (M^+, $C_{49}H_{77}ClO_{13}Si$)
^{1}H-NMR (300 MHz, $CDCl_3$):
3.07 ppm (dt, Jd = 2.5, Jt = 9) ($C_{25}H$)
4.00 ppm and 4.08* ppm (2s) (OH)
4.08 ppm (s) (CH_2Cl)
4.41 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)
5.10* ppm (bt, J = 3) and 5.22 ppm
(dd, J = 5, J' = 2.5) ($OC\underline{H}(CH_2)O$)

H9. Preparation of milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-(2""-(chloroacetoxy)-ethoxy)-ethoxy)-ethoxy)-tetrahydrofuran]

26 mg (75 %) of product, in the form of a mixture of epimers at C5' (isomer A:isomer B approximately 3:1), were obtained from 39 mg of 5-O-tert.-butyldimethylsilyl-milbemycin A4-13-spiro-2'-[5'-(2"-(2"'-(2""-(chloroacetoxy)-ethoxy)-ethoxy)-ethoxy)-tetrahydrofuran] [mixture of epimers at C5' (isomer A:isomer B approximately 3:1)] analogously to Preparation Example H3.

MS: (m/e): 822 (M+, $C_{43}H_{63}ClO_{13}$)
1H-NMR (300 MHz, $CDCl_3$):
3.07 ppm (dt, J_d = 2.5, J^t = 9) ($C_{25}H$)
4.00 ppm and 4.10* ppm (2s) (OH)
4.08 ppm (s) (CH_2Cl)
4.27 ppm (t, J = 7) (C_5H)
5.11* ppm (bt, J = 2.5) and 5.22 ppm (m) ($OC\underline{H}(CH_2)O$)

In accordance with the processes described above it is also possible to prepare, for example, the following compounds of formula I:

H10. 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-benzyloxytetrahydrofuran]

a) Isomer A:
MS: (m/e): 818 (M^+, $C_{48}H_{70}O_9Si$)
^{1}H-NMR (300 MHz, CDCl3):
3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
4.09 ppm (s) (OH)
4.42 ppm (bs, $w_{\frac{1}{2}}$ = 11) (C_5H)
4.48 ppm (d, J = 11.5) ($OC\underline{H}C_6H_5$)
4.82 ppm (d, J = 11.5) ($OCH\underline{H}C_6H_5$)
5.20 ppm (bt, J = 2.5) ($OC\underline{H}(CH_2)O$)
7.33 ppm (m) (C_6H_5)

b) Isomer B
MS: (m/e): 818 (M^+, $C_{48}H_{70}O_9Si$)
^{1}H-NMR (300 MHz, $CDCl_3$):
3.00 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
4.12 ppm (s) (OH)
4.41 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)
4.57 ppm (d, J = 11.5) ($OC\underline{H}C_6H_5$)
4.86 ppm (d, J = 11.5) ($OCH\underline{H}C_6H_5$)
5.54 ppm (dd, J = 10, J' = 5) ($C_{15}H$)
7.32 ppm (m) (C_6H_5)

H11: Milbemycin A_4-13-spiro-2'-[5'-benzyloxytetrahydro-furan]

a) Isomer A:

MS: (m/e): 704 (M^+, $C_{42}H_{56}O_9$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

4.10 ppm (s) (OH)

4.28 ppm (t, J = 7) (C_5H)

4.48 ppm (d, J = 11.5) ($OCHHC_6H_5$)

4.82 ppm (d, J = 11.5) ($OCHHC_6H_5$)

5.20 ppm (bt, J = 2.5) ($OCH(CH_2)O$)

7.33 ppm (m) (C_6H_5)

b) Isomer B

MS: (m/e): 704 (M^+, $C_{42}H_{56}O_9$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.00 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

4.10 ppm (s) (OH)

4.27 ppm (t, J = 7) (C_5H)

4.57 ppm (d, J = 11.5) ($OCHHC_6H_5$)

4.85 ppm (d, J = 11.5) ($OCHHC_6H_5$)

5.30 ppm (bt, J = 2.5) ($OCH(CH_2)O$)

7.31 ppm (m) (C_6H_5)

H12: 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-cyclohexyloxytetrahydrofuran]

a) Isomer A:

MS: (m/e): 810 (M^+, $C_{47}H_{74}O_9Si$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.60 ppm (m) ($OCH(CH_2)CH_2$)

4.09 ppm (s) (OH)

4.41 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)

b) Isomer B

MS: (m/e): 810 (M^+, $C_{47}H_{74}O_9Si$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.01 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.62 ppm (m) ($OC\underline{H}(CH_2)CH_2$)

4.08 ppm (s) (OH)

4.40 ppm (bs, $w_{\frac{1}{2}}$ = 10) (C_5H)

5.55 ppm (bs, J = 8) ($C_{15}H$)

H13: Milbemycin A_4-13-spiro-2'-[5'-cyclohexyloxytetra-hydrofuran]

a) Isomer A:

MS: (m/e): 696 (M^+, $C_{41}H_{60}O_9$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.08 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.62 ppm (m) ($OC\underline{H}(CH_2)CH_2$)

4.10 ppm (s) (OH)

4.28 ppm (t, J = 7) (C_5H)

b) Isomer B

MS: (m/e): 696 (M^+, $C_{41}H_{60}O_9$)

^{1}H-NMR (300 MHz, $CDCl_3$):

3.02 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.62 ppm (m) ($OC\underline{H}(CH_2)CH_2$)

4.07 ppm (s) (OH)

4.27 ppm (t, J = 7) (C_5H)

5.56 ppm (dd, J = 10, J' = 5) ($C_{15}H$)

H14: 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-methoxy-ethoxy)-ethoxy)-tetrahydro- furan]

Mixture of epimers at C5' (isomer A:isomer B approx. 3:1)

MS: (m/e): 830 (M^+, $C_{46}H_{74}O_{11}Si$)

1H-NMR (300 MHz, $CDCl_3$):

3.08 ppm (bt, J = 9) ($C_{25}H$)

3.36 ppm (s) (CH_3O)

4.02 and 4.09* ppm (2s) (OH)
4.41 ppm (bs, $w_{\frac{1}{2}}$ = 11) (C_5H)
5.12* ppm (bs, $w_{\frac{1}{2}}$ = 6) and 5.23 ppm (bs, $w_{\frac{1}{2}}$ = 6) ($OC\underline{H}(CH_2)O$)

H15: Milbemycin A_4-13-spiro-2'-[5'-(2"-(2"'-methoxy-ethoxy)-ethoxy)-tetrahydrofuran]

Mixture of epimers at C5' (isomer A:isomer B approx. 2:3)

MS: (m/e): 716 (M^+, $C_{40}H_{60}O_{11}$)
1H-NMR (300 MHz, $CDCl_3$):
3.08 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
3.38 ppm (s) (CH_3O)
4.01* and 4.10 ppm (2s) (OH)
4.29 ppm (t, J = 7) (C_5H)
5.12 ppm (bs, $w_{\frac{1}{2}}$ = 7) and 4.23* ppm (bs, $w_{\frac{1}{2}}$ = 6)
($OC\underline{H}(CH_2)O$)

H16: 5-O-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-((3"-methyl-oxetan-3"-yl)-methoxy)-tetrahydrofuran]

Mixture of epimers at C5' (isomer A:isomer B approx. 1:1)

MS: (m/e): 812 (M^+, $C_{46}H_{72}O_{10}Si$)
^{1}H-NMR (300 MHz, $CDCl_3$):
3.02 and 3.07 ppm (2dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
3.40 and 3.47 ppm (2d, J = 10) ($OC\underline{H}HC$)
3.87 and 3.88 ppm (2d, J = 10) ($OCH\underline{H}C$)
4.09 and 4.10 ppm (2s) (OH)
5.12 ppm (bd, J = 3.5) and 5.20 ppm
(dd, J = 4.5, J' = 2) ($OC\underline{H}(CH_2)O$)

H17: Milbemycin A_4-13-spiro-2'-[5'-((3"-methyloxetan-3"-yl)-methoxy)-tetrahydrofuran]

Mixture of epimers at C5' (isomer A:isomer B approx. 1:1)

MS: (m/e): 698 (M^+, $C_{40}H_{58}O_{10}$)
1H-NMR (300 MHz, $CDCl_3$):
3.02 and 3.07 ppm (2dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
3.40 and 3.46 ppm (2d, J = 10) (OCHHC)
3.86 and 3.88 ppm (2d, J = 10) (OCHHC)
4.09 and 4.10 ppm (2s) (OH)
4.28 ppm (t, J = 7) (C_5H)
5.12 ppm (bd, J = 3.5) and 5.20 ppm
(dd, J = 5, J' = 2) ($OCH(CH_2)O$)

H18: 5-tert.-butyldimethylsilyl-milbemycin A_4-13-spiro-2'-[5'-(2"-hydroxyethoxy)-tetrahydrofuran]

Mixture of epimers at C5' (isomer A:isomer B approx. 1:1)

MS: (m/e): 772 (M^+, $C_{43}H_{68}O_{10}Si$)
1H-NMR (300 MHz, $CDCl_3$):
3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
3.98 and 4.06* ppm (2s) (OH)
4.41 ppm (bs, $w_{\frac{1}{2}}$ = 11) (C_5H)
5.13* ppm (d, J = 4.5) and 5.22 ppm
(dd, J = 5, J' = 3) ($OCH(CH_2)O$)

H19: Milbemycin A_4-13-spiro-2'-[5'-(2"-hydroxyethoxy)-tetrahydrofuran]

a) Isomer A
MS: (m/e): 658 (M^+, $C_{37}H_{54}O_{10}$)
1H-NMR (300 MHz, $CDCl_3$):
3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)
4.06 ppm (s) (OH)
4.27 ppm (t, J = 7) (C_5H)
5.13 ppm (d, J = 4.5) ($OCH(CH_2)O$)

b) Isomer B:
MS: (m/e): 658 (M^+, $C_{37}H_{54}O_{10}$)
1H-NMR (300 MHz, $CDCl_3$):
3.07 ppm (dt, J_d = 2.5, J_t = 9) ($C_{25}H$)

3.98 ppm (s) (OH)
4.27 ppm (t, J = 7) (C_5H)
5.22 ppm (dd, J = 5, J' = 3) ($OC\underline{H}(CH_2)O$)
5.53 ppm (dd, J = 10.5, J' = 4.5) ($C_{15}H$)

H20. Preparation of 5-oximino-milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethoxypropoxy)-tetrahydrofuran]

a) A solution of 50 mg of milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethoxypropoxy)-tetrahydrofuran] in 3 ml of dichloromethane is stirred with 95 mg of manganese dioxide for 5 hours at room temperature. The manganese dioxide is filtered off over kieselguhr, and after concentration of the solution, 47 mg of crude 5-oxo-milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethylpropoxy)-tetrahydrofuran] are obtained.
MS: (m/e): 682 (M^+, $C_{40}H_{58}O_9$)

b) This crude product is dissolved together with 47 mg of hydroxylamine hydrochloride in 1.0 ml of pyridine. After stirring for 1 hour at room temperature, the mixture is worked up with diethyl ether and 1N HCl. Chromatography of the crude product on silica gel with ethyl acetate/hexane 1:3 yields 35 mg of the title compound.
MS: (m/e): 697 (M^+, $C_{40}H_{59}NO_9$)
^{1}H-NMR (300 MHz, $CDCl_3$):
0.88 ppm (s) ($C(CH_3)_3$)
2.96 ppm (d, J = 9.5) ($OC\underline{H}HC(CH_3)_3$)
3.08 ppm (dt, J_d = 2.5, J_t = 9.5) ($C_{25}H$)
3.48 ppm (d, J = 9.5) ($OC\underline{H}HC(CH_3)_3$)
4.64 ppm (s) (C6H)
7.62 ppm (s) (N-OH)

H21. Preparation of 5-oximino-milbemycin A_4-13-spiro-2'-[5'-cyclohexyloxytetrahydrofuran]

a) 56 mg of manganese dioxide are added to a solution of 30 mg of milbemycin A_4-13-spiro-2'-[5'-cyclohexyloxy-tetrahydrofuran] in 3 ml of dichloromethane. After stirring for 2 hours at room temperature, the reaction mixture is filtered over kieselguhr. After concentration of the solution 30 mg of crude 5-oxo-milbemycin A_4-13-spiro-2'-[5-cyclohexyloxy-tetrahydrofuran] are obtained.

MS: (m/e): 694 (M^+, $C_{41}H_{58}O_9$)

b) 29 mg of this crude product and 30 mg of hydroxylamine hydrochloride in 1.0 ml of pyridine are stirred for 2 hours at room temperature. The reaction mixture is worked up with diethyl ether and 1N HCl and after chromatography of the crude product on silica gel with ethyl acetate/hexane 1:3, 23 mg of the title compound are obtained.
MS: (m/e): 709 (M^+, $C_{41}H_{59}NO_9$)
^{1}H-NMR (300 MHz, $CDCl_3$):
3.09 ppm (dt, J_d = 2.5, J_t = 9.5) ($C_{25}H$)
3.62 ppm (m) ($OC\underline{H}(CH_2)CH_2$)
4.55 ppm (s) (C_6H)
7.65 ppm (s) (N-OH)

H22. Preparation of 5-oximino-milbemycin A_4-13-spiro-2'-[5'-(2"-methylbutoxy)-tetrahydrofuran]

a) 57 mg of manganese dioxide are added to a solution of 30 mg of milbemycin A_4-13-spiro-2'-[5'-(2"-methylbutoxy)-tetrahydrofuran] in 3 ml of dichloromethane. After stirring for 2 hours at room temperature, the reaction mixture is filtered over kieselguhr and, after concentration of the solution, 27 mg of crude 5-oxo-milbemycin A_4-13-spiro-2'-[5'-(2"-methylbutoxy)-tetrahydrofuran] are obtained.
MS: (m/e): 682 (M^+, $C_{40}H_{58}O_9$)

b) 26 mg of this crude product are dissolved together with 26 mg of hydroxylamine hydrochloride in 1.0 ml of pyridine. After stirring for 90 minutes at room temperature, the mixture is worked up with diethyl ether and 1N HCl. Chromatography of the crude product on silica gel with ethyl acetate/hexane 1:3 yields 21 mg of the title compound.
MS: (m/e): 697 (M^+, $C_{40}H_{59}NO_9$)
^{1}H-NMR (300 MHz, $CDCl_3$):
3.10 ppm (dd, J_1 = 6, J_2 = 9.5) ($OC\underline{H}HCH(CH_3)C_2H_5$)
3.66 ppm (dd, J_1 = 6, J_2 = 9.5) ($OCH\underline{H}CH(CH_3)C_2H_5$)
4.64 ppm (s) (C_6H)
7.68 ppm (s) (N-OH)

H23. Preparation of 5-oximino-milbemycin A_3-13-spiro-2'-[5'-(2"-ethoxy-ethoxy)-tetrahydrofuran]

a) 60 mg of manganese dioxide are added to a solution of 14.5 mg of milbemycin A_3-13-spiro-2'-[5'-(2"-ethoxyethoxy)-tetrahydrofuran] in 3 ml of dichloromethane. After stirring for 90 minutes at room temperature the reaction mixture is filtered over kieselguhr and, after concentration of the solution, 14 mg of crude 5-oxo-milbemycin A3-13-spiro-2'-[5'-(2"-ethoxyethoxy)-tetrahydrofuran] are obtained.
MS: (m/e): 670 (M^+, $C_{38}H_{54}O_{10}$)

b) This crude product is dissolved together with 20 mg of hydroxylamine hydrochloride in 1.0 ml of pyridine. After stirring for one hour at room temperature, the mixture is worked up with diethyl ether and 1N HCl. Chromatography of the crude product on silica gel with ethyl acetate/hexane 1:3 yields 10 mg of the title compound.
MS: (m/e): 685 (M^+, $C_{38}H_{55}NO_{10}$)

It is also possible to prepare the following compounds analogously to the procedures described above:

Table 1 Compounds of formula I

in which X = $-CH(OR_1)-$, R_1 = H and R_2 = CH_3

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
1.1	CH_3	A	
1.2	CH_3	B	
1.3	CH_3	A/B	m/e: 614 (M^+, $C_{35}H_{50}O_9$)
1.4	C_2H_5	A	
1.5	C_2H_5	B	
1.6	C_2H_5	A/B	
1.7	C_3H_7-n	A	
1.8	C_3H_7-n	B	
1.9	C_3H_7-n	A/B	
1.10	C_3H_7-i	A	
1.11	C_3H_7-i	B	
1.12	C_3H_7-i	A/B	
1.13	C_4H_9-n	A	
1.14	C_4H_9-n	B	
1.15	C_4H_9-n	A/B	
1.16	C_6H_{13}-n	A/B	
1.17	$C_{10}H_{21}$-n	A/B	
1.18	CH_2OCH_3	A	
1.19	CH_2OCH_3	B	
1.20	CH_2OCH_3	A/B	
1.21	CH_2CH_2OH	A	
1.22	CH_2CH_2OH	B	
1.23	CH_2CH_2OH	A/B	
1.24	$CH_2C(CH_3)_3$	A	m/e: 670 (M^+, $C_{39}H_{50}O_9$)
1.25	$CH_2C(CH_3)_3$	B	m/e: 670 (M^+, $C_{39}H_{50}O_9$)
1.26	$CH_2C(CH_3)_3$	A/B	
1.27	Phenyl	A	
1.28	Phenyl	B	
1.29	Phenyl	A/B	
1.30	Benzyl	A	
1.31	Benzyl	B	
1.32	Benzyl	A/B	
1.33	$CH_2CH_2OCH_3$	A	
1.34	$CH_2CH_2OCH_3$	B	
1.35	$CH_2CH_2OCH_3$	A/B	
1.36	$CH_2CH_2OC_2H_5$	A	m/e: 672 (M^+, $C_{38}H_{56}O_{10}$)
1.37	$CH_2CH_2OC_2H_5$	B	m/e: 672 (M^+, $C_{38}H_{56}O_{10}$)
1.38	$CH_2CH_2OC_2H_5$	A/B	
1.39	$CH_2CH_2OCH_2CH_2OCH_3$	A	
1.40	$CH_2CH_2OCH_2CH_2OCH_3$	B	
1.41	$CH_2CH_2OCH_2CH_2OCH_3$	A/B	

Table 1 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
1.42	$CH_2CH_2(OCH_2CH_2)_2OH$	A	
1.43	$CH_2CH_2(OCH_2CH_2)_2OH$	B	
1.44	$CH_2CH_2(OCH_2CH_2)_2OH$	A/B	
1.45	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A	
1.46	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	B	
1.47	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A/B	
1.48	Cyclohexyl	A	m/e: 682 (M^+, $C_{40}H_{58}O_9$)
1.49	Cyclohexyl	B	m/e: 682 (M^+, $C_{40}H_{58}O_9$)
1.50	Cyclohexyl	A/B	
1.51		A	
1.52		B	
1.53		A/B	
1.54	CH_2Cl_3	A	
1.55	CH_2Cl_3	B	
1.56	CH_2Cl_3	A/B	
1.57	$CH_2C(CH_3)(CH_2Cl)_2$	A	
1.58	$CH_2C(CH_3)(CH_2Cl)_2$	B	
1.59	$CH_2C(CH_3)(CH_2Cl)_2$	A/B	
1.60	CH_2CBr_3	A	
1.61	CH_2CBr_3	B	
1.62	CH_2CBr_3	A/B	
1.63	CH_2-Cyclobutyl	A	m/e: 668 (M^+, $C_{39}H_{56}O_9$)
1.64	CH_2-Cyclobutyl	B	m/e: 668 (M^+, $C_{39}H_{56}O_9$)
1.65	CH_2-Cyclobutyl	A/B	
1.66	$CH_2CH(CH_3)CH_2CH_3$	A	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
1.67	$CH_2CH(CH_3)CH_2CH_3$	B	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
1.68	$CH_2CH(CH_3)CH_2CH_3$	A/B	
1.69	$CH_2CH_2SCH_3$	A	
1.70	$CH_2CH_2SCH_3$	B	
1.71	$CH_2CH_2SCH_3$	A/B	
1.72	1-Adamantylmethyl	A	
1.73	1-Adamantylmethyl	B	
1.74	1-Adamantylmethyl	A/B	
1.75	CH_2-(2-Furyl)	A	
1.76	CH_2-(2-Furyl)	B	
1.77	CH_2-(2-Furyl)	A/B	

Table 1 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
1.78	(+)-2-Methyl-6-isopropyl-cyclohexyl	A	
1.79	(+)-2-Methyl-6-isopropyl-cyclohexyl	B	
1.80	(+)-2-Methyl-6-isopropyl-cyclohexyl	A/B	
1.81	$CH_2CH_2OCOCH_3$	A	
1.82	$CH_2CH_2OCOCH_3$	B	
1.83	$CH_2CH_2OCOCH_3$	A/B	m/e: 686 (M^+, $C_{38}H_{54}O_{11}$)
1.84	$CH_2CH_2OCH_2C_6H_5$	A	
1.85	$CH_2CH_2OCH_2C_6H_5$	B	
1.86	$CH_2CH_2OCH_2C_6H_5$	A/B	
1.87	CH_2CH_2Cl	A	
1.88	CH_2CH_2Cl	B	
1.89	CH_2CH_2Cl	A/B	
1.90	$CH_2CH_2OCH_2CH_2Cl$	A	
1.91	$CH_2CH_2OCH_2CH_2Cl$	B	
1.92	$CH_2CH_2OCH_2CH_2Cl$	A/B	
1.93	CH_2-(2-Thienyl)	A	
1.94	CH_2-(2-Thienyl)	B	
1.95	CH_2-(2-Thienyl)	A/B	
1.96	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A	
1.97	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	B	
1.98	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A/B	
1.99	H	A	
1.100	H	B	
1.101	H	A/B	
1.102	Cyclopentyl	A	
1.103	Cyclopentyl	B	
1.104	Cyclopentyl	A/B	
1.105	Cycloheptyl	A	
1.106	Cycloheptyl	B	
1.107	Cycloheptyl	A/B	
1.108	$CH_2C(CH_3)_2CH_2Cl$	A	
1.109	$CH_2C(CH_3)_2CH_2Cl$	B	
1.110	$CH_2C(CH_3)_2CH_2Cl$	A/B	
1.111	$CH(CH_3)CH_2CH_3$ (S)	A	
1.112	$CH(CH_3)CH_2CH_3$ (S)	B	
1.113	$CH(CH_3)CH_2CH_3$ (S)	A/B	
1.114	$CH_2CH_2OCOCH_2Cl$	A	
1.115	$CH_2CH_2OCOCH_2Cl$	B	
1.116	$CH_2CH_2OCOCH_2Cl$	A/B	
1.117	$CH_2CH(CH_2CH_2CH_3)_2$	A	

Table 1 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
1.118	$CH_2CH(CH_2CH_2CH_3)_2$	B	
1.119	$CH_2CH(CH_2CH_2CH_3)_2$	A/B	
1.120	$CH(CH_3)CH_2CH_3$ (R)	A	
1.121	$CH(CH_3)CH_2CH_3$ (R)	B	
1.122	$CH(CH_3)CH_2CH_3$ (R)	A/B	
1.123	3-Phenoxy-benzyl	A	
1.124	3-Phenoxy-benzyl	B	
1.125	3-Phenoxy-benzyl	A/B	
1.126	CH_2-Cyclohexyl	A	m/e: 696 (M^+, $C_{41}H_{60}O_9$)
1.127	CH_2-Cyclohexyl	B	m/e: 696 (M^+, $C_{41}H_{60}O_9$)
1.128	CH_2-Cyclohexyl	A/B	
1.129	3,4-Dimethoxybenzyl	A	
1.130	3,4-Dimethoxybenzyl	B	
1.131	3,4-Dimethoxybenzyl	A/B	
1.132	$CH(CH_3)C_6H_5$ (R)	A	
1.133	$CH(CH_3)C_6H_5$ (R)	B	
1.134	$CH(CH_3)C_6H_5$ (R)	A/B	
1.135	$CH(CH_3)C_6H_5$ (S)	A	
1.136	$CH(CH_3)C_6H_5$ (S)	B	
1.137	$CH(CH_3)C_6H_5$ (S)	A/B	
1.138	$CH_2CH(C_2H_5)_2$	A	
1.139	$CH_2CH(C_2H_5)_2$	B	
1.140	$CH_2CH(C_2H_5)_2$	A/B	
1.141	$CH_2CH(CH_3)_2$	A	
1.142	$CH_2CH(CH_3)_2$	B	
1.143	$CH_2CH(CH_3)_2$	A/B	
1.144	$CH_2C(CH_3)=CH_2$	A	
1.145	$CH_2C(CH_3)=CH_2$	B	
1.146	$CH_2C(CH_3)=CH_2$	A/B	
1.147	CH_2-1-Methylcyclopropyl	A	
1.148	CH_2-1-Methylcyclopropyl	B	
1.149	CH_2-1-Methylcyclopropyl	A/B	

Table 2 Compounds of formula I
in which X = $-CH(OR_1)-$, R_1 = H und R_2 = C_2H_5

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
2.1	CH_3	A	
2.2	CH_3	B	
2.3	CH_3	A/B	H1
2.4	C_2H_5	A	
2.5	C_2H_5	B	
2.6	C_2H_5	A/B	
2.7	C_3H_7-n	A	
2.8	C_3H_7-n	B	
2.9	C_3H_7-n	A/B	
2.10	C_3H_7-i	A	
2.11	C_3H_7-i	B	
2.12	C_3H_7-i	A/B	
2.13	C_4H_9-n	A	
2.14	C_4H_9-n	B	
2.15	C_4H_9-n	A/B	
2.16	C_6H_{13}-n	A/B	
2.17	$C_{10}H_{21}$-n	A/B	
2.18	CH_2OCH_3	A	
2.19	CH_2OCH_3	B	
2.20	CH_2OCH_3	A/B	
2.21	CH_2CH_2OH	A	H19
2.22	CH_2CH_2OH	B	H19
2.23	CH_2CH_2OH	A/B	
2.24	$CH_2C(CH_3)_3$	A	H5
2.25	$CH_2C(CH_3)_3$	B	H5
2.26	$CH_2C(CH_3)_3$	A/B	H5
2.27	Phenyl	A	m/e: 690 (M^+, $C_{41}H_{54}O_9$)
2.28	Phenyl	B	m/e: 690 (M^+, $C_{41}H_{54}O_9$)
2.29	Phenyl	A/B	
2.30	Benzyl	A	H11
2.31	Benzyl	B	H11
2.32	Benzyl	A/B	H11
2.33	$CH_2CH_2OCH_3$	A	
2.34	$CH_2CH_2OCH_3$	B	
2.35	$CH_2CH_2OCH_3$	A/B	
2.36	$CH_2CH_2OC_2H_5$	A	H3
2.37	$CH_2CH_2OC_2H_5$	B	H3
2.38	$CH_2CH_2OC_2H_5$	A/B	H3
2.39	$CH_2CH_2OCH_2CH_2OCH_3$	A	m/e: 716 (M^+, $C_{40}H_{60}O_{11}$)
2.40	$CH_2CH_2OCH_2CH_2OCH_3$	B	
2.41	$CH_2CH_2OCH_2CH_2OCH_3$	A/B	H15
2.42	$CH_2CH_2(OCH_2CH_2)_2OH$	A	

Table 2 (continuation)

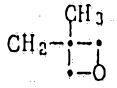
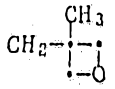
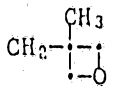
Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
2.43	$CH_2CH_2(OCH_2CH_2)_2OH$	B	
2.44	$CH_2CH_2(OCH_2CH_2)_2OH$	A/B	H7
2.45	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A	
2.46	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	B	
2.47	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A/B	H9
2.48	Cyclohexyl	A	H13
2.49	Cyclohexyl	B	H13
2.50	Cyclohexyl	A/B	H13
2.51		A	
2.52		B	
2.53		A/B	H17
2.54	CH_2Cl_3	A	
2.55	CH_2Cl_3	B	
2.56	CH_2Cl_3	A/B	
2.57	$CH_2C(CH_3)(CH_2Cl)_2$	A	m/e: 752 (M^+, $C_{40}H_{58}Cl_2O_9$)
2.58	$CH_2C(CH_3)(CH_2Cl)_2$	B	m/e: 752 (M^+, $C_{40}H_{58}Cl_2O_9$)
2.59	$CH_2C(CH_3)(CH_2Cl)_2$	A/B	
2.60	CH_2CBr_3	A	m/e: 880, 878 (M^+, $C_{37}H_{51}Br_3O_9$)
2.61	CH_2CBr_3	B	m/e: 880, 878 (M^+, $C_{37}H_{51}Br_3O_9$)
2.62	CH_2CBr_3	A/B	
2.63	CH_2-Cyclobutyl	A	m/e: 682 (M^+, $C_{40}H_{58}O_9$)
2.64	CH_2-Cyclobutyl	B	m/e: 682 (M^+, $C_{40}H_{58}O_9$)
2.65	CH_2-Cyclobutyl	A/B	
2.66	$CH_2CH(CH_3)CH_2CH_3$	A	m/e: 684 (M^+, $C_{40}H_{60}O_9$)
2.67	$CH_2CH(CH_3)CH_2CH_3$	B	m/e: 684 (M^+, $C_{40}H_{60}O_9$)
2.68	$CH_2CH(CH_3)CH_2CH_3$	A/B	

Table 2 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
2.69	$CH_2CH_2SCH_3$	A	m/e: 688 (M^+, $C_{39}H_{56}O_9S$)
2.70	$CH_2CH_2SCH_3$	B	m/e: 688 (M^+, $C_{39}H_{56}O_9S$)
2.71	$CH_2CH_2SCH_3$	A/B	
2.72	1-Adamantylmethyl	A	m/e: 762 (M^+, $C_{46}H_{66}O_9$)
2.73	1-Adamantylmethyl	B	m/e: 762 (M^+, $C_{46}H_{66}O_9$)
2.74	1-Adamantylmethyl	A/B	
2.75	CH_2-(2-Furyl)	A	m/e: 694 (M^+, $C_{40}H_{54}O_{10}$)
2.76	CH_2-(2-Furyl)	B	m/e: 694 (M^+, $C_{40}H_{54}O_{10}$)
2.77	CH_2-(2-Furyl)	A/B	
2.78	(+)-2-Methyl-6-isopropyl-cyclohexyl	A	m/e: 752 (M^+, $C_{45}H_{68}O_9$)
2.79	(+)-2-Methyl-6-isopropyl-cyclohexyl	B	m/e: 752 (M^+, $C_{45}H_{68}O_9$)
2.80	(+)-2-Methyl-6-isopropyl-cyclohexyl	A/B	
2.81	$CH_2CH_2OCOCH_3$	A	m/e: 700 (M^+, $C_{39}H_{56}O_{11}$)
2.82	$CH_2CH_2OCOCH_3$	B	
2.83	$CH_2CH_2OCOCH_3$	A/B	
2.84	$CH_2CH_2OCH_2C_6H_5$	A	m/e: 748 (M^+, $C_{44}H_{60}O_{10}$)
2.85	$CH_2CH_2OCH_2C_6H_5$	B	m/e: 748 (M^+, $C_{44}H_{60}O_{10}$)
2.86	$CH_2CH_2OCH_2C_6H_5$	A/B	
2.87	CH_2CH_2Cl	A	
2.88	CH_2CH_2Cl	B	
2.89	CH_2CH_2Cl	A/B	
2.90	$CH_2CH_2OCH_2CH_2Cl$	A	
2.91	$CH_2CH_2OCH_2CH_2Cl$	B	
2.92	$CH_2CH_2OCH_2CH_2Cl$	A/B	
2.93	CH_2-(2-Thienyl)	A	
2.94	CH_2-(2-Thienyl)	B	
2.95	CH_2-(2-Thienyl)	A/B	
2.96	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A	
2.97	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	B	
2.98	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A/B	

Table 2 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
2.99	H	A	
2.100	H	B	
2.101	H	A/B	m/e: 573 (M^+, $C_{35}H_{50}O_9$)
2.102	Cyclopentyl	A	m/e: 682 (M^+, $C_{40}H_{58}O_9$)
2.103	Cyclopentyl	B	m/e: 682 (M^+, $C_{40}H_{58}O_9$)
2.104	Cyclopentyl	A/B	
2.105	Cycloheptyl	A	m/e: 710 (M^+, $C_{42}H_{62}O_9$)
2.106	Cycloheptyl	B	m/e: 710 (M^+, $C_{42}H_{62}O_9$)
2.107	Cycloheptyl	A/B	
2.108	$CH_2C(CH_3)_2CH_2Cl$	A	m/e: 718 (M^+, $C_{40}H_{59}ClO_9$)
2.109	$CH_2C(CH_3)_2CH_2Cl$	B	m/e: 718 (M^+, $C_{40}H_{59}ClO_9$)
2.110	$CH_2C(CH_3)_2CH_2Cl$	A/B	
2.111	$CH(CH_3)CH_2CH_3$ (S)	A	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
2.112	$CH(CH_3)CH_2CH_3$ (S)	B	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
2.113	$CH(CH_3)CH_2CH_3$ (S)	A/B	
2.114	$CH_2CH_2OCOCH_2Cl$	A	m/e: 734 (M^+, $C_{39}H_{55}ClO_{11}$)
2.115	$CH_2CH_2OCOCH_2Cl$	B	m/e: 734 (M^+, $C_{39}H_{55}ClO_{11}$)
2.116	$CH_2CH_2OCOCH_2Cl$	A/B	
2.117	$CH_2CH(CH_2CH_2CH_3)_2$	A	m/e: 726 (M^+, $C_{43}H_{66}O_9$)
2.118	$CH_2CH(CH_2CH_2CH_3)_2$	B	m/e: 726 (M^+, $C_{43}H_{66}O_9$)
2.119	$CH_2CH(CH_2CH_2CH_3)_2$	A/B	
2.120	$CH(CH_3)CH_2CH_3$ (R)	A	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
2.121	$CH(CH_3)CH_2CH_3$ (R)	B	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
2.122	$CH(CH_3)CH_2CH_3$ (R)	A/B	
2.123	3-Phenoxy-benzyl	A	m/e: 796 (M^+, $C_{48}H_{60}O_{10}$)
2.124	3-Phenoxy-benzyl	B	m/e: 796 (M^+, $C_{48}H_{60}O_{10}$)
2.125	3-Phenoxy-benzyl	A/B	

Table 2 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
2.126	CH_2-Cyclohexyl	A	m/e: 710 (M^+, $C_{42}H_{62}O_9$)
2.127	CH_2-Cyclohexyl	B	m/e: 710 (M^+, $C_{42}H_{62}O_9$)
2.128	CH_2-Cyclohexyl	A/B	
2.129	3,4-Dimethoxybenzyl	A	m/e: 764 (M^+, $C_{44}H_{60}O_{11}$)
2.130	3,4-Dimethoxybenzyl	B	m/e: 764 (M^+, $C_{44}H_{60}O_{11}$)
2.131	3,4-Dimethoxybenzyl	A/B	
2.132	$CH(CH_3)C_6H_5$ (R)	A	m/e: 718 (M^+, $C_{43}H_{58}O_9$)
2.133	$CH(CH_3)C_6H_5$ (R)	B	m/e: 718 (M^+, $C_{43}H_{58}O_9$)
2.134	$CH(CH_3)C_6H_5$ (R)	A/B	
2.135	$CH(CH_3)C_6H_5$ (S)	A	m/e: 718 (M^+, $C_{43}H_{58}O_9$)
2.136	$CH(CH_3)C_6H_5$ (S)	B	m/e: 718 (M^+, $C_{43}H_{58}O_9$)
2.137	$CH(CH_3)C_6H_5$ (S)	A/B	
2.138	$CH_2CH(C_2H_5)_2$	A	
2.139	$CH_2CH(C_2H_5)_2$	B	
2.140	$CH_2CH(C_2H_5)_2$	A/B	
2.141	$CH_2CH(CH_3)_2$	A	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
2.142	$CH_2CH(CH_3)_2$	B	m/e: 670 (M^+, $C_{39}H_{58}O_9$)
2.143	$CH_2CH(CH_3)_2$	A/B	
2.144	$CH_2C(CH_3)=CH_2$	A	
2.145	$CH_2C(CH_3)=CH_2$	B	
2.146	$CH_2C(CH_3)=CH_2$	A/B	
2.147	CH_2-1-Methylcyclopropyl	A	
2.148	CH_2-1-Methylcyclopropyl	B	
2.149	CH_2-1-Methylcyclopropyl	A/B	

and the corresponding compounds 3.1 to 3.149 in which X, R_1 and R_3 have the meanings given for compounds 2.1 to 2.149 in Table 2, and R_2 represents isopropyl; and also the corresponding compounds 4.1 to 4.149 in which X, R_1 and R_3 have the meanings given for compounds 2.1 to 2.149 in Table 2, and R_2 represents sec.-butyl.

Table 3 Compounds of formula I

in which X = $-CH(OR_1)-$, $R_1 = Si(CH_3)_2C(CH_3)_3$ and $R_2 = CH_3$

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
5.1	CH_3	A	
5.2	CH_3	B	
5.3	CH_3	A/B	
5.4	C_2H_5	A	
5.5	C_2H_5	B	
5.6	C_2H_5	A/B	
5.7	C_3H_7-n	A	
5.8	C_3H_7-n	B	
5.9	C_3H_7-n	A/B	
5.10	C_3H_7-i	A	
5.11	C_3H_7-i	B	
5.12	C_3H_7-i	A/B	
5.13	C_4H_9-n	A	
5.14	C_4H_9-n	B	
5.15	C_4H_9-n	A/B	
5.16	C_6H_{13}-n	A/B	
5.17	$C_{10}H_{21}$-n	A/B	
5.18	CH_2OCH_3	A	
5.19	CH_2OCH_3	B	
5.20	CH_2OCH_3	A/B	
5.21	CH_2CH_2OH	A	
5.22	CH_2CH_2OH	B	
5.23	CH_2CH_2OH	A/B	
5.24	$CH_2C(CH_3)_3$	A	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
5.25	$CH_2C(CH_3)_3$	B	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
5.26	$CH_2C(CH_3)_3$	A/B	
5.27	Phenyl	A	
5.28	Phenyl	B	
5.29	Phenyl	A/B	
5.30	Benzyl	A	
5.31	Benzyl	B	
5.32	Benzyl	A/B	
5.33	$CH_2CH_2OCH_3$	A	
5.34	$CH_2CH_2OCH_3$	B	
5.35	$CH_2CH_2OCH_3$	A/B	
5.36	$CH_2CH_2OC_2H_5$	A	m/e: 786 (M^+, $C_{44}H_{71}O_{10}Si$)
5.37	$CH_2CH_2OC_2H_5$	B	m/e: 786 (M^+, $C_{44}H_{71}O_{10}Si$)
5.38	$CH_2CH_2OC_2H_5$	A/B	
5.39	$CH_2CH_2OCH_2CH_2OCH_3$	A	
5.40	$CH_2CH_2OCH_2CH_2OCH_3$	B	
5.41	$CH_2CH_2OCH_2CH_2OCH_3$	A/B	
5.42	$CH_2CH_2(OCH_2CH_2)_2OH$	A	
5.43	$CH_2CH_2(OCH_2CH_2)_2OH$	B	

Table 3 (continuation)

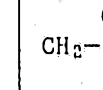
Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
5.44	$CH_2CH_2(OCH_2CH_2)_2OH$	A/B	
5.45	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A	
5.46	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	B	
5.47	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A/B	
5.48	Cyclohexyl	A	m/e: 796 (M^+, $C_{46}H_{72}O_9Si$)
5.49	Cyclohexyl	B	m/e: 796 (M^+, $C_{46}H_{72}O_9Si$)
5.50	Cyclohexyl	A/B	
5.51		A	
5.52		B	
5.53		A/B	
5.54	CH_2Cl_3	A	
5.55	CH_2Cl_3	B	
5.56	CH_2Cl_3	A/B	
5.57	$CH_2C(CH_3)(CH_2Cl)_2$	A	
5.58	$CH_2C(CH_3)(CH_2Cl)_2$	B	
5.59	$CH_2C(CH_3)(CH_2Cl)_2$	A/B	
5.60	CH_2CBr_3	A	
5.61	CH_2CBr_3	B	
5.62	CH_2CBr_3	A/B	
5.63	CH_2-Cyclobutyl	A	m/e: 782 (M^+, $C_{45}H_{70}O_8Si$)
5.64	CH_2-Cyclobutyl	B	m/e: 782 (M^+, $C_{45}H_{70}O_8Si$)
5.65	CH_2-Cyclobutyl	A/B	
5.66	$CH_2CH(CH_3)CH_2CH_3$	A	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
5.67	$CH_2CH(CH_3)CH_2CH_3$	B	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
5.68	$CH_2CH(CH_3)CH_2CH_3$	A/B	
5.69	$CH_2CH_2SCH_3$	A	
5.70	$CH_2CH_2SCH_3$	B	
5.71	$CH_2CH_2SCH_3$	A/B	
5.72	1-Adamantylmethyl	A	
5.73	1-Adamantylmethyl	B	
5.74	1-Adamantylmethyl	A/B	
5.75	CH_2-(2-Furyl)	A	
5.76	CH_2-(2-Furyl)	B	
5.77	CH_2-(2-Furyl)	A/B	
5.78	(+)-2-Methyl-6-isopropyl-cyclohexyl	A	

Table 3 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
5.79	(+)-2-Methyl-6-isopropyl-cyclohexyl	B	
5.80	(+)-2-Methyl-6-isopropyl-cyclohexyl	A/B	
5.81	$CH_2CH_2OCOCH_3$	A	
5.82	$CH_2CH_2OCOCH_3$	B	
5.83	$CH_2CH_2OCOCH_3$	A/B	
5.84	$CH_2CH_2OCH_2C_6H_5$	A	
5.78	(+)-2-Methyl-6-isopropyl-cyclohexyl	A	
5.79	(+)-2-Methyl-6-isopropyl-cyclohexyl	B	
5.80	(+)-2-Methyl-6-isopropyl-cyclohexyl	A/B	
5.81	$CH_2CH_2OCOCH_3$	A	
5.82	$CH_2CH_2OCOCH_3$	B	
5.83	$CH_2CH_2OCOCH_3$	A/B	
5.84	$CH_2CH_2OCH_2C_6H_5$	A	
5.85	$CH_2CH_2OCH_2C_6H_5$	B	
5.86	$CH_2CH_2OCH_2C_6H_5$	A/B	
5.87	CH_2CH_2Cl	A	
5.88	CH_2CH_2Cl	B	
5.89	CH_2CH_2Cl	A/B	
5.90	$CH_2CH_2OCH_2CH_2Cl$	A	
5.91	$CH_2CH_2OCH_2CH_2Cl$	B	
5.92	$CH_2CH_2OCH_2CH_2Cl$	A/B	
5.93	CH_2-(2-Thienyl)	A	
5.94	CH_2-(2-Thienyl)	B	
5.95	CH_2-(2-Thienyl)	A/B	
5.96	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A	
5.97	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	B	
5.98	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A/B	
5.99	H	A	
5.100	H	B	
5.101	H	A/B	
5.102	Cyclopentyl	A	
5.103	Cyclopentyl	B	
5.104	Cyclopentyl	A/B	
5.105	Cycloheptyl	A	
5.106	Cycloheptyl	B	
5.107	Cycloheptyl	A/B	
5.108	$CH_2C(CH_3)_2CH_2Cl$	A	
5.109	$CH_2C(CH_3)_2CH_2Cl$	B	
5.110	$CH_2C(CH_3)_2CH_2Cl$	A/B	

Table 3 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
5.111	$CH(CH_3)CH_2CH_3$ (S)	A	
5.112	$CH(CH_3)CH_2CH_3$ (S)	B	
5.113	$CH(CH_3)CH_2CH_3$ (S)	A/B	
5.114	$CH_2CH_2OCOCH_2Cl$	A	
5.115	$CH_2CH_2OCOCH_2Cl$	B	
5.116	$CH_2CH_2OCOCH_2Cl$	A/B	
5.117	$CH_2CH(CH_2CH_2CH_3)_2$	A	
5.118	$CH_2CH(CH_2CH_2CH_3)_2$	B	
5.119	$CH_2CH(CH_2CH_2CH_3)_2$	A/B	
5.120	$CH(CH_3)CH_2CH_3$ (R)	A	
5.121	$CH(CH_3)CH_2CH_3$ (R)	B	
5.122	$CH(CH_3)CH_2CH_3$ (R)	A/B	
5.123	3-Phenoxy-benzyl	A	
5.124	3-Phenoxy-benzyl	B	
5.125	3-Phenoxy-benzyl	A/B	
5.119	$CH_2CH(CH_2CH_2CH_3)_2$	A/B	
5.120	$CH(CH_3)CH_2CH_3$ (R)	A	
5.121	$CH(CH_3)CH_2CH_3$ (R)	B	
5.122	$CH(CH_3)CH_2CH_3$ (R)	A/B	
5.123	3-Phenoxy-benzyl	A	
5.124	3-Phenoxy-benzyl	B	
5.125	3-Phenoxy-benzyl	A/B	
5.126	CH_2-Cyclohexyl	A	m/e: 810 (M^+, $C_{47}H_{74}O_9Si$)
5.127	CH_2-Cyclohexyl	B	m/e: 810 (M^+, $C_{47}H_{74}O_9Si$)
5.128	CH_2-Cyclohexyl	A/B	
5.129	3,4-Dimethoxybenzyl	A	
5.130	3,4-Dimethoxybenzyl	B	
5.131	3,4-Dimethoxybenzyl	A/B	
5.132	$CH(CH_3)C_6H_5$ (R)	A	
5.133	$CH(CH_3)C_6H_5$ (R)	B	
5.134	$CH(CH_3)C_6H_5$ (R)	A/B	
5.135	$CH(CH_3)C_6H_5$ (S)	A	
5.136	$CH(CH_3)C_6H_5$ (S)	B	
5.137	$CH(CH_3)C_6H_5$ (S)	A/B	
5.138	$CH_2CH(C_2H_5)_2$	A	
5.139	$CH_2CH(C_2H_5)_2$	B	
5.140	$CH_2CH(C_2H_5)_2$	A/B	
5.141	$CH_2CH(CH_3)_2$	A	
5.142	$CH_2CH(CH_3)_2$	B	
5.143	$CH_2CH(CH_3)_2$	A/B	
5.144	$CH_2C(CH_3)=CH_2$	A	
5.145	$CH_2C(CH_3)=CH_2$	B	
5.146	$CH_2C(CH_3)=CH_2$	A/B	
5.147	CH_2-1-Methylcyclopropyl	A	
5.148	CH_2-1-Methylcyclopropyl	B	
5.149	CH_2-1-Methylcyclopropyl	A/B	

Table 4 Compounds of formula I
in which X = $-CH(OR_1)-$, $R_1 = Si(CH_3)_2C(CH_3)_3$ and $R_2 = C_2H_5$

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
6.1	CH_3	A	
6.2	CH_3	B	
6.3	CH_3	A/B	
6.4	C_2H_5	A	
6.5	C_2H_5	B	
6.6	C_2H_5	A/B	
6.7	C_3H_7-n	A	
6.8	C_3H_7-n	B	
6.9	C_3H_7-n	A/B	
6.10	C_3H_7-i	A	
6.11	C_3H_7-i	B	
6.12	C_3H_7-i	A/B	
6.13	C_4H_9-n	A	
6.14	C_4H_9-n	B	
6.15	C_4H_9-n	A/B	
6.16	C_6H_{13}-n	A/B	
6.17	$C_{10}H_{21}$-n	A/B	
6.18	CH_2OCH_3	A	
6.19	CH_2OCH_3	B	
6.20	CH_2OCH_3	A/B	
6.21	CH_2CH_2OH	A	
6.22	CH_2CH_2OH	B	
6.23	CH_2CH_2OH	A/B	H18
6.24	$CH_2C(CH_3)_3$	A	H4
6.25	$CH_2C(CH_3)_3$	B	H4
6.26	$CH_2C(CH_3)_3$	A/B	H4
6.27	Phenyl	A	
6.28	Phenyl	B	
6.29	Phenyl	A/B	
6.30	Benzyl	A	H10
6.31	Benzyl	B	H10
6.32	Benzyl	A/B	H10
6.33	$CH_2CH_2OCH_3$	A	
6.34	$CH_2CH_2OCH_3$	B	
6.35	$CH_2CH_2OCH_3$	A/B	
6.36	$CH_2CH_2OC_2H_5$	A	H2
6.37	$CH_2CH_2OC_2H_5$	B	H2
6.38	$CH_2CH_2OC_2H_5$	A/B	
6.39	$CH_2CH_2OCH_2CH_2OCH_3$	A	
6.40	$CH_2CH_2OCH_2CH_2OCH_3$	B	
6.41	$CH_2CH_2OCH_2CH_2OCH_3$	A/B	H14
6.42	$CH_2CH_2(OCH_2CH_2)_2OH$	A	
6.43	$CH_2CH_2(OCH_2CH_2)_2OH$	B	
6.44	$CH_2CH_2(OCH_2CH_2)_2OH$	A/B	H6
6.45	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A	
6.46	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	B	

Table 4 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
6.47	$CH_2CH_2(OCH_2CH_2)_2OCOCH_2Cl$	A/B	H8
6.48	Cyclohexyl	A	H12
6.49	Cyclohexyl	B	H12
6.50	Cyclohexyl	A/b	H12
6.51		A	
6.52		B	
6.53		A/B	H16
6.54	CH_2Cl_3	A	
6.55	CH_2Cl_3	B	
6.56	CH_2Cl_3	A/B	
6.57	$CH_2C(CH_3)(CH_2Cl)_2$	A	m/e: 868 (M^+, $C_{46}H_{72}Cl_2O_9Si$)
6.58	$CH_2C(CH_3)(CH_2Cl)_2$	B	m/e: 868 (M^+, $C_{46}H_{72}Cl_2O_9Si$)
6.59	$CH_2C(CH_3)(CH_2Cl)_2$	A/B	
6.60	CH_2CBr_3	A	m/e: 992, 994 (M^+, $C_{43}H_{65}Br_3O_9Si$)
6.61	CH_2CBr_3	B	m/e: 992, 994 (M^+, $C_{43}H_{65}Br_3O_9Si$)
6.62	CH_2CBr_3	A/B	
6.63	CH_2-Cyclobutyl	A	m/e: 796 (M^+, $C_{46}H_{72}O_8Si$)
6.64	CH_2-Cyclobutyl	B	m/e: 796 (M^+, $C_{46}H_{72}O_8Si$)
6.65	CH_2-Cyclobutyl	A/B	
6.66	$CH_2CH(CH_3)CH_2CH_3$	A	m/e: 798 (M^+, $C_{46}H_{74}O_9Si$)
6.67	$CH_2CH(CH_3)CH_2CH_3$	B	m/e: 798 (M^+, $C_{46}H_{74}O_9Si$)
6.68	$CH_2CH(CH_3)CH_2CH_3$	A/B	

Table 4 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
6.69	$CH_2CH_2SCH_3$	A	
6.70	$CH_2CH_2SCH_3$	B	
6.71	$CH_2CH_2SCH_3$	A/B	
6.72	1-Adamantylmethyl	A	m/e: 876 (M^+, $C_{52}H_{80}O_9Si$)
6.73	1-Adamantylmethyl	B	m/e: 876 (M^+, $C_{52}H_{80}O_9Si$)
6.74	1-Adamantylmethyl	A/B	
6.75	CH_2-(2-Furyl)	A	m/e: 808 (M^+, $C_{46}H_{68}O_{10}Si$)
6.76	CH_2-(2-Furyl)	B	m/e: 808 (M^+, $C_{46}H_{68}O_{10}Si$)
6.77	CH_2-(2-Furyl)	A/B	
6.78	(+)-2-Methyl-6-isopropyl-cyclohexyl	A	m/e: 866 (M^+, $C_{51}H_{82}O_9Si$)
6.79	(+)-2-Methyl-6-isopropyl-cyclohexyl	B	m/e: 866 (M^+, $C_{51}H_{82}O_9Si$)
6.80	(+)-2-Methyl-6-isopropyl-cyclohexyl	A/B	
6.81	$CH_2CH_2OCOCH_3$	A	
6.82	$CH_2CH_2OCOCH_3$	B	
6.83	$CH_2CH_2OCOCH_3$	A/B	
6.84	$CH_2CH_2OCH_2C_6H_5$	A	m/e: 862 (M^+, $C_{50}H_{74}O_{10}Si$)
6.85	$CH_2CH_2OCH_2C_6H_5$	B	m/e: 862 (M^+, $C_{50}H_{74}O_{10}Si$)
6.86	$CH_2CH_2OCH_2C_6H_5$	A/B	
6.87	CH_2CH_2Cl	A	
6.88	CH_2CH_2Cl	B	
6.89	CH_2CH_2Cl	A/B	
6.90	$CH_2CH_2OCH_2CH_2Cl$	A	
6.91	$CH_2CH_2OCH_2CH_2Cl$	B	
6.92	$CH_2CH_2OCH_2CH_2Cl$	A/B	
6.93	CH_2-(2-Thienyl)	A	
6.94	CH_2-(2-Thienyl)	B	
6.95	CH_2-(2-Thienyl)	A/B	
6.96	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A	
6.97	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	B	
6.98	(-)-2-Methyl-5-(1-methyl-vinyl)-2-cyclohexen-2-yl	A/B	

Table 4 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
6.99	H	A	
6.100	H	B	
6.101	H	A/B	m/e: 728 (M^+, $C_{41}H_{64}O_9Si$)
6.102	Cyclopentyl	A	m/e: 796 (M^+, $C_{46}H_{72}O_9Si$)
6.103	Cyclopentyl	B	m/e: 796 (M^+, $C_{46}H_{72}O_9Si$)
6.104	Cyclopentyl	A/B	
6.105	Cycloheptyl	A	
6.106	Cycloheptyl	B	
6.107	Cycloheptyl	A/B	
6.108	$CH_2C(CH_3)_2CH_2Cl$	A	m/e: 832 (M^+, $C_{46}H_{73}ClO_9Si$)
6.109	$CH_2C(CH_3)_2CH_2Cl$	B	m/e: 832 (M^+, $C_{46}H_{73}ClO_9Si$)
6.110	$CH_2C(CH_3)_2CH_2Cl$	A/B	
6.111	$CH(CH_3)CH_2CH_3$ (S)	A	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
6.112	$CH(CH_3)CH_2CH_3$ (S)	B	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
6.113	$CH(CH_3)CH_2CH_3$ (S)	A/B	
6.114	$CH_2CH_2OCOCH_2Cl$	A	m/e: 848 (M^+, $C_{45}H_{69}ClO_{11}Si$)
6.115	$CH_2CH_2OCOCH_2Cl$	B	m/e: 848 (M^+, $C_{45}H_{69}ClO_{11}Si$)
6.116	$CH_2CH_2OCOCH_2Cl$	A/B	
6.117	$CH_2CH(CH_2CH_2CH_3)_2$	A	m/e: 840 (M^+, $C_{49}H_{80}O_9Si$)
6.118	$CH_2CH(CH_2CH_2CH_3)_2$	B	m/e: 840 (M^+, $C_{49}H_{80}O_9Si$)
6.119	$CH_2CH(CH_2CH_2CH_3)_2$	A/B	
6.120	$CH(CH_3)CH_2CH_3$ (R)	A	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
6.121	$CH(CH_3)CH_2CH_3$ (R)	B	m/e 784 (M^+, $C_{45}H_{72}O_9Si$)
6.122	$CH(CH_3)CH_2CH_3$ (R)	A/B	
6.123	3-Phenoxy-benzyl	A	m/e: 910 (M^+, $C_{54}H_{74}O_{10}Si$)
6.124	3-Phenoxy-benzyl	B	m/e: 910 (M^+, $C_{54}H_{74}O_{10}Si$)
6.125	3-Phenoxy-benzyl	A/B	

Table 4 (continuation)

Comp.No.	R_3	Epimer	Physic. constant or Preparation Example
6.126	CH_2-Cyclohexyl	A	m/e: 824 (M^+, $C_{48}H_{76}O_9Si$)
6.127	CH_2-Cyclohexyl	B	m/e: 824 (M^+, $C_{48}H_{76}O_9Si$)
6.128	CH_2-Cyclohexyl	A/B	
6.129	3,4-Dimethoxybenzyl	A	m/e: 878 (M^+, $C_{50}H_{74}O_{11}Si$)
6.130	3,4-Dimethoxybenzyl	B	m/e: 878 (M^+, $C_{50}H_{74}O_{11}Si$)
6.131	3,4-Dimethoxybenzyl	A/B	
6.132	$CH(CH_3)C_6H_5$ (R)	A	m/e: 832 (M^+, $C_{49}H_{72}O_9Si$)
6.133	$CH(CH_3)C_6H_5$ (R)	B	m/e: 832 (M^+, $C_{49}H_{72}O_9Si$)
6.134	$CH(CH_3)C_6H_5$ (R)	A/B	
6.135	$CH(CH_3)C_6H_5$ (S)	A	m/e: 832 (M^+, $C_{49}H_{72}O_9Si$)
6.136	$CH(CH_3)C_6H_5$ (S)	B	m/e: 832 (M^+, $C_{49}H_{72}O_9Si$)
6.137	$CH(CH_3)C_6H_5$ (S)	A/B	
6.138	$CH_2CH(C_2H_5)_2$	A	
6.139	$CH_2CH(C_2H_5)_2$	B	
6.140	$CH_2CH(C_2H_5)_2$	A/B	
6.141	$CH_2CH(CH_3)_2$	A	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
6.142	$CH_2CH(CH_3)_2$	B	m/e: 784 (M^+, $C_{45}H_{72}O_9Si$)
6.143	$CH_2CH(CH_3)_2$	A/B	
6.144	$CH_2C(CH_3)=CH_2$	A	
6.145	$CH_2C(CH_3)=CH_2$	B	
6.146	$CH_2C(CH_3)=CH_2$	A/B	
6.147	CH_2-1-Methylcyclopropyl	A	
6.148	CH_2-1-Methylcyclopropyl	B	
6.149	CH_2-1-Methylcyclopropyl	A/B	

and the corresponding compounds 7.1 to 7.149 in which X, R_1 and R_3 have the meanings given for compounds 6.1 to 6.149 in Table 6, and R_2 represents isopropyl; and also the corresponding compounds 8.1 to 8.149 in which X, R_1 and R_3 have the meanings given for compounds 6.1 to 6.149 in Table 6, and R_2 represents sec.-butyl.

Formulation examples for active ingredients of formula I
(throughout, percentages are by weight)

Wettable powders	a)	b)	c)
active ingredient from the Tables	25 %	50 %	75 %
sodium lignosulphonate	5 %	5 %	-
sodium laurylsulphate	3 %	-	5 %
sodium diisobutylnaphthalene-sulphonate	-	6 %	10 %
octylphenol polyethylene glycol ether (7-8 moles of ethylene oxide)	-	2 %	-
highly dispersed silicic acid	5 %	10 %	10 %
kaolin	62 %	27 %	-

The active ingredient is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording wettable powders which can be diluted with water to give suspensions of any desired concentration.

Emulsifiable concentrate	
active ingredient from the Tables	10 %
octylphenol polyethylene glycol ether (4-5 moles of ethylene oxide)	3 %
calcium dodecylbenzenesulphonate	3 %
castor oil polyglycol ether (36 moles of ethylene oxide)	4 %
cyclohexanone	30 %
xylene mixture	50 %

Emulsions of any required concentration can be obtained from this concentrate by dilution with water.

Dusts	a)	b)
active ingredient from the Tables	5 %	8 %
talcum	95 %	-
kaolin	-	92 %

Ready for use dusts are obtained by mixing the active ingredient with the carrier and grinding the mixture in a suitable mill.

Extruder granulate

active ingredient from the Tables	10 %
sodium lignosulphonate	2 %
carboxymethylcellulose	1 %
kaolin	87 %

The active ingredient is mixed and ground with the adjuvants, and the mixture is moistened with water. The mixture is extruded and then dried in a stream of air.

Tablets or boli

I	an active ingredient from the Tables	33.0 %
	methyl cellulose	0.80 %
	highly dispersed silicic acid	0.80 %
	maize starch	8.40 %

The methyl cellulose is stirred in water and allowed to swell; the silicic acid is then stirred in to give a homogeneous suspension. The active ingredient and the maize starch are mixed and the aqueous suspension is added to this mixture, which is kneaded to a paste. This paste is granulated through a sieve (12M mesh width) and the granulate is then dried.

II	crystalline lactose	22.50 %
	maize starch	17.00 %
	microcrystalline cellulose	16.50 %
	magnesium stearate	1.00 %

All four adjuvants are thoroughly mixed.

Phases I and II are mixed and compressed to form tablets or boli.

Injectable formulations

A. Oily vehicle (slow release)

an active ingredient from the Tables	0.1-1.0 g
groundnut oil	ad 100 ml
an active ingredient from the Tables	0.1-1.0 g
sesame oil	ad 100 ml

Preparation: The active ingredient is dissolved in a portion of the oil while stirring and, if necessary, while heating gently; after cooling the solution is made up to the required volume and sterile-filtered through a suitable 0.22 µm membrane filter.

B. Water-miscible solvent (medium rate of release)

an active ingredient from the Tables	0.1-1.0 g
4-hydroxymethyl-1,3-dioxolan (glycerol formal)	40 g
1,2-propanediol	ad 100 ml
an active ingredient from the Tables	0.1-1.0 g
glycerol dimethyl ketal	40 g
1,2-propanediol	100 ml

Preparation: The active ingredient is dissolved in a portion of the solvent while stirring and the solution is made up to the required volume and sterile-filtered through a suitable 0.22 µm membrane filter.

C. Aqueous solubilisate (rapid release)

an active ingredient from the Tables	0.1-1.0 g
polyethoxylated castor oil (40 ethylene oxide units)*	10 g
1,2-propanediol	20 g
benzyl alcohol	1 g
aqua ad. inject.	ad 100 ml

*Commercially available under the name CREMOPHOR® EL (BASF AG);

an active ingredient from the Tables	0.1-1.0 g
polyethoxylated sorbitan monooleate (20 ethylene oxide units)**	8 g
4-hydroxymethyl-1,3-dioxolan (glycerol formal)	20 g
benzyl alcohol	1 g
aqua ad. inject.	ad 100 ml

** Commercially available under the name TWEEN® 80 (ICI);

Preparation: The active ingredient is dissolved in the solvents and the surfactant and made up to the required volume with water. Sterile-filtration through a suitable membrane filter of 0.22 µm pore diameter.

The aqueous systems can be used advantageously also for oral and/or intraruminal administration.

If the active ingredients of formula I or compositions containing them are used for controlling endoparasitic nematodes, cestodes and trematodes in domestic animals and productive livestock, for example cattle, sheep, goats, cats and dogs, they can be administered to the animals in both single and repeated doses, and depending upon the species of animal, the individual doses are preferably from 0.1 to 10 mg/kg of body weight. A better action is often achieved by protracted administration, or lower total doses may also suffice. The active ingredient, or compositions containing it, can also be added to feeds or drinks. The ready-prepared feed contains the active ingredient combinations preferably in a concentration of from 0.005 to 0.1 % by weight. The compositions can be administered to the animals perorally in the form of solutions, emulsions, suspensions, powders, tablets, boli or capsules. If the physical and toxicological properties of solutions or emulsions permit it, the compounds of formula I, or compositions containing them, can also be administered to the animals, for example, by subcutaneous injection or

intraruminally, or can be applied to the bodies of the animals by the pour-on method. Administration of the active ingredient to animals by means of salt licks or molasses blocks is also possible.

Biological examples

B-1. Action against L_1 larvae of Lucilia sericata

1 ml of an aqueous suspension of test compound is mixed with 3 ml of a special larval culture medium at about 50°C such that a homogeneous composition containing 250 ppm or 125 ppm of active ingredient is obtained. About 30 Lucilia sericata larvae (L_1) are put into each test tube sample. A mortality count is made after 4 days. The compounds of formula I, such as, for example, Nos 3.2, 3.6, 3.7, 3.10, 3.34 and 3.38, achieved 100 % action at 125 ppm.

B-2. Aaricidal action against Boophilus microplus (Biarra strain)

Adhesive tape is so applied horizontally across a PVC plate that 10 female Boophilus microplus ticks (Biarra strain), fully replete with blood, can be affixed thereto, by their backs, side by side in a row. Each tick is injected from an injection needle with 1 µl of a liquid which represents a 1:1 mixture of polyethylene glycol and acetone, in which mixture a specific amount of active ingredient of 1.0 µg per tick is dissolved. Control ticks are injected with liquid that does not contain the active ingredient. After this treatment, the ticks are kept in an insectarium under normal conditions at about 28°C and 80 % relative humidity until oviposition has taken place and the larvae have hatched from the eggs of the control ticks.

Compounds of formula I, such as, for example, those of the Preparation Examples, at this concentration have the effect that even after 30 days 9 out of 10 female ticks (= 90 %) lay eggs from which larvae are unable to hatch.

B-3. Trial with sheep infected with nematodes
(Haemonchus contortus and Trichostrongylus colubri formis)

The test compound is administered in the form of a suspension with a stomach probe or by intraruminal injection to sheep which have been artificially infected with Haemonchus contortus and Trichostrongylus colubriformis. 1 to 3 animals are used for each dose. Each sheep is treated only once with a single dose of 1 mg or 0.2 mg/kg of body weight. Evaluation is made by comparing the number of worm eggs excreted in the faeces of the sheep before and after treatment. Sheep injected simultaneously and in the same manner but untreated are used as controls. In this test, compounds of formula I, such as, for example, those of the Preparation Examples, exhibit a good action at a dose of 0.2 mg/kg, that is to say in comparison with untreated and infected control groups, the treated sheep exhibit no nematode infestation (= complete reduction of the number of worm eggs in the faeces).

B-4. Larvicidal action against Aedes aegypti

A 0,1 % solution of the test compound in acetone is pipetted onto the surface of 150 ml of water in beakers in amounts sufficient to give concentrations of 10 ppm, 3,3 ppm and 1.6 ppm. After the acetone has evaporated, about 30 to 40 three day-old Aedes larvae are put into each beaker. Mortality counts are made after 1, 2 and 5 days.

In this test, compounds of formula I, such as, for example, those of the Preparation Examples, achieved complete kill of all larvae after 1 day at a concentration of 1.6 ppm.

B-5. Milbicidal action against Dermanyssus gallinae

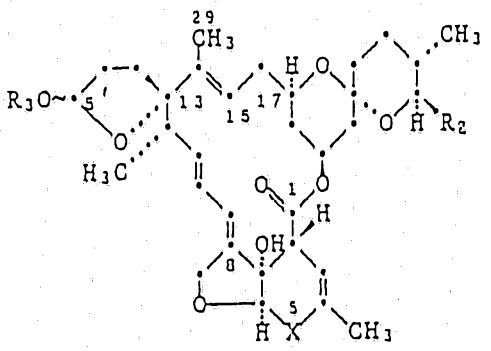
2 to 3 ml of a test solution (100, 10, 1 and 0.1 ppm of test compound) are put into a glass container which is open at the top, and about 200 mites in different stages of development are put into the container. The glass container is then sealed with cotton wool and shaken uniformly for 10 minutes until the mites are completely wetted. The container is then inverted until excess test solution has been absorbed by the cotton

wool. The container is again inverted and the treated mites are kept under observation for 3 days under laboratory conditions to evaluate the effectiveness of the test compounds, mortality being the criterion for effectiveness.

Compounds of formula I, such as, for example, those of the Preparation Examples, are 100 % effective at 100 ppm.

The claims defining the invention are as follows:

1. A compound of formula I



(I)

in which

X represents one of the groups $-CH(OR_1)-$, $-C(=O)-$ or $-C(=N-OH)-$;

R_1 represents hydrogen or a OH-protecting group;

R_2 represents methyl, ethyl, isopropyl or sec.-butyl or the group $-C(CH_3)=CH-A$ in which A represents methyl, ethyl or isopropyl; and

R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxy-alkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, C_1-C_3-alkyl-substituted C_3-C_7-cycloalkyl, hydroxy, benzyloxy, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen, and C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen, and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; 1-adamantylmethyl; menthyl; carveyl; phenyl, benzyl; naphthyl; a radical selected from the group consisting of phenyl,

benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to

three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

2. A compound of formula I according to claim 1, in which
X represents one of the groups -CH(OR_1)- and -C(=N-OH)-,
R_1 represents hydrogen or a OH-protecting group;
R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and
R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; an ethyl group substituted by benzyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

3. A compound of formula I according to claim 2, in which X represents $-CH(OR_1)-$; R_1 represents hydrogen or a OH-protecting group; and R_2 and R_3 have the meaning given in claim 2.

4. A compound of formula I according to claim 1, in which
X represents $-CH(OR_1)-$;
R_1 represents hydrogen or a OH-protecting group;
R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and
R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

5. A compound of formula I according to claim 4, in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, R_4-C(O)- or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical

selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_6-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents hydrogen, C_1-C_5-alkyl; C_1-C_5-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_3-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine and methyl; C_2-C_6-alkenyl; C_2-C_6-alkynyl; a radical selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl, which radical is substituted by fluorine, chlorine, bromine, C_1-C_3-alkoxy or by C_1-C_6-acyloxy; phenyl; benzyl; α-naphthyl; β-naphthyl; a radical selected from the group consisting of phenyl, benzyl, α-naphthyl and β-naphthyl, which radical is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, methoxy, CF_3, CF_3O, CH_3S, nitro and cyano; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, ethyl, CF_3, CH_3O, CF_3O, CH_3S, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

6. A compound of formula I according to claim 5, in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, R_4-C(O)- or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, inde-

pendently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents C_1-C_5-alkyl, or C_1-C_5-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_3-alkylthio, C_3-C_7-cycloalkyl, hydroxy and C_1-C_6-acyl, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy.

7. A compound of formula I according to claim 5, in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, R_4-C(O)- or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine and methyl; C_2-C_6-alkenyl; C_2-C_6-alkynyl; a radical selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl, which radical is substituted by fluorine, chlorine, bromine, C_1-C_3-alkoxy or by C_1-C_6-acyloxy; phenyl; benzyl; α-naphthyl; β-naphthyl; a radical selected from the group consisting of phenyl, benzyl, α-naphthyl and β-naphthyl, which radical is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, methoxy, CF_3, CF_3O, CH_3S, nitro and cyano; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, ethyl, CF_3, CH_3O, CF_3O, CH_3S, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

8. A compound of formula I according to claim 5, in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, $R_4-C(O)-$ or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents phenyl, benzyl, α-naphthyl, β-naphthyl or a radical selected from the group consisting of phenyl, benzyl, α-naphthyl and β-naphthyl, which radical is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, methoxy, CF_3, CF_3O, CH_3S, nitro and cyano.

9. A compound of formula I according to claim 5, in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, $R_4-C(O)-$ or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C_1-C_4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of fluorine, chlorine, bromine, methyl, ethyl, CF_3, CH_3O, CF_3O, CH_3S, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

10. A compound of formula I according to claim 9, in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen, $R_4-C(O)-$ or $-Si(R_5)(R_6)(R_7)$; wherein R_4 represents C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl or a radical selected from the group consisting of phenyl and benzyl, which radical is

unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, cyano and nitro, and R_5, R_6 and R_7, independently of one another, represent C1-C4-alkyl, benzyl or phenyl; R_2 represents methyl, ethyl, isopropyl or sec.-butyl; and R_3 represents a ~~unsaturated or preferably saturated~~ four-membered heterocyclic radical having a hetero atom selected from the group consisting of oxygen, nitrogen and sulphur, or represents furan, thiophene, pyrrole, isoxazole, isothiazole, furazan, imidazole, 1,2,4-triazole, 1,2,3-triazole, pyrazole, pyrroline, oxazole, thiazole, thiadiazoles, pyrazoline, thiazoline, pyrazolidine, pyrrolidine, oxazolidine, thiazolidine, oxadiazole, imidazoline, imidazolidine, pyrazolidine, tetrahydrofuran, pyridine, pyridazine, pyrimidine, pyrazine, thiazine, thiadiazines, pyrans, piperidine, piperazine, morpholine, perhydrothiazine or dioxan, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_4-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

11. A compound of formula I according to claim 1, in which X represents $-CH(OR_1)-$ and R_1 represents hydrogen; R_2 represents ethyl; and R_3 represents C_4-C_5-alkyl, C_4-C_6-cycloalkyl, C_4-C_6-cycloalkyl bonded via methyl, or phenyl, benzyl or α-methylbenzyl.

12. A compound of formula I according to claim 1 in which R_2 represents methyl or ethyl and X and R_3 have the meanings given in claim 1.

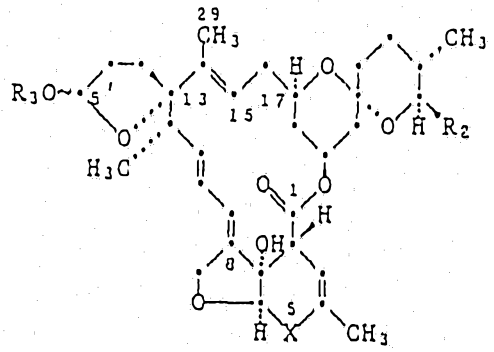
13. A compound of formula I according to claim 12, in which R_2 represents ethyl.

14. A compound of formula I according to claim 4, selected from the group:
milbemycin A_4-13-spiro-2'-[5'-(2"-ethoxyethoxy)-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-(2",2"-dimethylpropoxy)-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-cyclohexyloxytetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-benzyloxytetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-{2"-(2"'-(methoxyethoxy)-ethoxy}-tetrahydrofuran],

milbemycin A_4-13-spiro-2'-[5'-{2"-(2"'-hydroxymethoxy)-ethoxy)-ethoxy}-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-{2"-(2""-(chloroacetoxy)-ethoxy)-ethoxy)-ethoxy}-tetrahydrofuran],
milbemycin A_4-13-spiro-2'-[5'-methoxytetrahydrofuran], and
milbemycin A_4-13-spiro-2'-[5'-(2"-hydroxyethoxy)-tetrahydrofuran].

15. A compound of formula I according to claim 11, selected from the group: milbemycin A_4-13-spiro-2'-[5'-(2"-methylbutoxy)-tetrahydrofuran] and milbemycin A_4-13-spiro-2'-[5'-(1"-methylpropoxy)-tetrahydrofuran].

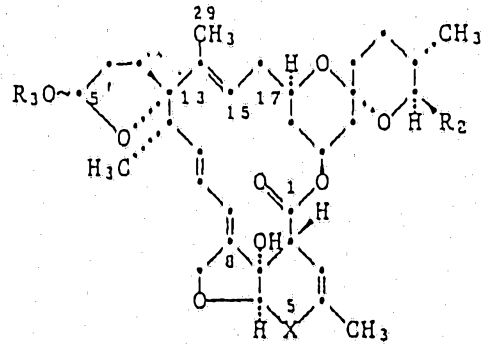
16. A process for the preparation of a compound of formula I



(I)

in which
X represents one of the groups $-CH(OR_1)-$, $-C(=O)-$ or $-C(=N-OH)-$;
R_1 represents hydrogen or a OH-protecting group;
R_2 represents methyl, ethyl, isopropyl or sec.-butyl or the group $-C(CH_3)=CH-A$ in which A represents methyl, ethyl or isopropyl; and
R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, C_1-C_3-alkyl-substituted C_3-C_7-cycloalkyl, hydroxy, benzyloxy, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen, and C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl derived from a straight-chain or branched alkanoic acid which is unsubstituted or substituted by halogen, or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one

substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy wherein the acyl moiety has the meaning given before; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring, characterised in that a compound of formula II

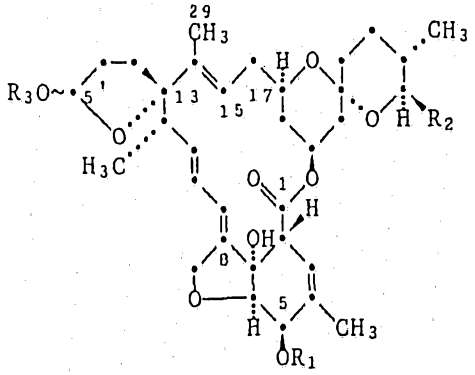


(II),

in which R_1 and R_2 have the definitions given under formula I and R_{10} and R_{11}, independently of one another, represent C_1-C_6-alkyl or together form a C_2-C_{10}-alkylene bridge, is reacted in the presence of an acid catalyst in an inert solvent with a compound of formula III

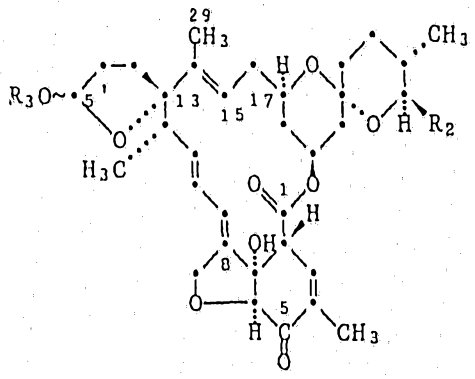
$$R_3OH \qquad \text{(III)},$$

in which R_3 has the definition given under formula I, and, if desired, the resulting compound of formula Ic



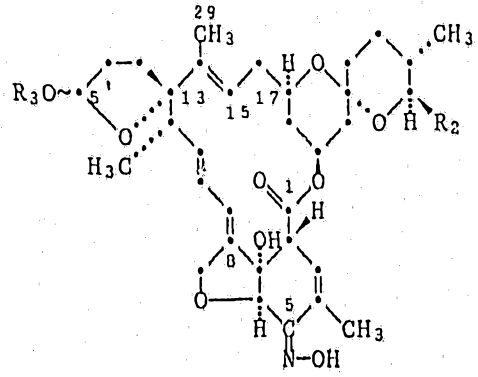
(Ic),

in which R_1, R_2 and R_3 have the meanings given for formula I, is converted by mild oxidation into a corresponding compound of formula Ib



(Ib),

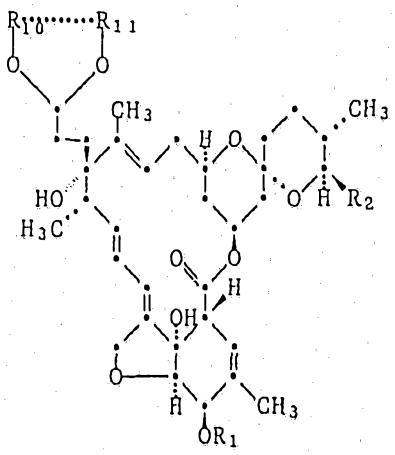
in which R_2 and R_3 have the meanings given for formula Ic, and, if desired, the compound of formula Ib is converted by reaction with hydroxylamine or a salt thereof into the corresponding compound of formula Ia



(Ia)

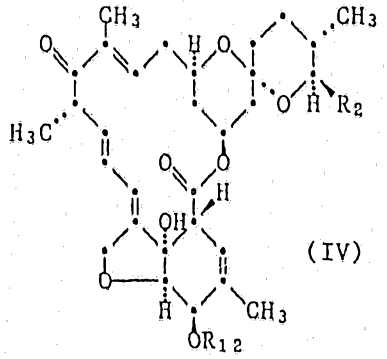
in which R_2 and R_3 have the meanings given for formula Ib.

17. A process for the preparation of a compound of formula II



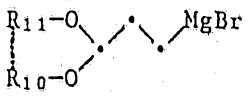
(II)

in which R_1 and R_2 have the definitions given under formula I and R_{10} and R_{11}, independently of one another, represent C_1-C_6-alkyl or together form a C_2-C_{10}-alkylene bridge, characterised in that a compound of formula IV



(IV)

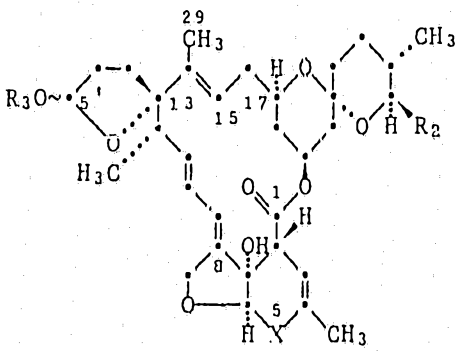
in which R_2 has the definition given under formula I and R_{12} represents hydrogen or a silyl group, is reacted in an inert solvent with a Grignard reagent of formula V



(V)

in which R_{10} and R_{11}, independently of one another, represent C_1-C_6-alkyl or together represent a C_2-C_{10}-alkylene bridge.

18. A composition for controlling ecto- and endo-parasites in productive livestock or for controlling pest insects, characterised in that, in addition to customary carriers and dispersing agents, it contains a compound of formula I



(I)

in which

X represents one of the groups $-CH(OR_1)-$, $-C(=O)-$ or $-C(=N-OH)-$;

R_1 represents hydrogen or a OH-protecting group;

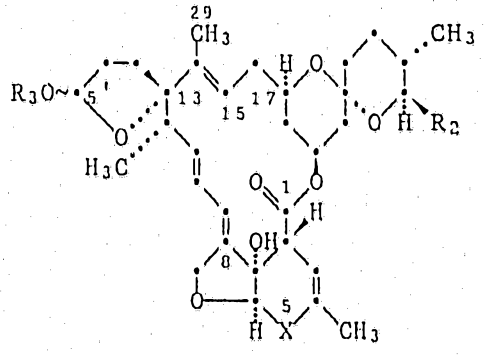
R_2 represents methyl, ethyl, isopropyl or sec.-butyl or the group $-C(CH_3)=CH-A$ in which A represents methyl, ethyl or isopropyl; and

R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, C_1-C_3-alkyl-substituted C_3-C_7-cycloalkyl, hydroxy, benzyloxy, C_1-C_6-acyl and C_1-C_6-acyloxy, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro

and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring.

19. A composition according to claim 18, characterised in that it contains as active ingredient a compound of formula I according to claim 11.

20. A method of controlling parasites in animals or of controlling insect pests, characterised in that a parasiticidally or insecticidally effective amount of a compound of formula I



(I)

in which

X represents one of the groups $-CH(OR_1)-$, $-C(=O)-$ or $-C(=N-OH)-$;

R_1 represents hydrogen or a OH-protecting group;

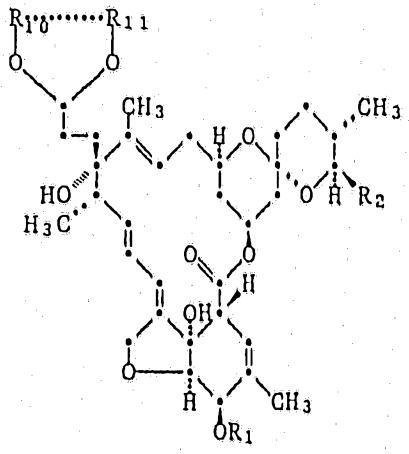
R_2 represents methyl, ethyl, isopropyl or sec.-butyl or the group $-C(CH_3)=CH-A$ in which A represents methyl, ethyl or isopropyl; and

R_3 represents hydrogen; C_1-C_{10}-alkyl; C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen, C_1-C_6-alkoxy, C_2-C_6-alkoxyalkoxy, C_3-C_9-alkoxyalkoxyalkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, C_1-C_3-alkyl-substituted C_3-C_7-cycloalkyl, hydroxy, benzyloxy, C_1-C_6-acyl and C_1-C_6-acyloxy, it being possible for each of the above-mentioned radicals representing or containing an alkoxy group to be terminally substituted at a terminal alkoxy group by hydroxy, halogen, C_1-C_6-acyl or by C_1-C_6-acyloxy; C_3-C_7-cycloalkyl; C_3-C_7-cycloalkyl substituted by at least one substituent selected from the group consisting of halogen and C_1-C_3-alkyl; C_3-C_7-cycloalkenyl; C_2-C_{10}-alkenyl; C_2-C_{10}-alkynyl; a radical selected from the group consisting of C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, which radical is substituted by

halogen, C_1-C_6-alkoxy or by C_1-C_6-acyloxy; 1-adamantylmethyl; menthyl; carveyl; phenyl; benzyl; naphthyl; a radical selected from the group consisting of phenyl, benzyl and naphthyl, which radical is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano; benzyl substituted by a phenoxy group; or a four- to six-membered heterocyclic radical that has from one to three hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen and that is unsubstituted or is substituted by at least one substituent selected from the group consisting of halogen, C_1-C_3-alkyl, C_1-C_3-haloalkyl, C_1-C_3-alkoxy, C_1-C_3-haloalkoxy, C_1-C_3-alkylthio, nitro and cyano, it being possible for the said heterocyclic radical also to be bonded via a C_1-C_6-alkylene bridge to the oxygen atom in the 5'-position of the tetrahydrofuran ring,
is applied to the parasite, the insect pest or to the locus thereof.

21. A process according to claim 20, characterised in that the parasites are nematodes.

22. A compound of formula II



(II)

in which R_1 and R_2 have the definitions given under formula I and R_{10} and R_{11}, independently of one another, represent C_1-C_6-alkyl or together represent a C_2-C_{10}-alkylene bridge.

FQ 7.5/SES/sm*

23. A 13-spiro-2'-[tetrahydrofuran]-milbemycin derivative, substantially as hereinbefore described with reference to any one of Examples H1 to H23, 1.1 to 1.149, 2.1 to 2.149, 3.1 to 3.149, 4.1 to 4.149, 5.1 to 5.149, 6.1 to 6.149, 7.1 to 7.149 or 8.1 to 8.149.

24. A process for preparing a 13-spiro-2'-[tetrahydrofuran]-milbemycin derivative, which process is substantially as herein described with reference to any one of Examples H1 to H23.

25. A 13-spiro-2'-[tetrahydrofuran]-milbemycin derivative, whenever prepared by the process of claim 16 or claim 24.

26. A composition for controlling ecto- and endo-parasites in productive livestock or for controlling pest insects comprising a compound as defined in claim 23 together with a parasiticidally or insecticidally acceptable carrier, diluent, excipient and/or adjuvant.

27. A composition for controlling ecto- and endo-parasites in productive livestock or for controlling plant insects, substantially as hereinbefore described with reference to any one of the Formulation Examples.

28. A method of controlling parasites in animals or of controlling insect pests wherein an parasiticidally or insecticidally effective amount of a compound as defined in claim 23 or a composition as defined in claim 24 or claim 25 is applied to the parasite, the insect pest or to the locus thereof.

29. A 13α-hydroxy-13β-substituted milbemycin derivative as defined in claim 22, substantially as hereinbefore described with reference to any one of Examples A1 to A4.

30. A process for preparing a 13α-hydroxy-13β-substituted milbemycin derivative as defined in claim 22, substantially as hereinbefore described with reference to any one of Examples A1 to A4.

31. A 13α-hydroxy-13β-substituted milbemycin derivative whenever prepared by the process of claim 17 or 30.

DATED this NINETEENTH day of JUNE 1991
Ciba-Geigy AG

Patent Attorneys for the Applicant
SPRUSON & FERGUSON

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