Kirk-Othmer Encyclopedia of Chemical Technology.

ANTIPARASITIC AGENTS, AVERMECTINS

In 1976 scientists at the Merck Corporation discovered a complex of eight closely related natural products, subsequently named avermectins A_{1a} through B_{2b}, in a culture of *Streptomyces avermitilis* MA-4680 (NRRL8165) originating from a soil sample collected at Kawana, Ito City, Shizuoka Prefecture, Japan and isolated by the Kitasato Institute. Their structures are shown in Figure 1 (1–6). They are among the most potent anthelmintic, insecticidal, and acaricidal compounds known.

The avermectins are closely related to another group of pesticidal natural products, the milbemycins. First described by Japanese workers, milbemycins were later found to be more abundant in nature than the avermectins (7–12). Both the avermectins and milbemycins are sixteen-membered lactones, with a spiroketal system containing two six-membered rings. The principal difference between them is that the avermectins have an α-L-oleandrosyl-α-L-oleandrosyl disaccharide attached at the 13-position whereas the milbemycins have no 13-substituent. Milbemycin structures are shown in Figure 2.

Two avermectins, abamectin (the avermectin B_1) [71751-41-2] and ivermectin [70288-86-7], which is saturated at C22–C23, have been commercialized to date. These two marketed avermectins have been described in considerable detail (Table 1) (13).

Avermectin	CAS Registry Number	Molecular formula
A_{1a}	[65195-51-9]	$C_{49}H_{74}O_{14}$
A_{1b}	[65195-52-0]	$C_{48}H_{72}O_{14}$
A_{2a}	[65195-53-1]	$C_{49}H_{76}O_{15}$
A_{2b}	[65195-54-2]	$C_{48}H_{74}O_{15}$
B_{1a}	[65195-55-3]	$C_{48}H_{72}O_{14}$
B_{1b}	[65195-56-4]	$C_{47}H_{70}O_{14}$
B_{2a}	[65195-57-5]	$C_{48}H_{74}O_{15}$
B_{2b}	[65195-58-6]	$C_{47}H_{72}O_{15}$

Name	CAS Registry Number	R_{25}	Molecular formula
milbemycin Alfa$_1$ (A_3)	[51596-10-2]	CH_3	$C_{31}H_{44}O_7$
milbemycin Alfa$_3$ (A_4)	[51596-11-3]	CH_2CH_3	$C_{32}H_{46}O_7$
milbemycin D	[77855-81-3]	$CH(CH_3)_2$	$C_{33}H_{48}O_7$
anthelmintic F-28249-Alpha (nemadectin)		$C(CH_3)CHCH(CH_3)_2$	$C_{36}H_{52}O_8$

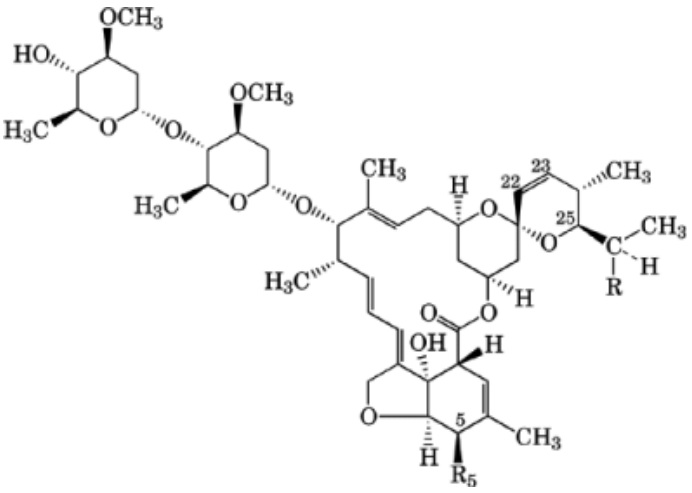


Fig. 1. The avermectins show variations at positions 5, 22–23, and 25. In the A series $R_5{=}OCH_3$; for the B series $R_5{=}OH$. The designation 1 corresponds to $\overset{22}{\underset{}{-}}\overset{}{CH=CH}\overset{}{\underset{}{-}}\overset{23}{}$ as shown. The designation 2 indicates $\overset{22}{\underset{}{-}}\overset{}{CH_2-CHOH}\overset{}{\underset{}{-}}\overset{23}{}$. In ivermectin, C-22–C-23 is saturated. The avermectins are isolated as mixtures wherein the major component a has a *sec*-butyl group at position 25 ($R{=}C_2H_5$), and component b has an isopropyl group ($R{=}CH_3$) at C-25.

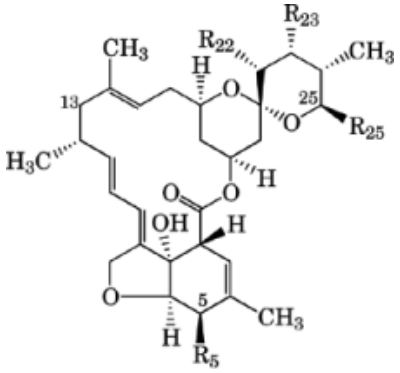
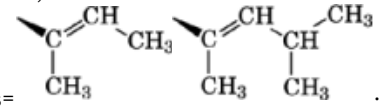


Fig. 2. Milbemycin structures in the milbemycin Alfa series. $R_5{=}OH$, OCH_3; $R_{22}{=}H$, OH; $R_{23}{=}H$, $OCOCH(CH_3)(CH_2)_3CH_3$; $R_{25}{=}CH_3$, C_2H_5. In the anthelmintic F-28249, antibiotics S541 series $R_5{=}OH$, OCH_3; $R_{22}{=}H$; $R_{23}{=}OH$; $R_{25}{=}$  .
Some specific examples follow; in all these examples $R_5{=}OH$ and $R_{22}{=}H$. For the milbemycins, $R_{23}{=}H$; $R_{23}{=}OH$ for nemadectin.

1. Abamectin

Avermectin B_1 is the most effective of the avermectin family of natural products against agriculturally important insects and mites (14). It has been commercialized for agricultural use under the nonproprietary name abamectin. This mixture of avermectins contains at least 80% of avermectin B_{1a} ($C_{48}H_{72}O_{14}$) and not more than

20% of avermectin B_{1b} ($C_{47}H_{70}O_{14}$). Abamectin for use in foliar spray applications is formulated as an emulsifiable concentrate. It is being developed for use in a number of horticultural and agronomic crops to control mites and insects. A summary of its biological activity is shown in Table 2 and a summary of its agricultural applications is shown in Table 3.

Table 1. Trade Name Registrations by the Merck Corporation[a]

Trade name	Delivery form	Recipient
Abamectin		
Avid	foliar spray	
Agri-Mek	foliar spray	
Vertimek	foliar spray	
Affirm	bait	fire ants
Avomec	injection	cattle
Duotin	injection	cattle
Ivermectin		
Ivomec	injection	cattle, sheep, goats, pigs, camels
	oral liquid	cattle, sheep
	paste, pour on	cattle
Ivomec F	injection	cattle
Oramec	oral liquid	sheep, goats
Eqvalan	paste	horses
	oral liquid	horses
Heartguard 30	tablet or chewable	dogs
Cardomec	tablet	dogs
Cardotek	tablet	dogs
Mectizan	tablet	humans

[a] Ref. 12.

Table 2. Biological Activity of Abamectin (Avermectin B_1) Against Mites and Insects[a]

Common name	Species name	LC_{90}(ppm)
Mite species[b]		
citrus rust mite	*Phyllocoptruta oleivora*	0.02
two-spotted spider mite	*Tetranychus urticae*	0.03
strawberry mite	*Tetranychus turkestani*	0.08
European red mite	*Panonychus ulmi*	0.04
citrus red mite	*Panonychus citri*	0.24
broad mite	*Polyphagotarsonemus*	0.03
Insect species[c]		
Colorado potato beetle	*Leptinotarsa decemlineata*	0.03
tomato hornworm	*Manduca secta*	0.02
Mexican bean beetle	*Epilachna varivestes*	0.20
pea aphid	*Acyrthosiphon pisum*	0.40
cabbage looper	*Trichoplusia ni*	1.0
corn earworm	*Heliothis zea*	1.5
southern armyworm	*Spodoptera eridania*	6.0

[a] Ref. 15.
[b] Contact effect against adult mites.
[c] Foliar residue bioassay.

Table 3. Principal Agricultural Applications of Abamectin Foliar Spray

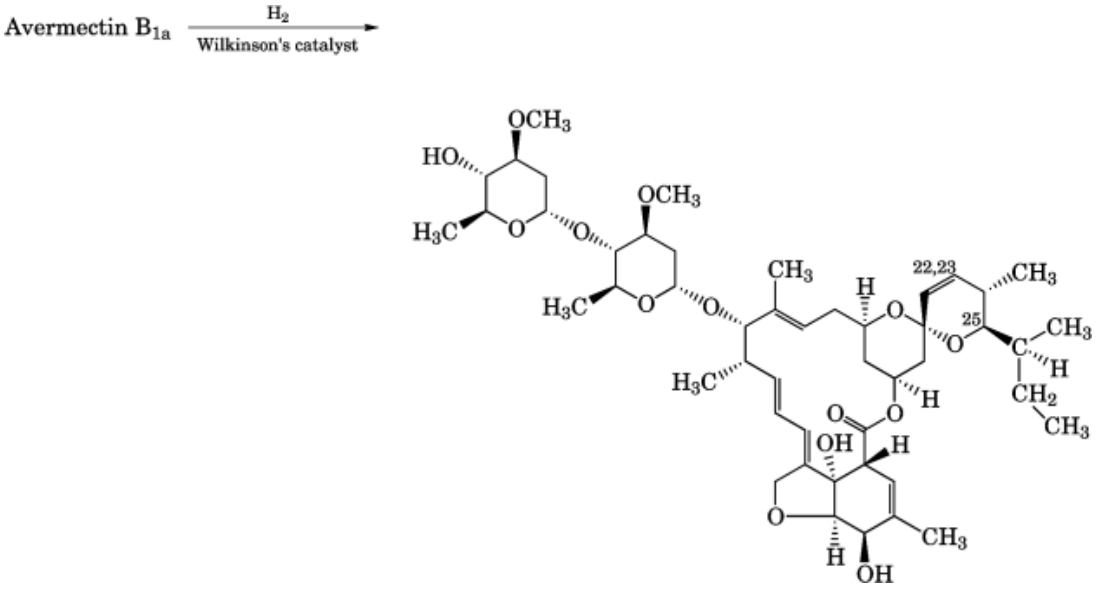
Common name	Species name	Application
armyworm	*Spodoptera exigua*	vegetables[a]
	Spodoptera eridania	
broad mite	*Polyphagotarsonemus latus*	citrus
citrus red mite	*Panonychus citri*	citrus
citrus rust mite	*Phyllocoptruta oleivora*	citrus
citrus thrip	*Scirtothrips citri*	citrus
cotton aphid	*Aphis gossypii*	cotton
deciduous tree nut		miscellaneous crops
European red mite	*Panonychus ulmi*	pears
leafminer	*Liriomyza trifolii*	ornamentals, vegetables[a]
	Liriomyza sativae	vegetables[a]
Lepidoptera		cotton
pear psylla	*Psylla pyricola*	pears
pear rust mite	*Epitrimerus pyri*	pears
strawberry		miscellaneous crops
spider mite	*Tetranychus urticae*	cotton
	Tetranychus turkestani	cotton
	Tetranychus pacificus	cotton
	Tetranychus cinnabarinus	cotton
thrips species		ornamentals
tomato pinworm	*Keiferia lycopersicella*	vegetables[a]
tomato russet mite	*Aculops lycopersici*	vegetables[a]
two-spotted spider mite	*Tetranychus urticae*	vegetables[a], pears, ornamentals

[a] Celery, tomato, pepper.

Abamectin is also used to control the imported red fire ant *Solenopsis invicta*. For this use abamectin is formulated as a bait together with soybean oil and corn grits. Worker ants transport the bait to the colony, the queen becomes sterile, and the colony is eliminated after 12 to 21 weeks. Similar effects on the fecundity of other female insects at nonlethal doses have been reported (16, 17).

2. Ivermectin

Selective reduction of the 22,23-olefin of avermectin B_1 yields the 22,23-dihydro derivative assigned the nonproprietary name ivermectin (18). The structure shown depicts the 25-*sec*-butyl derivative [70161-11-4], but it should be noted that both commercial products contain up to 20% of the 25-isopropyl analogue [70209-81-3].



Ivermectin is active against two significant phyla of animal parasite: the Nemathelminthes or nematodes (roundworms) and the Arthropoda (insects, ticks, and mites). Ivermectin is inactive against platyhelminthes (flukes and tapeworms).

Ivermectin has an extremely broad spectrum of antinematodal activity in a variety of domestic animals. Indeed, among the many nematodes against which it has been tested, none has been found that is not affected by ivermectin during at least one stage of the life cycle. In all but a few instances the drug is highly active against both immature and mature worms (19).

Perhaps the most striking aspect of the antinematodal action of ivermectin is its potency. This varies widely from species to species and stage to stage, but in all cases the minimum effective dosage is much less than that of other anthelmintics. Among the most sensitive parasites are immature. *Dirofilaria immitis* in dogs (0.001 mg/kg) and *Oesophagostomum radiatum* and *Dictyocaulus viviparus* in cattle (0.05 mg/kg). Among the least sensitive nematodes are *Nematodirus helvetianus* in cattle, and *Toxascaris leonina*, and perhaps immature *Trichuris vulpis*, in dogs. Two parasite life cycle forms against which activity has not been demonstrated even at high dosage (more than 1.0 mg/kg) are adult *Dirofilaria immitis* (heartworm) in dogs and immature *Trichinella spiralis* in the muscle of mice and pigs even though other life cycle stages are affected. The vast majority of nematodes, regardless of host species or stage of worm development, are highly susceptible to ivermectin when the drug is given as a single oral or parenteral dose at 0.1–0.2 mg/kg.

The activity of ivermectin against the filarial parasite *Dirofilaria immitis* in dogs suggested a possible role for the control of filarial parasites of humans (20). It has been extensively tested in human onchocerciasis and is now considered to be the drug of choice. In a single yearly oral dose, it suppresses microfilariae in the skin and eyes and, in most cases, prevents the progression of the disease to blindness. Table 4 shows the results of a 30-patient double-blind study recorded over one year.

Two forms of lymphatic filariasis are found in India. The Bancroftian form is the most common and accounts for more than 90% of the disease whereas Brugian filariasis accounts for the rest. In a study carried out in India (6) in 40 patients with *Wuchereria Bancrofti* filariasis treated with single oral doses, all of the dose levels chosen (25, 50, 100, and 200 mg/kg) were efficacious in clearing microfilariae from the blood of all patients treated. However, after three months some microfilaria recurred in the blood of most patients (Table 5).

Table 4. Ivermectin and Diethylcarbamazine Against *Onchocerca volvulus* Infections[a]

Study day	Placebo[b]	Ivermectin[c]	DEC[d]
−1	99.4	130.4	100.3
2	108.2	38.8	27.0
4	99.7	14.1	14.4
8	105.1	6.6	4.1
14	125.9	2.2	6.8
28	102.6	0.6	9.2
90	84.5	1.0	18.0
180	65.3	2.9	21.8
270	80.8	5.0	27.5
360	93.0	11.8	45.1

[a] Numbers represent the skin density of microfilariae (21).
[b] Ten patients received placebo.
[c] Ten patients received a single oral dose of ivermectin, 12 mg.
[d] Ten patients received diethylcarbamazine [90-89-1] (DEC) daily orally for eight days: total dose 1.3 g.

Table 5. Efficacy[a] of Ivermectin in the Treatment of *Wuchereria Bancrofti* Filariasis[b]

	Day						
Single oral dose, mg/kg	0	1.5	5	12	30	90	180
25	761	2.9	<1	<1	5.2	42.9	98
50	1154	3.3	<1	<1	3.5	103.6	92.3
100	610	3.0	<1	<1	<1	19.9	95.9
200	478	<1	<1	<1	1.5	43.7	70.8

[a] Geometric mean microfilariae/mL.
[b] Ref. 22.

Further studies are planned and some are underway using different doses and regimens. Ivermectin still appears to hold promise as a new treatment for lymphatic filariasis.

Ivermectin is widely used as an endectocide for cattle as an injectable, oral, topical, or slow release bolus; for sheep as an injectable or oral formulation; for swine as an injectable; for horses as a paste or drench; and for goats as an injectable or oral formulation. Ivermectin has recently been introduced for heartworm prophylaxis in dogs and it is being studied for use with cats, many other mammals, birds, fish, and reptiles.

Ivermectin is used in cattle, sheep and horses at 0.2 mg/kg; swine at 0.3 mg/kg; dogs at 0.006 mg/kg; and man at 0.05–0.2 mg/kg. It is effective against parasitic nematodes, grubs, lice, mites, ticks, and bots. Ivermectin is not active against tapeworms, flatworms, bacteria, or fungi.

3. Biosynthesis

The proposed pathway for the biosynthesis of the avermectins (Fig. 3) has been described in a review (23). Some of the details are yet to be elucidated, although the steps, in general, are based on firm evidence from four types of studies: incorporation of labeled precursors, conversion of putative intermediates by producing strains and blocked mutants, *in vitro* measurement of biosynthetic enzymes, and studies with enzyme inhibitors. The

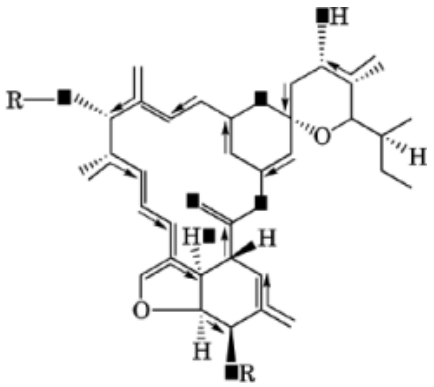


Fig. 3. Biosynthetic scheme of avermectins, ■=O^{18}, $\overrightarrow{CH_3COOH}$, $\overbrace{CH_3CH_2COOH}$.

biosynthesis of the oleandrose units was elucidated from studies using $^{3}H/^{14}C$ and ^{13}C labeled glucose, which indicated a direct conversion of glucose to oleandrose.

4. Chemistry

4.1. Stability

Avermectins are highly lipophilic substances and dissolve in most organic solvents such as chloroform, methylene chloride, acetone, alcohols, toluene, cyclohexane, dimethylformamide, dimethyl sulfoxide, and tetrahydrofuran. Their solubility in water is correspondingly low, only 0.006–0.009 ppm (= mg/L).

Chemical stability studies are monitored by silica gel thin-layer chromatography (tlc) or by high performance liquid chromatography (hplc) using a reverse-phase C_{18} coated column (24). Hplc peaks or tlc spots are visualized by their uv absorption at 245 nm; the tlc spots can also be detected by ceric sulfate or phosphomolybdic acid staining.

Avermectins are acid-sensitive. Although stable in anhydrous glacial acetic acid solution at room temperature, aqueous CH_3COOH and stronger acids, such as dilute HCl, H_2SO_4, and *p*-toluenesulfonic acid in methanol solution, more rapidly cleave off the first sugar. Stronger concentrations of methanolic or aqueous acids are necessary to hydrolyze off the second sugar to give the aglycone.

Strong bases such as methanolic potassium hydroxide, sodium methoxide, or 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU), cause epimerization at the C-2 carbon or shift the beta-gamma double bond into conjugation with the lactone carbonyl (Fig. 4) (25, 26).

Uv light below 280 nm rapidly isomerizes the (*E*) (*trans*) 8,9- and 10,11-double bonds to the 8,9- and 10,11-(*Z*)-isomers (Fig. 5) (27).

4.2. Reactivity

Avermectin B_1 and ivermectin both contain two secondary and one tertiary hydroxy group. The two secondary alcohols are readily acetylated with acetic anhydride in pyridine, although at 0°C, a fair amount of the 4″-monoacetate, but not the 5-monoacetate, is obtained. With more reactive acid chlorides, however, it is not possible to obtain the 4″-*O*-monoacyl derivative, and it is necessary to protect the 5-OH as a 5-*O*-*tert*-butyldimethysilyl (TBDMS) derivative. This can be prepared selectively because of the hindered C-4″ position (28). Removal of the 5-protecting group is accomplished with *p*-toluenesulfonic acid monohydrate

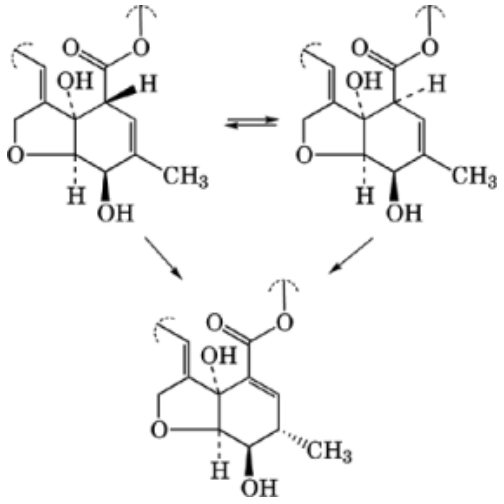


Fig. 4. Treatment of ivermectin with methanolic potassium hydroxide solution (25).

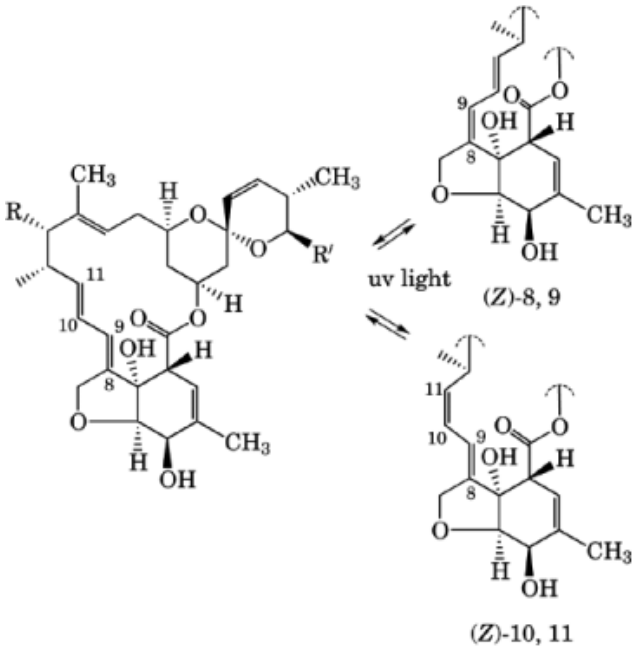


Fig. 5. Photoisomerization of avermectins. R=α−L−oleandrosyl−L−αoleandrosyl; R′=*sec*−C_4H_9 or *i*-C_3H_7 (see Fig. 1) (27).

(p − TsOH·H_2O) in CH_3OH (1% at RT for 20–30 min; longer reaction times generate substantial amounts of monosaccharide) or with an HF-pyridine-THF mixture (29). It is sometimes possible to prepare 5-monoacyl derivatives directly from unprotected ivermectin by careful use of one equivalent of acylation reagent, particularly when the latter is bulky (eg, bis(trichloroethoxy)phosphoryl chloride). Many 4″-*O*-substituted derivatives have been prepared as they retain considerable bioactivities; however, 5-*O*-substitution products lose most anthelmintic activities.

5. Analytical Procedures

Since the avermectins exhibit unprecedented potency, they are used at unusually low doses of 6–300 μg/kg, which makes the detection and isolation of residues and metabolites from animal tissue a new challenge. For this reason a sensitive analytical assay requires a derivative suitable for detection at concentrations down to 1/10 or 1/100 of one ppm. Ivermectin and avermectin B_1 are therefore converted into an aromatic derivative which allows detection by fluorescence absorbance. To achieve this derivatization, avermectin B_1, ivermectin, or their derivatives are heated with acetic anhydride in pyridine at 100°C for 24 h (30). The reaction time can be reduced to 1 h by using *N*-methylimidazole as a catalyst (31). The resultant 4″-*O*-acetyl-2,5,6,7-bisdehydro analogue is detected after hplc separation and characterized by a distinct retention time. Using a C_2-extraction cartridge, with 22,23-dihydro avermectin B_{1a} monosaccharide as an internal standard, it is possible to detect as little as 1 ng/mL of ivermectin in plasma or milk (32). This procedure was adapted as a confirmatory assay by hydrolysis of the avermectin derivatives to aglycone, monosaccharide, and parent disaccharide, subsequent aromatization, and finally detection of three distinct hplc peaks corresponding to the acetylated bisdehydro aglycone, monosaccharide, and parent compound peaks via fluorescence detection. A procedure using chemical ionization mass spectrometry-mass spectrometry (ms/ms) was developed for a confirmatory assay of ivermectin tissue residues in cattle (33). It is also possible to determine avermectins directly after extraction, using a synthetically isomerized avermectin derivative as an internal standard for hplc with uv detection (25). A hplc-reverse isotope dilution assay is available for the determination of ivermectin residues in animal tissue (34). A similar fluorescent derivative containing a 5-phenol group obtained by dehydration of the 5-keto derivative of ivermectin with ammonium acetate was also reported (35). An extraction procedure allowing direct hplc analysis with uv detection of ivermectin in bovine serum at concentrations as low as 2 ppb is available (36). Monoclonal antibodies for immunoassay of avermectins have been prepared (37).

6. Monosaccharides and Aglycones

The macrocyclic lactone of all avermectins has an α-L-oleandrosyl-α-L-oleandrosyloxy substituent at carbon 13, which is a 2-deoxy sugar glycoside, relatively sensitive to acid hydrolysis or alcoholysis. A solution of ivermectin in methanol containing a strong acid such as 1% sulfuric acid readily gives a good yield of the aglycone after 16–24 h at RT. When 2-propanol is substituted for methanol in this reaction, a good yield of the monosaccharide is obtained, as the bulkier 2-propanol preferentially attacks the sterically less hindered 1″-position over the 1′-position, which is attached directly to the C-13 of the macrocycle, which in turn is flanked on either side by the C-12 and C-14 methyl groups, respectively (Fig. 6) (38). These procedures readily yield the monosaccharides of ivermectin and avermectin B_1 and the aglycone of ivermectin. The preparation of the aglycone of avermectin B_1, however, is complicated: under the reaction conditions, addition of methanol to the 22,23-double bond occurs, yielding mainly the two epimeric 22,23-dihydro-23-methoxy monosaccharides and/or aglycones. The aglycone of the avermectin B_1 therefore must be prepared with aqueous acid; it can be obtained as a 1:1 mixture of aglycone and monosaccharide using 10% sulfuric acid in aqueous THF solution (38).

Removal of the 13-hydroxy group from avermectin aglycones gives 13-deoxyavermectin aglycones which are closely related to certain milbemycins. For example, ivermectin was converted into its aglycones (22,23-dihydroavermectin B_{1a} and B_{1b} aglycones); the 5-hydroxy group was then protected as an *O-tert*-butyldimethylsilyl group. The 13-hydroxy group was substituted by chloro; the 13-chloro group was removed by reduction; C-5-OH was deprotected; and, finally, the C-25 B_{1a} and B_{1b} homologues were separated into 13-deoxy-22,23-dihydroavermectin B_{1a} and B_{1b} aglycones (39). Interestingly, the latter was subsequently also obtained from a milbemycin fermentation and given the name milbemycin B41-D (see Fig. 2 for structure B_{1b}).

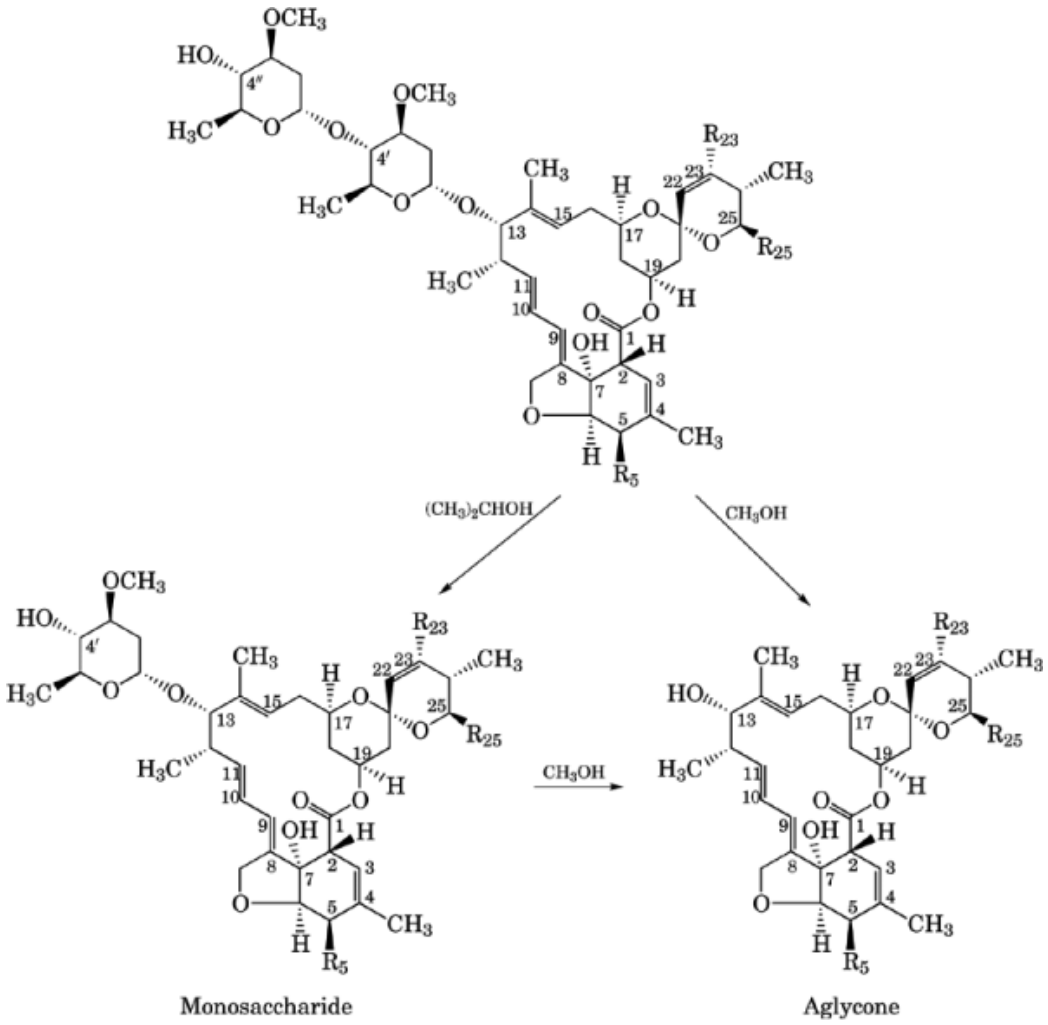


Fig. 6. Avermectin monosaccharides and aglycones. R_{25}=*sec*−C_4H_9; R_5=OCH_3 or OH; R_{23}=OH or H. The reaction conditions are 18°C, 16 h, 1% H_2SO_4 in the solvent indicated (38).

7. Chemical Reactions

7.1. Oxidations

Avermectin B_1 and ivermectin have two secondary hydroxy groups susceptible to oxidation to the corresponding ketones. Because of the allylic nature of the C-5 hydroxy group its selective oxidation to 5-oxoavermectin is readily accomplished with manganese dioxide (40). Although tautomerization to the enol and elimination of the remaining tertiary C-7 hydroxy group leads to a phenol (35), the 5-oxo derivatives are nonetheless stable enough to allow further chemical reactions. Particularly important is the stereospecific reduction with $NaBH_4$ to the 5-beta alcohol with natural configuration, which is used to prepare tritiated avermectin derivatives. Reaction with trifluoroacetic anhydride, however, gives the 2,5,6,7-tetradehydro phenol analogue. Use of mild oxidation procedures, such as oxalyl chloride-DMF (Swern oxidation), gives 4″,5-dioxo avermectin derivatives

or, after protection of the C-5 hydroxy group as a *tert*-butyldimethylsilyl derivative, 5-*O*-*tert*-butyldimethylsilyl-4″-oxoavermectins, which are valuable intermediates for further 4″-modified analogues. Sodium borohydride reduction of the 4″-keto function gives a mixture of 4″-epimeric hydroxy compounds, with the unnatural axial 4″-hydroxy group the major product and the natural epimer the minor one. Reductive amination with $NaCNBH_3$ and NH_4OOCCH_3 likewise yields an epimeric mixture of 4″-aminoderivatives with interesting biological properties (41).

The avermectins also possess a number of allylic positions that are susceptible to oxidative modification. In particular the 8a-methylene group, which is both allylic and alpha to an ether oxygen, is susceptible to radical oxidation. The primary product is the 8a-hydroperoxide, which has been isolated occasionally as an impurity of an avermectin B_1 reaction (such as the catalytic hydrogenation of avermectin B_1 with Wilkinson's rhodium chloride-triphenylphosphine catalyst to obtain ivermectin). An 8a-hydroxy derivative can also be detected occasionally as a metabolite (42) or as an impurity arising presumably by air oxidation. An 8a-oxo-derivative can be obtained by oxidizing 5-*O*-protected avermectins with pyridinium dichromate (43). This also can arise by treating the 8a-hydroperoxide with base.

The allylic 4a-methyl group can be oxidized with SeO_2-catalyzed *tert*-butylhydroperoxide to a 4a-hydroxy analogue (44).

The double bonds of avermectins react with *m*-chloroperbenzoic acid to give 3,4-, 8,9-, and 14,15-epoxides. The 8,9-epoxide is the primary product and can be isolated in good yield (45). The 8,9-epoxide was opened by aqueous acids to the 8,9-diol (46). The 3,4-diol can be obtained readily and regiospecifically by osmium tetroxide oxidation. Neither peracids nor OsO_4 will attack the 22,23-double bond.

8. Reductions Including Ivermectin Preparation

Reductions of avermectin B_1 containing five double bonds with Pd or Pt catalysts proceed at almost comparable rates at the two disubstituted 10,11- and 22,23-double bonds to give a mixture of 10,11- and 22,23-dihydro derivatives. Further hydrogenation leads to 10,11,22,23-tetrahydro- and 3,4,10,11,22,23-hexahydro-derivatives; exhaustive hydrogenation leads to 3,4,8,9,10,11,22,23-octahydro analogues. Under no circumstances is the 14,15-double bond hydrogenated. For the preparation of ivermectin (22,23-dihydro avermectin B_1), Wilkinson's homogeneous $[(C_6H_5)_3P]_3RhCl$ catalyst has been employed for the regiospecific hydrogenation of the avermectin B_1 22,23-double bond, which is the only disubstituted cis double bond (18). To prepare 10,11-dihydro avermectin B_1, the regioselective reaction with *N*-bromacetamide was used to make a 11,10-bromohydrin, which can then be dehalogenated and deoxygenated to the desired product (47).

9. Radiolabeled Derivatives

Since ivermectin (= 22,23-dihydroavermectin B_1) is obtained by catalytic reduction of avermectin B_1, the same procedure using tritium gas conveniently affords tritiated ivermectin (22,23-$^3[H]$-22,23-dihydroavermectin B_1). The preparation of a tritiated derivative containing a 22,23-double bond starts with the readily available 5-ketone, which is reduced with $^3[H]$-sodium borohydride stereospecifically to a 5-$^3[H]$-derivative (40). Carbon-14 labeled avermectins can be obtained by a biosynthetic process using sodium (1-^{14}C)propionate as labeled precursor (48).

10. Interconversions of Avermectins

Methylation of avermectins B_1 and B_2 leads to the corresponding derivatives of the A series (49). A procedure involving the oxidation of the 5-methoxy group with mercuric acetate and $NaBH_4$ reduction of the 5-keto-intermediate allows the conversion of the A to the B components (50). The 23-hydroxy group of the "2" components, after selective protection of the other secondary hydroxy groups, is converted to a thionocarbonate, which can be eliminated to give the 22,23-double bond of the "1" components; alternatively it can be reduced with tributyltin hydride to the 22,23-dihydro derivatives (= ivermectins) (51).

11. Syntheses

Avermectin aglycones, monosaccharides, and the naturally occurring disaccharides themselves have been further modified by attaching various sugars to the different hydroxy groups. Most of these methods have used 1-bromo sugars via the Konigs-Knorr procedure (52, 53). More recently, the use of 1-phenylthio and 1-fluoro sugars has resulted in better yields of those glycosides (54). A mixture of the two anomeric methyl glycosides of oleandrose is obtained by acid methanolysis of avermectins, and these have been converted to L-oleandrose (55) and the 1-phenylthio glycoside (54). Total synthesis of avermectins including the glycosylation of avermectin aglycones by interesting, new methods have been reported recently by several research groups (56–59). Two excellent reviews of partial and total synthesis of avermectins and milbemycins have been published (60, 61).

12. Economic Aspects

The worldwide acceptance of ivermectin in livestock production and health care of companion animals has made it the largest selling animal health drug. Abamectin is in commercial use as an agricultural pesticide and its applications are continuing to expand. Ivermectin under the trademark Mectizan is now considered the drug of choice for treatment of human onchocerciasis. There is no commercial return since it is provided free of charge to the World Health Organization. Ivermectin also shows considerable promise for the treatment of human lymphatic filariasisand strongyloidiasis.

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