

(22) Date de dépôt/Filing Date: 1990/09/07

(41) Mise à la disp. pub./Open to Public Insp.: 1991/03/12

(45) Date de délivrance/Issue Date: 2002/08/20

(30) **Priorité/Priority:** 1989/09/11 (07/405,808) US

(51) Cl.Int.⁵/Int.Cl.⁵ C07D 493/22, A01N 43/90, A61K 31/70

(72) Inventeurs/Inventors:

Buckwalter, Brian Lee, US;
Tseng, Shin-Shyong, US

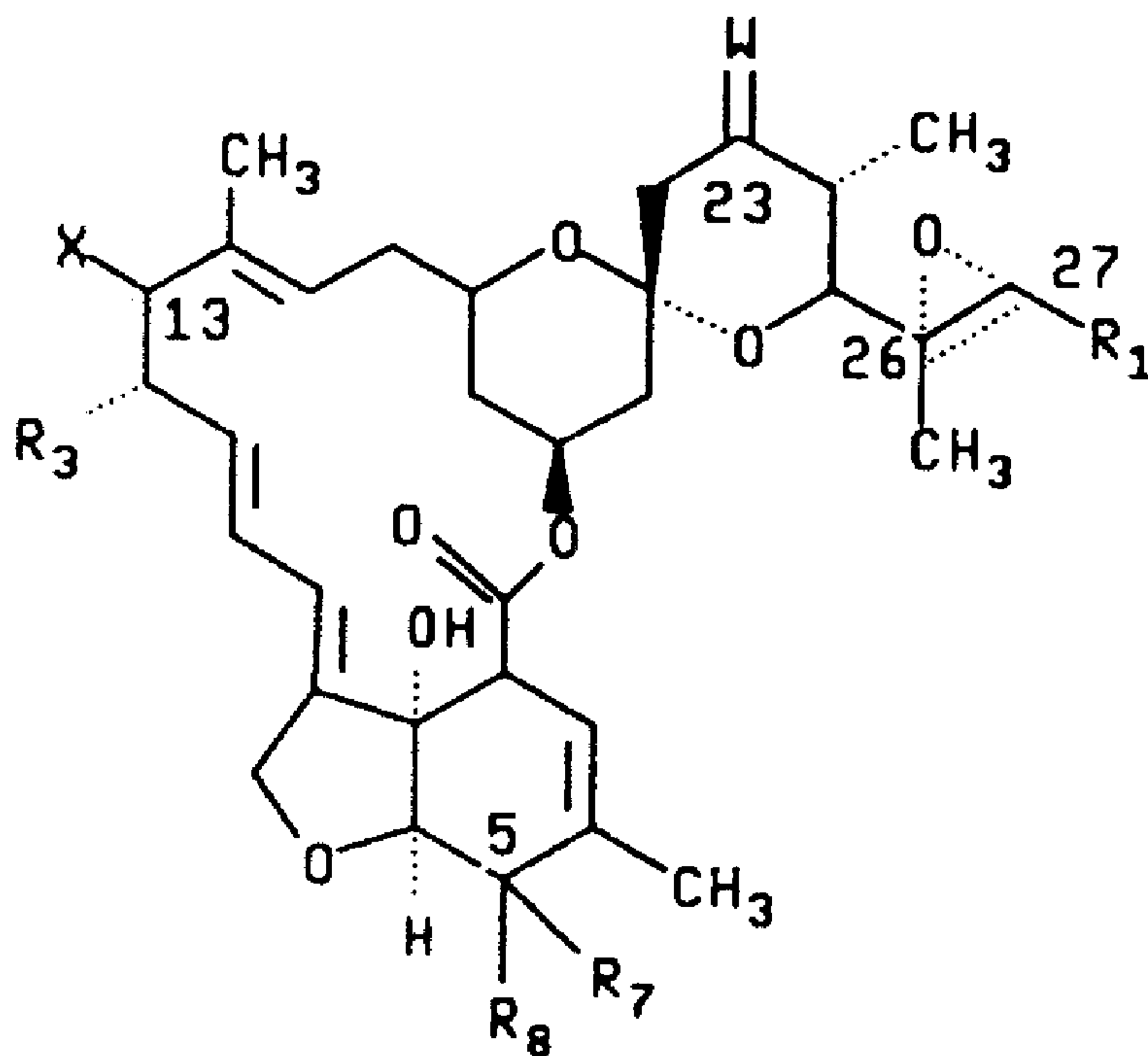
(73) Propriétaire/Owner:

AMERICAN CYANAMID COMPANY, US

(74) **Agent:** SMART & BIGGAR

(54) Titre : DERIVES 13-ALKYL-23-IMINO DE COMPOSES LL-F28249 ET LEUR UTILISATION COMME INSECTICIDES ENDO- ET ECTOPARASITICIDES, COMME ACARICIDES ET NEMATICIDES

(54) Title: 13-HALO-23-IMINO DERIVATIVES OF LL-F28249 COMPOUNDS AND THEIR USE AS ENDO- AND ECTOPARASITICIDAL INSECTICIDAL, ACARICIDAL AND NEMATOCIDAL AGENTS



(57) **Abrégé/Abstract:**

There are provided certain 13-halo-23-imino-LL-F28249 compounds which are useful for controlling endo- and ectoparasites, insects, acarids and nematodes.

2024825

13-HALO-23-IMINO DERIVATIVES OF LL-F28249 COMPOUNDS
AND THEIR USE AS ENDO- AND ECTOPARASITICIDAL,
INSECTICIDAL, ACARICIDAL AND NEMATOCIDAL AGENTS

ABSTRACT OF THE INVENTION

There are provided certain 13-halo-23-imino-LL-F28249 compounds which are useful for controlling endo- and ectoparasites, insects, acarids and nematodes.

61109-7797

- 1 -

5

10

13-HALO-23-IMINO DERIVATIVES OF LL-F28249 COMPOUNDS
AND THEIR USE AS ENDO- AND ECTOPARASITICIDAL,
INSECTICIDAL, ACARICIDAL AND NEMATOCIDAL AGENTS

15

The present invention relates to certain 13-halo-23-imino-LL-F28249 compounds and their use for controlling endo- and ectoparasitic infections in warm-blooded animals and controlling insect, acarid and nematode infestations in agricultural crops and controlling the housefly.

20

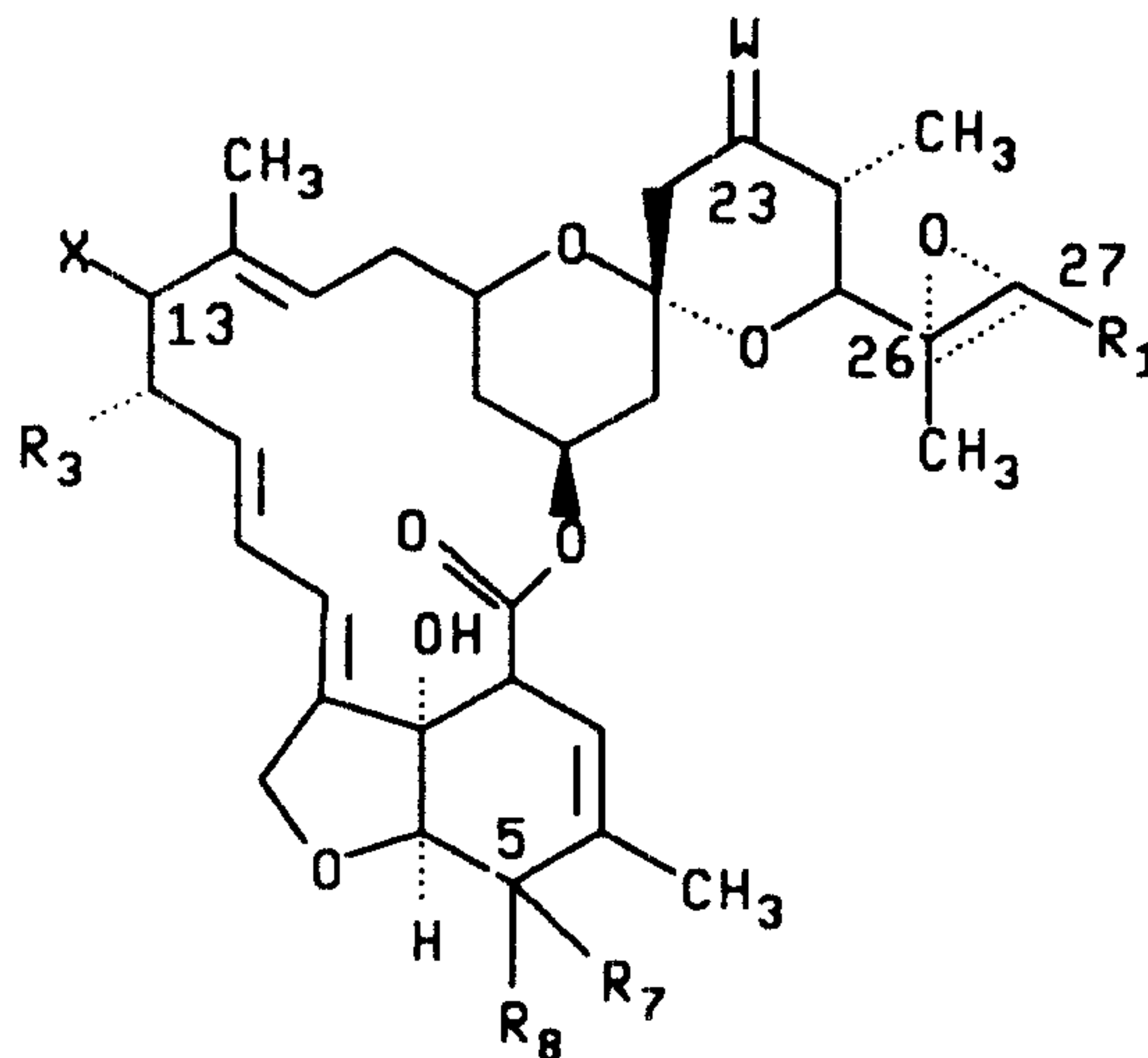
25

The designation LL-F28249 is used to describe compounds produced by the fermentation broth of Streptomyces cyaneogriseus, subspecies noncyanogenus, deposited in the NRRL collection under deposit accession number 15773. The morphological characteristics of said compounds and methods for the production thereof are described in United States Patent No. 5,106,994.

61109-7797

- 2 -

The compounds of the invention have the structural formula:



wherein

R_1 is methyl, ethyl or isopropyl;

R_7 is hydrogen and R_8 is OR_2 , or when taken together with the carbon atom to which they are attached R_7 and R_8 represent $C=O$;

R_2 is hydrogen, C_1-C_4 alkyl, or $C(=O)-R_4$;
 R_4 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, phenoxy, C_1-C_4 alkoxymethyl, phenoxymethyl, or phenyl optionally substituted with 1 nitro, 1-3 halogens, 1-3 C_1-C_4 alkyl, or 1-3 C_1-C_4 alkoxy;

R_3 is hydrogen, methyl or ethyl;

X is fluorine, bromine, chlorine or iodine;

W is oxygen or $N-Y$;

Y is OR_5 or NHR_6 ;

R_5 is C_1-C_4 alkyl or C_1-C_4 acyl; and

R_6 is C_1-C_4 acyl; and

the dotted triangular figure with oxygen at $C_{26}-C_{27}$

61109-7797

- 3 -

indicates that there is present
either a double bond or an epoxide.

A preferred group of 13-halo-23-imino-LL-F28249 compounds have the structural formula shown above wherein

R_1 is isopropyl;

R_7 is hydrogen and R_8 is OR_2 ;

R_2 is hydrogen, C_1-C_4 alkyl, or $C-R_4$;

R_4 is hydrogen, methyl, chloromethyl, dichloromethyl, trichloromethyl, or methoxymethyl;

R_3 is methyl;

X is fluorine;

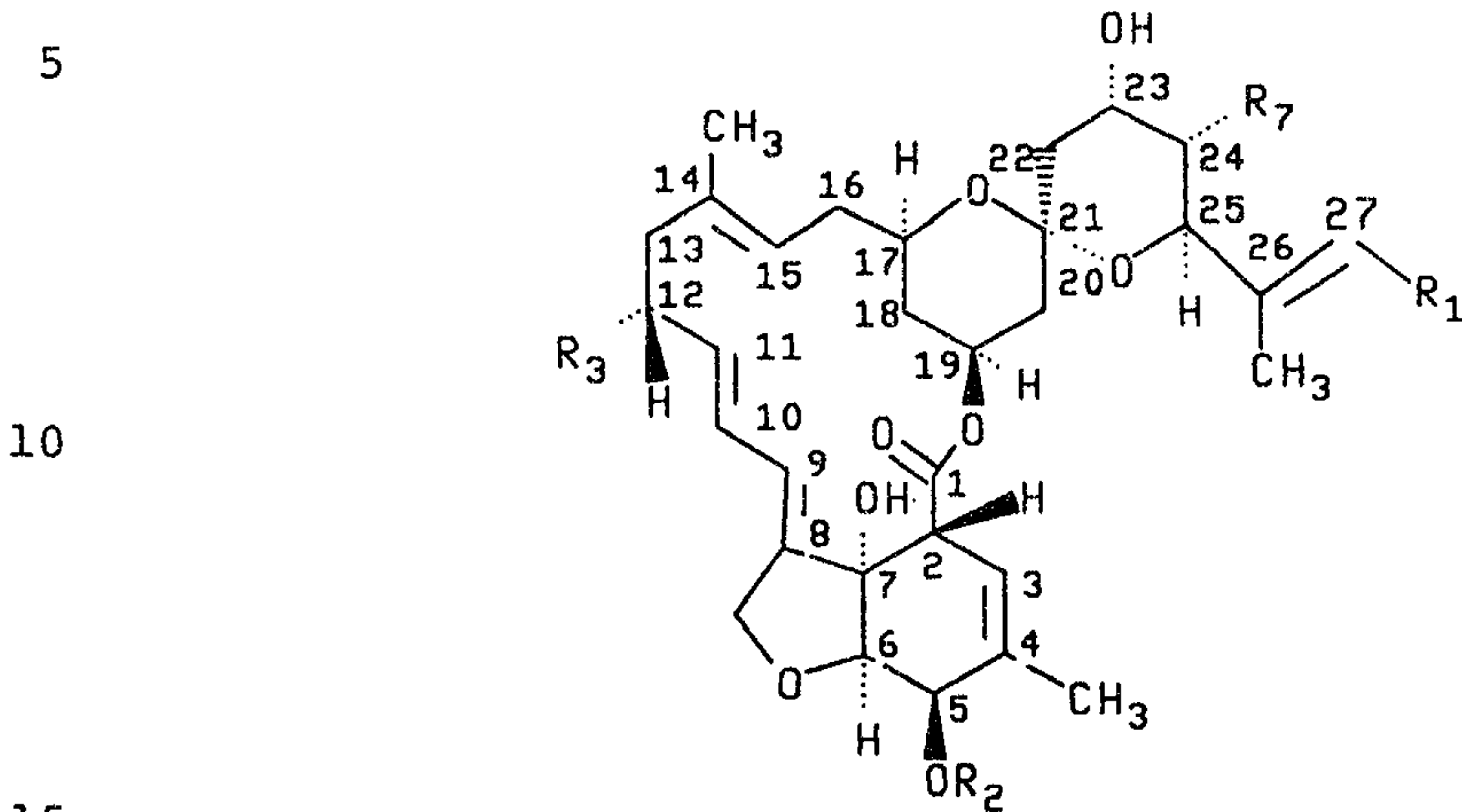
W is N-Y;

Y is OR_5 ; and

R_5 is C_1-C_4 alkyl.

The compounds of the invention are effective antiendoparasitic and antiectoparasitic agents and can be used to protect warm-blooded animals against infestations of the above-said pests. They may also be applied to a wide variety of agronomic crops and the surroundings in which said crops are grown or growing to protect said crops from the damage caused by insects, acarids and nematodes. They are highly effective for the control of the housefly when applied to the habitat, food source, or breeding ground of the housefly.

The LL-F28249 compounds are represented by the following structural formula:



20

Component	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	<u>R₇</u>
LL-F28249 α	CH(CH ₃) ₂	H	CH ₃	CH ₃
LL-F28249 β	CH ₃	H	CH ₃	CH ₃
LL-F28249 γ	CH ₃	CH ₃	CH ₃	CH ₃
LL-F28249 ϵ	CH(CH ₃) ₂	H	H	CH ₃
LL-F28249 ζ	CH ₂ CH ₃	H	CH ₃	CH ₃
LL-F28249 θ	CH(CH ₃) ₂	H	CH ₃	CH ₂ CH ₃
LL-F28249 ι	CH(CH ₃) ₂	H	CH ₂ CH ₃	CH ₃
LL-F28249 λ	CH(CH ₃) ₂	CH ₃	CH ₃	CH ₃

25

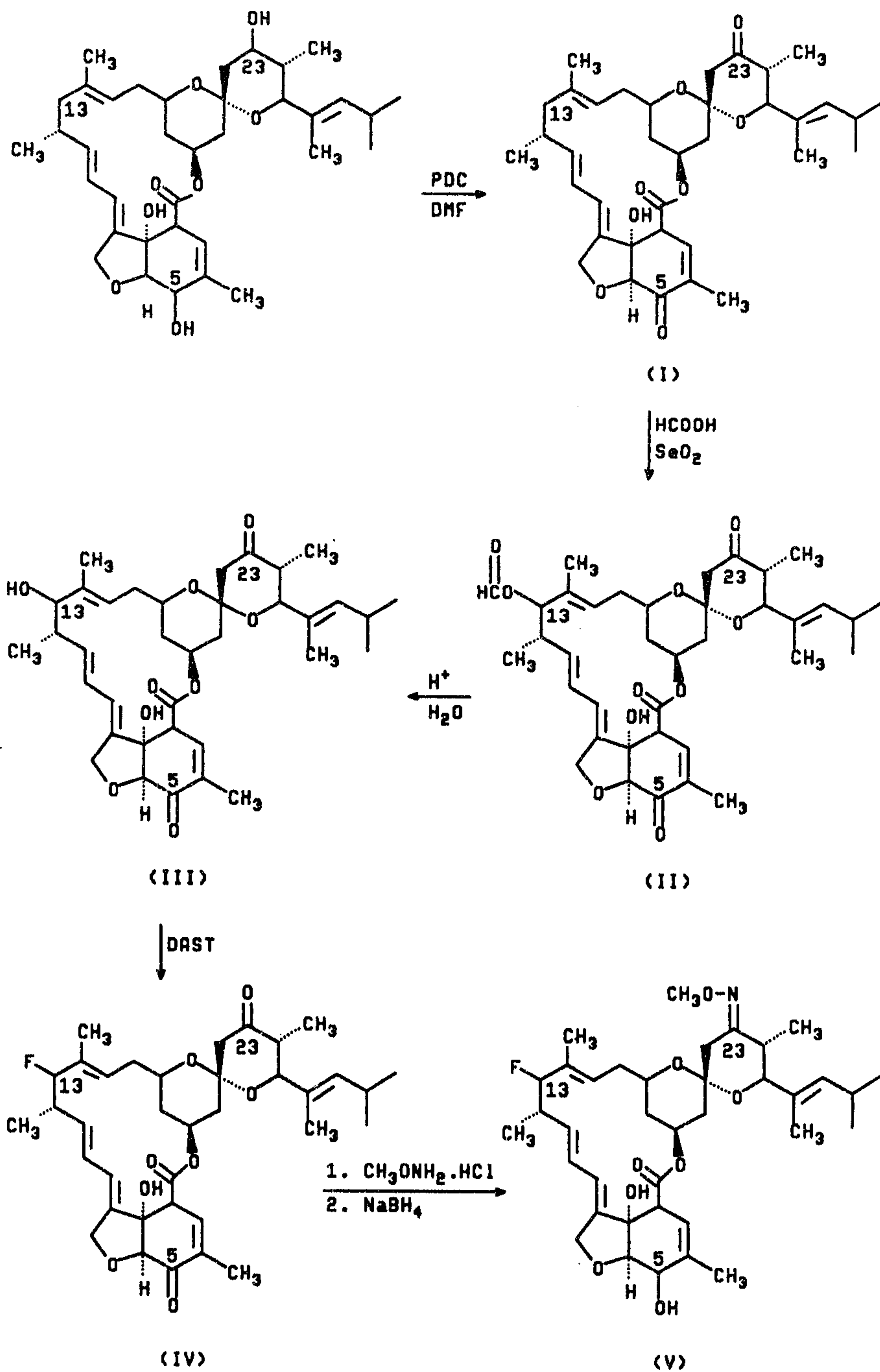
30

35

Surprisingly, it has been found that chemical modification at the 5, 13, 23, 26 and 27 positions of the LL-F28249 compounds shown above enhances the endo- and ectoparasiticidal, insecticidal, acaricidal and nematocidal activity of said compounds. More particularly, the 13-halo-23-imino derivatives of 5-hydroxy and 5-O-substituted-LL-F28249 and 26,27-epoxy-LL-F28249 compounds demonstrate potent endectocidal and insecticidal activity.

Functionalization at the 13 position of the above shown LL-F28249 compounds is achieved by oxidation of the 5 and 23 hydroxy groups with pyridinium dichromate in dimethylformamide to give the 5,23-dioxo-LL-F28249 compound (I) followed by reaction with selenium dioxide and formic acid to give the 13-(formyloxy)-5,23-dioxo-F28249 compound (II). The thus-obtained compound (II) is converted to the 13-hydroxy-5,23-dioxo-LL-F28249 compound (III) via acid hydrolysis and then reacted with diamino sulfur trifluoride (DAST) to give the 13-fluoro-5,23-dioxo-LL-F28249 compound (IV). Compound (IV) is reacted sequentially with methoxylamine hydrochloride and sodium borohydride to give the 13-fluoro-23-methoximino-LL-F28249 compound (VI). Using LL-F28249 α as the starting material, the above-described reaction sequence is illustrated in Flow Diagram I shown below.

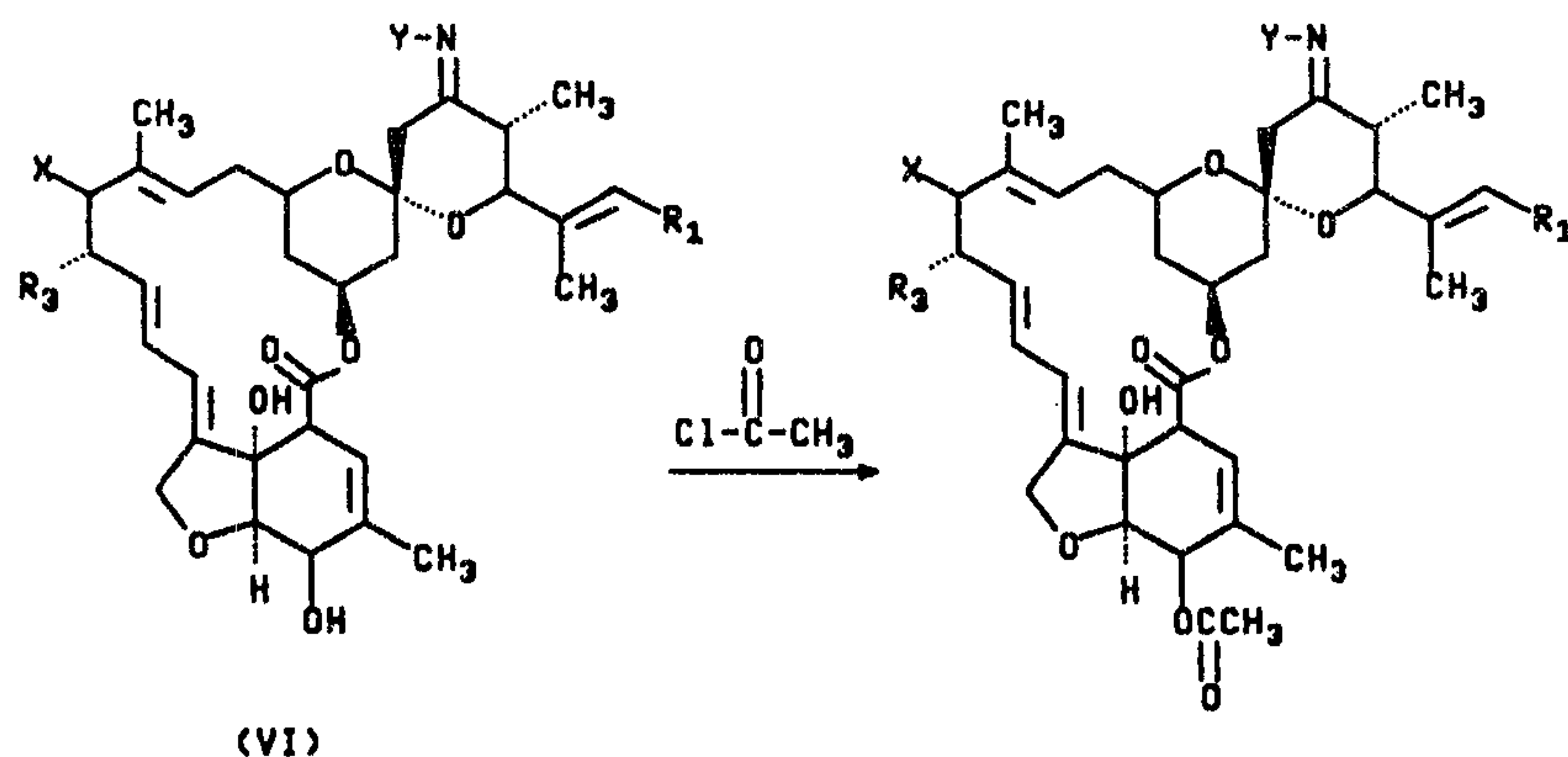
FLOW DIAGRAM I



Compound (III) is used as a common intermediate and reacted with halogenating reagents such as phosphorous tribromide and thionyl chloride to give the 13-bromo- or 13-chloro- or 13-iodo-5,23-dioxo-LL-F28249 compounds represented by compound (IV) wherein F is Br or Cl or I, and then reacted sequentially with an alkoxyamine, or hydroxylamine, and sodium borohydride to give the corresponding 13-halo-23-imino-LL-F28249 compounds represented by compound (V) wherein F is Br or Cl or I as shown in Flow Diagram I, above.

Derivatization of the 5-hydroxy moiety to give novel 5-alkoxy and 5-acyloxy-13-halo-23-imino-LL-F28249 compounds is achieved by reacting compound (VI) with an alkylating or acylating agent as illustrated in Flow Diagram II.

FLOW DIAGRAM II



R₁, R₃, X and Y are as described hereinabove.

Alternatively, compounds of the invention are prepared by reacting the LL-F28249 starting material with an acyl halide such as p-nitrobenzoylchloride followed by oxidation of the 23-hydroxy group and functionalization at the 13 carbon to give the intermediate compound (VII) as illustrated in Flow Diagram III.

FLOW DIAGRAM III

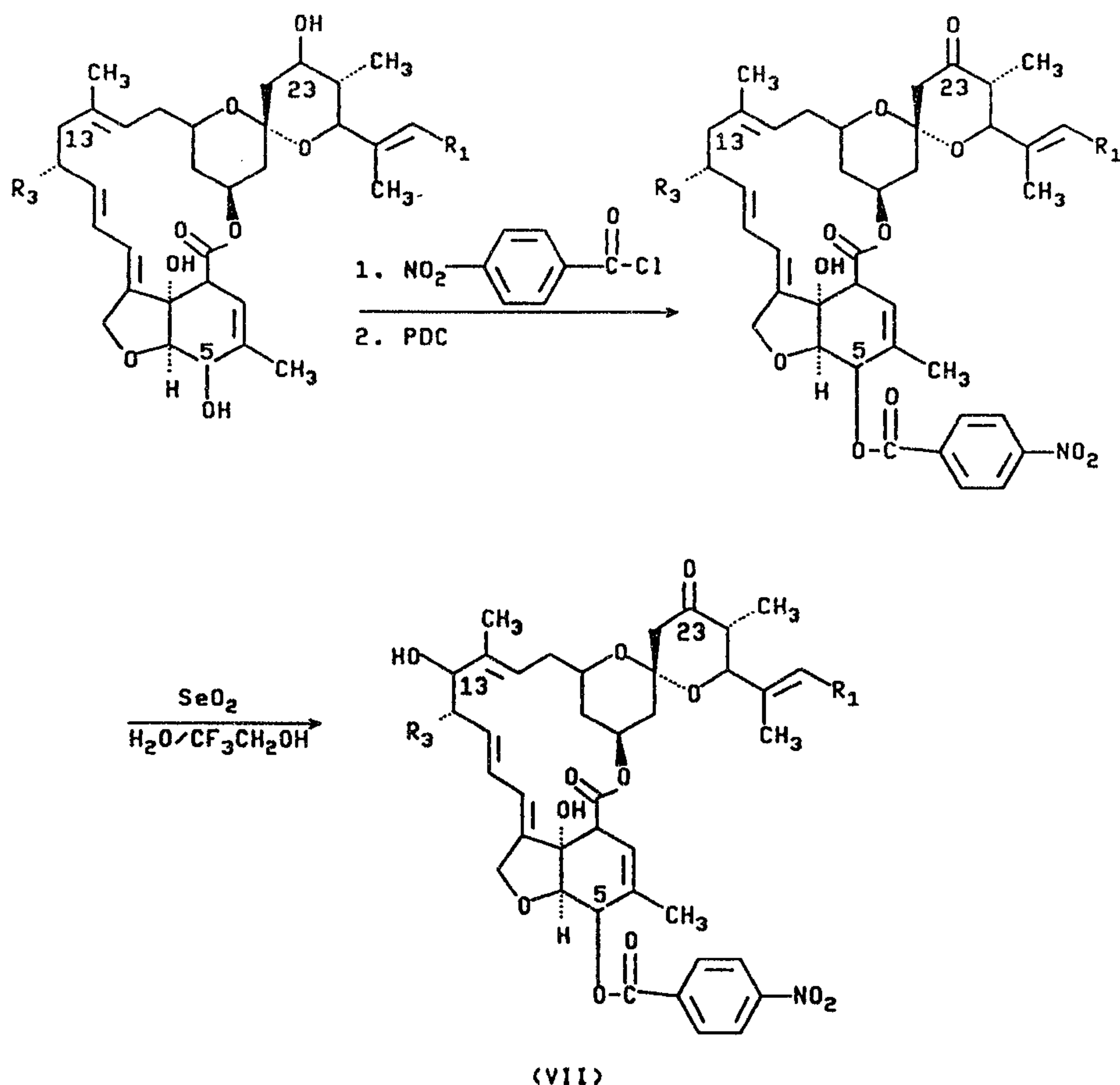
5

10

15

20

25

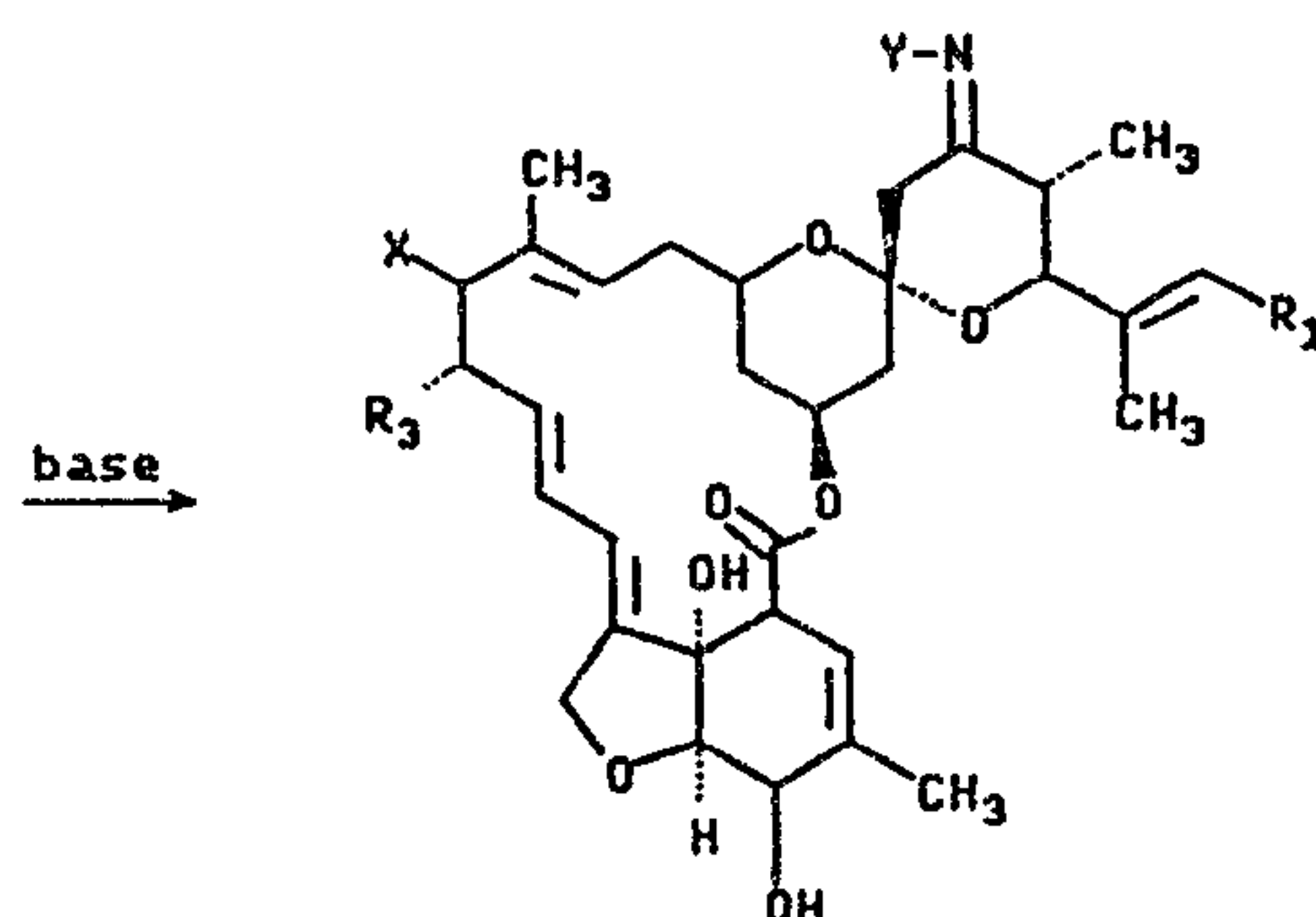
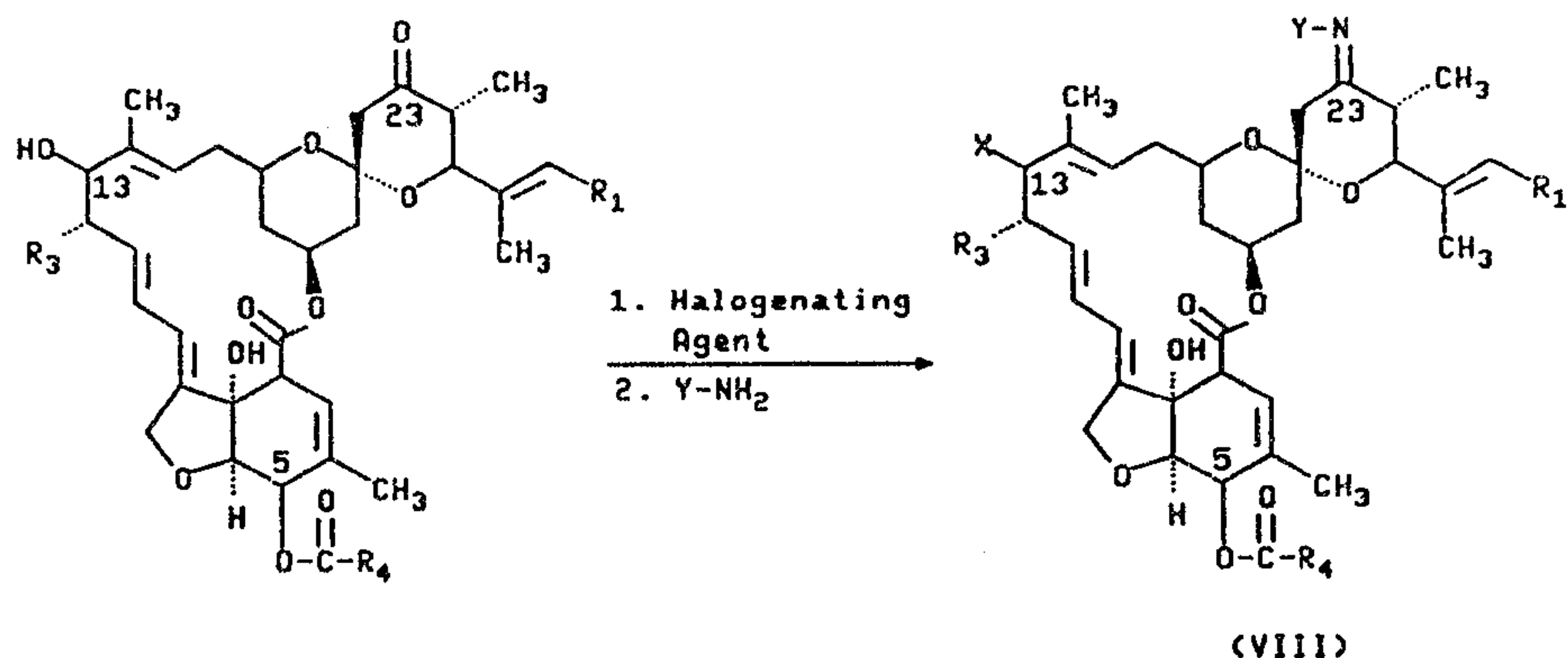


30

35

Compound (VII) is treated with an halogenating agent such as diamino sulfur trifluoride, thionyl chloride or phosphorous tribromide followed by reaction with an alkoxyl or hydroxylamine to give the desired 13-halo-23-imino-5-(acyloxy)-LL-F28249 compounds such as compound (VIII). Optionally, compound (VIII) is hydrolyzed in base to give the corresponding 13-halo-23-imino-LL-F28249 compounds. The reaction sequence is illustrated in Flow Diagram IV.

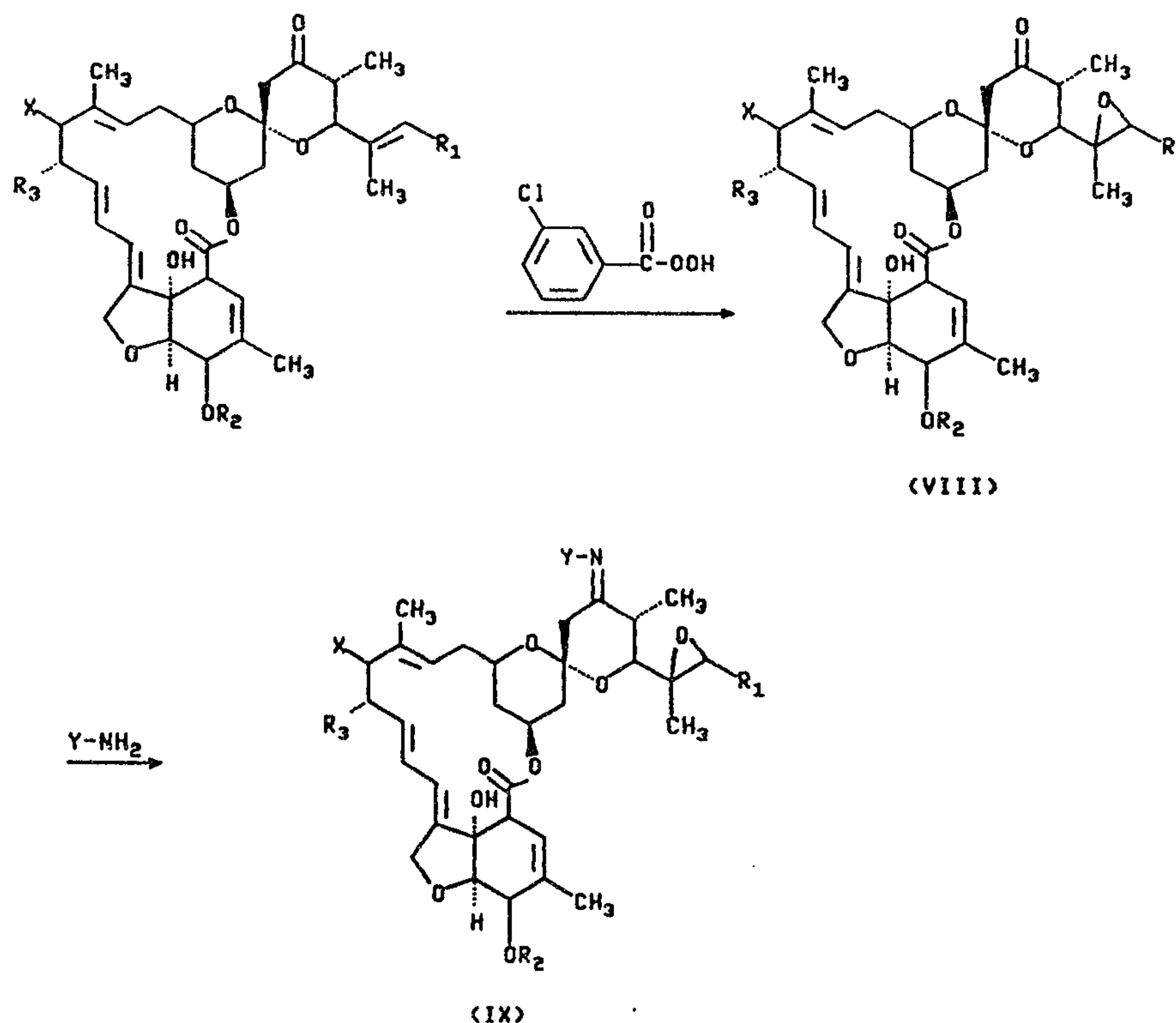
FLOW DIAGRAM IV



R₁, R₃, R₄, X and Y are as described hereinabove.

Advantageously, the 26,27 epoxide derivatives of 13-halo-23-imino-LL-F28249 compounds are prepared by reacting the 13-halo-23-oxo precursor with m-chloroperbenzoic acid followed by treatment of the 26,27 epoxide product with an alkoxyl, acyloxyl or hydroxyl-oxime to give the desired compounds (IX) as illustrated in Flow Diagram V.

FLOW DIAGRAM V



R_1 , R_2 , R_3 , X and Y are as described hereinabove.

Surprisingly, it has been found that the compounds of the invention are highly effective endo- and ectoparasiticial agents useful for treating warm-blooded animals. It has also been found that said compounds are excellent insecticidal, nematocidal and acaricidal agents useful for controlling said pests and protecting agronomic crops from damage caused by said pests.

For use in the treatment of warm-blooded animals such as cattle, sheep, swine, horses, dogs or

5 other mammals, the compounds of the invention may be administered orally in a dosage unit form such as a capsule, bolus or tablet, or as a liquid drench. The drench is normally a solution, suspension or dispersion of the active ingredient usually in water together with a suspending agent such as bentonite and a wetting agent or like excipient and an antifoaming agent. 10 Drench formulations generally contain from 0.001 to 0.5% by weight of the active compound. The capsules and boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate or di-calcium phosphate.

15 Where it is desired to administer the LL-F28249 derivatives in a dry, solid dosage unit form, capsules, boluses or tablets containing the desired amount of active compound usually are employed. These dosage forms are prepared by intimately and uniformly 20 mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such dosage unit formulations may be varied widely with respect to their 25 total weight and content of the antiparasitic agent depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

30 When the active compound is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top dressing or in the form of pellets which may then be added to the finished feed or optionally fed separately. Alternatively, the antiparasitic compounds of the invention may be admin- 35 istered to animals parenterally, for example, by intraruminal, intramuscular, intratracheal, or by subcutaneous injection, in which event the active ingredient

is dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active material is admixed with an acceptable vehicle, preferably a vegetable oil such as peanut oil, cotton seed oil or the like. Other parenteral vehicles such as organic preparations using solketal, propylene glycol, glycerol formal and aqueous parenteral compositions may also be used in the preparation of parenteral formulations for administration to warm-blooded animals.

In these formulations the active compound or compounds are dissolved or suspended in the formulation in sufficient amount to provide from 0.005% to 5% by weight of the active compound in said formulation.

The compounds of the invention are useful for treating endoparasites in warm-blooded animals such as helminths. Said compounds are also useful for the prevention and treatment of diseases caused by ectoparasites, for example, arthropod ectoparasites such as mites, ticks, lice, fleas and other biting insects in domesticated animals and poultry.

Further, the 13-halo-23-imino-LL-F28249 compounds described herein are excellent insecticidal, nematocidal and acaricidal agents useful for protecting, growing or harvested crops from attack by the above-said pests. The compounds of the invention may be formulated into dry compacted granules, flowable compositions, wettable powders, dusts, dust concentrates, microemulsions and the like, all of which lend themselves to soil, water and/or foliage application and provide the requisite plant protection. Such compositions include the compounds of the invention admixed with agronomically acceptable solid or liquid carriers.

In these compositions the active compounds are intimately mixed or ground together with the composition in sufficient amounts to provide from 3% to 20% by weight of the active compound in said composition.

The compositions of this invention are useful in combating agricultural pests that inflict damage upon crops while they are growing or while in storage. The compounds are applied using known techniques such as sprays, dusts, emulsions, wettable powders, flowables and the like to the growing or stored crops to provide protection against infestation by agricultural pests.

Still further, compounds of this invention are outstandingly effective for controlling pupation of housefly larvae thereby being useful in the control of the housefly in the habitat, food source or breeding ground of said housefly. The compounds can be applied using sprays, dusts, emulsions, wettable powders, flowables, microemulsion granular compositions and the like as described hereinabove to said habitat, food source or breeding ground of said housefly.

In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating certain more specific details thereof. The invention is not to be limited thereby except as defined in the claims.

Unless otherwise noted, all parts are by weight.

EXAMPLE 1Preparation of 5,23-dioxo-LL-F28249 α

A mixture of LL-F28249 α (10.0g, 0.016 mole) and diatomaceous earth (160.0 g) in dimethylformamide, under nitrogen, is treated portionwise with pyridinium dichromate (58.0g, 0.15 mole), stirred for 4 hours at room temperature, treated with 1L of diethyl ether, stirred for 15 minutes and filtered. The filtrate is washed with water followed by brine, dried over MgSO₄ and concentrated in vacuo to give a yellow oil residue. The residue is flash chromatographed (silica, methylene chloride:isopropanol 99:1 as eluent) to afford the title product as a light yellow solid (4.84 g, 49.7%), identified by ¹HNMR, ¹³CNMR and mass spectral analyses.

EXAMPLE 2Preparation of 13-(formyloxy)-5,23-dioxo-LL-F28249 α

A mixture of 5,23-dioxo-LL-F28249 α (2.6 g, 4.3 mmole) in 88% formic acid, under nitrogen, is treated with selenium dioxide (1.0 g, 9.0 mmole), stirred at 50° for 2 hours, cooled to room temperature, treated with 3 volumes of methylene chloride, stirred for 10 minutes and filtered through diatomaceous earth. The filtrate is separated and the organic phase is concentrated in vacuo to give a light brown solid residue. Flash column chromatography (silica, hexanes:ethyl acetate, 2:1 as eluent) of the residue affords the title product as a beige solid (1.3 g, 43%), identified by ¹HNMR and ¹³CNMR spectroscopy.

EXAMPLE 3**Preparation of 13-hydroxy-5,23-dioxo-LL-F28249 α**

A mixture of 13-(formyloxy)-5,23-dioxo-LL-F28249 α (800 mg, 1.1 mmole), methanol and dioxane, at 0-5°C is treated with 20 mL of 1.2N HCl, stirred at room temperature for 4 hours, allowed to stand at 40°C for 16 hours and concentrated in vacuo. The residue is taken up in ethyl acetate, washed with sodium bicarbonate solution followed by brine, dried over MgSO₄ and concentrated in vacuo, to give the title compound as a beige solid (700 mg, 91%), identified by ¹HNMR, ¹³CNMR and mass spectral analyses.

EXAMPLE 4**Preparation of 13-fluoro-5,23-dioxo-LL-F28249 α and 13-fluoro-23-oxo-LL-F28249 α**

A mixture of 13-hydroxy-5,23-dioxo-LL-F28249 α (100 mg, 0.15 mmole) in methylene chloride at -40°C, under nitrogen, is treated with dimethylaminosulfur trifluoride (40 μ l, 29.4 mg, 0.22 mmole) via a syringe and stirred at -40°C to -30°C for 3 hours. The reaction mixture is poured into ice water, and the phases are separated. The aqueous phase is extracted with ethyl acetate. The organic phases are combined, washed with water and brine, dried over MgSO₄ and concentrated in vacuo to give the title product mixture as a yellow solid, 112 mg. High pressure liquid chromatography (HPLC) analysis indicates 57% 13-fluoro-5,23-dioxo-LL-F28249 α and 13% 13-fluoro-23-oxo-LL-F28249 α is present in the mixture. Column chromatography (silica, hexanes:ethyl acetate, 4:1 as eluent) of the product mixture affords pure 13-fluoro-5,23-dioxo-LL-F28249 α as

a yellow solid, identified by ^1H , ^{13}C and ^{19}F NMR and mass spectral analyses.

5

EXAMPLE 5

Preparation of 13-fluoro-23-(O-methyloxime)-LL-F28249 α

10

15

20

25

A mixture of 13-fluoro-5,23-dioxo-LL-F28249 α (30 mg, 0.05 mmole) in absolute ethanol at -10°C to -5°C , under nitrogen, is treated with inidazole (10 mg, 0.15 mmole) followed by addition of methoxylamine hydrochloride (12.5 mg, 0.15 mmole), stirred for 2 hours at -10°C to -5°C , treated with sodium borohydride (12.0 mg, 0.30 mmole) and stirred for 1 hour at -10°C to -5°C . The reaction mixture is quenched with water, stirred for 15 minutes at ambient temperatures and concentrated in vacuo. The resultant residue is dispersed in ethyl acetate and water, the phases are separated and the organic phase is washed with water followed by brine, dried over MgSO_4 and concentrated in vacuo to give a residue. The residue is column chromatographed (silica, hexanes: ether, 4:1 as eluent) to afford the title product as a white solid, identified by ^1H , ^{13}C and ^{19}F NMR and mass spectral analysis.

EXAMPLE 6

30

Preparation of 13-fluoro-5-(formyloxy)-23-(O-methyloxime)-LL-F28249 α

35

A mixture of 13-fluoro-23-(O-methyloxime)-LL-F28249 α (80 mg, 0.12 mmole) in dry pyridine at 0°C , under nitrogen, is treated with 1.0 mL of the mixed anhydride of acetic acid and formic acid, stirred at room temperature for 1/2 hour then poured onto a mixture of ice and saturated sodium bicarbonate

5 solution. The reaction mixture is extracted with
ether, the ether extract is washed with cold dilute
hydrochloric acid solution, followed by a water wash
and a saturated sodium bicarbonate wash. The organic
phase is dried over Na_2SO_4 and concentrated in vacuo.
10 The resultant residue is flash chromatographed (silica,
methylene chloride:ethyl acetate, 40:1 as eluent) to
afford the title product as a white solid (34.4 mg,
42%) identified by ^1H and ^{13}C NMR and mass spectral
analyses.

15 EXAMPLE 7

Preparation of 5-(dichloroacetoxy)-13-fluoro-23-(O-met- hyloxime)-LL-F28249 α

20 A stirred mixture of 13-fluoro-23-(O-methyl-
oxime)-LL-F28249 α (85 mg, 0.12 mmole) and dimethyl-
aminopyridine (2.9 mg, 0.024 mmole) in methylene
chloride at 5-10°C, under nitrogen, is treated with
pyridine (501L, 0.62 mmole) followed by dichloroacetyl
chloride (0.02 1L, 0.208 mmole). After 2 hours at
5-10°C, the reaction mixture is poured onto saturated
25 sodium bicarbonate and ice and extracted with ether.
The organic phase is washed sequentially with dilute
(0.5%) hydrochloric acid, water and saturated sodium
bicarbonate solution, dried over Na_2SO_4 and concen-
trated in vacuo. The residue is flash chromatographed
30 (silica, 0.25% to 0.5% isopropanol in methylene chlo-
ride, gradient elution) to give the title product as a
white solid, identified by ^1H and ^{13}C NMR and mass
spectral analyses.

EXAMPLE 8**Preparation of 13-fluoro-23-(O-methyloxime)-5-(tri-chloroacetoxy)-LL-F28249 α**

5 A stirred mixture of 13-fluoro-23-(O-methyl-
oxime)-LL-F28249 α (80 mg, 0.12 mmole) and dimethyl-
aminopyridine (2.9 mg, 0.024 mmole) in methylene
10 chloride, at 5-10°C under nitrogen, is treated with
pyridine (50 lL, 0.62 mmole) followed by trichloro-
acetyl chloride (20 lL, 0.18 mmole). After 1 1/4 hours
at 5-10°C, the reaction mixture is poured into saturat-
ed sodium bicarbonate and ice and extracted with ether.
15 The organic phase is washed sequentially with dilute
(0.5%) hydrochloric acid, water and saturated sodium
bicarbonate, dried over Na₂SO₄ and concentrated in
vacuo to give a white foam residue. The residue is
flash chromatographed (silica, 0.10% to 0.25% isopro-
20 panol in methylene chloride, gradient elution) to
afford the title product as an off-white solid
(63.4 mg, 66%) identified by ¹H and ¹³C NMR and mass
spectral analyses.

EXAMPLE 9**Preparation of 5-[(p-nitrobenzoyl)oxy]-LL-F28249 α**

25 A mixture of LL-F28249 α (6.36 g, 10.4 mmole)
and pyridine (1.98 g, 25 mmole) in methylene chloride
30 at 20-25°C is treated with p-nitrobenzoyl chloride
(2.45 g, 13.2 mmole), stirred for 4 hours, allowed to
stand for 16 hours and treated with saturated sodium
bicarbonate and methylene chloride. The reaction
mixture is stirred for 5 minutes and the phases are
35 separated. The organic phase is washed sequentially
with saturated sodium bicarbonate, 5% hydrochloric acid
and brine, dried over MgSO₄ and concentrated in vacuo

to afford the title product as a white solid foam
(7.9 g, 93.5% purity) by liquid chromatography analysis) identified by ¹HNMR and mass spectral analyses and microanalysis.

EXAMPLE 10

Preparation of 5-[(p-nitrobenzoyl)oxy]-23-oxo-LL-F282-49α

A stirred mixture of 5-[(p-nitrobenzoyl)-oxy]-LL-F28249α (6.3 g, 8.4 mmole) in dimethylformamide is treated with pyridinium dichromate all at once at 20-25°C. The reaction mixture is stirred for 6 hours, poured into water, stirred for 15 minutes and filtered. The filter cake is washed with water, air-dried, taken up in refluxing ethyl acetate, treated with diatomaceous earth and filtered. The filtrate is concentrated in vacuo to give a red-brown solid residue. The residue is recrystallized from n-propanol to afford the title product as white crystals (3.3 g, 51.7%) identified by ¹HNMR and mass spectral analyses.

EXAMPLE 11

Preparation of 13-hydroxy-5-[(p-nitrobenzoyl)oxy]-23-oxo-LL-F28249α

A stirred mixture of 5-[(p-nitrobenzoyl)-oxy]-23-oxo-LL-F28249α (1.25 g, 1.36 mmole) and selenium dioxide (0.78 g, 7.02 mmol) in 20 mL of 9:1 trifluoroethanol:water is heated at 40°C for 4 hours, cooled to room temperature and filtered through diatomaceous earth. The filtrate is concentrated in vacuo; the resultant residue is taken up in methylene-chloride and filtered to remove any residual selenium dioxide and the filtrate is concentrated in vacuo; the resultant

residue is flash chromatographed (silica ethyl acetate:hexanes 1:2 as eluent) to afford the title product as a white solid (0.29 g, 27%) identified by ^1H and ^{13}C NMR and mass spectral analyses.

EXAMPLE 12

Preparation of 13-fluoro-5-[(p-nitrobenzoyl)oxy]-23-oxo-LL-F28249 α

A mixture of 13-hydroxy-5-[(p-nitrobenzoyl)oxy]-23-oxo-LL-F28249 α (0.5 mmole) in dry methylene chloride, under nitrogen, at -70°C is treated dripwise with dimethylamino sulfur trifluoride (80 μl , 0.60 mmole) via a syringe. After 20 minutes at -70°C , the reaction mixture is quenched with 1/2 mL of water and 1 mL of methanol and stirred for 15 minutes at -78°C to 0°C , allowed to warm to room temperature and concentrated in vacuo. The residue is flash chromatographed (silica, methylene chloride/ethyl acetate mixtures as eluent) to afford the title product as a white solid (236 mg, 58.7%) identified by ^1H , ^{13}C and APT NMR and mass spectral analyses.

EXAMPLE 13

Preparation of 13-fluoro-23-oxo-LL-F28249 α

A rapidly stirred mixture of 13-fluoro-5-[(p-nitrobenzoyl)oxy]-23-oxo-LL-F28249 α (187 mg, 0.24 mmole) in dioxane at 5°C is treated dropwise with 1N NaOH (0.35 mL, 0.35 mmol), stirred at $10-15^\circ\text{C}$ for 3 hours, diluted with ethyl acetate and water, and mixed well. The phases are separated and the organic phase is washed with water, dried over NaSO_4 and concentrated in vacuo. The residue is flash chromatographed (silica, ethyl acetate:hexane, 1:2-1:1 gradient elution) to

give the title product as a white powder (117 mg, 78%), identified by ^1H and ^{13}C NMR and mass spectral analyses.

EXAMPLE 14

Preparation of 26,27-epoxy-13-fluoro-23-oxo-LL-F28249 α (I) and 3,4:26,27-diepoxy- 13-fluoro-23-oxo-LL-F28249 α (II)

A stirred mixture of 13-fluoro-23-oxo-L-L-F28249 α (62.8 mg, 0.10 mmole) in methylene chloride at 5-10°C is treated with purified *m*-chloroperbenzoic acid (41.7 mg, 0.24 mmole), stirred for 3 hours at 5-10°C and quenched with 10% sodium bicarbonate solution. The phases are separated and the organic phase is concentrated in vacuo. The resultant residue is flash chromatographed (silica, hexanes:ethyl acetate gradient elution, 2:1-1:1) to give the title product mixture. The mixture is further purified by preparative, reverse phase, high pressure liquid chromatography (HPLC) (C-18 column, acetonitrile:water, 65:35) to afford title product (I) as a white powder (18 mg, 29%) and title product (II) as a white powder (16 mg, 26%). Both compounds (I) and (II) are identified by ^1H and ^{13}C NMR and mass spectral analyses.

EXAMPLE 15

Preparation of 26,27-epoxy-13-fluoro-23-(O-methyl-oxime)-LL-F28249 α

A mixture of 26,27-epoxy-13-fluoro-23-oxo-LL-F28249 α (7.6 mg, 0.012 mmole), hydroxylamine hydrochloride (4.5 mg, 0.05 mmole) and sodium acetate (6.6 mg, 0.08 mmole) in methanol is stirred at room temperature for 6 hours and concentrated in vacuo. The residue is partitioned between water and methylene

chloride. The organic phase is separated and concentrated in vacuo. The resultant residue is chromatographed (silica, ethyl acetate:hexanes, 1:1) to afford the title product as a white powder (6.0 mg, 76%) identified by ^1H and ^{13}C NMR and mass spectral analyses.

EXAMPLE 16

Preparation of 13-chloro-5,23-dioxo-LL-F28249 α

A mixture of 13-hydroxy-5,23-dioxo-LL-F28249 α (70 mg, 0.10 mmole) in methylene chloride, under nitrogen, at 5-10°C is treated dripwise with thionyl chloride (30 mL, 18.4 mg, 0.15 mmole) via a syringe, stirred at 5-10°C for 2 hours and at room temperature for 16 hours and concentrated in vacuo. The semi-solid residue is flash chromatographed (silica, hexane:ethyl acetate, 75:25) to afford the title product as a beige solid (38.5 mg, 60%) identified by ^1H NMR and mass spectral analyses.

EXAMPLE 17

Preparation of 13-bromo-5,23-dioxo-LL-F28249 α

A mixture of 13-hydroxy-5,23-dioxo-LL-F28249 α (97 mg, 0.15 mmole) in benzene, under nitrogen, at 5-10°C is treated with phosphorous tribromide (20 mL, 57.6 mg, 0.21 mmole) via a syringe, stirred for 1 hour at 5-10°C, poured into water and extracted with ethyl acetate. The organic phase is washed with brine, dried over MgSO_4 , and concentrated in vacuo. The semi-solid residue is chromatographed twice (silica, hexanes:ethyl acetate, 9:1) to afford the title product as a light yellow solid identified by mass spectral analysis.

EXAMPLE 185 Evaluation Of The Antiparasitic Activity Of Test
 Compounds.

 The antiparasitic activity of the compounds
of the present invention against helminths, acarids,
10 and arthropod ectoparasites at various concentrations
of active ingredient is determined by the following
test examples. The results of these tests are sum-
marized in Table I.

15 Evaluation of test compounds for controlling
 Trichostrongylus colubriformis in warm-blooded animals

 In these tests the active ingredient is
dissolved in polyethylene glycol and dimethylsulfoxide
(PEG:DMSO) (1:2 v/v) in sufficient quantity to provide
20 treatments that deliver from 0.0156 to 0.1250 mg/kg of
test compound to the animal.

 To evaluate the test compounds, 5 week old
male gerbils are infected with 400-600 infective
T. colubriformis larvae of sheep origin on day 0. On
day 7, the gerbils are weighed and treatment initiated.
25 Test compounds are administered by gavage on the 7th
day after treatment. The gerbils are sacrificed on the
11th day after treatment, and the remaining worms
counted. The percent efficacy is calculated by com-
paring worm counts in treated animals with those from
30 untreated infected controls using the following formu-
la.

$$\frac{\text{Control mean} - \text{treated mean}}{\text{control mean}} \times 100 = \% \text{ Efficacy}$$

35

Three replicates per treatment are employed in these
evaluations.

61109-7797

- 24 -

The data obtained are summarized in Table I.

5

Evaluation of test compounds for controlling
Psoroptes cuniculi (Ear Mites)

10

15

20

On the day prior to test, or the morning of test, test compounds are dissolved in acetone and diluted to the desired concentrations. The concentration should be calculated so that 400 μ L contains the amount to be placed on each filter paper. 400 μ L of this solution is pipetted onto a top (3.7 cm dia) and bottom (3.5 cm dia) filter paper disc which is then placed on a ceramic plate to dry. [NOTE: This should be done under a hood.] There is a rough and smooth side to the filter paper. The test solution should be applied to the rough side which is placed up while drying. When dry, the two discs are placed in a Petri dish with the rough sides facing in separated by a small piece of stiff paper folded in the shape of a tent. Dishes are held at room temperature overnight, if done the day before the test. A standard at 0.01, 0.1 and 1.0 μ L/cm² is run in each test.

25

30

Scab (containing mites) is collected from the ears of infested rabbits the morning of the test. This material is placed in a large Petri dish under an illuminated magnifier. Mites crawl out of the scab and are easily collected on the point of a dissecting needle or one prong of a pair of fine forceps. The top filter paper in each dish is removed and 12 mites are placed on the bottom disk and the top paper replaced. Before replacing the top of the Petri dish the rim of the dish is smeared with Vaseline* to trap any escaping mites.

35

For evaluation tests there are generally 4 replicates of each dose which are counted, 2 at 4 hours and 2 at 24 hours.

*Trade-mark

After mites are added to the dishes, the dishes in each replicate are placed in a tray which is then placed in a plastic bag with several wet towels and held at room temperature.

After 4 or 24 hours, dishes are examined under a dissecting scope as follows -

1. Open dish carefully, remove top filter paper and save.
2. Draw a small circle approximately 1/2 cm in diameter on bottom filter paper using a soft pencil.
3. Using a disposable pipette, gently wet the area in and around the circle.
4. Transfer all mites from the dish into this circle. Look carefully - on cover, top filter paper and under bottom paper for mites.
5. Count and record the number of mites in the circle.
6. Replace the top cover and set the dish aside.
7. A minimum of 15 minutes later, count the mites remaining in the circle (these are dead mites).
8. Calculate and record the number of live mites.
9. Calculate percent efficacy as follows:

$$\frac{\text{Total of Dead mites}}{\text{Total number of mites}} \times 100 = \% \text{ Efficacy}$$

The data obtained are summarized in Table I.

61109-7797

- 26 -

Evaluation of test compounds for controlling
Musca domestica

5 In this test system, newly emerged housefly larvae are grown on an undefined medium of fermented whole milk and dried beef blood. Test compounds are added to the milk and activity is determined by the failure of larvae to pupate.

10 The test is run in 1 oz plastic medicine cups. Paper toweling (Scott C-Fold^{*} towels, #150) is cut in pieces approximately 3.5 x 10 cm. Three of these pieces are folded accordion style and placed in each paper cup. Twenty-four hours before the initia-
15 tion of the test, 1/2 gallon of whole milk is divided into 5 1-liter beakers and placed in an incubator at 39°C. The morning of the test, the fermented milk is removed from the incubator, stirred and poured into small beakers (100 mL each). The 1 to 2 g of dried beef
20 blood is added to each beaker with stirring to distribute the blood and incubated.

 Doses of test compounds are calculated so that 0.1 mL contains the amount of test compound to be added to 100 mL of milk. Compounds should be dissolved
25 in acetone. 100 μ L of acetone is added to each control beaker.

 Each beaker is removed from incubator and placed on a magnetic stirrer. The test compound is added and thoroughly mixed. Then 20 mL portions are
30 removed and added to labelled test cups (4 reps/treatment). Using a fine paint brush, 20 larvae are transferred into each cup which is then sealed in a plastic bag with a few pinholes in it. Bags containing cups are placed on a flat tray and placed in a 27°C incu-
35 bator for one week.

 Trays are removed from incubator and the number of pupae in each bag recorded. The paper

*Trade-mark

5 toweling is removed and examined closely for any pupae
that have remained in the cups. Most of the pupae will
be loose in the bag. The percent efficacy is cal-
culated as follows:

10
$$\frac{\text{Number of pupae from 4 treatment cups}}{\text{Number of cups/treatment} \times 20} \times 100$$

15 The final results expressed as percent inhibition of
pupation are corrected for control mortality by using
Abbott's formula. Data obtained are summarized in
Table I.

20

25

30

35

TABLE I
Evaluation Of The Antiparasitic Activity Of Test Compounds

Test Compound	T. colubriformis				P. cuniculi				M. domestica	
	(mg/kg)				(micrograms/cm ²)				(ppm)	
	0.125	0.0625	0.0313	0.0156	4.0	1.0	0.1	0.01	10	1.0
13-Fluoro-23-(O-methyl-oxime)-LL-F28249alpha	100	100	83	66	100	100	100	96	100	62
13-Fluoro-5-(formyloxy)-23-(O-methyloxime)-LL-F28249alpha	100	86	82	-	100	100	100	38	-	-
26,27-Epoxy-13-fluoro-23-(O-methyloxime)-LL-F28249alpha	100	100	100	98	100	100	100	7	79	-
5-(Dichloroacetoxy)-13-fluoro-23-(O-methyl-oxime)-LL-F28249alpha	100	83	59	-	100	100	100	57	15	-
13-Fluoro-23-(O-methyl-oxime)-5-(trichloroacetoxy)-LL-F28249alpha	99	77	17	-	100	100	100	79	-	-

EXAMPLE 195 Evaluation Of The Insecticidal And Acaricidal Activity
 of Test Compounds

 In the following evaluations, test solutions
are prepared by dissolving the test compound in a 35%
acetone in water mixture to a concentration of
10 10,000 ppm. Subsequent dilutions are made with water
as needed.

Heliothis virescens, egg, tobacco budworm

 A young cotton leaf about 6-7 cm long is
15 dipped in the test solution with agitation for 3
seconds. Eggs are collected on a cheesecloth and the
cheesecloth is cut into 10-20 mm squares containing
about 50-100 eggs each (6-30 hours old). A square of
cheesecloth with eggs is also dipped in the test
20 solution and placed on the treated leaf. The combina-
tion is placed in a hood to dry, then placed in an 8 oz
paper cup, into which a 5 cm length of damp dental wick
has been placed. A clear plastic lid is put on the top
of the cup and the treatments are held for 3 days
25 before mortality counts are made.

Heliothis virescens, third-instar, tobacco budworm

 Cotton cotyledons are dipped in the test
solution and allowed to dry in a hood. When dry, each
30 is cut into quarters and 10 sections are placed,
individually, into 30 mL plastic medicine cups con-
taining a 5-7 mm long piece of damp dental wick. One
third-instar caterpillar is added to each cup, and a
cardboard lid placed on the cup. Treatments are
35 maintained for 3 days before mortality counts and
estimates of reduction in feeding damage are made.

Spondoptera eridania, third-instar larvae,
Southern armyworm

5 A Sieva lima bean leaf expanded to 7-8 cm in
length is dipped in the test solution with agitation
for 3 seconds and placed in a hood to dry. The leaf is
then placed in a 100 x 10 mm petri dish containing a
damp filter paper on the bottom and 10 third instar
10 caterpillars. Observations of mortality, reduced
feeding, or any interference with normal moulting are
made at 3 days and 5 days.

Aphis fabae, mixed instar, bean aphid

15 Pots containing single nasturtium plants
(Tropaeolum sp.) about 5 cm tall, are infested with
about 100-200 aphids 1 day before the test. Each pot
is sprayed with the test solution for 2 revolutions of
a 4 rpm turn-table in a hood, using a #154 DeVilbiss
20 atomizer. The spray tip is held about 15 cm from the
plant, and the spray directed so as to give complete
coverage of the plants and the aphids. The sprayed
pots are set on their sides on white enamel trays and
held for 2 days, following which mortality estimates
25 are made.

Empoasca abrupta, adults, western potato leafhopper

30 A sieva lima bean leaf about 5 cm long is
dipped in the test solution for 3 seconds with agita-
tion and placed in a hood to dry. The leaf is placed
in a 100 x 10 mm petri dish containing a moist filter
paper on the bottom. About 10 adult leafhoppers are
added to each dish, and the treatments are kept for 3
days before mortality counts are made.

35

Tetranychus urticae (P-resistant strain) 2-spotted
spider mite

5 Sieva lima bean plants with primary leaves
expanded to 7-8 cm are selected and cut back to one
plant per pot. A small piece is cut from a leaf taken
from the main colony of mites and placed on each leaf
10 of the test plants. This is done about 2 hours before
treatment to allow the mites to move over to the test
plant and to lay eggs. The size of the cut piece is
varied to obtain about 100 mites per leaf. At the time
of the treatment, the piece of leaf used to transfer
the mites is removed and discarded. The mite-infested
15 plants are dipped in the test solution for 3 seconds
with agitation and set in the hood to dry. Plants are
kept for 2 days before estimates of adult kill are made
using the first leaf. The second leaf is kept on the
plant for another 5 days before observations are made
20 of the kill of eggs and/or newly emerged nymphs.

Rating Scale

	0 = no effect	5 = 56-65% kill
	1 = 10-25% kill	6 = 66-75% kill
25	2 = 26-35% kill	7 = 76-85% kill
	3 = 36-45% kill	8 = 86-99% kill
	4 = 46-55% kill	9 = 100% kill

30 The data obtained are summarized in Table II.

35

TABLE II

Evaluation Of The Insecticidal And Acaricidal Activity Of Test Compounds

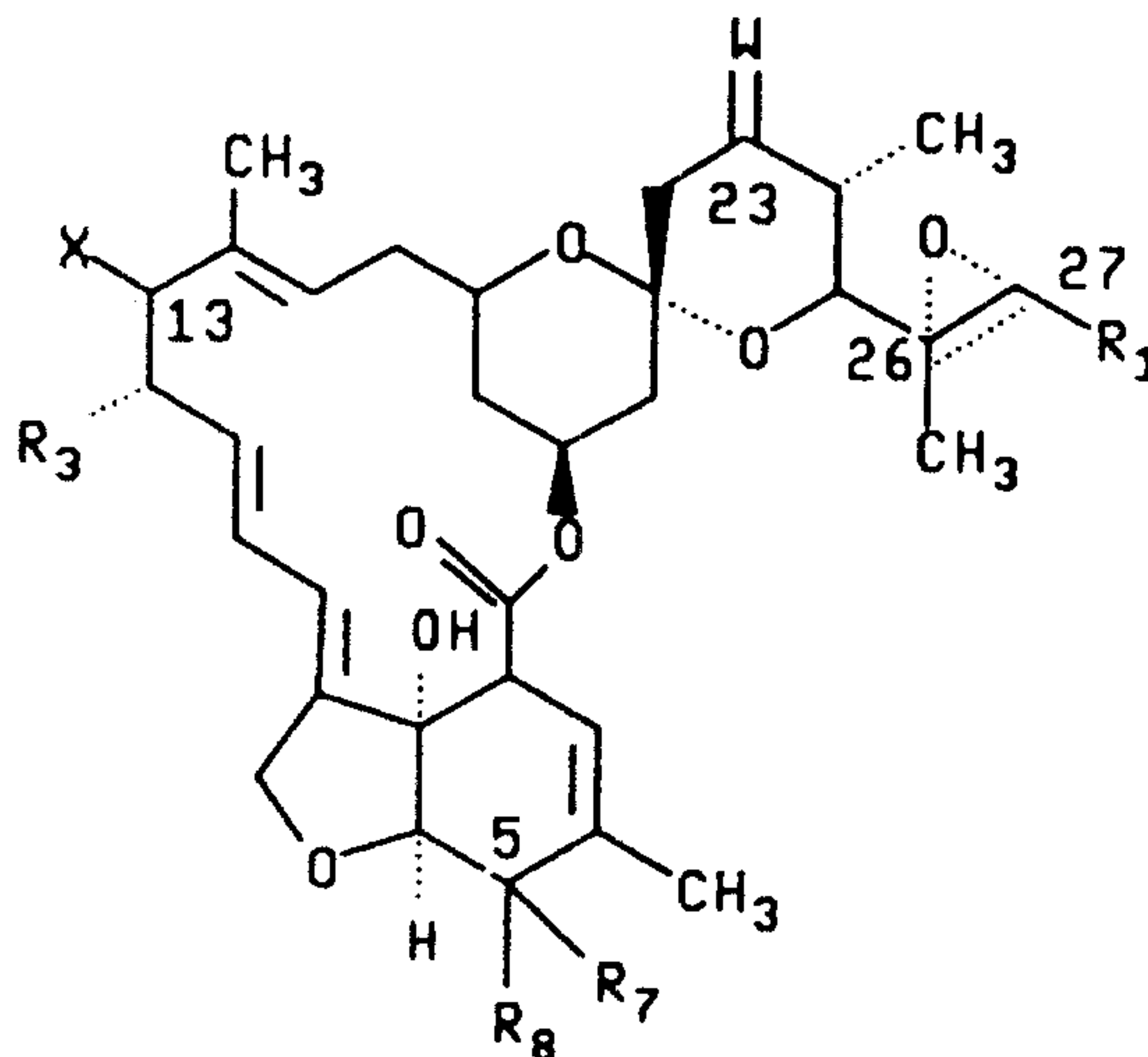
Test Compound	Tobacco Budworm		Southern Armyworm		Bean Aphid		Leafhopper		P-resistant Mites	
	egg		Day 3		Day 5		(ppm)		(ppm)	
	100	10	100	10	100	10	100	10	1000	100
13-Fluoro-23-(O-methylloxime)-LL-F28249alpha	8	0	9	9	9	9	7	6	9	8
5-(Dichloro-acetoxy)-13-fluoro-23-(O-methylloxime)-LL-F28249alpha	0	0	9	9	9	9	7	0	9	8
13-Fluoro-23-(O-methylloxime)-5-(trichloro-acetoxy)-LL-F28249alpha	8	0	9	9	9	9	0	0	9	8
13-Fluoro-5-(formyloxy)-23-(O-methylloxime)-LL-F28249alpha	0	0	9	8	9	9	0	0	9	8

61109-7797

- 33 -

CLAIMS:

1. A compound having the structural formula:



wherein

R₁ is methyl, ethyl or isopropyl;

R₇ is hydrogen and R₈ is OR₂, or when taken together with the carbon atom to which they are attached R₇ and R₈ represent C=O;

R₂ is hydrogen, C₁-C₄ alkyl, or C(=O)-R₄;
 R₄ is hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxymethyl, phenoxymethyl, or phenyl optionally substituted with 1 nitro, 1-3 halogens, 1-3 C₁-C₄ alkyl, or 1-3 C₁-C₄ alkoxy;

R₃ is hydrogen, methyl or ethyl;

X is fluorine, bromine, chlorine or iodine;

W is N-Y;

Y is OR₅ or NHR₆;R₅ is C₁-C₄ alkyl or C₁-C₄ acyl;R₆ is C₁-C₄ acyl; and

the dotted triangular figure with oxygen at C₂₆-C₂₇ indicates that there is present either

61109-7797

- 34 -

a double bond or an epoxide.

2. The compound according to claim 1,
wherein R_1 is isopropyl;

R_7 is hydrogen and R_8 is OR_2 ;

5 R_2 is hydrogen, C_1-C_4 alkyl, or $C \begin{array}{c} O \\ || \end{array} R_4$;
 R_4 is hydrogen, methyl, chloromethyl, dichloromethyl,
trichloromethyl, or methoxymethyl;

R_3 is methyl;

X is fluorine;

10 W is N-Y;

Y is OR_5 ; and

R_5 is C_1-C_4 alkyl.

3. The compound according to claim 1,
wherein

15 R_1 is isopropyl;

R_7 and R_8 taken together with the carbon atom to which
they are attached represent $C=O$,

R_3 is methyl;

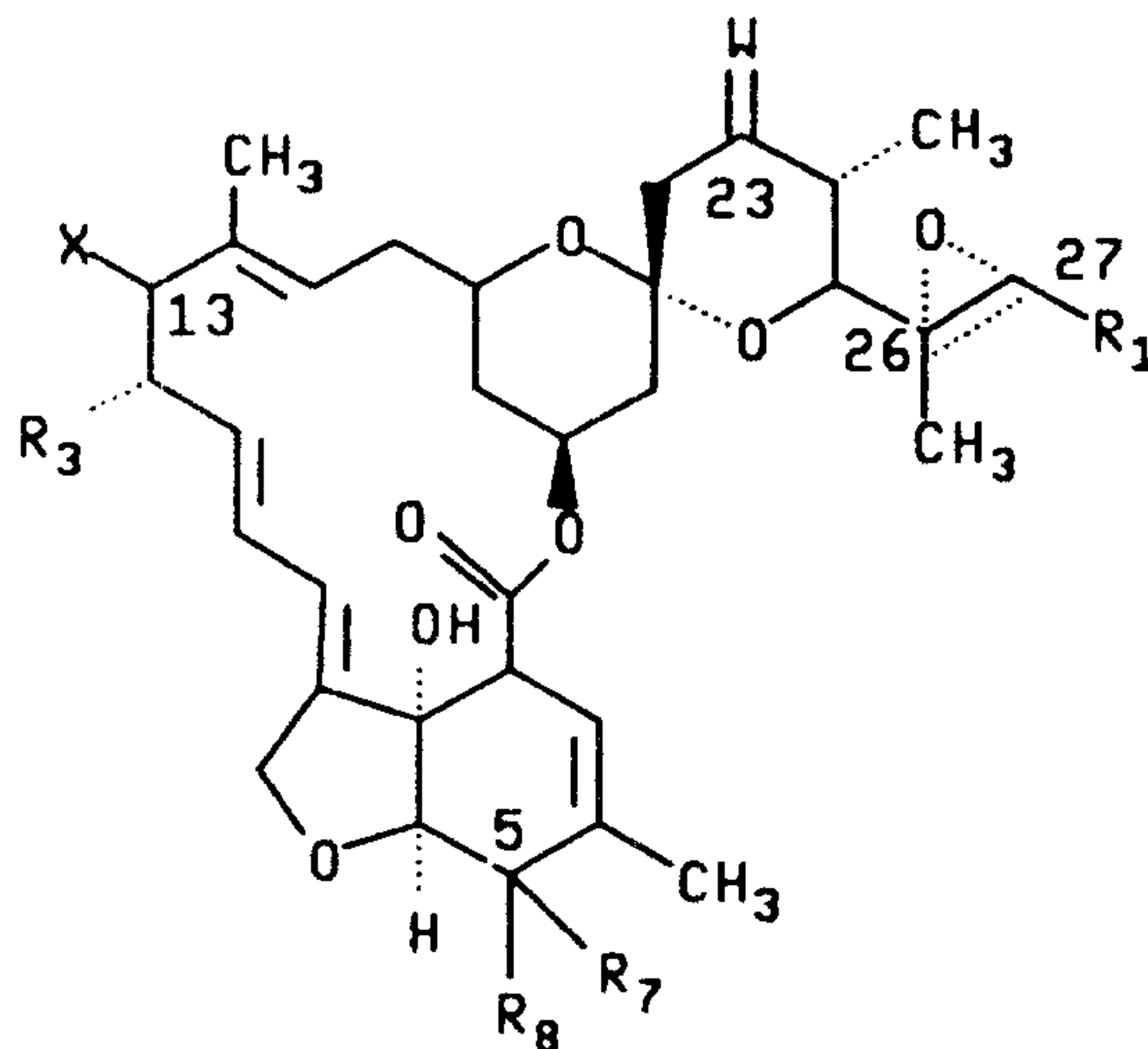
X is fluorine;

20 and W is N-Y.

4. Use of an endo- or ectoparasitically
effective amount of a compound having the structural
formula:

61109-7797

- 35 -



wherein

R₁ is methyl, ethyl or isopropyl;

R₇ is hydrogen and R₈ is OR₂, or when taken together with the carbon atom to which they are attached R₇ and R₈ represent C=O;

R₂ is hydrogen, C₁-C₄ alkyl, or C(=O)-R₄;
 R₄ is hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxymethyl, phenoxymethyl, or phenyl optionally substituted with 1 nitro, 1-3 halogens, 1-3 C₁-C₄ alkyl, or 1-3 C₁-C₄ alkoxy;

R₃ is hydrogen, methyl or ethyl;

X is fluorine, bromine, chlorine or iodine;

W is N-Y;

Y is OR₅ or NHR₆;

R₅ is C₁-C₄ alkyl or C₁-C₄ acyl;

R₆ is C₁-C₄ acyl; and

the dotted triangular figure with oxygen at the

C₂₆-C₂₇ indicates that there is present either a double bond or an epoxide, for preventing, treating or controlling an endoparasitic or ectoparasitic infection in a warm-blooded animal.

61109-7797

- 36 -

5. The use according to claim 4, wherein said compound has the structural formula as described in claim 4 and

R_1 is isopropyl;

R_7 is hydrogen; R_8 is OR_2 ;

R_2 is hydrogen, C_1-C_4 alkyl, or $C(=O)-R_4$;

R_4 is hydrogen, methyl, chloromethyl, dichloromethyl, trichloromethyl, or methoxymethyl;

R_3 is methyl;

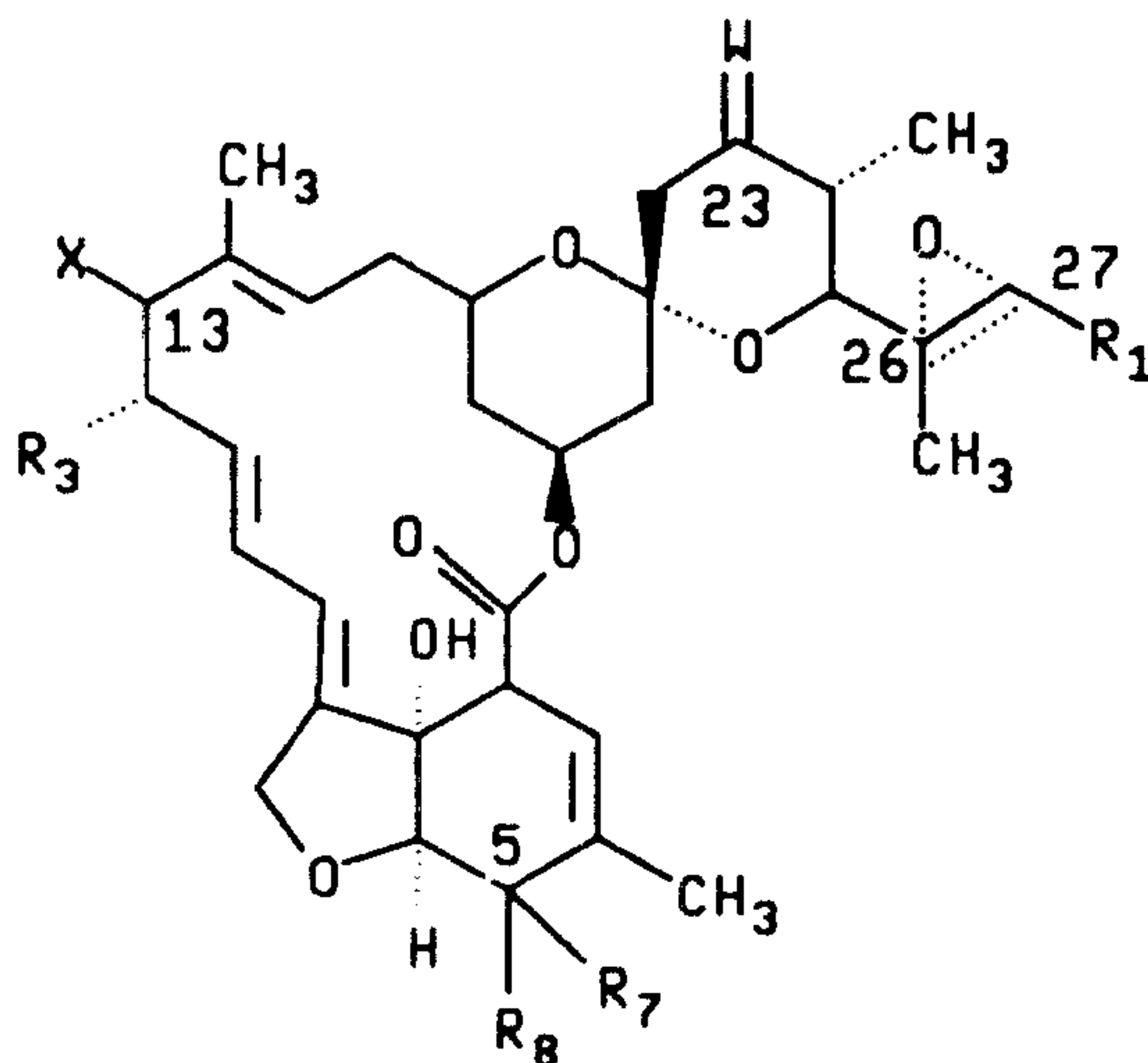
X is fluorine;

W is N-Y;

Y is OR_5 ; and

R_5 is C_1-C_4 alkyl.

6. A method for protecting crops, trees, shrubs, stored grain and ornamental plants from attack by an insect, acarid and nematode which comprises applying to said crops, trees, shrubs, stored grain and ornamental plants an insecticidally, acaricidally or nematocidally effective amount of a compound having the structural formula:



61109-7797

- 37 -

wherein

R_1 is methyl, ethyl or isopropyl;

R_7 is hydrogen and R_8 is OR_2 , or when taken together with the carbon atom to which they are attached R_7 and R_8 represent $C=O$;

R_2 is hydrogen, C_1-C_4 alkyl, or $C(=O)-R_4$;

R_4 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxymethyl, phenoxymethyl, or phenyl optionally substituted with 1 nitro, 1-3 halogens, 1-3 C_1-C_4 alkyl, or 1-3 C_1-C_4 alkoxy;

R_3 is hydrogen, methyl or ethyl;

X is fluorine, bromine, chlorine or iodine;

W is $N-Y$;

Y is OR_5 or NHR_6 ;

R_5 is C_1-C_4 alkyl or C_1-C_4 acyl;

R_6 is C_1-C_4 acyl; and

the dotted triangular figure with oxygen at $C_{26}-C_{27}$ indicates that there is present either a double bond or an epoxide.

61109-7797

- 38 -

7. The method according to claim 6, wherein the compound has the structural formula as described in claim 6 and

R_1 is isopropyl;

R_7 is hydrogen; R_8 is OR_2 ;

R_2 is hydrogen, C_1-C_4 alkyl, or $C(=O)-R_4$;

R_4 is hydrogen, methyl, chloromethyl, dichloromethyl, trichloromethyl, or methoxymethyl;

R_3 is methyl;

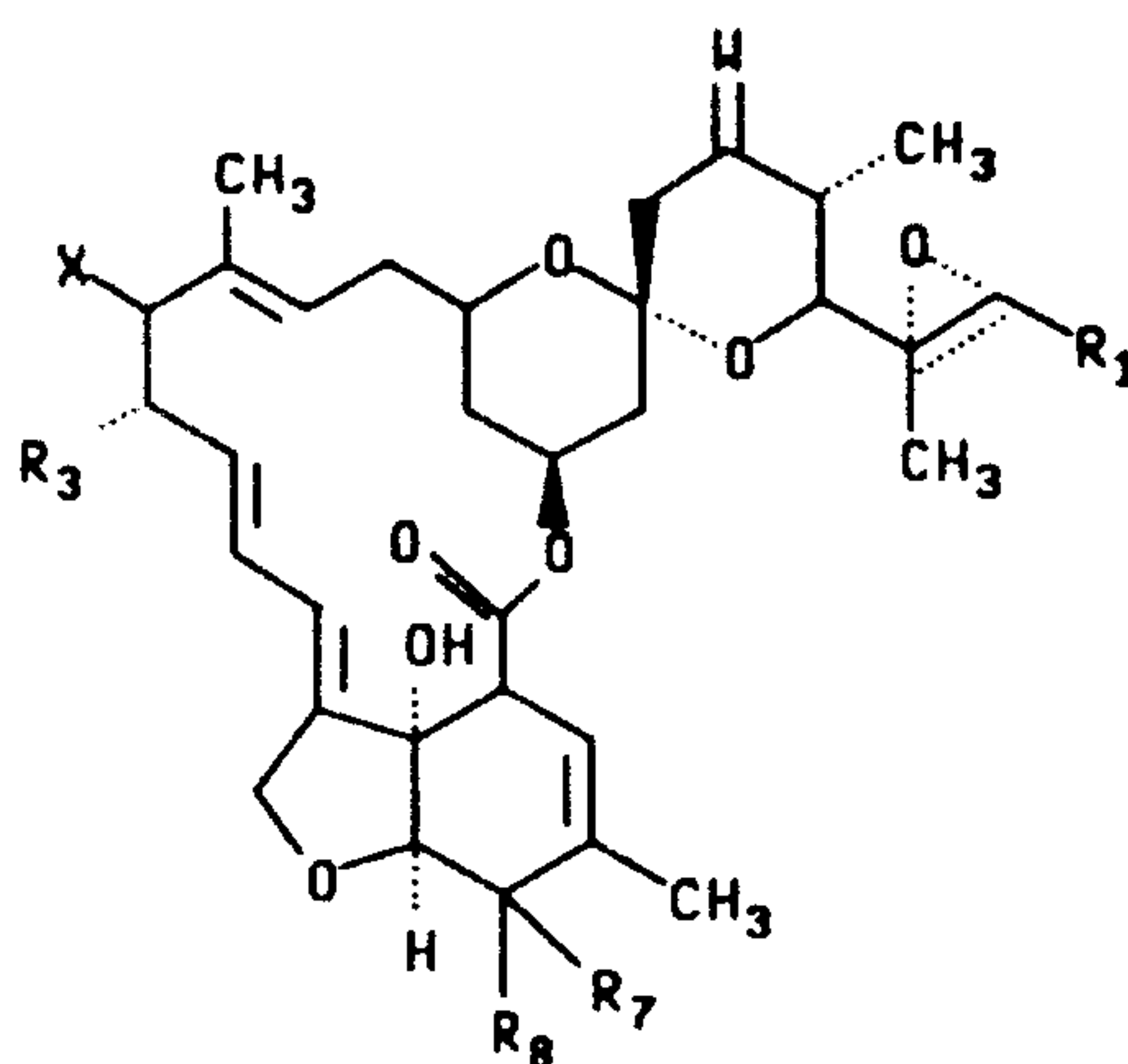
X is fluorine;

W is N-Y;

Y is OR_5 ; and

R_5 is C_1-C_4 alkyl.

8. A composition for controlling endo- and ectoparasites, insects, acarids and nematodes comprising an agronomically acceptable carrier containing a prophylactically, therapeutically, pharmaceutically or insecticidally effective amount of a compound having the structural formula:



wherein

R_1 is methyl, ethyl or isopropyl;

R_7 is hydrogen and R_8 is OR_2 , or when taken together with the carbon atom to which they are attached R_7 and R_8 represent $C=O$;

61109-7797

- 39 -

O
||

R_2 is hydrogen, C_1-C_4 alkyl, or $C-R_4$;
 R_4 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl,
 C_1-C_4 alkoxymethyl, phenoxymethyl,
 or phenyl optionally substituted with 1 nitro, 1-3
 5 halogens, 1-3 C_1-C_4 alkyl, or 1-3 C_1-C_4 alkoxy;
 R_3 is hydrogen, methyl or ethyl;
 X is fluorine, bromine, chlorine or iodine;
 W is N-Y;
 Y is OR_5 or NHR_6 ;
 10 R_5 is C_1-C_4 alkyl or C_1-C_4 acyl;
 R_6 is C_1-C_4 acyl; and
 the dotted triangular figure with oxygen at $C_{26}-C_{27}$
 indicates that there is present either
 a double bond or an epoxide.

- 15 9. Use of an endo- or ectoparasitically effective amount of a compound according to any one of claims 1 to 3 for preparing a medicament for preventing, treating or controlling an endoparasitic or ectoparasitic infection in a warm-blooded animal.
- 20 10. A composition for controlling endo- and ectoparasites, insects, acarids and nematodes comprising an agronomically acceptable carrier containing a prophylactically, therapeutically, pharmaceutically or insecticidally effective amount of a compound according to
 25 claim 2 or 3.

