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Recent advances in avermectin chemistry

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One half of the 2015 Nobel Prize in Physiology or Medicine was awarded to Satoshi Ōmura and William Campbell for the discovery of natural avermectins in 1976, which has revolutionized the treatment of endo- and ectoparasitic diseases. The published reviews on avermectins are primarily concerned with their biological activity and applications. This is the first review that analyzes the main advances and trends in the development of avermectin chemistry. The strategies for the total synthesis of natural avermectins are described. Considerable attention is given to the methods of chemical modification of avermectins giving new semisynthetic derivatives. The established structure–biological activity relationships for the products are discussed. The review considers the optimal strategies for chemical modification of avermectins in order to increase their biological activity and stability, reduce toxicity for warm-blooded animals and expand their field of application.
The bibliography includes 241 references.

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1. Introduction

Parasitic infections caused by protozoa, helminths and ectoparasites are distributed worldwide and pose a serious health risk to humans and animals, in particular livestock.[1–7] Avermectins are currently considered as the most effective nematicides, insecticides and acaricides.[8–12]

Avermectins were isolated for the first time in 1976 in Japan from the soil actinomycetes *Streptomyces avermitilis* and their activity was evaluated against the nematode *Nematospiroidesdubius*.[13] The investigations demonstrated that avermectins showed high broad-spectrum antiparasitic activity. Different avermectin derivatives, primarily ivermectin, which were synthesized in subsequent studies, have become widely used as drugs and in agriculture.[8, 13–15]

Avermectins have brought a therapeutic revolution in the fight against parasites and they are currently the most commonly applied antiparasitic drugs, which probably most

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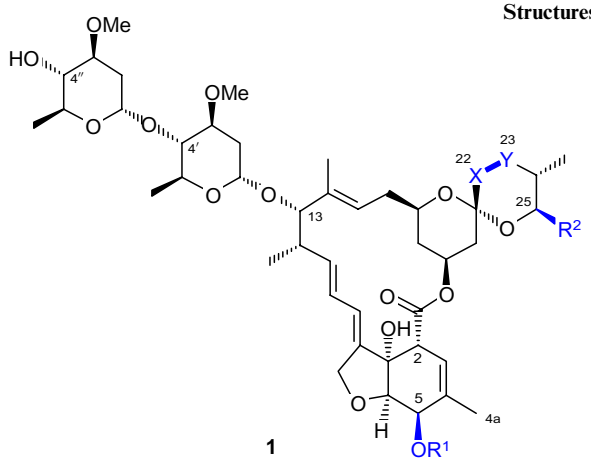
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effectively combat endo- and ectoparasites of plants, animals and humans. For the discovery of avermectins, Satoshi Ōmura and William Campbell were awarded the 2015 Nobel Prize in Physiology or Medicine.[16–18]

Avermectins (AVM, **1**) belong to the 16-membered macrolide family. Formally, these compounds can be represented as milbemycin derivatives (*e.g.*, compounds **2**) with the disaccharide 4′-α-L-oleandrosyl-4″-α-L-oleandrosyl (L-oleandrose is 2,6-dideoxy-3-*O*-methyl-L-arabinohexose) attached at the 13 position. The strain *S. avermitilis* found in Japan produces a mixture of eight avermectins consisting of four major and four minor compounds (four pairs of homologous compounds) designated as avermectins A_{1a}, A_{1b}, A_{2a}, A_{2b}, B_{1a}, B_{1b}, B_{2a} and B_{2b}.† The structural differences between the homologous avermectins are presented in Table 1. The designations A and B refer to the presence of the methoxy or hydroxy group, respectively, at the C5 position. Besides, the homologues differ by the moieties at the C22 and C23 positions. Thus, the number 1 in the name of the avermectin indicates that the C22 and C23 atoms are bonded by a C–C single bond and the C23 atom carries an *S*-configured α-hydroxy group; the number 2 indicates the presence of the C=C double bond between the C22 and C23 atoms. Finally, the a and b series designate the presence of a sec-butyl or isopropyl substituent, respectively, at the C25 atom. In each homologous pair, the ratio of the major (represented by the lowercase letter a) to minor (represented by the lowercase letter b) components generally varies from 80 : 20 to 90 : 10.[19]

Milbemycins structurally differ from avermectins in that the former compounds are missing the C-13 disaccharide.

Structures 1



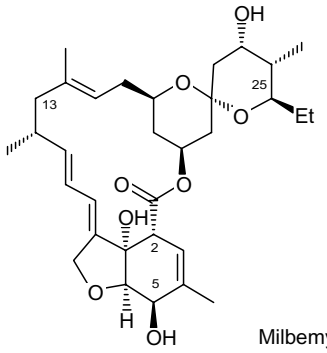
1

Table 1. Avermectin homologues **1**.

Avermectin	R^1	X–Y	R^2
A_{1a}	OMe	CH=CH	Bu^s
A_{1b}	OMe	CH=CH	Pr^i
A_{2a}	OMe	CH_2–CH(α-OH)	Bu^s
A_{2b}	OMe	CH_2–CH(α-OH)	Pr^i
B_{1a}	OH	CH=CH	Bu^s
B_{1b}	OH	CH=CH	Pr^i
B_{2a}	OH	CH_2–CH(α-OH)	Bu^s
B_{2b}	OH	CH_2–CH(α-OH)	Pr^i

† Presently, the two last symbols are often not subscripted for the sake of simplicity, *i.e.*, avermectins are denoted as A1a, A1b, *etc.*

Structure 2



Milbemycin α19 (**2**)

Milbemycins and avermectins have a common pharmacophore, the 16-member macrocyclic lactone ring fused both with hexahydrobenzofuran and spiroketal moieties (see Structure **1**). This pharmacophore binds at specific glutamate-gated chloride channel (GluCl-channel) receptors. Avermectins and milbemycins have similar but not identical spectra of biological activity.[20] Milbemycins are more abundant in nature than avermectins; however, the former compounds are generally less active or inactive.[21,22]

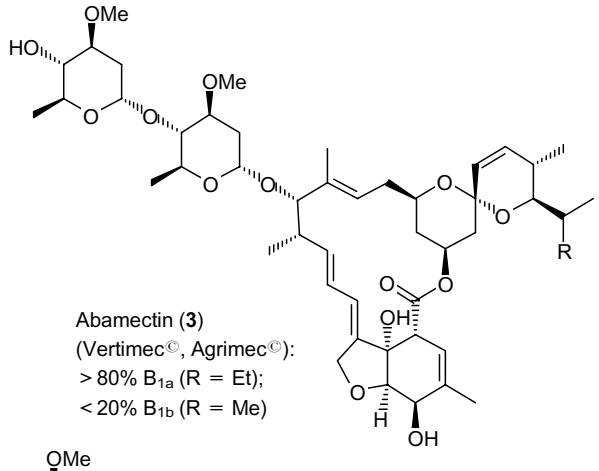
All individual avermectins exhibit high antiparasitic activity, the highest activity being observed for avermectins B_1 containing a hydroxy group at the C5 position. A pair of avermectins B_1, *i.e.*, a mixture of avermectins B_{1a} (> 80%) and B_{1b} (< 20%), is marketed under the trade name Abamectin (**3**).[19,22] Tenvermectins A and B (**4**) and doramectin (**5**), which contains the cyclohexyl group instead of the *sec*-butyl group (avermectin B_{1a}) at the C25 position, are also produced by microbiological methods.

Commercially available semisynthetic avermectins, such as ivermectin (IVM, **6**), emamectin benzoate (**7**), eprinomectin (EPM, **8**) and sumectin (**9**), are derived from abamectin; therefore, they exist as mixtures of the major (B_{1a}) and minor (B_{1b}) homologues.[23,24] The doramectin-based drug selamectin (**10**) shows systemic broad-spectrum nematicidal, insecticidal and acaricidal effects.

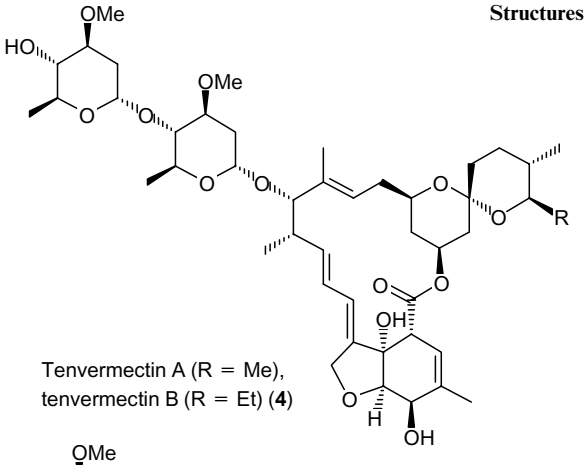
Avermectins have attracted great attention of researchers interested in designing new agents effective against endo- and ectoparasites due to the unique structure of these compounds and their high cost-effectiveness as drugs and plant protection products. One area of research on avermectins is based on the improvement of biotechnology of their production. Another area involves not only the preparation of synthetic avermectins but also the chemical modification of the known compounds of this family, which are performed in order to increase their biological activity and stability, decrease the toxicity and improve other properties, thereby allowing the extension of their use.[25] Apart from the widely used ivermectin, eprinomectin and avermectin, other derivatives with high anthelmintic activity were synthesized. Therefore, there is a need for a more in-depth analysis of how different chemical modifications of avermectins affect the biological activity (primarily anthelmintic) of the resulting products, their stability and properties.[26] Besides, avermectins are extensively evaluated for other types (in addition to those mentioned above) of biological activity (see Section 6).

Monographs and reviews on the chemistry of avermectins are lacking in the literature. In the small-circulation monograph[27] written with the participation of the authors of this review, the data on avermectins are mainly of a historical character and are considered in relation to milbe-

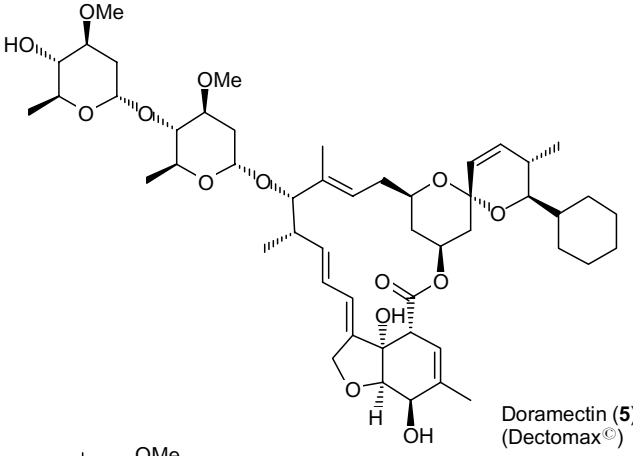
Structures 3 – 10



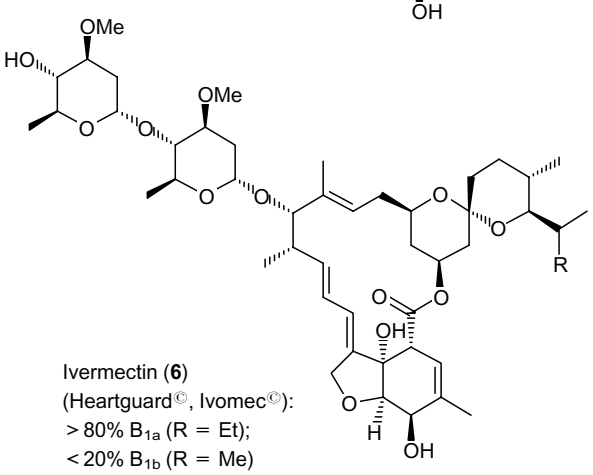
Abamectin (**3**)
(Vertimec©, Agrimec©):
> 80% B_{1a} (R = Et);
< 20% B_{1b} (R = Me)



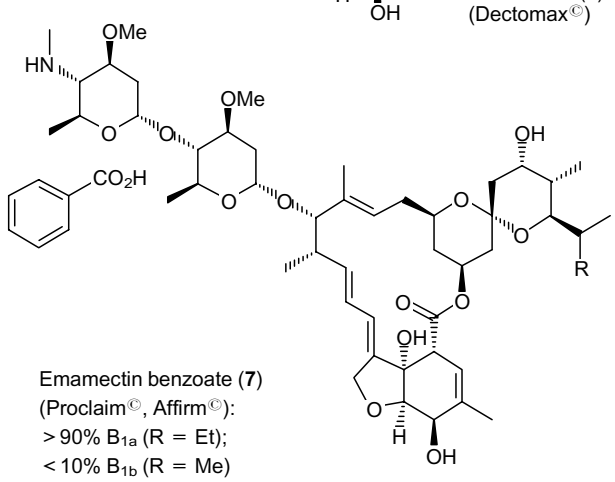
Tenvermectin A (R = Me),
tenvermectin B (R = Et) (**4**)



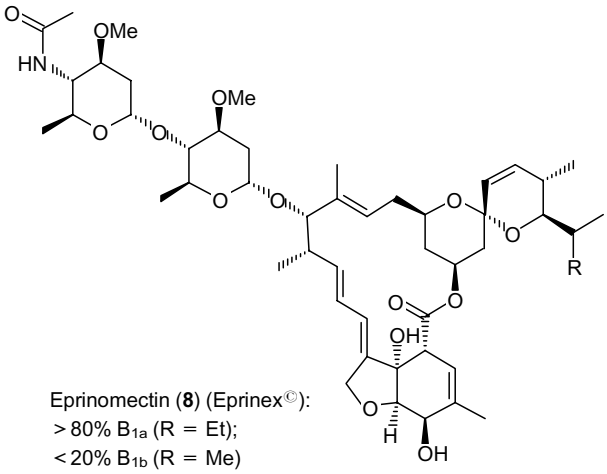
Doramectin (**5**)
(Dectomax©)



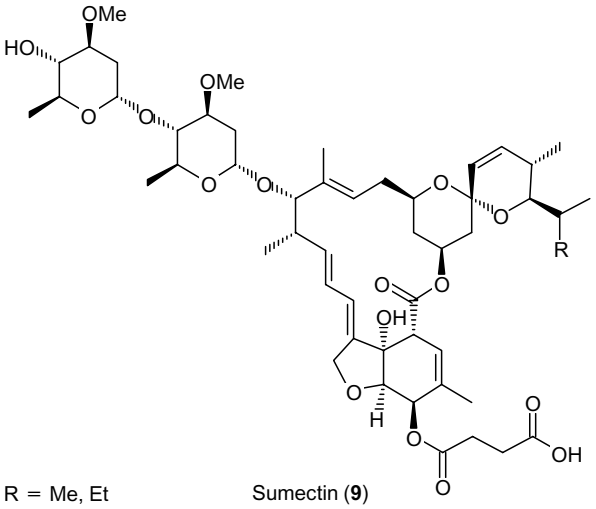
Ivermectin (**6**)
(Heartguard©, Ivomec©):
> 80% B_{1a} (R = Et);
< 20% B_{1b} (R = Me)



Emamectin benzoate (**7**)
(Proclaim©, Affirm©):
> 90% B_{1a} (R = Et);
< 10% B_{1b} (R = Me)

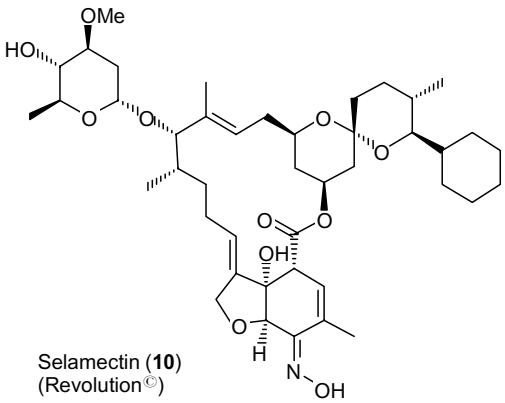


Eprinomectin (**8**) (Eprinex©):
> 80% B_{1a} (R = Et);
< 20% B_{1b} (R = Me)



R = Me, Et

Sumectin (**9**)



Selamectin (**10**)
(Revolution©)

mycins. This is the first review that summarizes and analyzes the main advances and trends in the development of avermectin chemistry and describes methods for the preparation of natural avermectins and their semisynthetic derivatives. Considerable attention is given to the methods of chemical modification of natural avermectins. The structure–biological activity relationships for the products are discussed. These data will allow the synthesis of avermectin-based effective agents with low toxicity and broad-spectrum activity.

2. Synthesis of avermectins

Microbiological methods remain the most used for industrial synthesis of natural avermectins. The modern biotechnology for the production of avermectins implies the creation of high-performance strains that produce not only the most effective avermectins B_1 (B_{1a} and B_{1b}) but also highly active semisynthetic avermectin analogues.[28] Presently, the industrial synthesis of avermectins relies on the fermentation, the microsomal oxidation of early-stage fermentation products and semisynthetic approaches.[29] The synthetic biology methods and tools for the preparation of target products (*e.g.*, ivermectin) were extensively developed in the past years.[30]

Another area of research is concerned with the development of the total chemical synthesis of natural products. First strategies for the synthesis of avermectins B_{1a} and A_{1a}, proposed at the end of the 20th century, involved many steps and afforded target products in very low yields (0.08%).[31] Attempts are being continued to develop efficient procedures for the total chemical synthesis of avermectins.[32] Synthetic strategies were proposed for the preparation of abamectin[33] and ivermectin.[34–36] The total synthesis of avermectins B_{1a} (see Refs 32 and 37) and A_{1a},[38] as well as of their aglycones, was described in the publications.[39,40]

2.1. Microbiological method

Natural avermectins are produced on the industrial scale by the aerobic fermentation using a broth of the high-producing strain *S. avermitilis*. The most significant progress in the improvement of biotechnological production of avermectins was made in China. Thus, Chinese researchers[41,42] succeeded in increasing the titer of the product, avermectin B_1 (abamectin), from 0.009 to 9 g L^{-1}, *i.e.*, by 1000 times. To date, China is the only avermectin producing country in the world, the avermectin generating about $0.5 billion annual sale (3 billion RMB).[41]

The avermectin complex produced in Russia under the trade name Aversectin C is a mixture of eight homologues with the following percentage of components: B_1 (42%), B_2 (22%), A_1 (13%) and A_2 (23%).[28]

As mentioned above, doramectin (**5**)[43] is structurally related to avermectin B_{1a} with the only difference that it contains a cyclohexyl substituent instead of the *sec*-butyl group at the C25 position, which is not typical of the wild-type strain. This avermectin derivative is produced by the fermentation using the avermectin-producing mutant strain *S. avermitilis*, which is capable of introducing the cyclohexyl substituent, that is present in the reagent added to the fermentation broth, at the C25 position.[44,45] The use of the synthesized gene *aveC* during the fermentation made to possible to significantly increase the purity of doramectin and reduce its cost.[46–48]

The long-term mass use of avermectin and ivermectin led to the widespread emergence of resistance of parasites to these drugs. Therefore, there is a need for the design of new avermectin analogues with high biological activity. Among these products are tenvermectins A and B (**4**), which were isolated from the fermentation broth of the genetically engineered strains *S. avermitilis* MHJ1011 and AVE-H39.[49–53] These 16-membered macrolides showed better insecticidal properties compared to avermectin and ivermectin. Tenvermectins have attracted particular attention also because they are structurally similar to the semisynthetic ivermectin, the most commercially successful member of the avermectin drug family.

The discovery of tenvermectin and a series of other natural avermectins and milbemycins bearing, like ivermectin, a 22,23-saturated bond has stimulated an extensive search for ivermectin-producing strains. These studies resulted in the construction of genetically engineered strains producing ivermectin and other 22,23-dihydroavermectins.[54–58] The results of these studies opened a route to the production of industrial ivermectin-producing strains because the biosynthesis of such 16-membered lactones is much more economical and technically more affordable compared to the chemical synthesis based on available avermectins. Currently, ivermectin is industrially produced by the selective hydrogenation of the 22,23-double bond of abamectin.[8]

2.2. Chemical synthesis

There are two lines of development of strategies for the chemical synthesis of avermectins. One lines involves the synthesis of the most active isomers of avermectins from by-products or biologically less active products of biosynthesis. In particular, the conversion of less active isomers of avermectin B_2 into avermectin B_1 made it possible to significantly increase the efficacy of the agents.[34,59] These studies have attracted considerable attention in early stages of the research on avermectins since the complexity of their structures makes the total synthesis of these compounds a challenging problem. However, due to the progress in the selective biotechnological production of the most effective avermectins B_1, these studies became irrelevant. Currently, these methods are used only for special purposes, *e.g.*, for the introduction of isotope labels.[60]

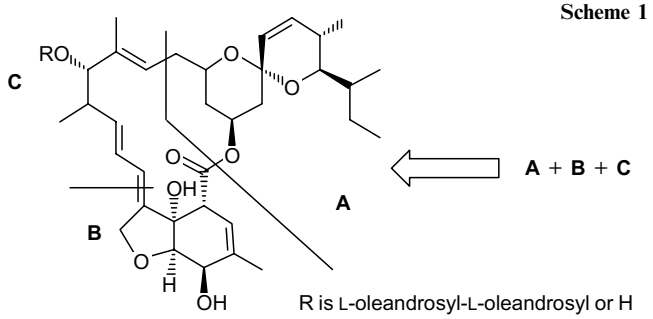
Another area of research is concerned with the development of methods for the total synthesis of natural avermectins. Strategies for the synthesis generally involve several independent components, which provide the construction of particular moieties of the complex molecule. Studies are focused on the development of new methods and the improvement of known methods for the formation of the spiroketal and hexahydrobenzofuran moieties and the acyclic portion involving the C9–C15 atoms. Besides, approaches are developed to assemble the avermectin aglycone from individual segments followed by the formation of the target product from the aglycone.

The first total synthesis of (+)-avermectin B_{1a} was reported in 1986.[37] The transformation sequence is based on the stereoselective synthesis of the northern segment (C11–C28) of the molecule derived from (*S*)-malic acid and L-isoleucine followed by the coupling with the functionalized southern segment, macrolactonization and stereocontrolled glycosylation.

Later, the total synthesis of avermectins B_{1a} (see Refs 61–63) and A_{1a} (see Ref. 38) was described. Avermec-

tin B_1 aglycone, a key intermediate in the synthesis of avermectin B_{1a},[62] is assembled from three subunits: the spiroketal segment (**A**), the hexahydrobenzofuran moiety (**B**) and the acyclic portion (**C**) comprising the C9–C15 atoms (Scheme 1).

Scheme 1



Each segment is synthesized separately and then they are connected to form the avermectin aglycone in the following sequence:

A + **B** ⟶ **A**–**B**

A–**B** + **C** ⟶ **AVM**

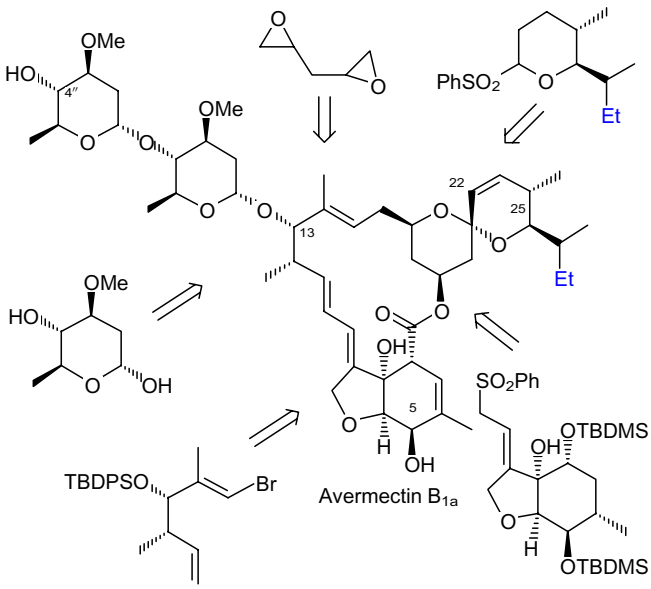
Therefore, the first step involves the connection of the spiroketal and hexahydrobenzofuran moieties followed by the coupling of the resulting unit to the acyclic portion and the cyclization to form macrolide, the avermectin aglycone. The total synthesis is completed with the attachment of the disaccharide L-oleandrosyl-L-oleandrose to the aglycone (Scheme 2).

Several approaches were developed for the formation of the hexahydrobenzofuran moiety.[64] For example, the following reactions were used as the key step: the condensation of 2-lithioxymethyl-1,3-dithiane with epoxy ketone,[65] the free-radical cyclization,[66,67] the Michael aldol condensation of an enoate–ketone by the action of an aluminium thiophenoxy complex[68] or other reactions.[69–71]

A number of enantiospecific methods, both biosynthetic[72] and chemical,[73–80] were proposed for the preparation of the spiroketal moiety of avermectin B_{1a}. For example, the 16-step synthesis of the spiroketal moiety of avermectin B_1 was accomplished.[33] Transformations involving the Wittig condensation as a key step were proposed in the publication.[81] A larger subunit of the avermectin aglycone (C11–C25 segment) containing the spiroketal unit was synthesized in the studies.[82,83]

The stereodivergent approach to the spiroketal moiety of avermectins A_1[84] utilizes a sequence of three aldol reactions involving the tris(trimethylsilyl)silyl group. The

Scheme 2



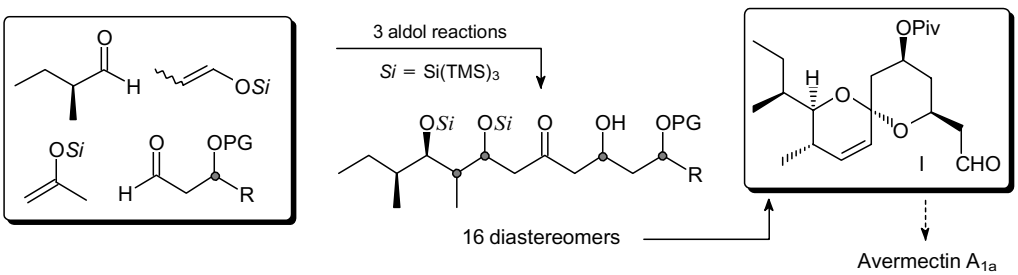
TBDPS is *tert*-butyldiphenylsilyl, TBDMS is *tert*-butyldimethylsilyl

distinguishing feature of this method is that each aldol reaction can be controlled to allow the highly stereoselective formation of either diastereomer, thereby giving 16 diastereomers along the same linear skeleton. The aldol products can be transformed into spiroketals, including the key intermediate **I** in the total synthesis of avermectin A_{1a} (Scheme 3).[84]

Oligosaccharides required for the synthesis of avermectin B_{1a} can be prepared *via* different routes. For example, a general method was developed for the stereoselective synthesis of oligosaccharides under mild conditions from D-glucose using 2-deoxy-2-pyridyl-1-thioglycosides as glycosyl donors and methyl iodide as the activator.[85] The haloetherification reaction was used to synthesize fully functionalized disaccharides.[86] Other multistep transformations giving various disaccharide derivatives were developed.[33,37,87,88] An alternative method is based on the preparation of oleandrosyl oleandrose (**11**) through the chemical degradation of natural avermectin.[89,90] A two-step procedure was proposed for the isolation of the target disaccharide using ozone, methyl sulfide and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 4).[90]

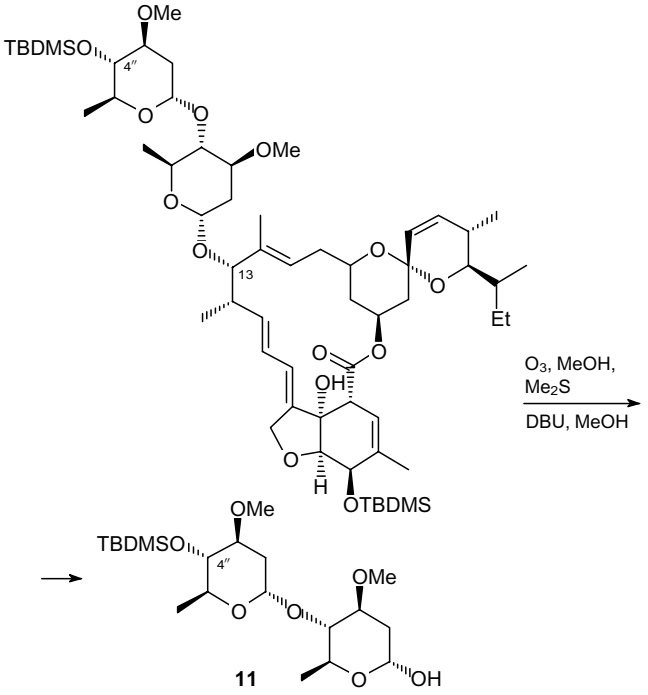
In the final step, avermectin is produced by the iterative glycosylation, *i.e.*, through the formation of a bond with oligosaccharides. The tandem addition of different sugar residues catalyzed by oleandrosyl disaccharides, which occurs without the total biochemical synthesis of avermec-

Scheme 3



PG is protecting group, TMS is trimethylsilyl, Piv is pivaloyl

Scheme 4



tin, was described in the study.[91] This investigation greatly extends the repertoire of known carbohydrates destined for nucleotide substrates and provides a rapid one-pot strategy for the generation of 50 differentially glycosylated avermectins.

Subsequently, a more efficient and straightforward route to avermectin B_{1a} was proposed, with each step being optimized by the authors (Scheme 5).[32]

The strategy for the synthesis involves the following transformations: 1) the stereoselective construction of the hexahydrobenzofuran and spiroacetal segments, as well as *E*,*E*-diene (C8 – C11); and 2) the macrolactone cyclization without disturbing the readily epimerizable C2 stereocentre and the C3 – C4 double bond, which is prone to migrate to the C2 position (Scheme 6).[32]

The distinguishing feature of this total synthesis of avermectin B_{1a} is the unique protection of hydroxy aldehyde with the trityl group. This allows the authors to synthesize the hexahydrobenzofuran segment and retain it without isomerization or decomposition throughout the transformation sequence.[32]

3. Semisynthetic avermectins

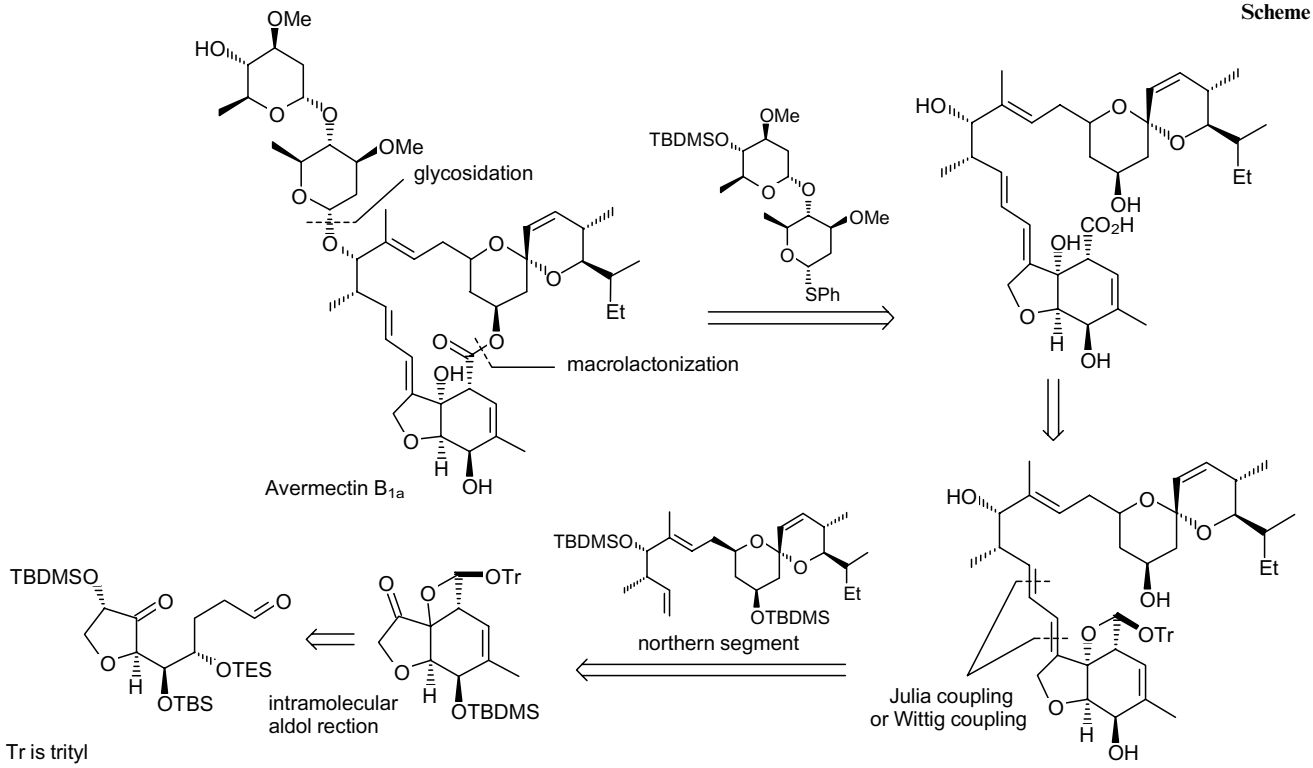
Secondary metabolites of living organisms are often used as active ingredients of drugs only after chemical modification in order to increase their activity and bioavailability and also to impart required physicochemical properties to these compounds and reduce side effects.

More effective analogues were synthesized based on natural avermectins. The strategy for chemical modification was derived from the data on biological activity of the components of the avermectin complex.[92,93] A series of avermectin B_1 derivatives thus synthesized are used in veterinary, agricultural protection and medicine. The technology of the production of semisynthetic avermectins, such as ivermectin, emamectin and eprinomectin, is based on the hydrogenation of the 22,23-double bond, amination and acetoxyamination of natural avermectin B_1, respectively; the production of selamectin, on the sequential demonoglycosylation, hydrogenation of the 22,23-double bond and 5-oxyamination of doramectin (Scheme 7).

3.1. Ivermectin

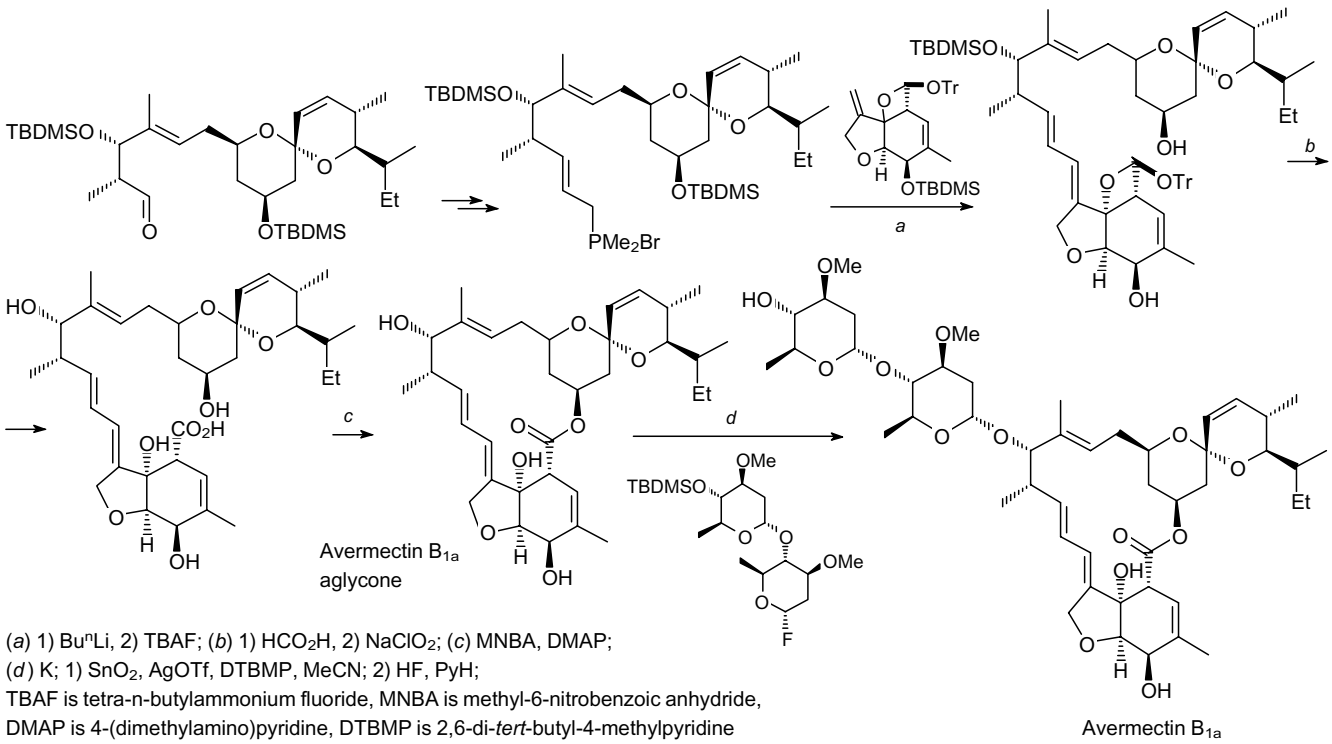
Ivermectin (**6**) is a semisynthetic macrocyclic lactone, which was prepared for the first time from abamectin (using the

Scheme 5



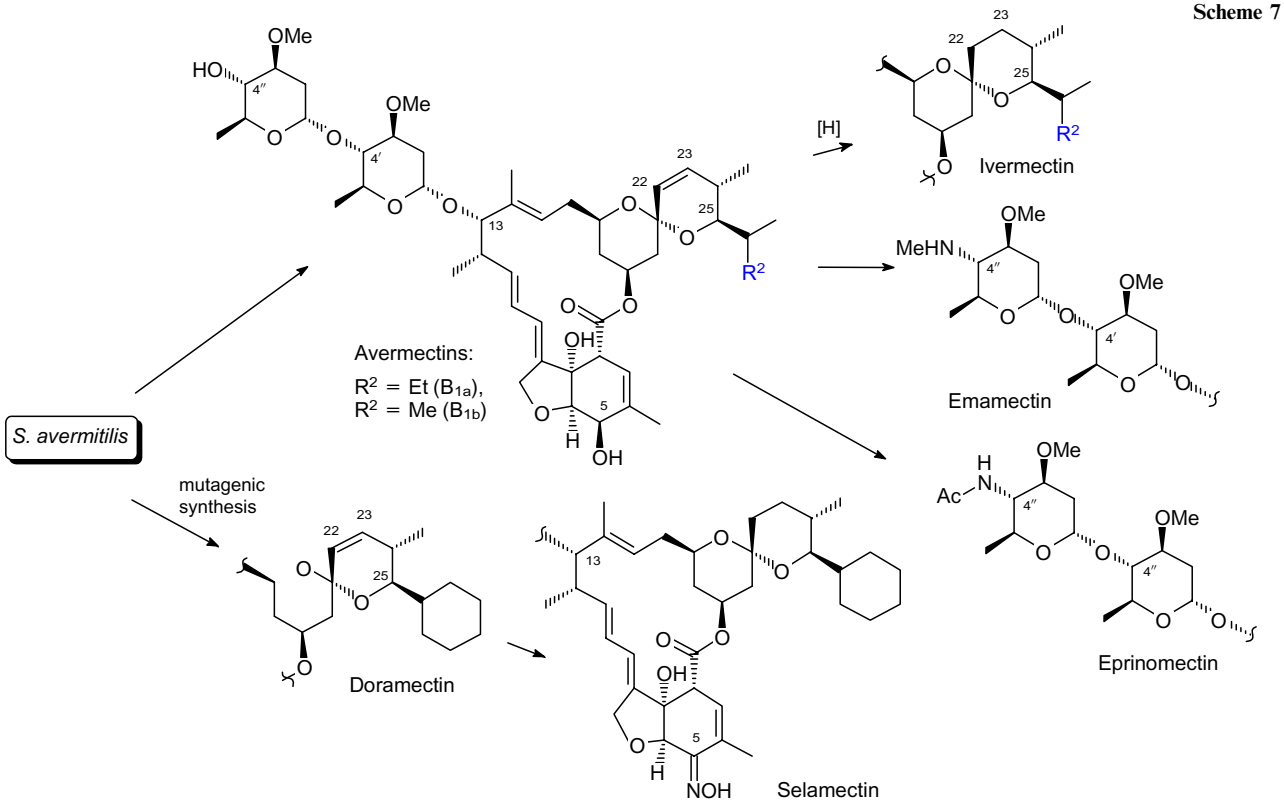
Tr is trityl

Scheme 6



(*a*) 1) Bu^{n}Li, 2) TBAF; (*b*) 1) HCO_2H, 2) $NaClO_2$; (*c*) MNBA, DMAP;
(*d*) K; 1) SnO_2, AgOTf, DTBMP, MeCN; 2) HF, PyH;
TBAF is tetra-n-butylammonium fluoride, MNBA is methyl-6-nitrobenzoic anhydride,
DMAP is 4-(dimethylamino)pyridine, DTBMP is 2,6-di-*tert*-butyl-4-methylpyridine

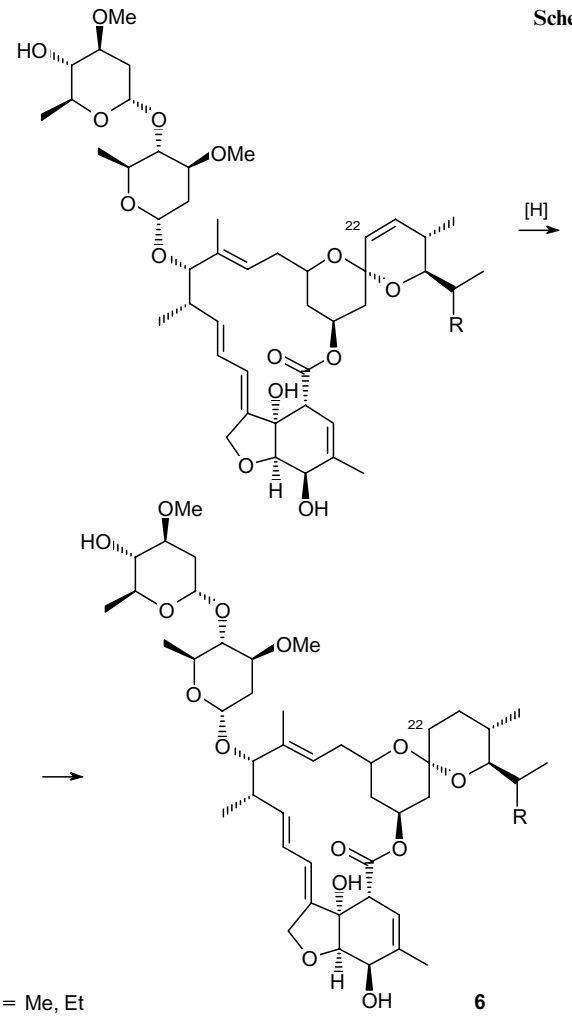
Scheme 7



producer strain *S. avermitilis*) by the selective hydrogenation of the 22,23-double bond. This compound, like abamectin, is a mixture of homologues B_{1a} (> 80%) and B_{1b} (< 20%).[8] Ivermectin is effective against a wide range of ecto- and exoparasites, except for trematodes and cestodes.[94]

As mentioned above, the synthesis of ivermectin was an important step towards designing antiparasitic agents.[95] It should be noted that avermectin B_1 is rather rapidly decomposed when exposed to sunlight under field conditions, while ivermectin (lacking the 22,23-double bond) is stable under these conditions. Consequently, the selective

Scheme 8



R = Me, Et **6**

hydrogenation of the 22,23-double bond allows the preparation of a more photostable compound compared to avermectin (Scheme 8).

Ivermectin is synthesized by the hydrogenation of avermectin B_1 in the presence of different catalysts.[93,96–102] The selectivity of the process depends on both the catalyst used and the reaction conditions (solvent, temperature, duration). Thus, the hydrogenation of abamectin in the presence of $RuCl_3$ or sodium 3-(diphenylphosphino)benzenesulfonate (TPPMS) affords ivermectin in 75 or 77% yield, respectively.[102] The catalytic hydrogenation of avermectin in aqueous ethanol in the presence of tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst) gives ivermectin in 95% yield.[96,99] Among γ-Al_2O_3-supported Ir-, Ru-, Pd-, Pt-based heterogeneous catalysts for the hydrogenation of avermectins, Ir/γ-Al_2O_3 showed the highest catalytic activity and high selectivity.[103]

Currently, ivermectin is one of the most commonly used antiparasitic drugs, making more than $1 billion in sales annually.[8]

3.2.Eprinomectin and emamectin

Eprinomectin (4″-acetylamino-4″-deoxyavermectin B_1, **8**) is used as a broad-spectrum veterinary parasiticide.[23,43,104] This compound is derived from avermectin B_1, in which the OH group at C4″ is replaced by the amide group (Scheme 9).[104,105] The transformation sequence involves four main steps: the protection of the OH group at the C5 position, the oxidation of the hydroxy group at the C4″ position to the keto group using phenyl dichlorophosphate or oxalyl chloride in DMSO (Swern oxidation), the reductive amination of ketone and the deprotection.

Emamectin is an avermectin derivative, in which the β-OH group at the C4″ position is replaced by the β-methylamino group.[22] Since emamectin is generally derived from abamectin,[22,106,107] it also exists as a mixture of two homologues (B_{1a} and B_{1b}). Emamectin is synthesized similarly to eprinomectin (see Scheme 9 for R = Me). The commercial drug based on emamectin is the benzoic acid salt (compound **7**).[22]

3.3. Sumectin

The Russian drug sumectin (**9**) is prepared by the acylation of natural abamectin (avermectins B_1) with succinic anhydride in the presence of dimethylaminopyridine (DMAP) as the catalyst (Scheme 10).[108,109] This compound is also referred to as 5-*O*-succinyl avermectin B_1, avermectin B_1 hemisuccinate or avermectin.

3.4. Selamectin

Selamectin (**10**) is the monosaccharide oxime derivative of avermectin[43] prepared from doramectin (Scheme 11).[110–113] In terms of chemical structure, this compound is an intermediate between disaccharide avermectins and milbemycins.

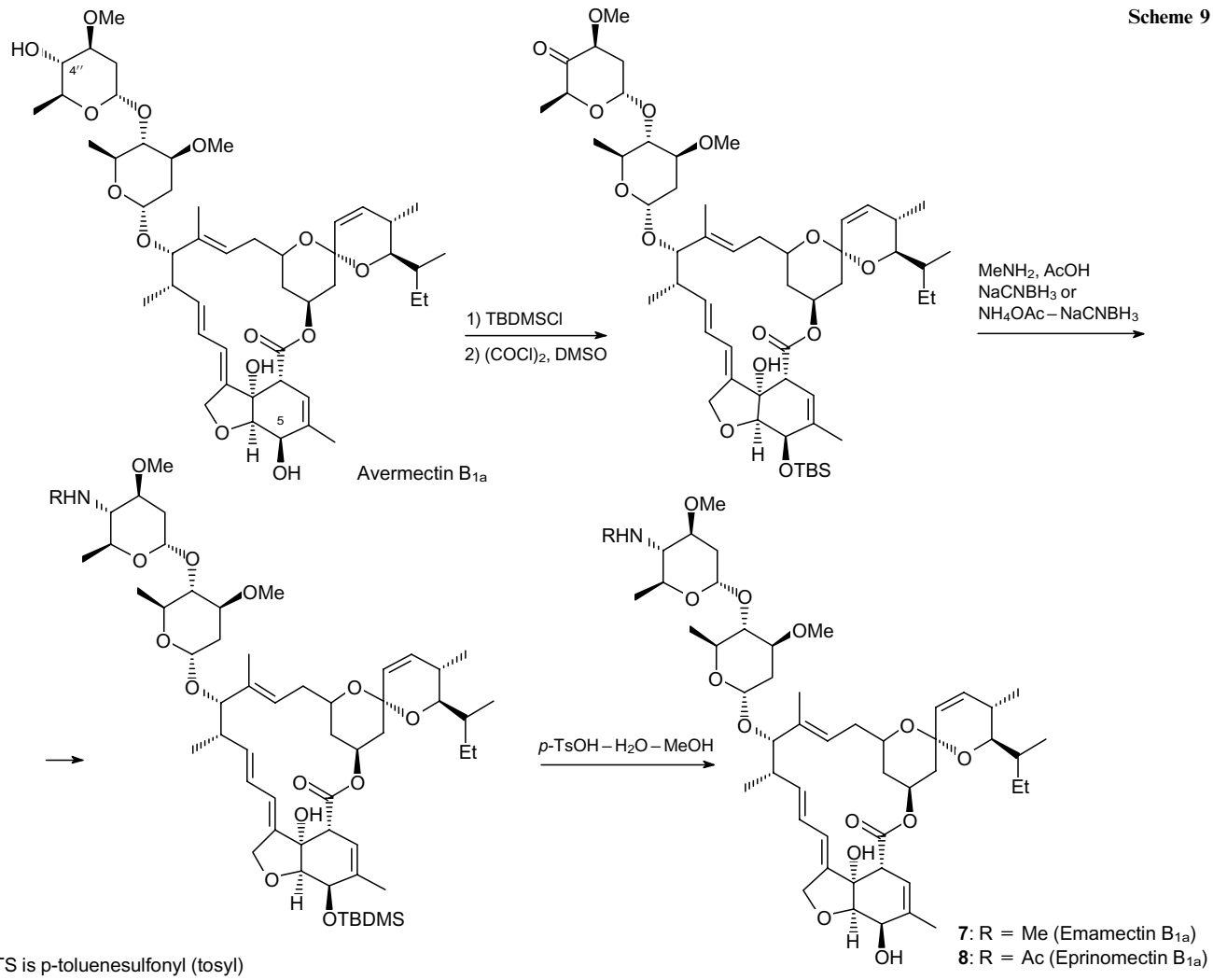
4. Chemical modification of avermectins

After the discovery of avermectins, many attempts were made to prepare their new stable and highly active derivatives with low toxicity.[114] Most studies in this area dealt with the modification of the most active avermectin B_{1a}, which resulted in the development of a large number of commercial drugs based on this compound. Much less attention was given to the chemical modification of avermectin B_{2a}, which also exhibits high biological activity and is a safer alternative.[115,116]

The avermectin molecule is characterized by the presence of a large number of reactive sites accessible to chemical modifications. Hydroxy substituents are one of the most easily accessible groups, among which stands out the hydroxy group of L-oleandrose at the C4″ position. Besides, the hydroxy groups of the macrocyclic lactone moiety at the C(5) atom, as well at the C(7) and C(23) atoms, are also chemically accessible sites. The axial hydroxy group at the C23 position is the most inert and it is much more difficult to subject this group to modification compared to the most active secondary allylic OH group at the C5 position adopting a pseudoequatorial configuration. Therefore, there are only a few studies on the functionalization of the C(23)—OH moiety. Apart from the hydroxy groups, the avermectin molecule contains other reactive sites, in particular, labile double bonds and a rather acidic hydrogen atom at the C2 position of the hexahydrobenzofuran moiety. The diversity of reactive sites in the avermectin molecule provides great possibilities for its chemical modification. At the end of the 20th century, chemical modifications of all possible reactive sites of avermectin were performed in a lot of studies. However, most of the synthesized derivatives proved to be inactive or weakly active.[23,114,117]

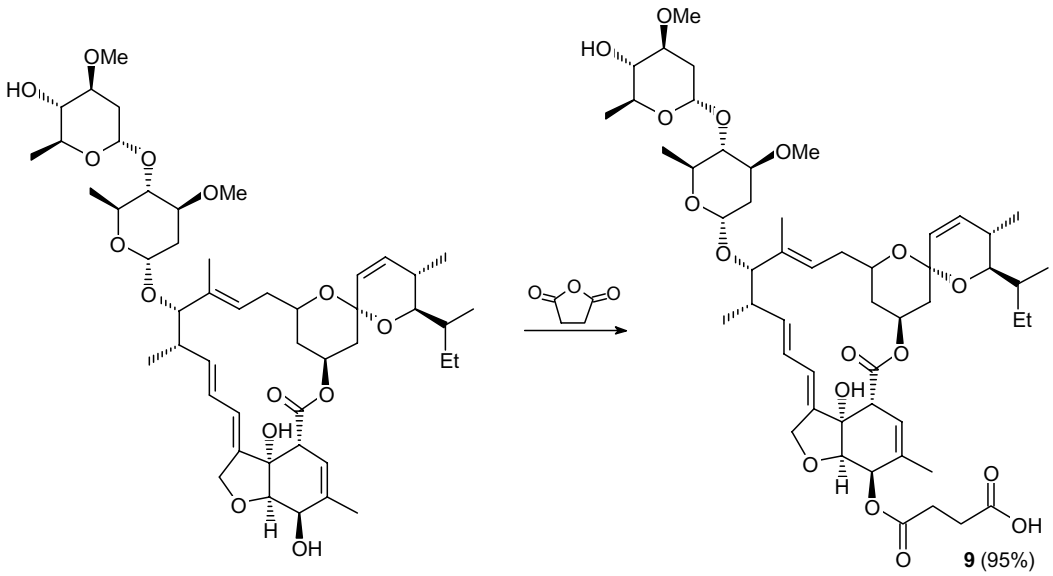
This Section is focused on methods of chemical modification of avermectins to form compounds that retain high

Scheme 9



p-TS is p-toluenesulfonyl (tosyl)

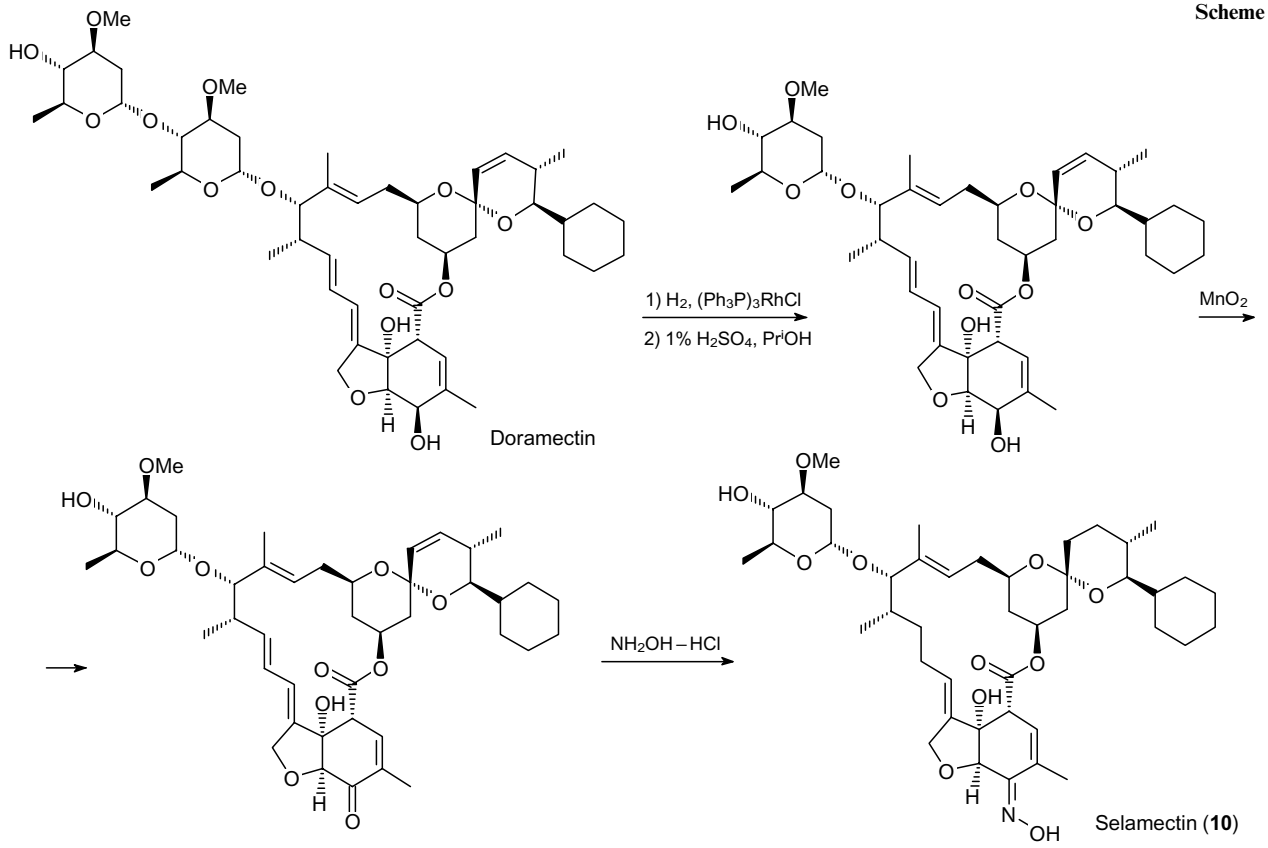
Scheme 10



biological activity. Modification products of hydroxy groups at the C4″ atom of L-oleandrose and at the C5 position are most important. Besides, the transformations leading to a strong decrease in the biological activity are briefly considered.

Currently, there are two main relevant research areas: (1) the development and improvement of methods for modification of avermectins at the specified position and (2) the synthesis of new derivatives, including those containing particular functional groups. The design of new

Scheme 11



derivatives involves the introduction of groups, which most frequently occur in known drugs but are not present in natural avermectins. These are, *e.g.*, ester, hydrazide, hydrazone, oxime and *O*-acyloxime groups. It is worth noting that studies on the modification and synthesis of avermectin derivatives are closely related to the analysis of structure–property relationships (see Section 5).

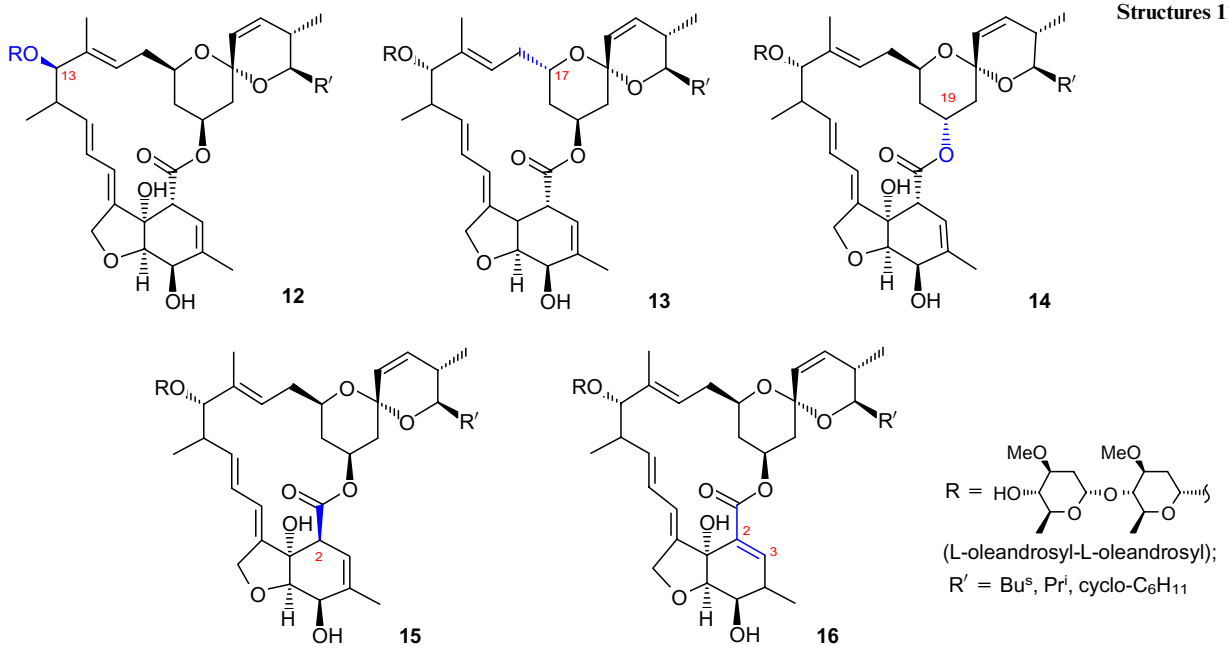
4.1. Epimerization of chiral centres

Even slight structural modifications significantly affect the biological activity of avermectins. In particular, products of epimerization of avermectins at the C13 (compound **12**),[118] C17 (**13**) and C19 (**14**) atoms[119,120] and also at the C2 position (**15**)[121–124] do not exhibit pronounced antiparasitic activity. Similarly, the migration of the C3=C4 double bond to the position conjugated to the carbonyl group (**16**)[121–125] led to the partial or complete loss of biological activity.

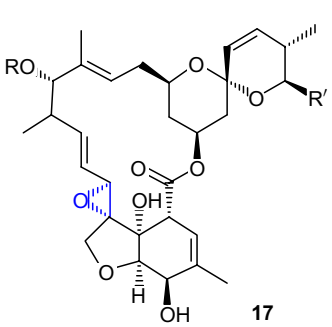
4.2. Double bond modification

Several reactions of avermectins involving double bonds are known, such as the epoxidation, hydration, oxidation, *etc.*

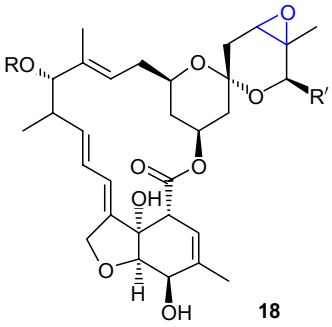
Structures 12–16



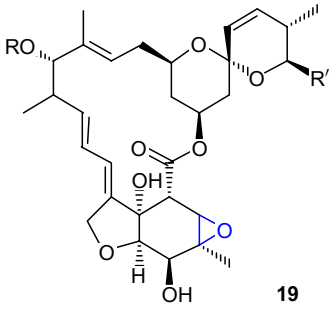
Structures 17 – 19



17



18



19

R is L-oleandrosyl-L-oleandrosyl; R′ = Pr^i, Bu^s, cyclo-C_6H_{11}

However, almost all derivatives synthesized by these methods proved to be weakly active.

The first example of the epoxidation of double bonds of avermectins was described in the patent.[126] Products of epoxidation at the C8═C9 and C14═C15 bonds were prepared by the reaction of avermectins with *m*-chloroperoxybenzoic acid. Avermectin B_1 8,9-oxide (**17**) exhibited high biological activity,[126, 127] which has stimulated the synthesis of other avermectin epoxides. In particular, 23,24- (**18**)[128] and 3,4-oxides (**19**)[129] of this homologue were prepared. However, subsequent studies did not reveal highly active compounds among other epoxidation products of avermectins at double bonds.

Products of oxirane ring cleavage of avermectin B_1 epoxides, in particular compounds that are formed through the formal hydration of double bonds, also proved to be inactive.[128]

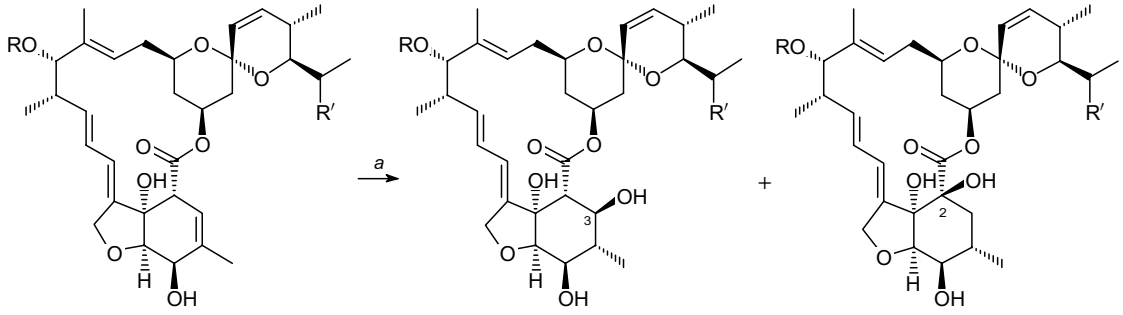
The Mukaiyama reaction of avermectin B_1 in the presence of Mn^{III} compounds as the catalyst afforded derivatives bearing hydroxy groups, *e.g.*, 3-hydroxy-3,4-dihydroavermectin B_1 (**20**).[130] Besides, the authors synthesized 2-hydroxy-3,4-dihydroavermectin B_1 (**21**), the first representative of 2-substituted avermectins (Scheme 12).

Hypobromic acid generated from *N*-bromoacetamide (NBA) was used as the selective reagent for the attack at the 10,11-double bond of avermectins.[131] The reaction afforded 10,11- bromohydrin (**22**), which was easily reduced to 10-hydroxyavermectin B_{1a} (**23**) (Scheme 13).

An investigation of the oxidation of avermectins demonstrated[132] that mercuric acetate selectively reacted with the 3,4-double bond of avermectin A_{2a}, to form 3α-acetoxy-4,5-enol methyl ether **24**, which was then transformed into 5-keto avermectin B_{2a} (**25**) accompanied by the elimination of the 3-acetoxy group. Ketone **25** can also be synthesized by the oxidation of avermectin with manganese(IV) oxide (Scheme 14).[132]

The intramolecular free-radical cyclization of bromoethyl(dimethyl)silyl ether of avermectin at the 3,4-double

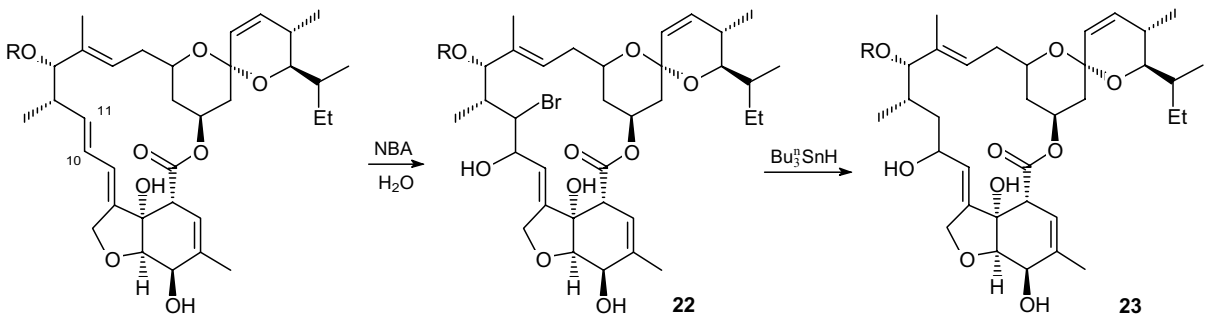
Scheme 12



Avermectin B_1 **20** **21**

R is L-oleandrosyl-L-oleandrosyl; R′ = Me, Et; (*a*) $Mn(dpm)_3$ (3 mol.%), $PhSiH_3$ (1.5 equiv.), Pr^{i}OH (0.2 M), O_2 (1 atm), from 0 to 20 °C (71% yield); dpm is dipivaloylmethanate

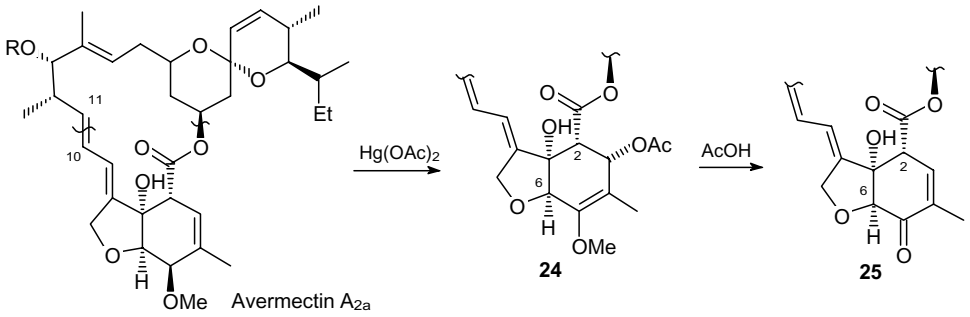
Scheme 13



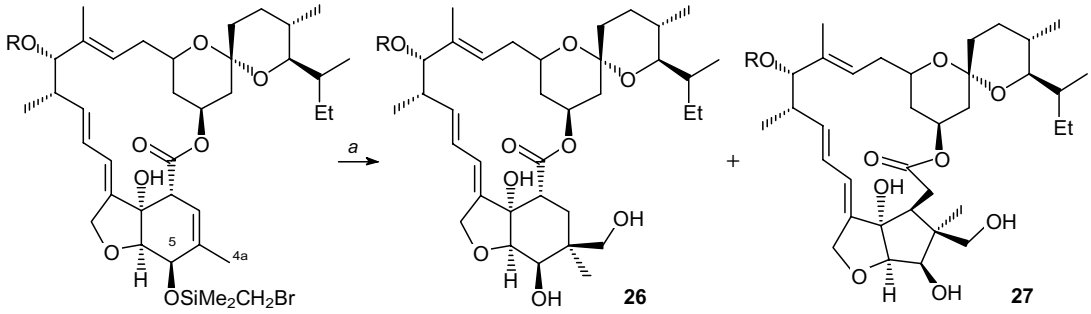
22 **23**

R is L-oleandrosyl-L-oleandrosyl

Scheme 14



Scheme 15



R is L-oleandrosyl-L-oleandrosyl; (*a*) 1) $NaCNBH_3$, Bu^n_3SnCl (cat), AIBN, Bu^tOH; 2) H_2O_2, KF, $KHCO_3$, THF, MeOH, rt; AIBN is azobis(isobutyronitrile), cat is catalyst, rt is room temperature

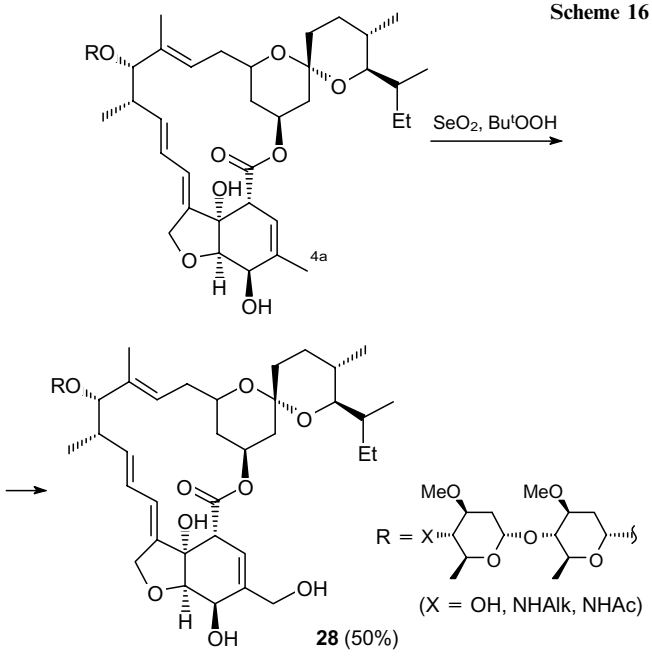
bond followed by the oxidation of the product with hydrogen peroxide was performed in order to prepare diol **26**.[133] However, the reaction was accompanied by an intramolecular rearrangement. As a result, diol **26** was obtained in a yield $<5\%$, while 17-membered cyclic lactone **27** was unexpectedly isolated as the major reaction product (46% yield) (Scheme 15).[133]

An important research area is the search for reagents and catalysts providing the selective hydrogenation of double bonds of the avermectin molecule. The hydrogenation of avermectin with hydrogen using different catalysts afforded a series of reduction products. Among these products, only ivermectin derived from avermectin by the hydrogenation at the 22,23-double bond was found to have high activity.

4.3. Synthesis of C4a derivatives

The synthesis of C4a avermectin derivatives involves the introduction of a reactive functional substituent (generally the hydroxy group) at the C4 methyl group followed by the transformation of the resulting compound into the target product. One of the methods most commonly used for the synthesis of C4a-hydroxyavermectins **28** is based on the oxidation of the methyl group at the C4a position with selenium oxide in the presence of *sec*-butyl hydroperoxide (Scheme 16).[134, 135]

Scheme 16



A series of C4a derivatives **29** were synthesized from C4a-hydroxyavermectins **28** (Scheme 17).[135]

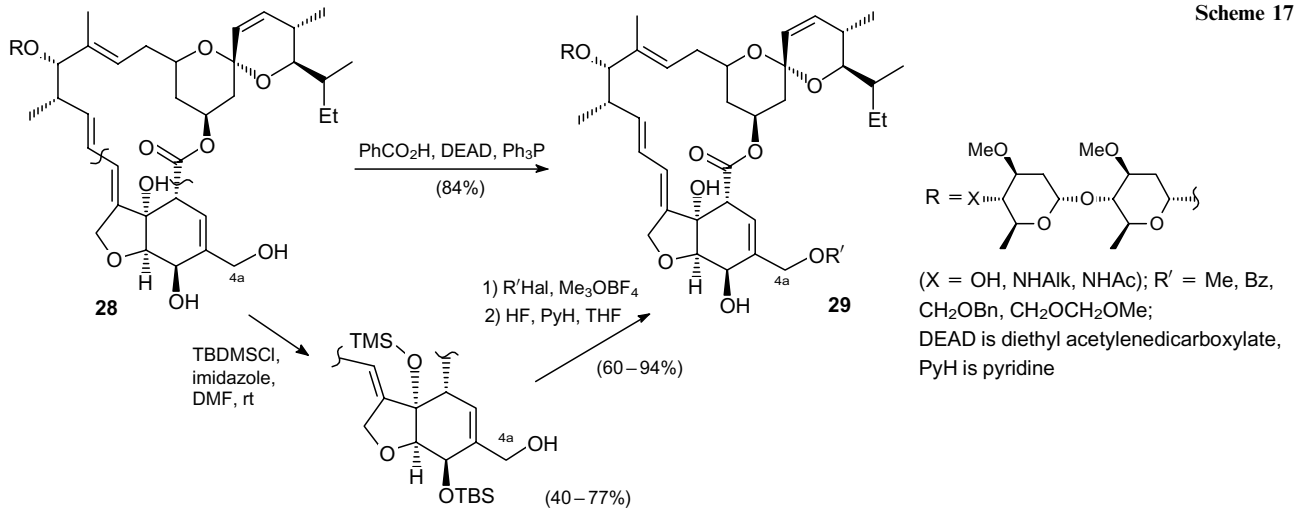
The $\Delta^{4,4a}$-isomer of avermectin B_{1a} (**30**) bearing the exo methylene group at the C4 position was synthesized from 4a-hydroxyavermectin B_{1a} in a similar way.[136] The final steps of this synthesis involve the sequential treatment of the corresponding intermediate with *N*-phenylselenophthalimide (NPSP) in the presence of Bu^n_3P and with tri-n-butylstannane and the removal of the phenoxyacetyl (PA) protection. In this case, a mixture of target C4-methylene derivative **30** and the starting avermectin B_{1a} was obtained in a ratio of 1: 2.5 (Scheme 18).

The $\Delta^{4,4a}$-isomer of avermectin B_{1a} **30**, like avermectin B_{1a} and ivermectin, exhibits antiparasitic activity against gastrointestinal helminths. The configuration control and the stereo control at the C2 position are challenging problems in this transformation sequence.[136]

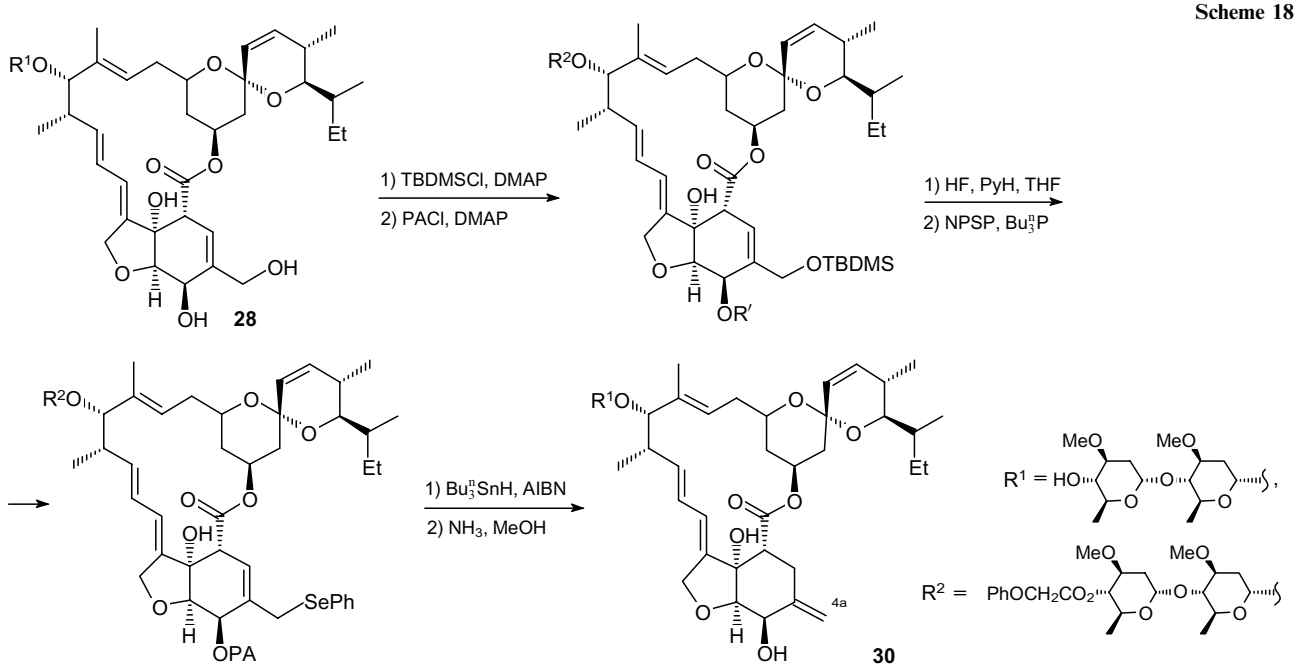
4.4. Synthesis of C4′ derivatives

The discovery of highly active eprinomectin and emamectin has stimulated the synthesis of avermectin analogues, in which the terminal oleandrosyl moiety of disaccharide is

Scheme 17



Scheme 18



either modified or replaced by another carbohydrate. The synthesis of these compounds is based on monosaccharides.

Avermectin derivative **31** contains methylated α-L-fucopyranoside instead of the oleandrosyl moiety at the C4′ position (Scheme 19).[137] When performing the synthesis of this compound, it was unexpectedly found that the reaction affords the target product only using thioglycosyl donors but not L-fucopyranosyl trichloroacetimidate. Compound **31** was found to have high biological activity.

A series of 4′-modified avermectins **32** were synthesized through a similar protocol (Scheme 20).[138] This synthesis was performed using unusual thioglycosyl derivatives of sugars, which readily react with carbohydrate-substituted macrolides in the presence of *N*-iodosuccinimide (NIS) or I_2 in *N*-methylpyrrolidone (NMP) at room temperature.[138]

Some compounds **32** exhibited higher *in vivo* biological activity against cabbage larvae compared to avermectin B_{1a}.

4.5. Synthesis of C4″ derivatives

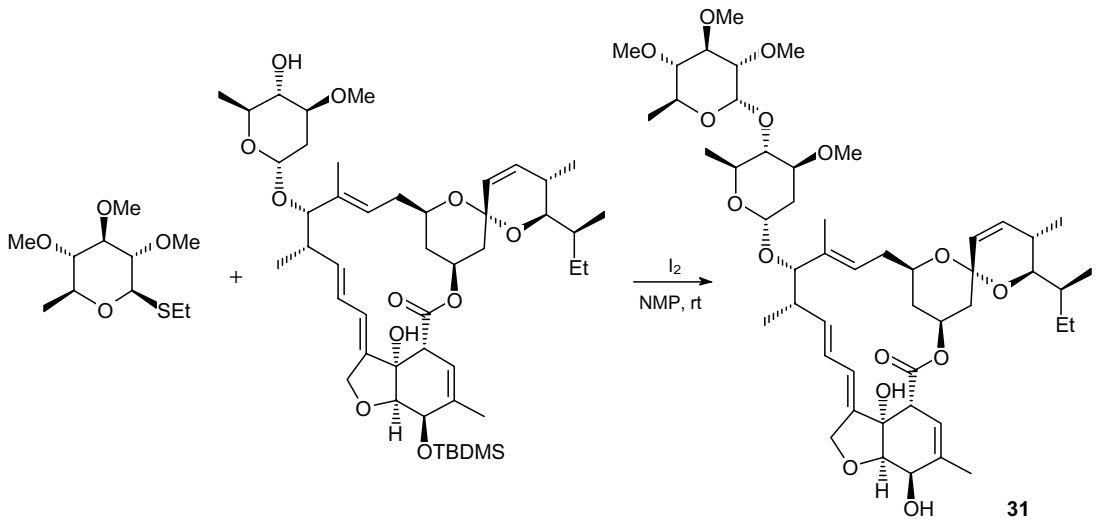
The chemical modification of avermectins at the C4″ atom of the L-oleandrose moiety is the most commonly used because the biological activity of the modified products is generally not decreased and in some cases is even increased. It is this method that was applied to synthesize the largest number of known avermectin derivatives and analogues. Among them, we can mention eprinomectin and emamectin, which are the major components of commercial drugs. As mentioned above, the hydroxy groups at the C4″ and C5 atoms have similar reactivity. Therefore, in order to achieve the selective transformation of the C4″-hydroxy group, the OH group at the C5 atom is generally protected by conversion into an ester group.

The acylation of the OH group at the C4″ position and the oxidation of this group to ketone, which is then subjected to amination, play a key role in the synthesis of modified avermectins.

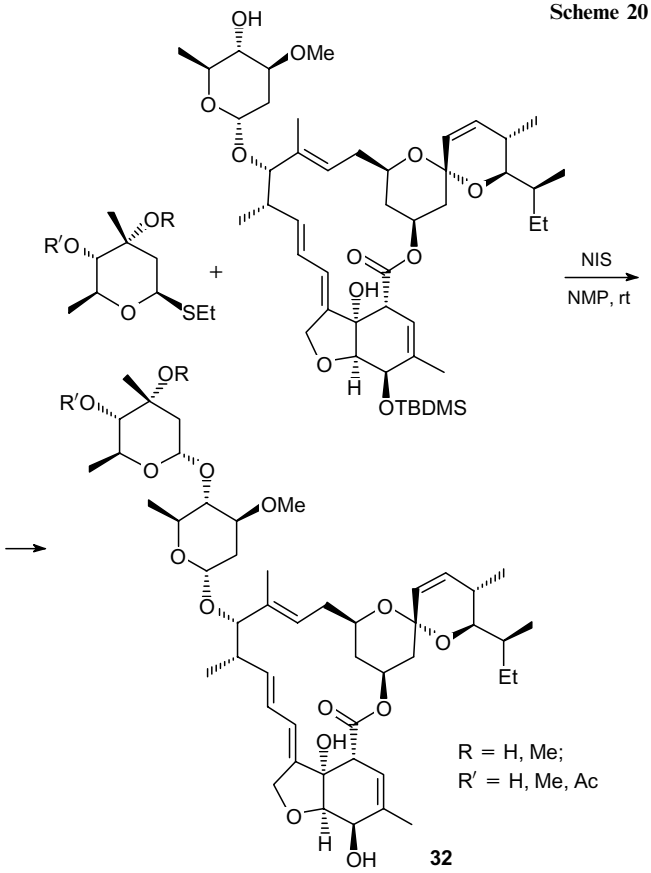
4.5.1. Acylation

The direct acylation of avermectin B_{1a} is nonselective because of similar reactivity of two secondary hydroxy groups at the C4″ and C5 atoms. Thus, the reaction with acetic anhydride in pyridine affords a mixture of mono- and

Scheme 19



Scheme 20



diacetates, 4″-*O*-acetyl and 4″,5-di-*O*-acetyl avermectins B_{1a}, in 39 and 21% yields, respectively,[115] which are separated by chromatography. The rapid treatment of the diacetate with sodium methoxide in methanol gives 4″-*O*-acetyl avermectin B_{1a} in good yield, however, an increase in the basicity of the reaction mixture leads to the complete decomposition of the product. 4″-*O*-Acetyl avermectins exhibited high antiparasitic activity.

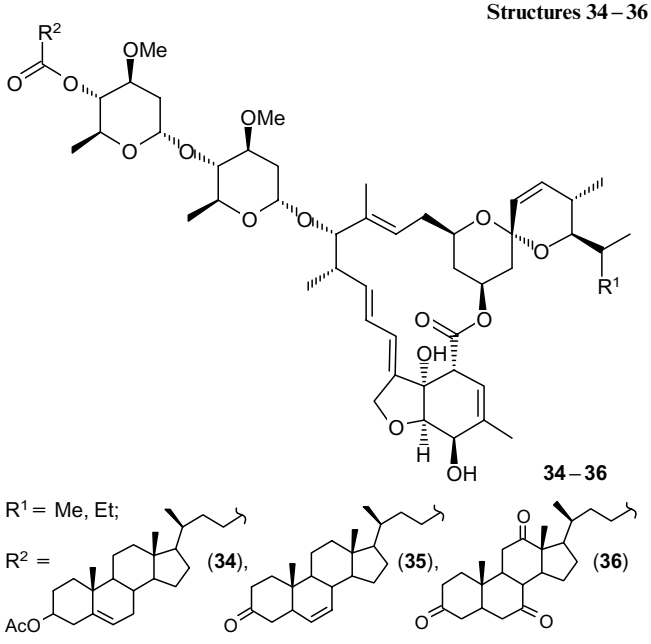
The selective synthesis of 4″-acyl derivatives was performed starting from avermectins, in which the hydroxy groups at the C5 and C23 positions (if the latter is present) were protected with ester or silyl groups. The final step of the synthesis dealt with the deprotection. This synthesis afforded a series of 4″-*O*-acyl avermectin derivatives **33**. Protected 5-*O*-*tert*-butyldimethylsilyl avermectin B_1 was reacted with vicinal 1,2-dicarboxylic anhydrides (Scheme 21).[139]

Steroidal esters of 4″-*O*-avermectin B_1 were synthesized through a similar protocol.[140] The acylation of 5-*O*-silyl-substituted avermectin B_1 with anhydrides of cholanic acid derivatives produced 3β-acetoxychol-5-en-24-oic (**34**), 3-oxochol-4-en-24-oic (**35**) and 3,7,12-trioxocholan-24-oic esters (**36**).[140]

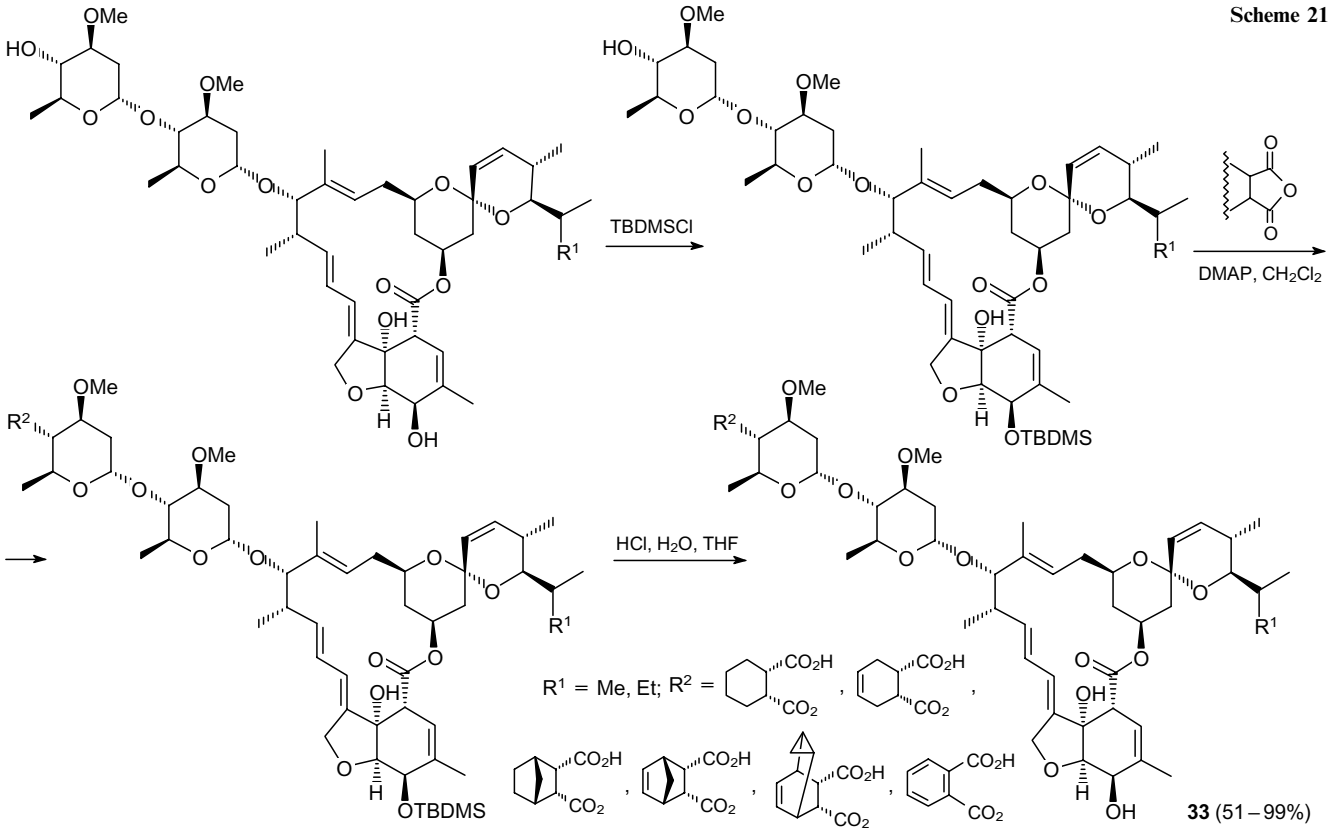
The same strategy (see Scheme 21) for the four-step synthesis, involving the protection of the hydroxy group at the C5 position, was applied to prepare 4″-substituted ivermectin **37** in the presence of succinic anhydride (Scheme 22).[141] Product **37** showed high antileishmanial activity.

Numerous doramectin derivatives **38** containing carbamate, ester, sulfonate, acylcarbamide or acylthiocarbamide groups at the C4″ position were synthesized by the acylation.[142, 143]

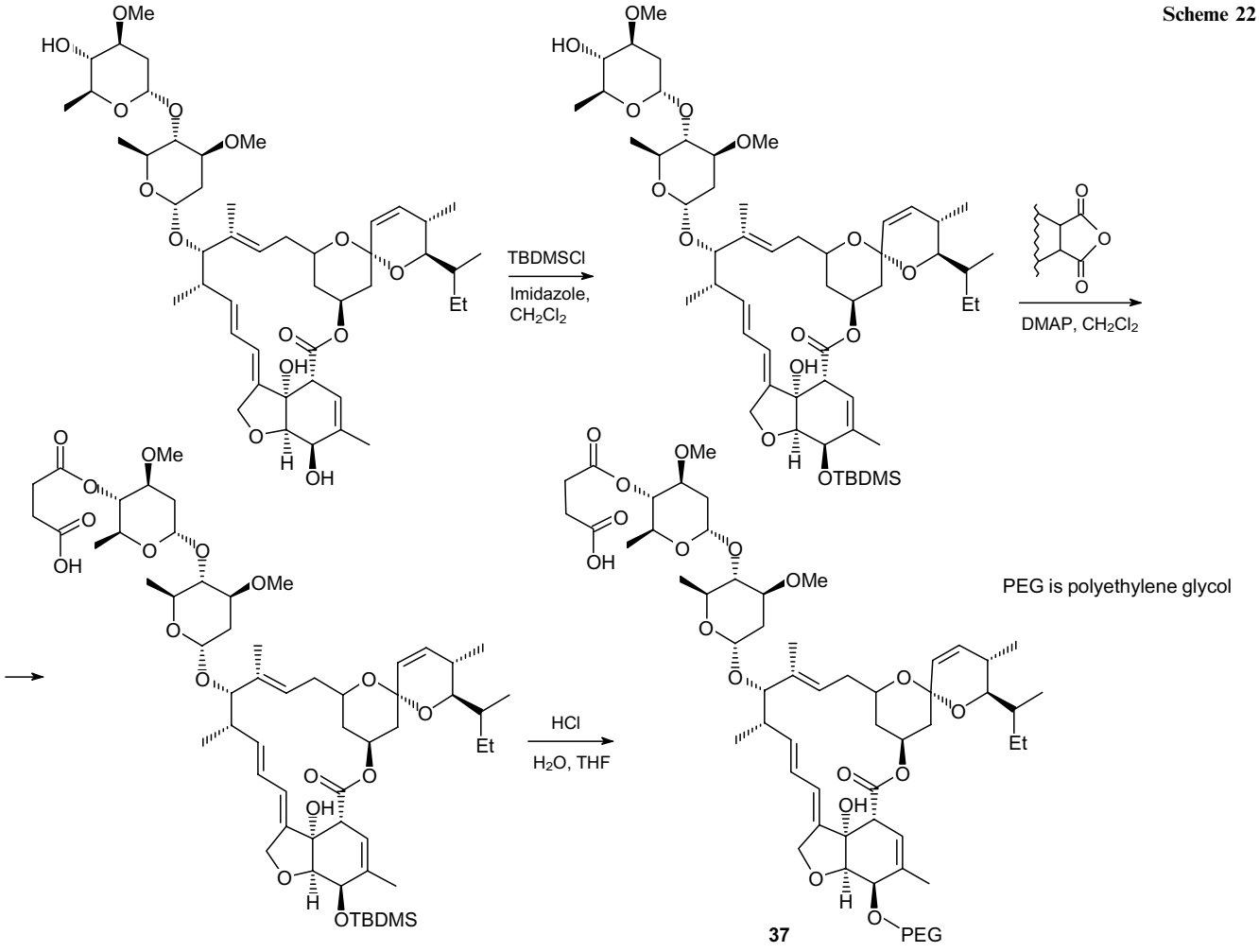
Structures 34 – 36



Scheme 21



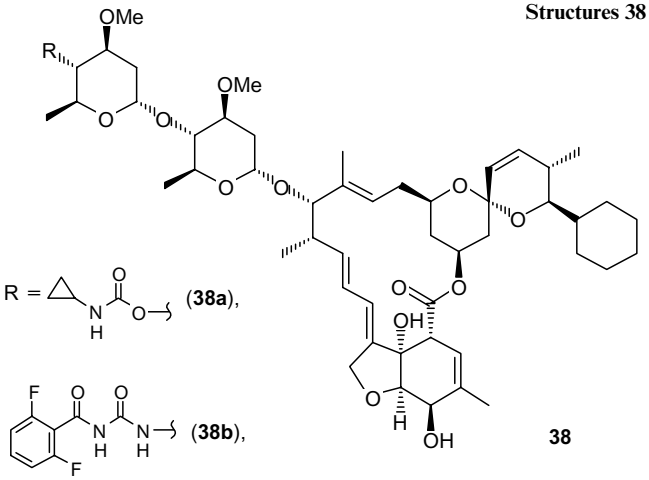
Scheme 22



The above substituents are often present as active groups in different classes of pesticides. Doramectin was modified according to a standard procedure. First, the OH group at the C5 position was protected with *tert*-butyldimethylsilyl chloride followed by the reaction at the C4″-OH group and the selective transformation of the latter into the target group. In the final step, the TBS protection was removed. Among the synthesized compounds, the doramectin derivatives with R = cyclo-$C_3H_5NHCO_2$ (**38a**) and 2,4-$F_2C_6H_3C(O)NHC(O)NH$ (**38b**) exhibited the highest biological activity. It was demonstrated that the presence of hydrogen bonds at the C4″ position of the avermectin molecule with the target protein γ-aminobutyric acid (GABA) receptor was crucial for retaining high activity.

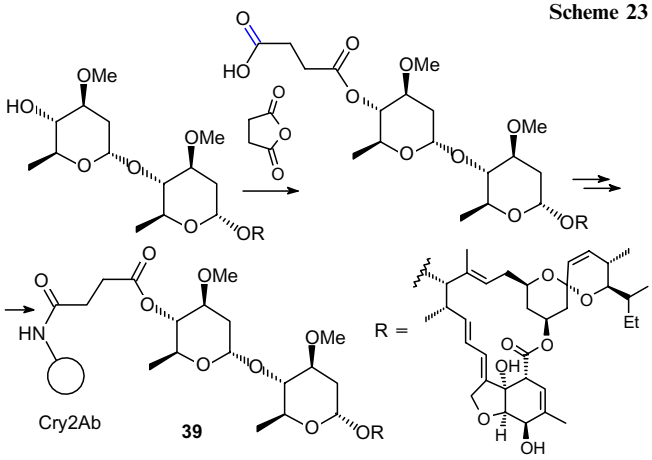
The synthesis of bioconjugate **39** is also worth mentioning. In this bioconjugate, the C4″ position of avermectin is attached through a linker to the toxin Cry2Ab (Scheme 23).[144]

Structures 38



$AlkNHCO_2$, cyclo-$AlkNHCO_2$, $AllNHCO_2$, $BnNHCO_2$, 4-$MeOC_6H_4CH_2NHCO_2$, $XC_6H_4NHCO_2$ (X = H, 4-F, 4-Cl, 4-Br, 2-Me, 3-Cl, 4-OMe, 4-Me, 4-CF_3), 1-$NaphNHCO_2$, $AlkCO_2$, $CH_2{=}CHCO_2$, $BnCO_2$, $AlkSO_2$, AlkC(O)NHC(O)NH, ArC(O)NHC(O)NH, AlkC(O)NHC(S)NH, ArC(O)NHC(SNH), *etc.*; Naph is naphthyl

Scheme 23



4.5.2. Oxidation – amination

The selective formation of nitrogen-containing functional groups in the molecule (synthesis of amines, oximes, *etc.*) was accomplished according to the following procedure. The C5 hydroxy group was protected, the C4″ hydroxy group was oxidized with phenyl dichlorophosphate and the target substituents were introduced followed by the deprotection.[145–147] The reductive amination of 4″-oxo-5-*O*-*tert*-butyldimethylsilyl derivatives **40** affords a mixture of epimeric 4″-deoxy-4″-amino analogues, in which the 4″-amino group of major component **41** is in the axial β-orientation (Scheme 24).[145–147]

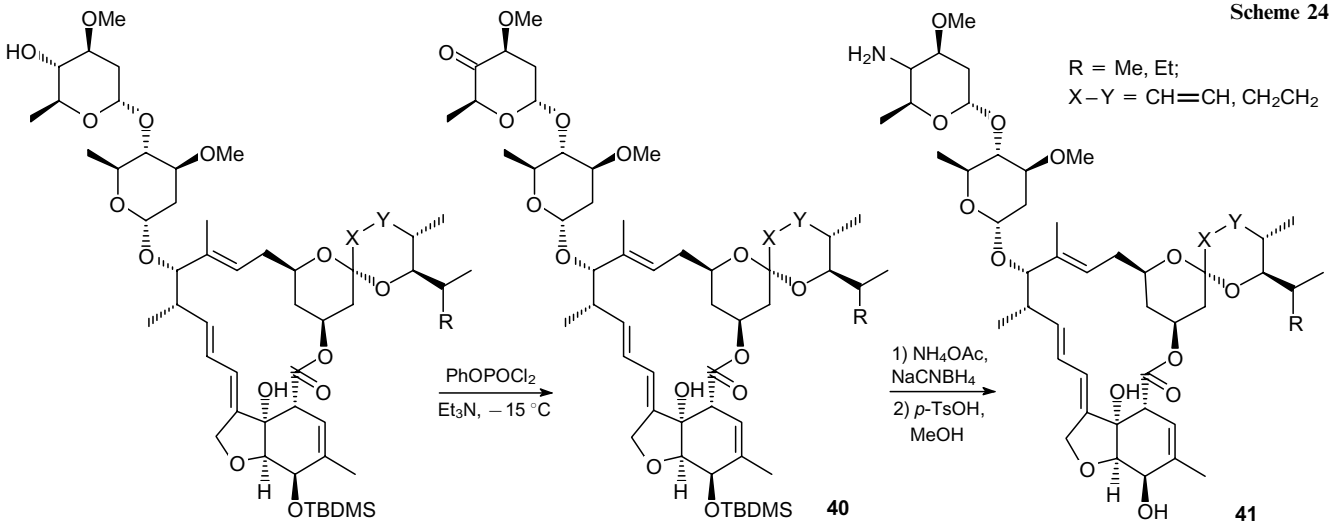
The subsequent acylation of amino derivative **41** gives eprinomectin.[104, 105, 147]

A series of 4″-alkylidene 5-*O*-*tert*-butyldimethylsilyl derivatives of avermectin B_{1a} were prepared from ketone **40a** (X–Y = CH=CH; R = Et) by the Horner–Emmons reaction with phosphorus ylides (Scheme 25).[148]

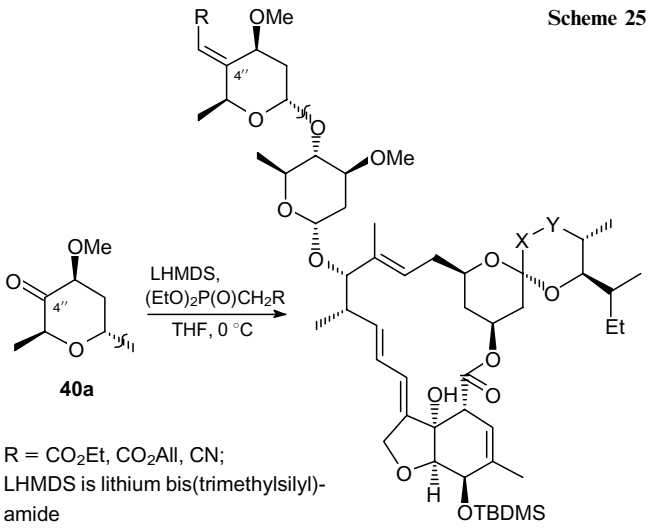
Then various 4″-substituted derivatives were synthesized from the 4″-alkylidene-5-*O*-TBDMS-avermectins B_{1a} (Schemes 26 and 27).[148]

A large number of avermectin derivatives containing sulfonyl groups at the C4″ atom, the corresponding sulfonylamidines, sulfonylureas and sulfonylamines, are easily produced from 4″-*epi*-amino-4″-deoxyavermectin B_1 (**42**) (Scheme 28).[146] Some 4″-*epi*-(sulfonylamidino)-4″-deoxyavermectins B_1 showed high biological activity against

Scheme 24

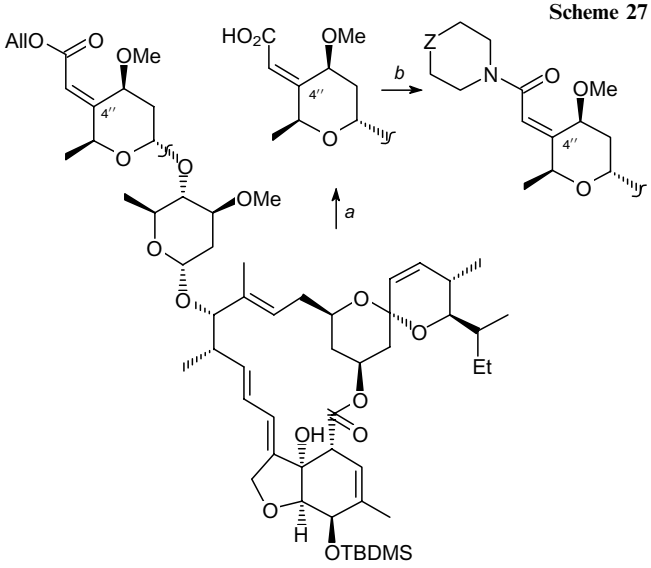


Scheme 25



R = CO_2Et, CO_2All, CN;
LHMDS is lithium bis(trimethylsilyl)-amide

Scheme 27



Z = CH_2, O, NH; (*a*) $Pd(Ph_3P)_4$, $NaBH_4$, EtOH, 0 °C (90%); (*b*) EDCI, HOBt, CH_2Cl_2, rt (74–99%); EDCI is *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide, HOBt is 1-hydroxybenzotriazole

three species of arachnids, insects and nematodes, namely, *Tetranychus cinnabarinus*, *Aphis craccivora* and *Bursaphelenchus xylophilus*.

Another series of (4″*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-alkylcarbamoyl derivatives of avermectin B_1 (**43**) were synthesized by the diastereoselective Ugi reaction based on (*S*)-phenylsulfinimines. In this case, the phenylsulfinimine moiety at the C4″ position acts as the activating group (Scheme 29).[149]

Simple and efficient methods were developed for the synthesis of (4″*R* or 4″*S*)-4″-deoxy-4″-amino-4″-C-substituted avermectins B_1 (**44**) (Scheme 30).[150] In these methods, the (*S*)-phenylsulfinimines moiety was also utilized as the activating group at the C4″ position. These avermectin derivatives showed high activity against mites, dipterous leafminers, thrips and lepidoptera.[150]

4.5.3. Miscellaneous 4″ derivatives

4″-(Ethoxycarbonylmethyl) avermectins and ivermectins **45a** were synthesized using ethyl diazoacetate in the presence of $Rh_2(OAc)_4$ as the catalyst (Scheme 31).[151, 152] Prior to the reaction, the C5 and C7 hydroxy groups were protected with silyl groups, namely, the *tert*-butyldimethylsilyl and trimethylsilyl groups, respectively.

The reactions were catalyzed by $Rh_2(OAc)_4$, $Rh_2(O_2CC_7H_{15}\text{-n})_4$, $Rh_2(O_2CCF_3)_4$, $Cu(OTf)_2$ [Tf is trifluoromethanesulfonyl (triflyl)], $BF_3 \cdot Et_2O$, $Sc(OTf)_3$ and also by the $Rh_2(OAc)_4$–1,1,3,3-tetramethylthiourea (TMU) and $Rh_2(OAc)_4$–Me_2S systems. The highest yields and purity of the products were achieved in the $Rh_2(OAc)_4$-catalyzed reaction.

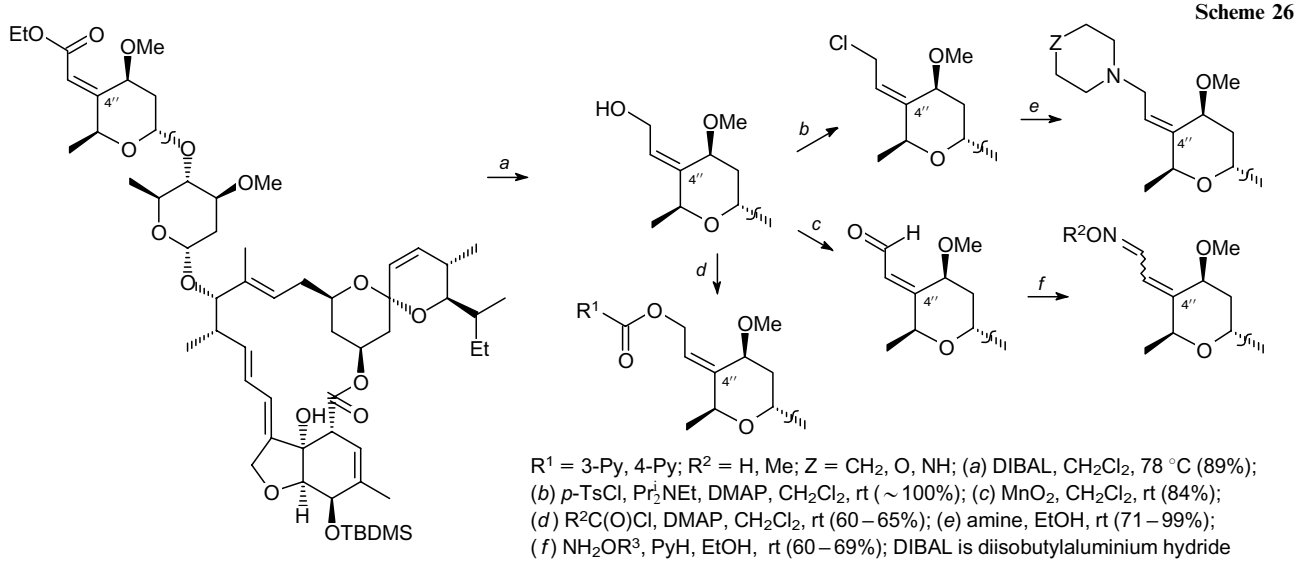
Different transformations of 4″-(ethoxycarbonylmethyl) avermectins and ivermectins **45a** afforded numerous alkoxy derivatives **45** at the 4″ position (Scheme 32).[152]

Most of these compounds exhibit high insecticidal and nematicidal activity against the mematodes *Caenorhabditis elegans* and the brine shrimp *Artemia salina*.[152]

4.6. Synthesis of 5-O derivatives

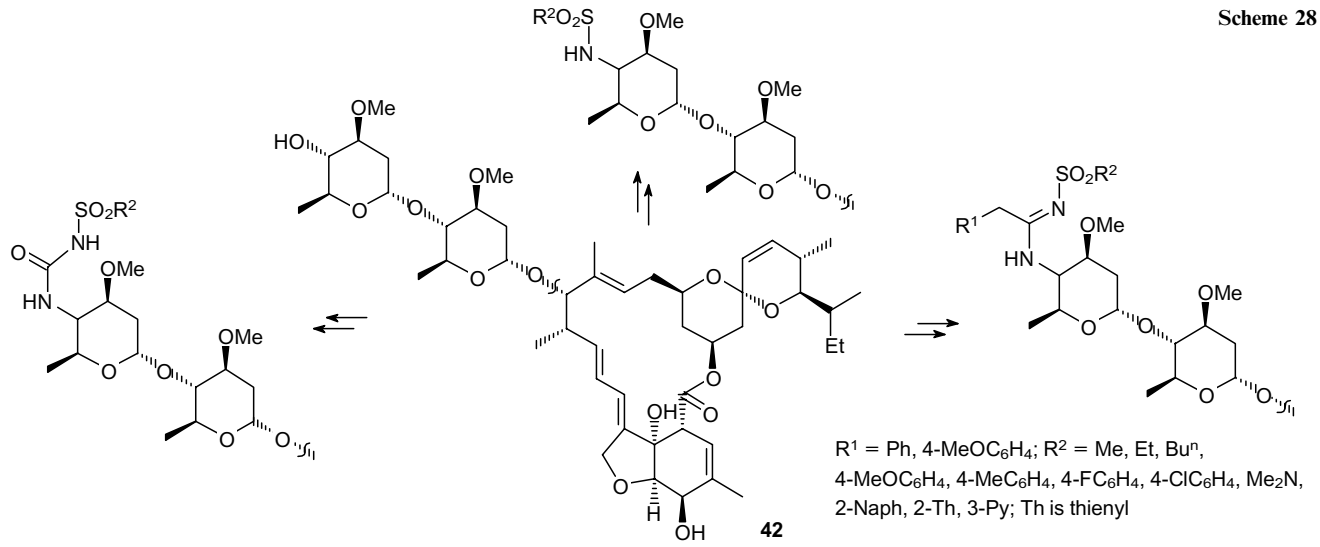
Only the acylation of avermectins with acetic anhydride was investigated in the first studies on the acylation reactions. Based on the results of these studies, it was concluded that the presence of a free hydroxy group at the most reactive C5

Scheme 26



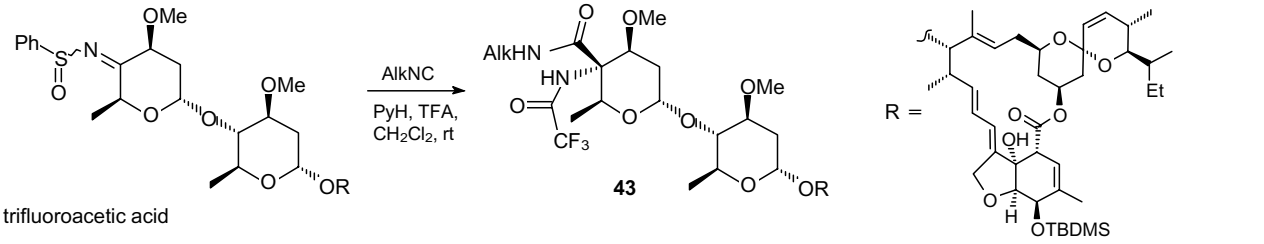
R^1 = 3-Py, 4-Py; R^2 = H, Me; Z = CH_2, O, NH; (*a*) DIBAL, CH_2Cl_2, 78 °C (89%); (*b*) *p*-TsCl, Pr^i_2NEt, DMAP, CH_2Cl_2, rt (~100%); (*c*) MnO_2, CH_2Cl_2, rt (84%); (*d*) $R^2C(O)Cl$, DMAP, CH_2Cl_2, rt (60–65%); (*e*) amine, EtOH, rt (71–99%); (*f*) NH_2OR^3, PyH, EtOH, rt (60–69%); DIBAL is diisobutylaluminium hydride

Scheme 28



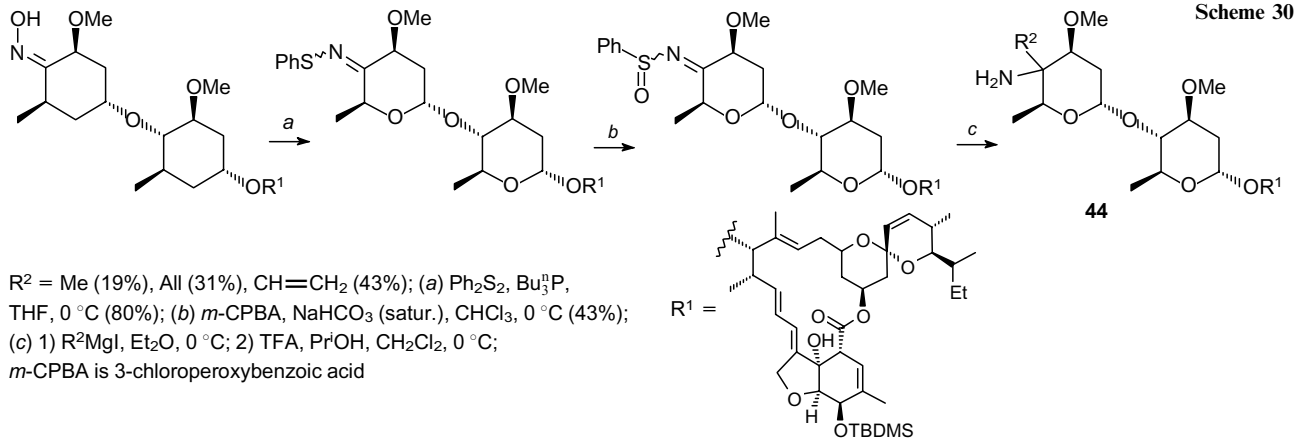
R^1 = Ph, 4-$MeOC_6H_4$; R^2 = Me, Et, Bu^n, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, Me_2N, 2-Naph, 2-Th, 3-Py; Th is thienyl

Scheme 29



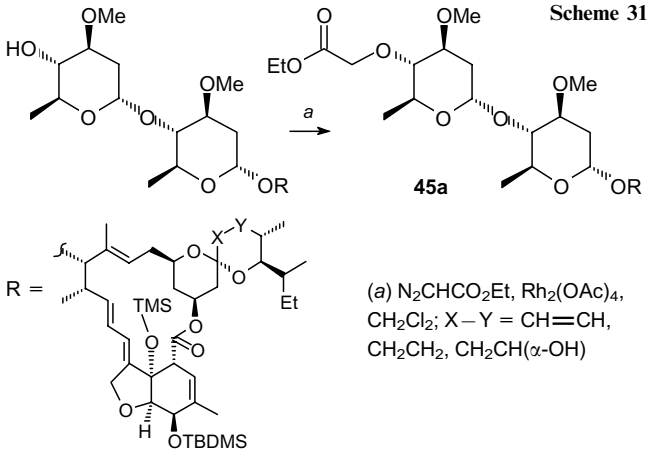
TFA is trifluoroacetic acid

Scheme 30



R^2 = Me (19%), All (31%), CH═CH_2 (43%); (*a*) Ph_2S_2, Bu^n_3P, THF, 0 °C (80%); (*b*) *m*-CPBA, $NaHCO_3$ (satur.), $CHCl_3$, 0 °C (43%); (*c*) 1) R^2MgI, Et_2O, 0 °C; 2) TFA, Pr^iOH, CH_2Cl_2, 0 °C;
m-CPBA is 3-chloroperoxybenzoic acid

Scheme 31

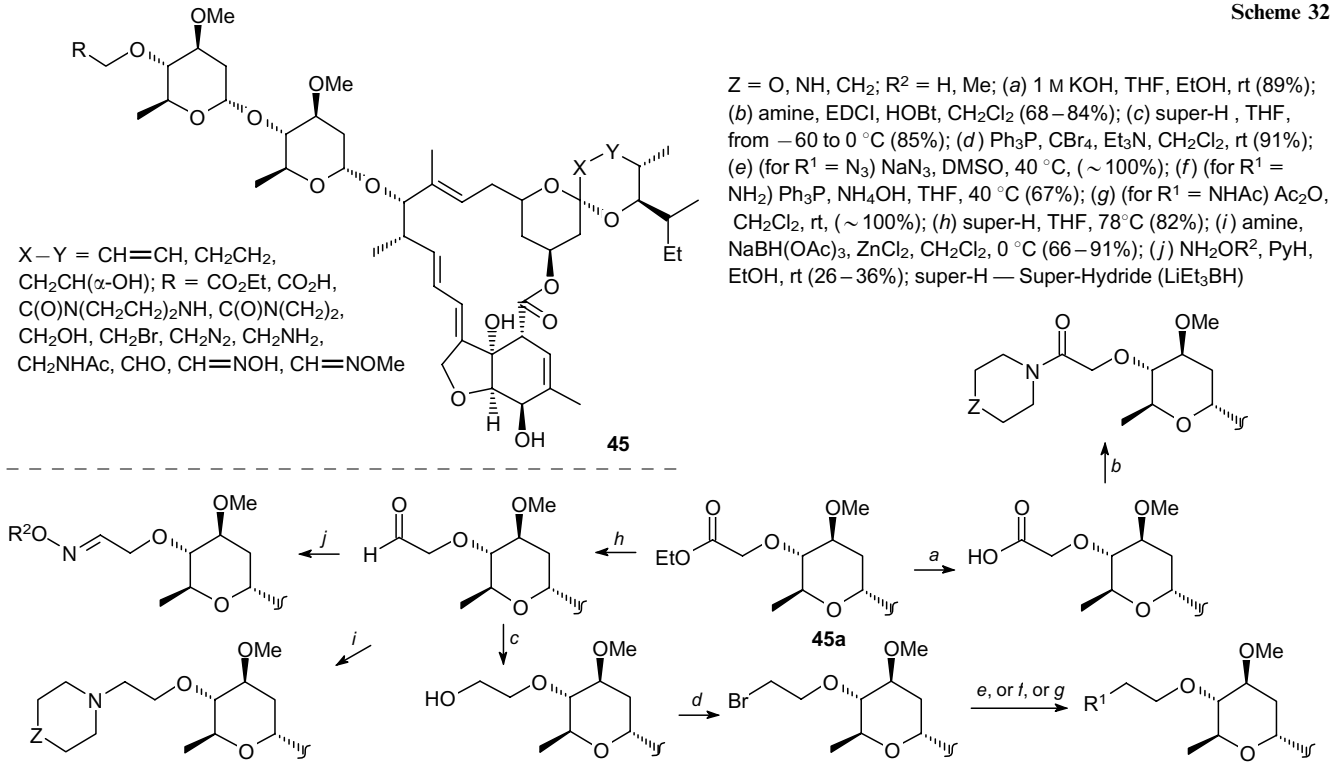


(*a*) N_2CHCO_2Et, $Rh_2(OAc)_4$, CH_2Cl_2; X−Y = CH═CH, CH_2CH_2, CH_2CH(α-OH)

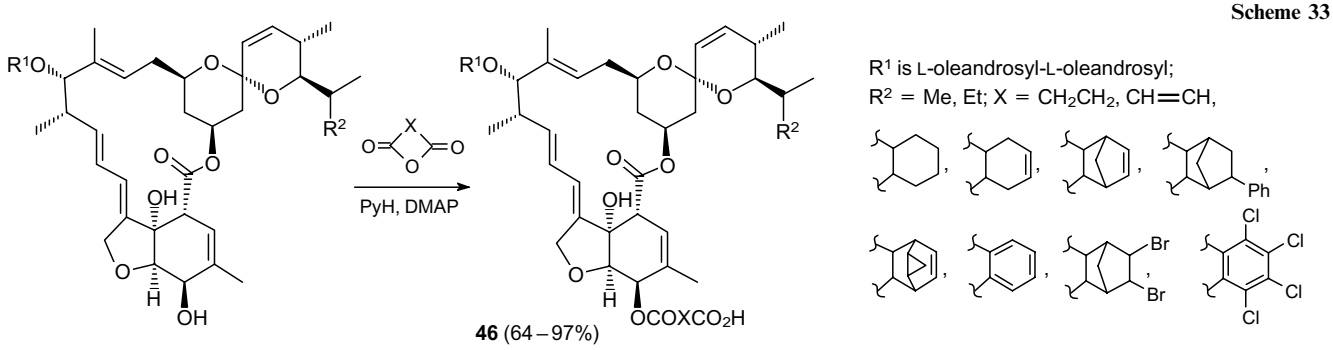
position of the macrocycle is required for the antiparasitic activity.[115] However, this conclusion turned out to be wrong. Later it was demonstrated [108, 139, 153] that 5-*O* derivatives of avermectin B_1 (compounds **46**), prepared by the reaction with different anhydrides of vicinal dicarboxylic acids, also showed high antiparasitic activity (Scheme 33).

Since avermectin B_1 contains two reactive hydroxy groups, at the C5 and C4″ positions, it can be suggested that the acylation would occur nonselectively to form a mixture of products. An excess of the anhydride theoretically should provide the acylation at both OH groups giving 5,4″-disubstituted products.[139] However, under standard conditions, the acylation with anhydrides of vicinal dicarboxylic acids occurs selectively only at the C5 hydroxy group. Even in the presence of a large excess of anhydride, the simultaneous acylation at the C5 and C4″ positions of the macrolide ring was not observed. This result

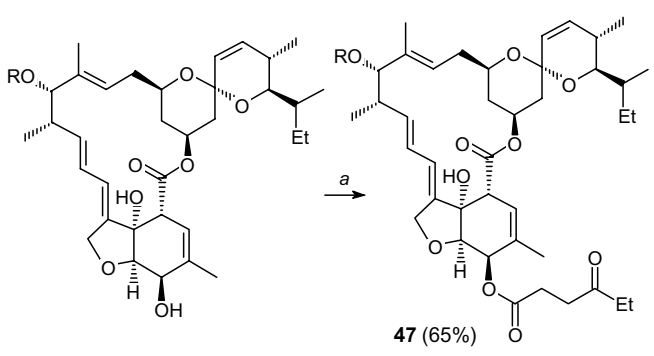
Scheme 32



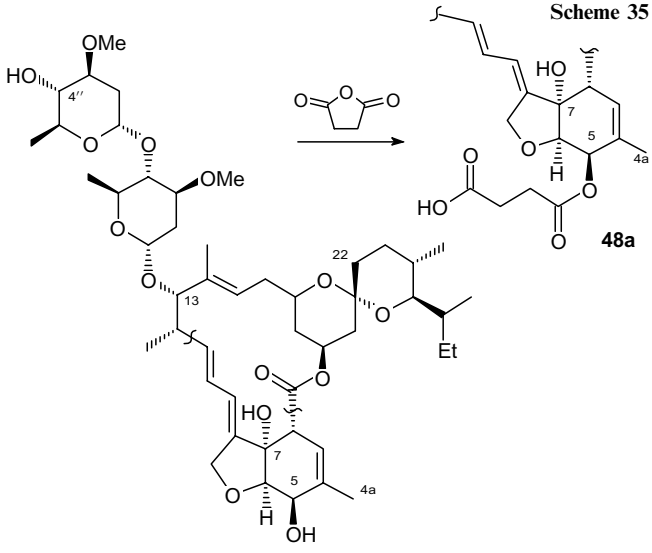
Scheme 33



Scheme 34



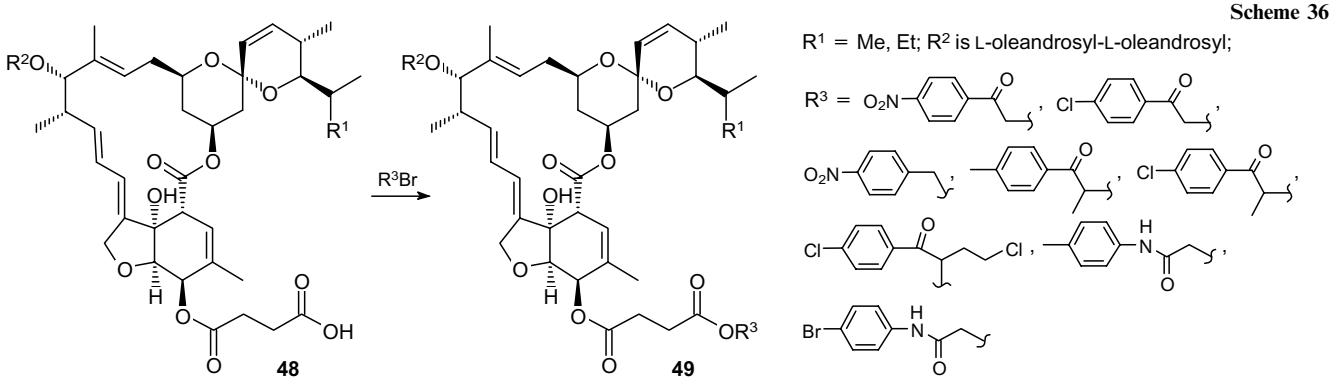
Scheme 35



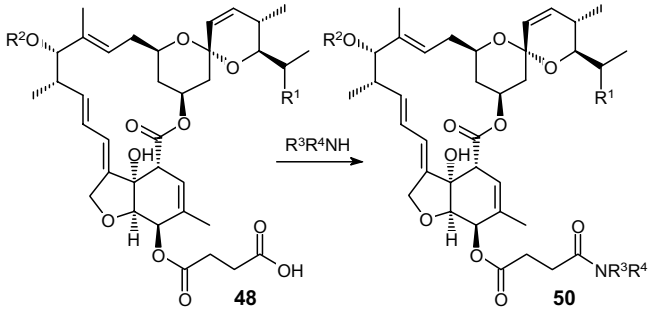
is of great practical importance because it enables the synthesis of C5-acylated avermectins.

The 2,6-lutidine-catalyzed reaction of avermectin B_1 with succinic acid monoethyl ester chloride affords exclusively 5-*O*-(succinoyl) avermectin B_1 (**47**). The regioselectivity of the process is attributed to the fact that the 4″ hydroxy group of avermectin is sterically more hindered compared to the C5 hydroxy group (Scheme 34).[154]

Scheme 36

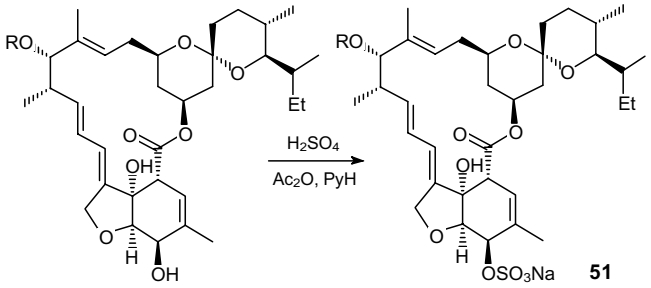


Scheme 37



R^1 = Me, Et; R^2 is L-oleandrosyl-L-oleandrosyl; R^3 = Alk, 3-Py, $MeOCH_2CH(Me)$; R^4 = H, Alk; R^3R^4N is morpholino

Scheme 38



R is L-oleandrosyl-L-oleandrosyl

Ivermectin is acylated at the C5 OH group with acid anhydrides in organic solvents in the presence of amines as the catalyst to give 5-*O*-hemisuccinate **48a**. At room temperature, the reaction is completed in 7 days (Scheme 35).[108, 139, 154]

Compounds **48** are convenient intermediates in the synthesis of a number of other 5-*O* derivatives. Thus, their reactions with phenacyl halides, bromoacetanilides and benzyl bromides as the alkylating agents afford esters of 5-*O*-succinoyl avermectin B_1 (**49**) (Scheme 36).[155]

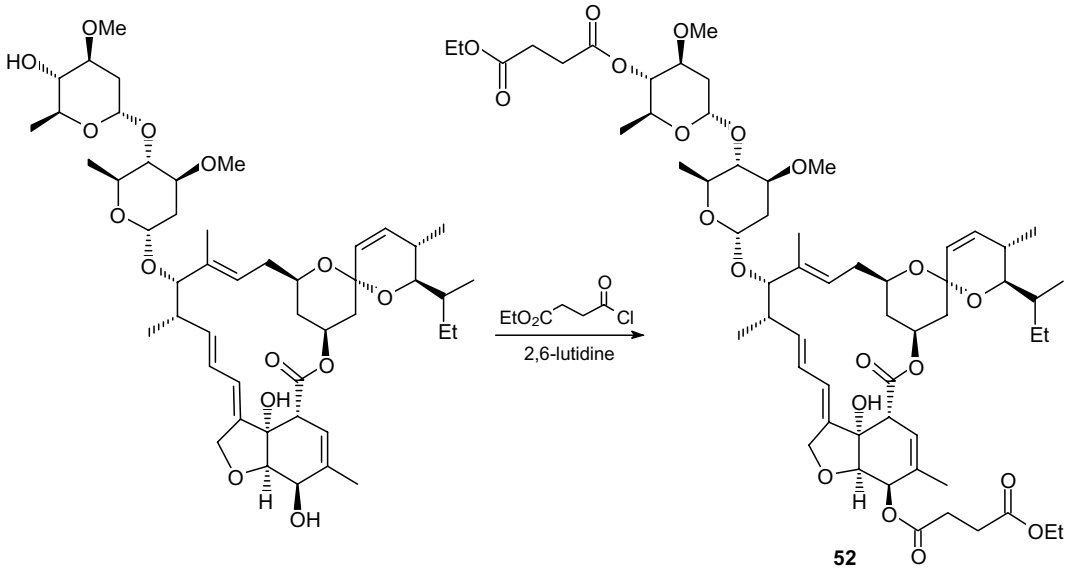
A series of [1-(avermectin-5-yl)] succinic acid ester amides (**50**) were synthesized in a similar way (Scheme 37).[156]

The synthesis of ivermectin 5-*O*-sulfate sodium salt (**51**) is based on the sulfation of ivermectin under mild conditions.[157] The formation of the 4″-*O*-sulfate salt was not observed because, as demonstrated above, the C5 hydroxy group is more reactive than the sterically hindered OH group at the C4″ position (Scheme 38).

4.7. Synthesis of 4″,5-disubstituted avermectins

The direct modification of a hydroxy group (acylation, sulfation) using a large excess of the reagent under catalytic conditions can afford avermectin derivatives containing substituents at the C4″ and C5 positions. As mentioned above, avermectin B_1 can be acylated at both hydroxy groups with succinic acid monoethyl ester chloride. Thus, bisuccinate **52** was synthesized by the 2,6-lutidine-catalyzed

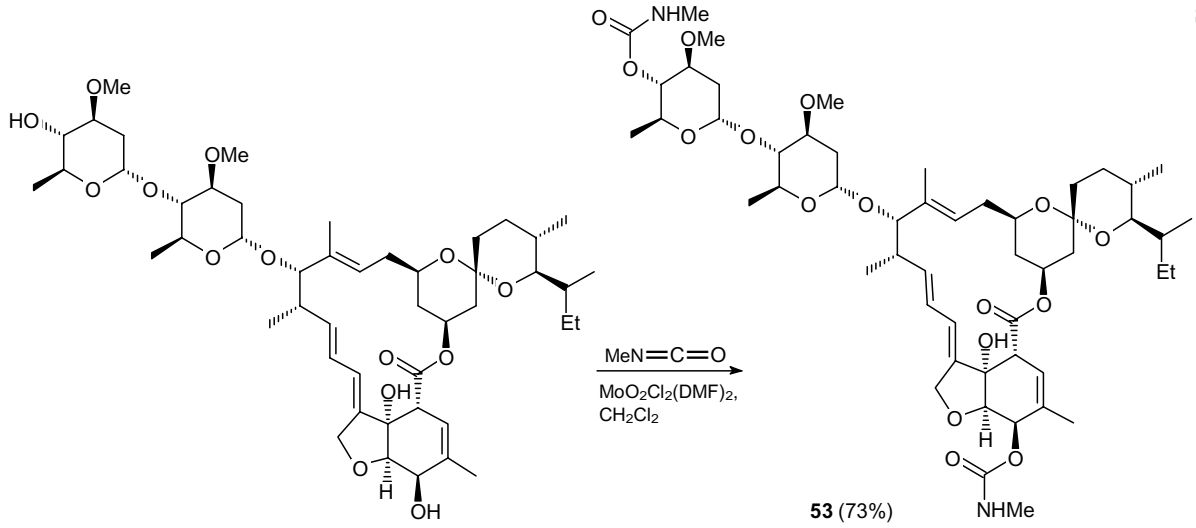
Scheme 39



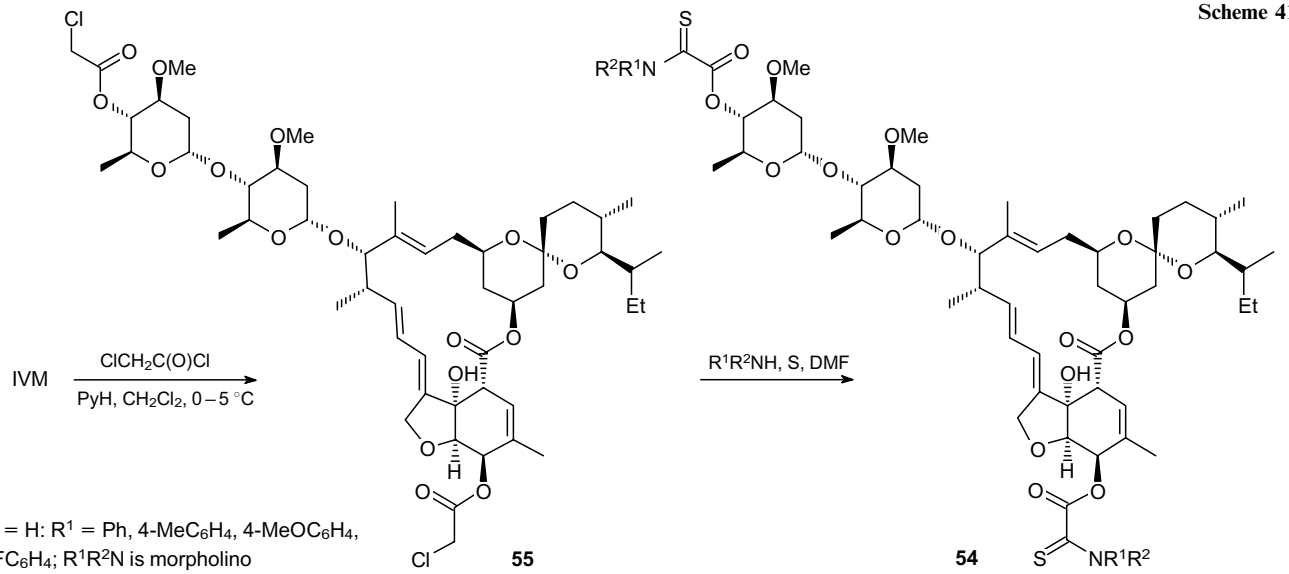
reaction of avermectin with a 15-fold excess of succinic acid monoethyl ester chloride. The yield of 4″,5-bis-[(4-ethoxy-4-oxobutanoyl)oxy] avermectin B_1 was 49% (Scheme 39).[154]

A similar reaction of avermectin B_1 with an excess of succinic anhydride was described in the study.[141] Under ambient pressure, the reaction afforded only the monoacylation product, whereas the double acylation product of avermectin B_1, 5,4″-bis(*O*-succinoyl) avermectin B_1 was obtained in 65% yield at ultrahigh pressure (10 kBar).

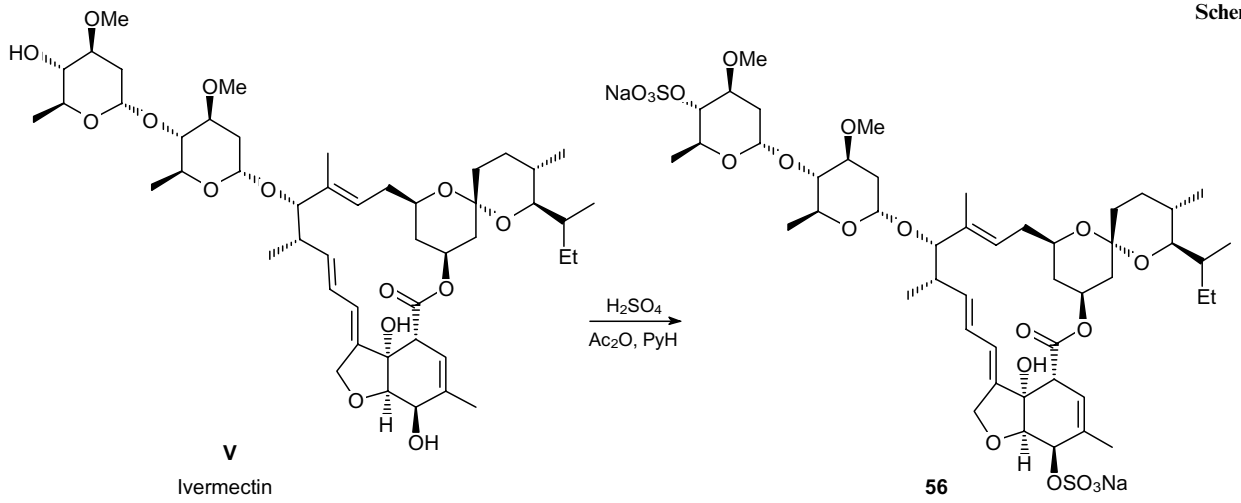
Scheme 40



Scheme 41



Scheme 42



Another 4″,5-disubstituted product, 4″,5-bis(*N*-methylcarbamoyl) ivermectin **53**, was synthesized by the reaction of ivermectin with methyl isocyanate in the presence of $MoO_2Cl_2(DMF)_2$ as the catalyst (Scheme 40).[158]

It is worth noting that the standard method for the synthesis of carbamates *via* the reaction of isocyanates with appropriate alcohols in the presence of a catalyst (acidic and basic hydrolysis) did not afford the target product.[158]

Among the 4″,5-disubstitution products, we also note 5,4″-bis[2-amino-2-(thioxo)acetyl] ivermectins **54**,[159] which were prepared by the reaction of 5,4″-bis(chloroacetyl) ivermectin (**55**) with amines in the presence of sulfur. These compounds are hybrid molecules combining ivermectin B_1 with a monothiooxamide moiety. The latter moiety contains the ester and thioamide groups in close proximity to each other, thereby offering a great synthetic potential for the preparation of systematic sets of hybrid molecules with valuable biological properties (Scheme 41).[159]

Besides, the sulfation of ivermectin for 6 h afforded a mixture of mono- (**51**) and bis-products (**56**) in a ratio of 6 : 1, which was separated by chromatography.[157] Ivermectin 4″,5-*O*-disulfate sodium salt was obtained in a low yield of 10% (Scheme 42).

4.8. Synthesis of C5-oximes

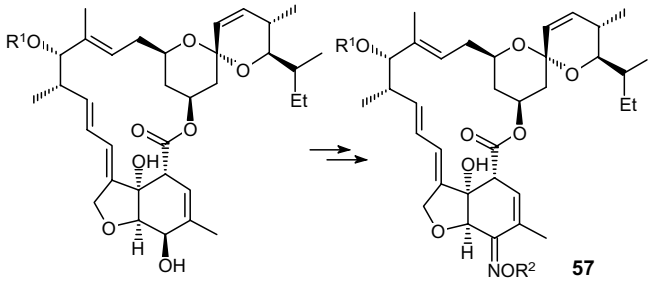
As mentioned above, for a long time it was believed that the C5 hydroxy group is of crucial importance for broad-spectrum high activity.[115] Therefore, the synthesis of 4″ derivatives has attracted great attention of researchers. However, later it was found that avermectin analogues containing oxime groups, as well as the corresponding esters, at the C(5) atoms exhibit high antiparasitic activity and can be effectively used in clinical practice.[160, 161]

For instance, 5-acyloxyimino-5-deoxyavermectin B_1 derivatives (**57**) were synthesized by the selective oxidation of the hydroxy group at C5 followed by the oximation and esterification (Scheme 43).[162]

Nearly all derivatives **57** show antiparasitic activity at a level of the starting avermectin B_1; butyric- or *cis*-chrysanthemic acid-based ester groups enhance biological activity.[162]

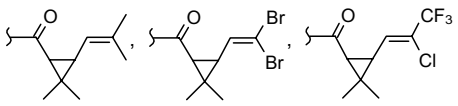
A series of 5-deoxyavermectin B_{2a} oxime ester derivatives (**58**) were synthesized according to a similar procedure.[163] The oximation was followed by the esterification with benzoic acids containing various substituents on the aromatic ring.

Scheme 43

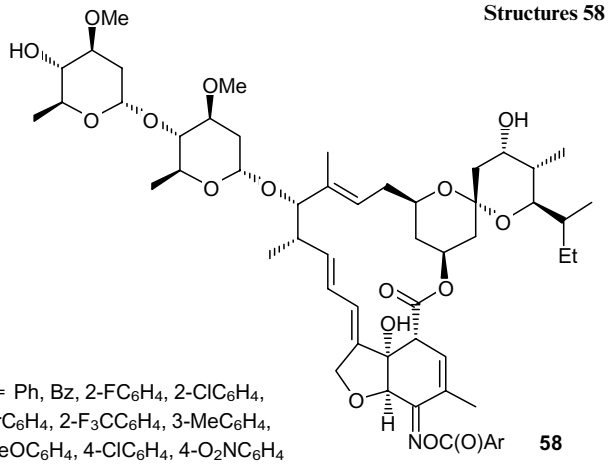


Avermectin B_1

R^1 is L-oleandrosyl-L-oleandrosyl; R^2 = C(O)Pr^n,



Structures 58



Ar = Ph, Bz, 2-FC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 2-$F_3CC_6H_4$, 3-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$

Among the synthesized compounds, the *O*-(4-chlorobenzoyl)oxime exhibited higher antiparasitic activity compared to avermectin B_{2a} and, consequently, this derivative can be considered as a potential lead compound for the design of new avermectin B_{2a} derivatives.[163] The positions of the substituent on the aromatic ring and its electronic properties significantly influence the biological activity of the product, which is important for the subsequent structural optimization of avermectin B_{2a} derivatives.[163]

The investigation of the acylation of 5-deoxyivermectin B_1 oxime (**59**) demonstrated[164] that this reaction can occur at two reactive sites, the hydroxy groups of the oxime moiety at the C5 position and at the C4″ atom of the disaccharide unit. The reaction of compound **59** with an excess of acyl chloride in dichloromethane in the presence of DMAP or *N*,*N*′-di(cyclohexyl)carbodiimide (DCC) at room temperature led to the selective monoacylation of the 5-NOH group giving **60**, whereas diacylation products **61** were isolated upon slight heating. The yields of 5-alkyl(aryl)carbonyloximino-5-deoxyivermectins **60** were 60–65% (Scheme 44). The acylation of oxime **59** with acids in the presence of DMAP or DCC in dichloromethane at room temperature also results in the monoacylation of the NOH group at the 5 position giving products in 80–90% yields (see Scheme 44).

Doramectin oxime **62** was synthesized by the regioselective hydrogenation of doramectin followed by the oxidation of the C5 hydroxy group with manganese dioxide and the treatment of intermediate ketone with hydroxylamine (Scheme 45).[160]

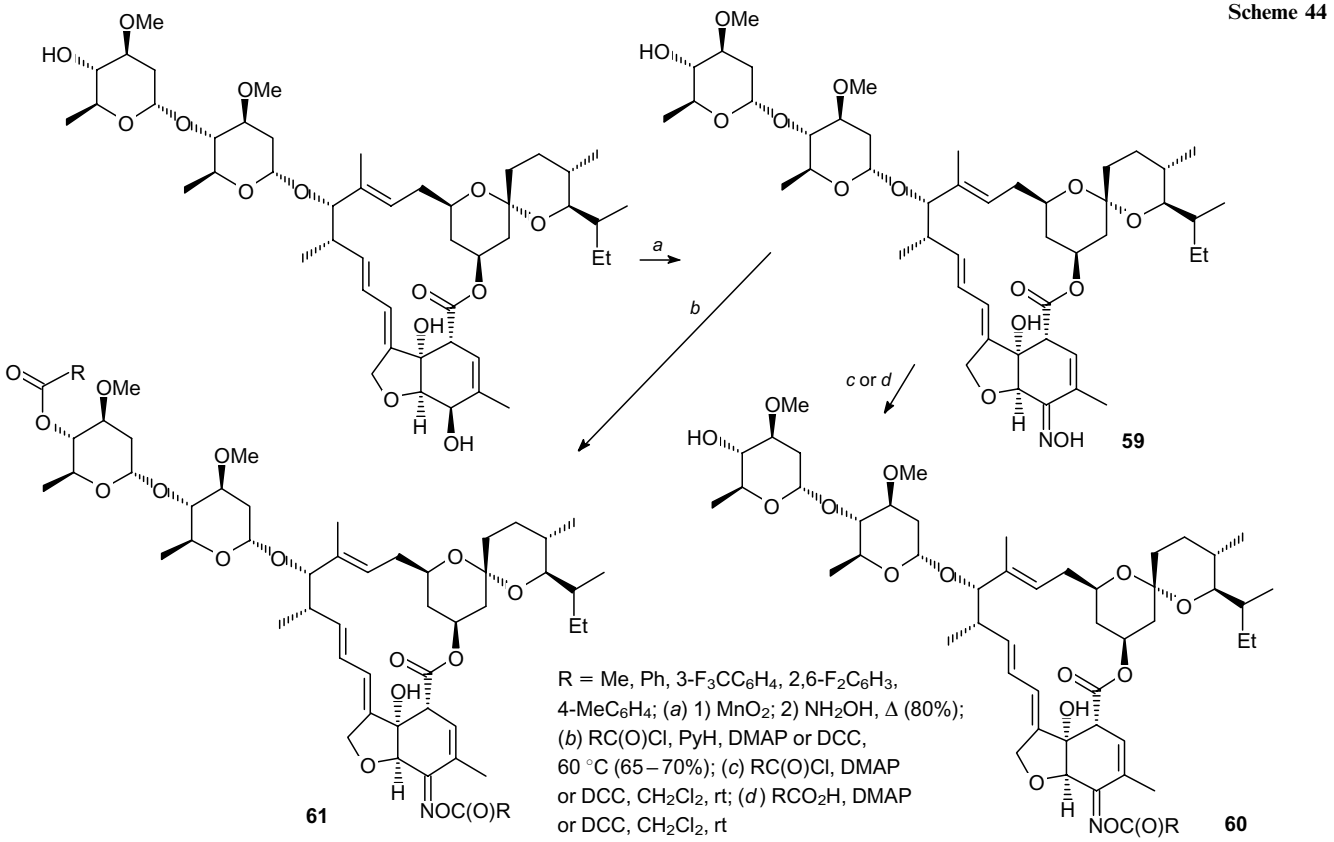
4.9. Modification of the spiroketal moiety

The spiroketal moiety of avermectin can also be subjected to modification; however, investigations of these transformations are scarce.

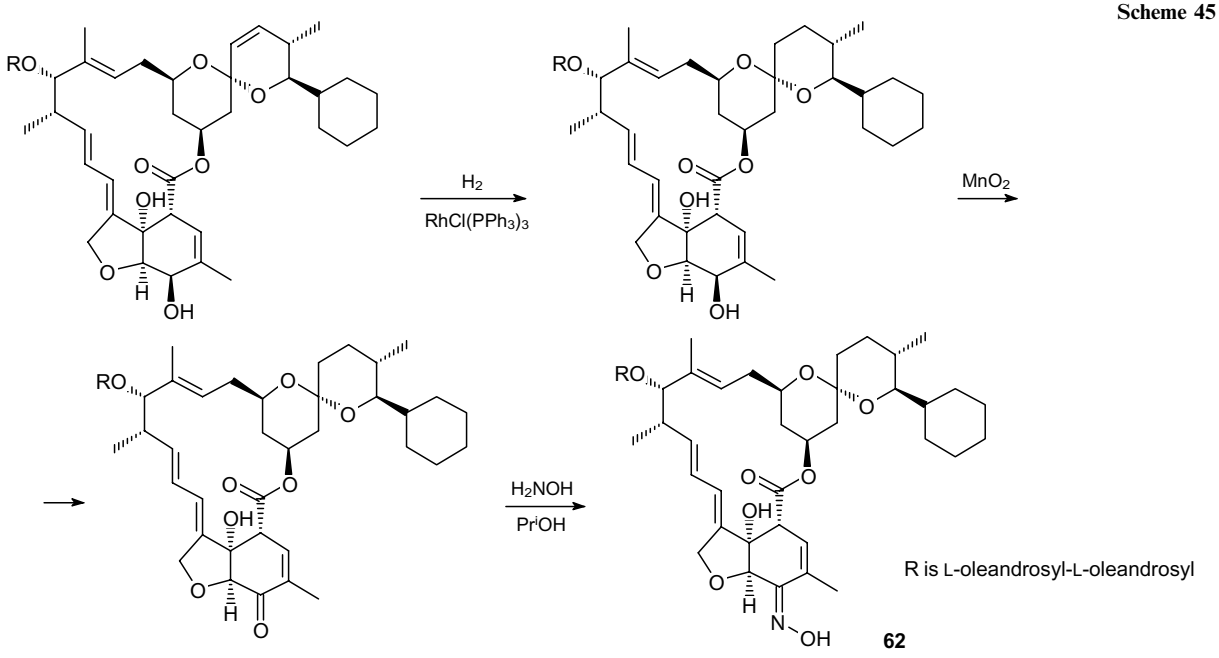
For example, a versatile strategy was developed for the synthesis of 25-nor-6,5-spiroketal avermectin analogues **63** containing different substituents at the C24 atom of the five-membered ring.[165] These compounds show high biological activity comparable to that of natural avermectins (Scheme 46).

A series of 5,6-spiroketal avermectin analogues **64** containing a triazole functional group were synthesized by the modification of the spiroketal moiety of avermectin B_{2a}.[166] Some of these products exhibit antinematicidal activity comparable to that of ivermectin (Scheme 47).

Scheme 44



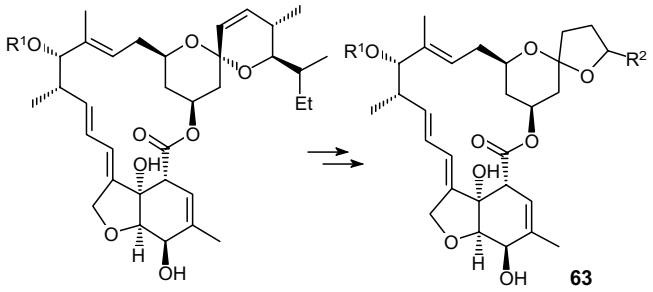
Scheme 45



Another modification of the spiroketal moiety of avermectin is based on the replacement of the C23 carbon atom by oxygen or sulfur to form 23-nor-23-oxa or 23-nor-23-thiaavermectins **65**.[167] Heteroatom-substituted avermectins can be represented as isosteres of 22,23-dihydroavermectin B_{1a} and the corresponding sulfoxides and sulfones are isosteric to avermectin B_{2a}. Therefore, these derivatives bear diverse functionality at C24 and C25 of avermectins. However, these compounds were not evaluated for biological activity.

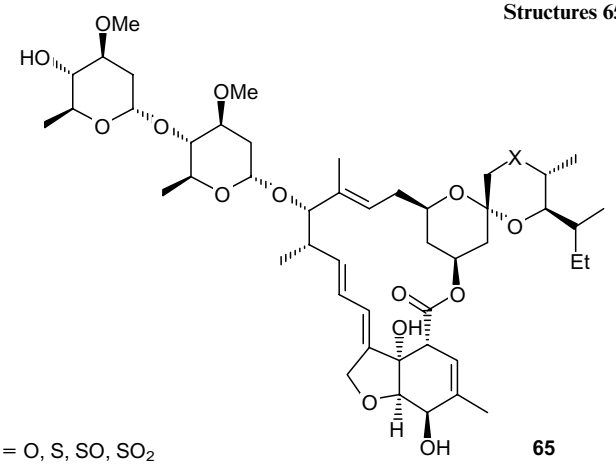
Currently, none of the modification products of the spiroketal moiety of avermectins are of commercial interest. Nevertheless, investigations of these transformations hold promise because the commercially available moxidectin is a C23 derivative of the 6,6-spiroketal moiety of the related milbemycin.[20, 23]

Scheme 46



R^1 is L-oleandrosyl-L-oleandrosyl; R^2 = H, Alk, CH_2OH, CH_2OMe, Ph, Ar, OMe

Structures 65



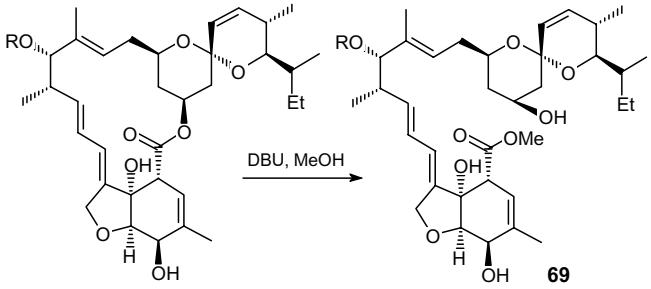
X = O, S, SO, SO_2

4.10. Avermectins as precursors

Apart from chemical modifications through the introduction of various functional groups, other fields of application of avermectins in organic synthesis were developed. For example, a series of functionalized segments were derived from avermectins. These segments can be used as precursors for the design of new hybrid molecules or semisynthetic analogues of natural products and also in order to confirm the structures of intermediates. Thus, the degradation of avermectin B_{1a} affords building blocks **66**–**68** serving as intermediates in the total synthesis of avermectins (Scheme 48).[89, 168]

The degradation of avermectin with DBU in methanol gives a mixture of other products.[125] $\Delta^{2,3}$-Seco acid methyl ester **69** that was isolated as the major product can be used as the starting compound for the synthesis of avermectin analogues (Scheme 49).

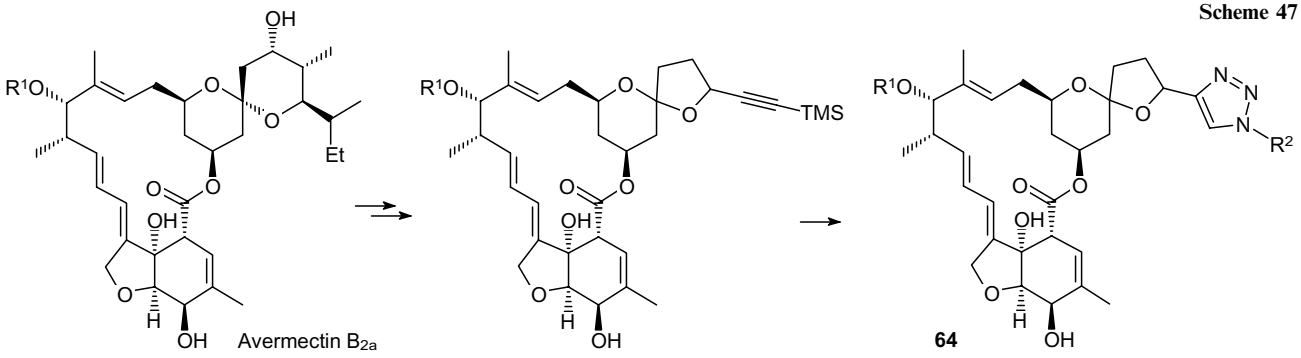
Scheme 49



R is L-oleandrosyl-L-oleandrosyl

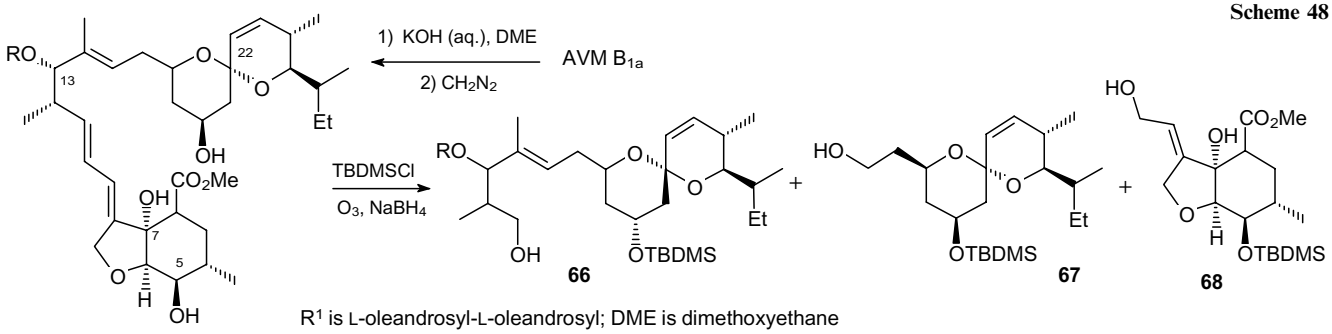
Among other types of degradation, the most well studied is the acidic hydrolysis of avermectins, which promotes the sequential deglycosylation of monosaccharide **70** and then aglycone **71** (Scheme 50). The selective elimination of carbon, *i.e.*, of the α-L-oleandrose moiety, at the C4′ position of avermectin occurs under mild acidic con-

Scheme 47



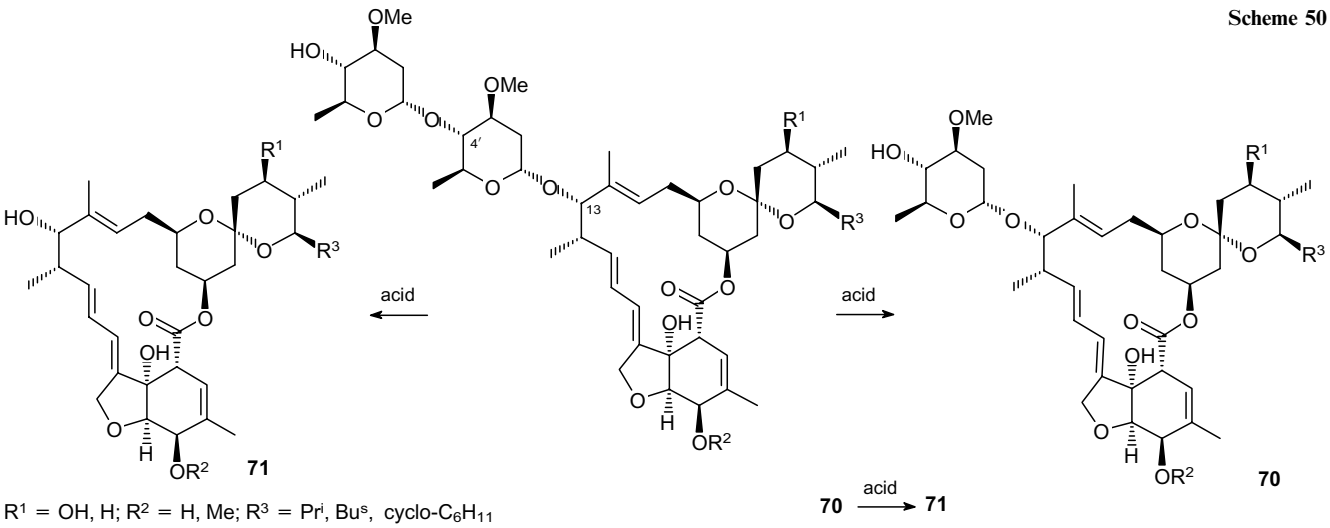
R^1 is L-oleandrosyl-L-oleandrosyl; R^2 = Bz, 4-$HO_2CC_6H_4$, Ad, $CH_2CH(OH)CH_2OH$

Scheme 48



R^1 is L-oleandrosyl-L-oleandrosyl; DME is dimethoxyethane

Scheme 50



ditions, while the whole disaccharide is eliminated under more severe conditions to form aglycones.[169] At lower concentrations of sulfuric acid (from 0.01 to 0.1%), the degradation affords monosaccharides as the major products, while aglycones are produced at higher concentrations of the acid (from 1 to 10%). At intermediate concentrations of sulfuric acid, the degradation generally gives mixtures of these products.[169] The acidic hydrolysis of avermectins depends also on the nature of the solvent. In particular, the hydrolysis of avermectins with 1% sulfuric acid in methanol produces the corresponding aglycone **71**; in isopropyl alcohol, the reaction results in the selective formation of monosaccharides **70**.[29] Similarly, doramectin undergoes sequential deglycosylation in acetonitrile under moderately acidic conditions to form doramectin monosaccharide (within 1 h) and aglycone (18 h), respectively.[124]

5. Structure – property relationships for avermectins: the influence of the structure on the biological activity, stability and toxicity

Understanding the structure – property relationships is necessary for a more meaningful search for new derivatives with high biological activity and other properties required for the design of commercial drugs. These investigations are conducted along two paths: the analysis of relationships between the activity of natural products and their structures and the analysis of the data on biological activity of chemically modified derivatives obtained by computer methods (SAR/QSAR, where SAR is the structure – activity relationship and QSAR is the quantitative structure – activity relationship) and(or) molecular docking. In some cases, the data on metabolism of avermectins[170] are used to account for the structure – property relationships.

5.1. Diversity of natural compounds

As mentioned above, one area of research on structure – property relationships involves the analysis and comparison of the structures of known natural compounds of the avermectin (or milbemycin) family, the identification of the moieties responsible for their physicochemical properties and pharmacological activity and the modification of available compounds (primarily commercial products) based on the analysis of the obtained data. In order to make significant progress in this area, it is necessary to isolate as many as possible natural compounds of these families, which is reflected in an increasing number of studies.

The range of natural compounds of the 16-membered macrolide family, which are formally avermectin (or milbemycin) derivatives, is constantly expanded. Apart from avermectins (isolated from *Streptomyces avermitilis*), milbemycins (from *S. hygroscopicus*, subsp. *aureolacrimosus*) and nemadectins (from *S. hygroscopicus*, subsp. *noncyanogenus*) structurally related to milbemycins, the following 16-membered macrolides were isolated: tenvermectins C, D (see Ref. 171) and $\Delta^{2,3}$-tenvermectin A (see Ref. 172) from the stain *S. avermitilis* MHJ1011, melingmycin from *S. nanchangensis* (structurally related to α(11)-milbemycin),[173] milbemycin analogues from *S. microflavus* neau3 Y-3,[174] aglycones from the strains *S. avermitilis* NEAU1069 (see Ref 175 and 176) and AVE-H39,[177] milbemycin R from the mutant strain *S. bingchenggensis* BCJ60B11,[178] avermectin B_1 homologues from the Beibu Gulf gorgonian coral *Anthogorgia caerulea* (China),[179] avermectin analogues from the mutant strain *S. avermectinius* ΔaveCDE,[180] *etc.* (Fig. 1).[181,182]

The presence of 5-*O*-methyl-22,23-dihydrovermectin B_{1a} (and avermectin B_{2a}), *i.e.*, natural 5-*O*-ivermectin (semisynthetic ivermectin is derived from avermectin B_1, see Section 3.1), in tenvermectin and among metabolites produced by *Anthogorgia caerulea* is of interest in relation to the production of ivermectin by synthetic biology methods. Apparently, other, currently unknown producers of ivermectin-like compounds occur in nature.

All known avermectins and structurally related milbemycins, as well melingmycin, 28-homo avermectin B_{1a} and 28-isopropyl avermectin B_{1a}, exhibit high antiparasitic activity at very low concentrations. Numerous examples of practically important natural avermectin-like compounds and their semisynthetic analogues containing various substituents in different positions (C4, C5, C13, C22, C23, C25) of the pentacyclic core (pharmacophore of these substances) modulate their biological activity only to some extent.

The diversity of natural avermectins (milbemycins) and structurally related compounds demonstrates possible chemical modifications aimed at the synthesis of their semisynthetic analogues with improved properties.

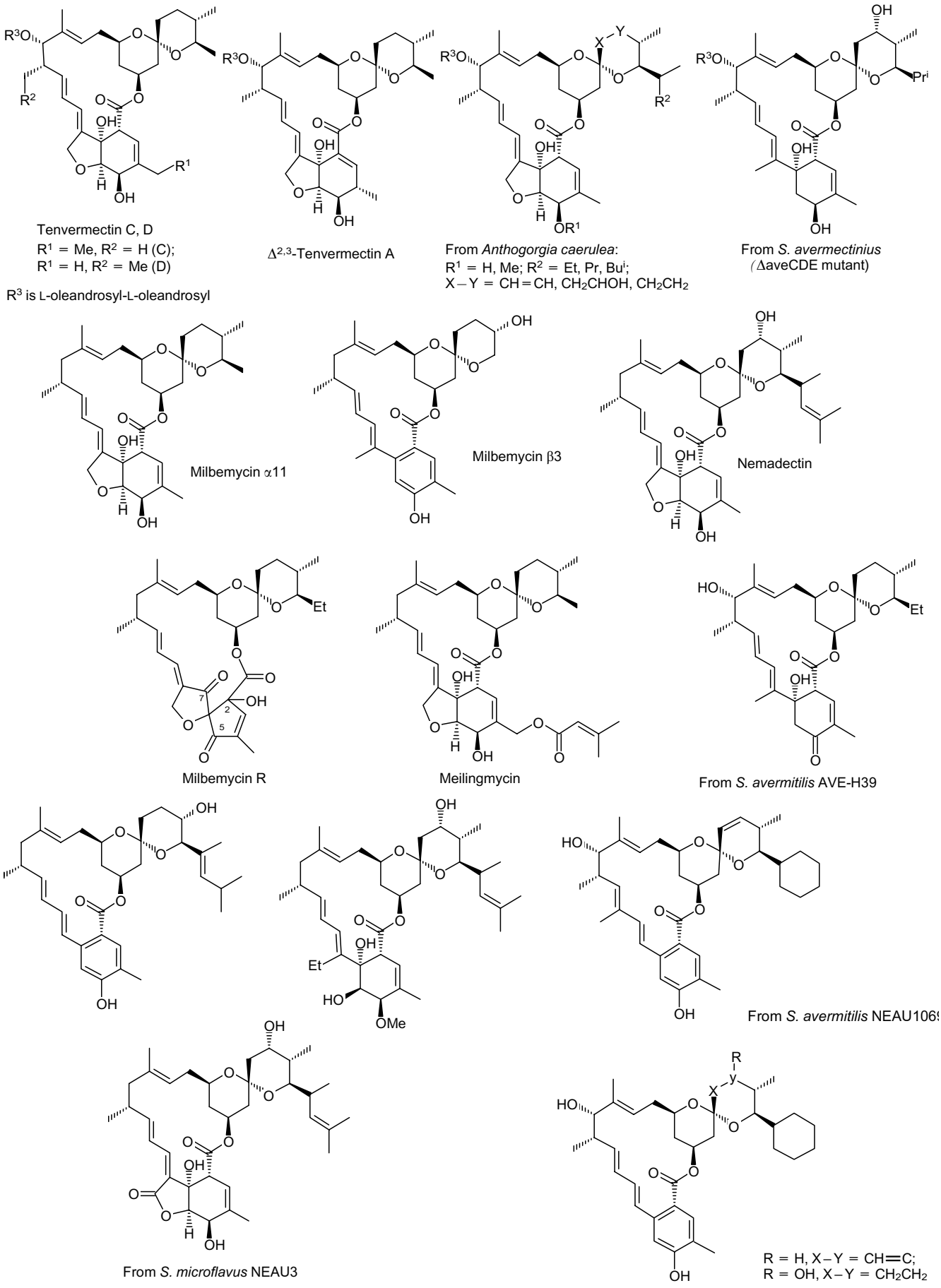


Figure 1. Structures and natural sources of avermectins and milbemycins isolated in 2002–2021.[171–182]

5.2. Effect of substituents at the C(4″) atom on the activity

Investigations of avermectin derivatives demonstrated that the presence of lipophilic bis(oleandrosyl) disaccharide at the C13 position of the macrocycle is not required for the biological activity. However, this moiety is a convenient target for subsequent chemical modification. The analysis of the influence of the structure on the antiparasitic activity demonstrated that substituted avermectins, modified at the C4″ position, have the highest activity. The synthesis of these derivatives presents no difficulty due to the easy accessibility of the hydroxy group at the C4″ atom as the reactive site.

The synthesis produced functional derivatives containing acyl,[115] amino (see Ref. 183) or thio groups[184] at the C4″ positions, the substituents in which affect the properties of the synthesized compounds (stability, solubility and the biological activity spectrum), retaining the efficacy of the starting molecule.[185] Besides, substituents bearing alkylamino, oxyiminoalkyl, alkylsilyl, alkylthio, *etc*. groups were introduced at the C4″ position of avermectins.[91, 135, 148, 150–152, 184, 186, 187] It was found that some 4″-N-substituted analogues exhibit higher activity compared to that of avermectin B_{1a}.[105, 106, 147, 188, 189] The synthesis of 4″-amino-4″-deoxyavermectins was the major breakthrough in this research. For example, emamectin bearing the *epi*-methylamino group at the C4″ position is one of the most effective compounds. Its insecticidal activity is 1500 times higher than that of avermectin B_1. Eprinomectin, in which the 4″ hydroxy group is replaced by the *epi*-acetylamino group, also shows high antiparasitic activity. In general, these derivatives also have good solubility, high biodistribution, good chemical stability and broad-spectrum activity, thereby allowing the structural optimization of avermectins through rational modifications at the C4″ position. A series of sulfonyl-containing 4″-N-substituted derivatives, such as the corresponding sulfonylamidines, sulfonylureas and sulfonylamines, were synthesized.[146] Most of the synthesized compounds exhibited high biological activity. The SAR analysis of the influence of the structure of the sulfonyl groups on the biological activity of the compound demonstrated that the size, electron density and the distribution of substituents in the sulfonyl side chain play a crucial role in the manifestation of activity of these derivatives.[146] Besides, the data on the activity of the synthesized compounds were used to construct a quantitative structure–activity relationship (QSAR) model, which predicted that the insecticidal activity of avermectin analogues is mainly affected by such factors as the molecular shape, the size of the substituent, the degree of branching and the number of double bonds.[146]

The SAR analysis of a series of 4″-aminoavermectins against the spider mite (*Tetranychus urticae*) and the southern armyworm (*Spodoptera eridania*) was performed in the study.[117] It was demonstrated that 4″-amino-4″-deoxyavermectin B_1 [(*S*)-**72**], in which the C4″ atom has an *S* configuration, is five times less active against *S. eridania* compared to the *R* isomer, 4″-*epi*-amino-4″-deoxyavermectin B_1 [(*R*)-**72**]. Among the 4″-amino derivatives, emamectin benzoate (**7**) is the most active against *S. eridania*. Meanwhile, all 4″-amino derivatives are less active against the spider mite compared to abamectin (**3**) (Table 2).

The synthesis and SAR analysis of new avermectin derivatives **73e**–**f** were described in the study.[19] The activity of these derivatives was evaluated against the Egyptian cotton leafworm (*S. littoralis*), the western flower thrips (*Frankliniella occidentalis*) and the spider mite (*T. urticae*).

Structures 72, 73

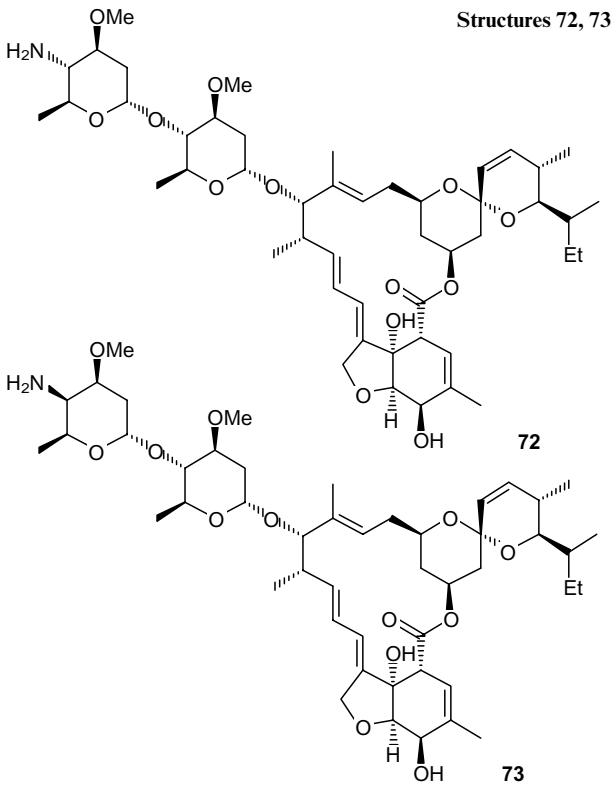


Table 2. Activity of avermectins against the spider mite and the southern armyworm.[117]

Compound	Activity (EC_{90}), ppm	
	T. urticae	*S. eridania*
Abamectin (**3**)	0.03	8.0
Emamectin benzoate (**7**)	0.25	0.004
(*S*)-**72**	0.25	0.10
(*R*)-**72**	0.25	0.02

EC_{90} is the 90% effective concentration.

Structures 73

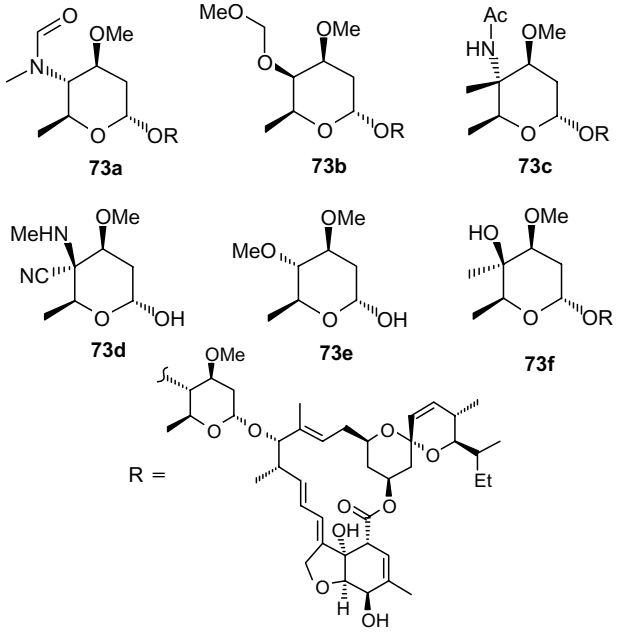


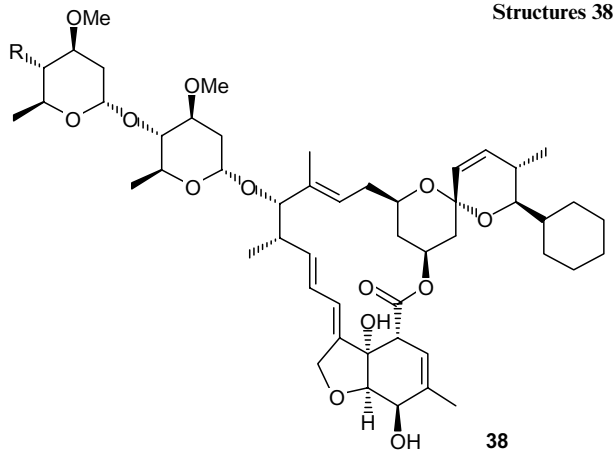
Table 3. Antiparasitic activity and toxicity of selected avermectin derivatives.[117]

Compound	Activity, ppm			Toxicity	
	S. littoralis	*F. occidentalis*	*T. urticae*	in rats, mg kg^{-1}	in daphnia, μg L^{-1}
Abamectin (**3**)	0.8	3.0	0.03	221	0.34
Emamectin benzoate (**7**)	0.05	3.0	0.2	76	0.99
73a	0.8	0.8	0.01	< 50	1.7
73b	0.05	0.8	0.003	> 200	2.7
73c	3	0.8	0.01	> 50	0.8
73d	> 3	3	0.01	> 50	Non-toxic
73e	3	0.8	0.01	> 50	5
73f	0.8	3	0.01	50	Non-toxic

The structures and biological activity of these avermectins and the data on their toxicity evaluated in rats and daphnia are given in Table 3. It was found that the type of the substituent significantly affects the biological activity spectrum, the high activity against insects and mites generally causing no increase in the toxicity of the modified derivatives.

The evaluation of the structure–activity relationship was also performed for a wide range of carbamate, ester and sulfonate doramectin derivatives **38** modified at the C4″ position.[142]

Structures 38



38

R = $AlkNHCO_2$, cyclo-$AlkNHCO_2$, $AllNHCO_2$, $BnNHCO_2$, 4-$MeOC_6H_4CH_2NHCO_2$, $XC_6H_4NHCO_2$ (X = H, 4-F, 4-Cl, 4-Br, 2-Me, 3-Cl, 4-OMe, 4-Me, 4-CF_3), 1-$NaphNHCO_2$, $AlkCO_2$, $CH_2{=}CHCO_2$, $BnCO_2$, $AlkSO_2$, *etc*.

It was demonstrated that the type of substitution at the C4″ atom of doramectin has a significant effect on the insecticidal activity of its derivatives. The following general patterns were found:

— the activity decreases in the series carbamate > ester ≈ sulfonate derivatives;

— compounds containing short alkyl groups are more active than those bearing long substituents;

— alkyl-substituted compounds are more active than aromatic compounds;

— derivatives with normal (unbranched) substituents are more active than those with branched substituents, and cyclopropyl-substituted compounds are more active than cyclohexyl-substituted derivatives.

Among the tested compounds, derivative **38a** bearing the cyclopropyl carbamate moiety (R = cyclo-$C_3H_5NHCO_2$) showed the highest activity, which is higher than that of doramectin and commercial avermectins.[142] Besides, doramectins containing methyl or allyl carbamate moieties (R = $MeNHCO_2$, $AllNHCO_2$) have high activity.[142]

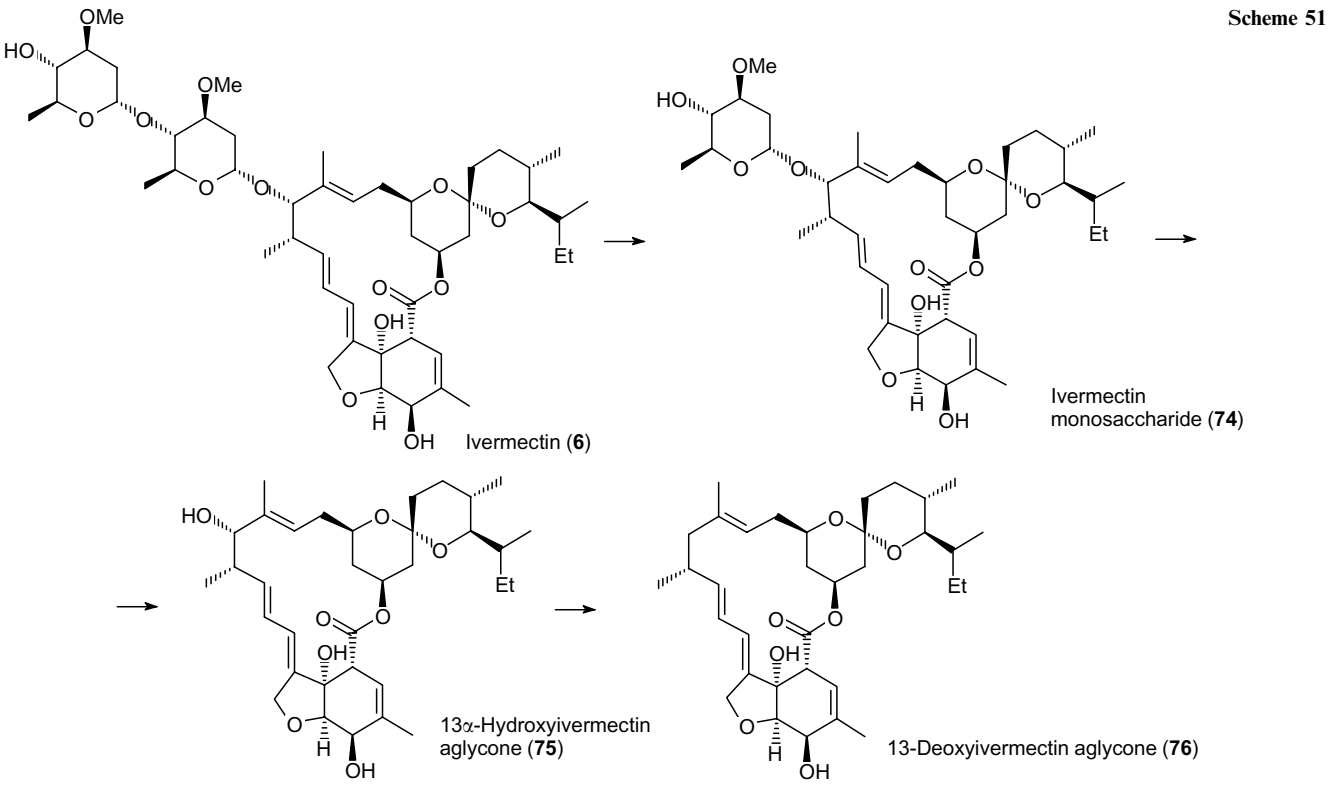
To get a better insight into the structure–activity relationship for the doramectin derivatives, molecular docking simulations for this series of compounds was performed using the GABA receptor from *Plutella xylostella*. The calculations demonstrated that cyclopropyl carbamate **38a** has the highest binding affinity for the GABA receptor. The results of docking of compounds **38**, doramectin and a number of avermectins are in good agreement with the data on their insecticidal activity. Thus, the activity of carbamates is higher than that of esters, the activity of the latter is similar to that of sulfonates.[142]

5.3. Effect of substituents at the C13 atom on the activity

Ivermectin (22,23-dihydroavermectin B_1, **6**) shows almost as high antiparasitic efficacy as avermectin B_1. The discovery of this compound has given a great boost to further studies of avermectins. In particular, chemical methods were developed for the successive removal of the bis(oleandrosyl) moiety. Deglycosylated avermectin analogues were studied in comparison with milbemycins. Thus, the removal of terminal oleandrose from ivermectin v*ia* acid hydrolysis gave monosaccharide **74**, which is only slightly less active than the starting ivermectin. Meanwhile, the removal of both oleandroses afforded virtually inactive aglycone **75** containing the 13α-hydroxy group. This naturally gave rise to a question as to whether 13-deoxyivermectin aglycone **76** and related milbemycins exhibit nematicidal activity. The main structural difference between the ivermectin aglycone and milbemycins is that the former contains the α-hydroxy group at the C13 position. It is this group that is responsible for the absence of activity of these avermectin derivatives. The removal of this group affords less polar 13-deoxyivermectin aglycone **76**, which is structurally more similar to milbemycins and has higher anthelmintic activity. Actually, the resulting component of 13-deoxy-22,23-dihydroavermectin B_{1b} (**76**) is natural milbemycin D (Scheme 51).[185]

The data on the effect of substituents at the C13 atom of avermectin aglycone on the biological activity are summarized in the review.[22] The following main conclusions were made. The activity of avermectin B_1 monosaccharide (**77**) against the spider mite (*T. urticae*) was comparable with that of the starting avermectin B_1, whereas avermectin B_1 aglycone (**78**) was 30 times less active. Surprisingly, but the aglycones of both 13-deoxyavermectin B_1 (**79**) and 13-deoxy-22,23-dihydroavermectin B_1 (**80**) were three times

Scheme 51



more active than avermectin B_1. On the contrary, the acaricidal activity of ivermectin (22,23-dihydroavermectin B_1, **6**) was 3 times lower compared to that of abamectin (**3**). Monosaccharide **81** and aglycone **82** proved to be virtually inactive against *T. urticae*. It is worth noting that avermectin B_1 is the most active acaricide among the naturally occurring avermectins, whereas avermectins B_2, A_1 and A_2 are almost ten times less active.

The results of other studies [117, 190] also confirm the fact that the presence of the disaccharide unit of the avermectin molecule is not necessary for high acaricidal activity. Generally, compounds containing lipophilic substituents at the C(13) atom (or unsubstituted at this position) are highly active, whereas the introduction of polar substituents leads to a decrease in the activity of the derivatives.[22]

5.4. Effect of the modification of the spiroketal moiety

Chemical modifications of the spiroketal moiety have attracted great attention after the discovery of ivermectin produced by the hydrogenation of the C22–C23 double bond of avermectin B_1.[95]

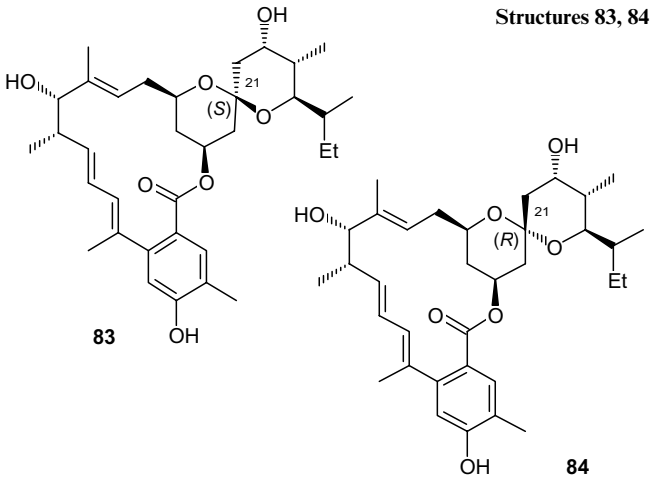
The presence of substituents at the C23 position, such as the 23-hydroxy group in avermectin B_2 or the 23-oxo or 23-methoxime group in milbemycin, leads to a change in the biological activity spectrum but does not increase the overall efficacy compared to avermectin B_1.[185, 191] Other external modifications in the spiroketal moiety of avermectins, such as that between the homologues B_{1a} and B_{1b}, has almost no effect on the activity.[185, 191]

Lipophilic substituents at the C25 position, such as five- or six-membered alicycles, can produce longer tissue half-lives of these compounds, but they did not show fundamental improvement of the activity compared to avermectin B_1.[185, 191] However, the introduction of the lipophilic but-2-en-2-yl group or polar substituents causes a decrease in the activity of the corresponding derivatives.[185]

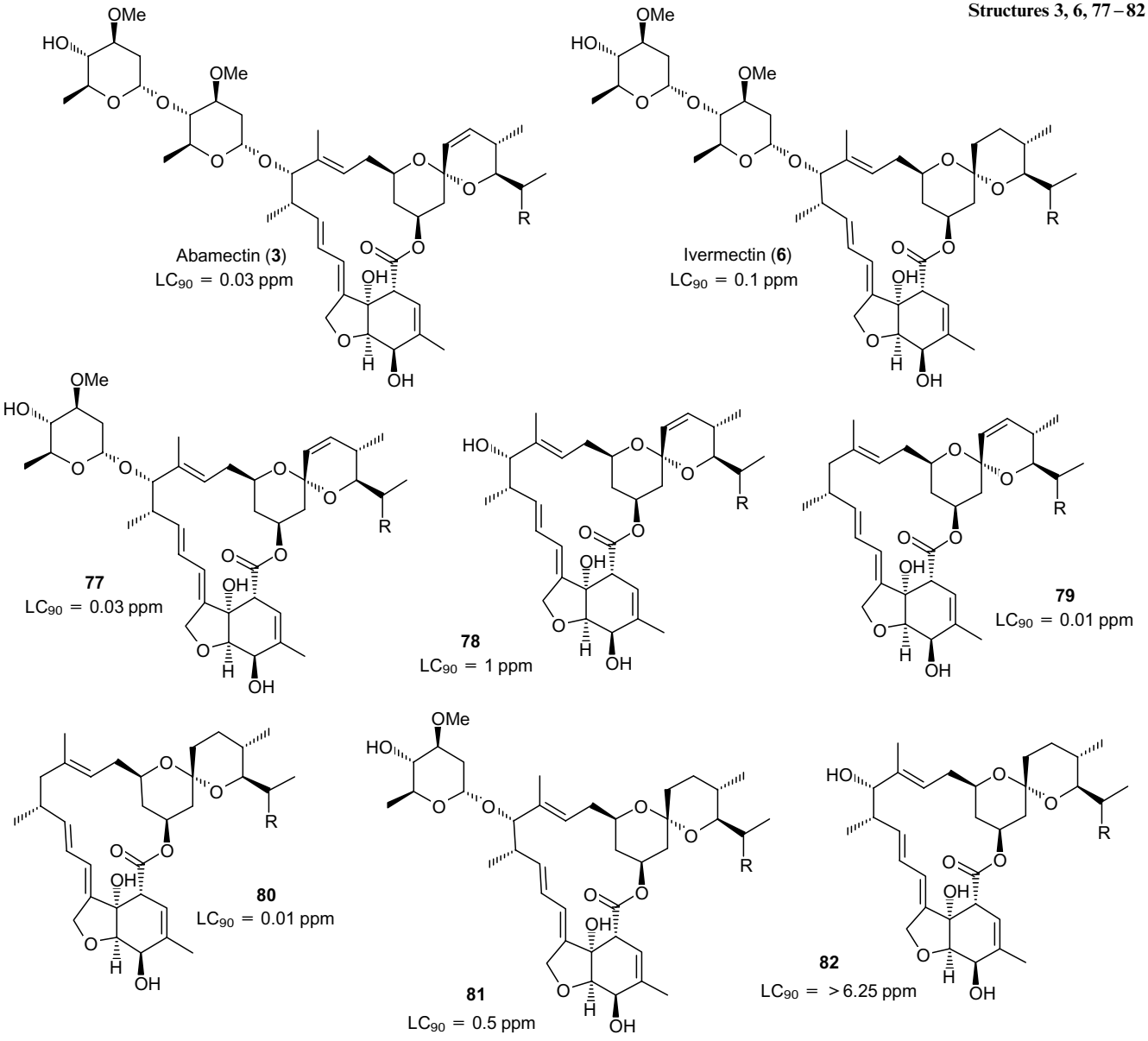
Apart from investigations of the effect of substituents in the spiroketal moiety, attempts were made to evaluate the dependence of biological activity of the synthesized compounds on the configuration at the spirocyclic junction. Natural avermectins have a 6,6-spiroketal moiety with an exclusive *R* configuration at the C21 spirocyclic atom. To evaluate the effect of stereochemistry of this moiety on the biological activity, avermectin aglycones, spiroketals **83** and **84** with the *S* and *R* configuration at the asymmetric centre, respectively, were isolated from fermentation products of the mutant strain *S. Avermectinius* VL1004.[192]

Stereoisomers **83** and **84** were evaluated for different types of insecticidal activity. It was found that the spiroketal with the native *R* configuration at the C21 atom has a broader biological activity spectrum. However, both compounds were, as expected, much less active than avermectin B_{1a}.[192]

Structures 83, 84



Structures 3, 6, 77 – 82



R = Et (> 80%), Me (< 20%); LD_{90} is the dose required to kill 90% of the exposed population

5.5. Structure – activity relationship

Studies aimed at chemical modifications of natural avermectins revealed a number of derivatives with higher biological activity compared to natural sources. This served as an impetus to investigation of the relationship between the chemical structure and activity (structure – activity relationship, SAR) for this class of compounds. These studies were complicated by a broad spectrum of their biological activity. Nevertheless, a number of structure – property relationships were established.[92, 117, 185]

The avermectin molecule contains several chemically active sites accessible to modification. Derivatives bearing substituents at different positions were synthesized and evaluated for their biological activities (primarily, for antiparasitic activity). The results of these studies are summarized in the monograph.[92] Based on these data, the following conclusions can be drawn.

1. 4″-*O*-Substituted avermectins retain high biological activity, the modification of the carbohydrate moiety being possible at other positions as well.

2. The presence of a disaccharide residue at the C13 position of avermectins is necessary for high biological activity. Thus, the removal of the oleandrosyl moiety giving the corresponding monosaccharide leads to a decrease in the activity of the derivatives by 25 – 50% compared to the activity of the starting compound. The removal of the second oleandrosyl moiety affords the corresponding aglycone characterized by even lower activity. For example, dihydroavermectin B_1 aglycone is 30 times less active than the staring avermectin. However, the removal of the hydroxy group at the C13 atom of the aglycone gives 13-deoxyavermectin aglycones (milbemycins), some of which exhibit high anthelmintic activity.

3. Avermectins of the A series bearing the methoxy group at the C5 position have lower activity compared to avermectins of the B series bearing a hydroxy substituent at this position. Other 5-*O*-alkoxy avermectins containing bulkier alkyl groups exhibited weak activity or were inactive.

4. 5-Acylated derivatives, as well as 5-deoxyavermectin 5-oximes and esters, show high antiparasitic activity.[108, 156, 160–164]

5. The reduction of the 22,23-double bond of avermectins giving the corresponding 22,23-dihydroavermectins (ivermectins) does not lead to a significant change in the biological activity, the stability of the products being increased and their toxicity being reduced.

6. The aliphatic natures of the six-membered ring of the hexahydrobenzofuran moiety containing an OH or OMe group at the C5 position is important for high antiparasitic activity. The aromatization of this ring leads to the loss of activity. Apart from avermectins bearing the natural OH group at the C5 atom, 5-oxime derivatives and their esters are also highly active.[160, 161]

7. Other types of modifications of avermectins at the C5, C13, C22, C23 and C26 positions generally lead to a decrease in the biological activity of the products.

6. Prospects of application

A number of reviews and monographs address the use of avermectins as antiparasitic drugs (primarily, anthelmintic drugs and nematicides) in agriculture and medicine.[29, 193–202] In recent years, extensive research efforts were concentrated on expanding the area of application of avermectins, in particular for the treatment and prevention of previously unknown diseases.

All avermectins exhibit unprecedented activity against every invertebrate, including nematodes, mites and insects. The mechanism of their biochemical action is described in detail in reviews and monographs.[29, 107, 193, 195, 196, 203, 204] Avermectins block the glutamate-gated chloride channels and can be effective against not only helminths but also against other invertebrates, including arthropods, mites, shellfish, *etc*. Hence, there is growing interest in using avermectins to combat other diseases caused by parasites, in particular scabies and malaria, and by soil-transmitted helminths. Thus, ivermectin is extensively studied as a malaria control tool since it was proved to be effective against malaria vectors.[205] It was demonstrated that ivermectin has mosquito-lethal and sporontocidal properties, preventing the sporozoite maturation and development in mosquitoes, thereby rendering mosquitoes incapable of transmitting malaria.[206] Therefore, ivermectin has strong potential for reducing infection transmission. The results of the use of ivermectin for fighting malaria are summarized in the review.[207]

Ivermectin was also found to be highly effective against visceral leishmaniasis.[208, 209] This drug is also expected to control insect vectors of parasitic diseases and kill subcutaneous mites and Cheyletiella mite and also can be used to treat a number of parasitic diseases.[210]

The discovery of antiviral and anticancer activity of avermectins has provided additional impetus to studies on their application for the treatment of other diseases. It was found that ivermectin has antiviral properties,[211] in particular it is effective against a steadily increasing number of RNA viruses, including influenza, HIV, Zika and Hendra viruses, dengue and West Nile fever.[212–218] Among other viral diseases, which can be treated with ivermectin, mention should be made of Newcastle disease virus (avian paramyxovirus).[219] Abamectin was found to be highly active against yellow fever virus and flavivirus.[215]

After the emergence of SARS-CoV-2 pandemic, researchers began searching for effective treatment for novel coronavirus infection. Ivermectin appears useful in all stages of the disease.[220–224] This drug was approved by the World Health Organization for the prophylaxis and treatment of COVID-19.[220]

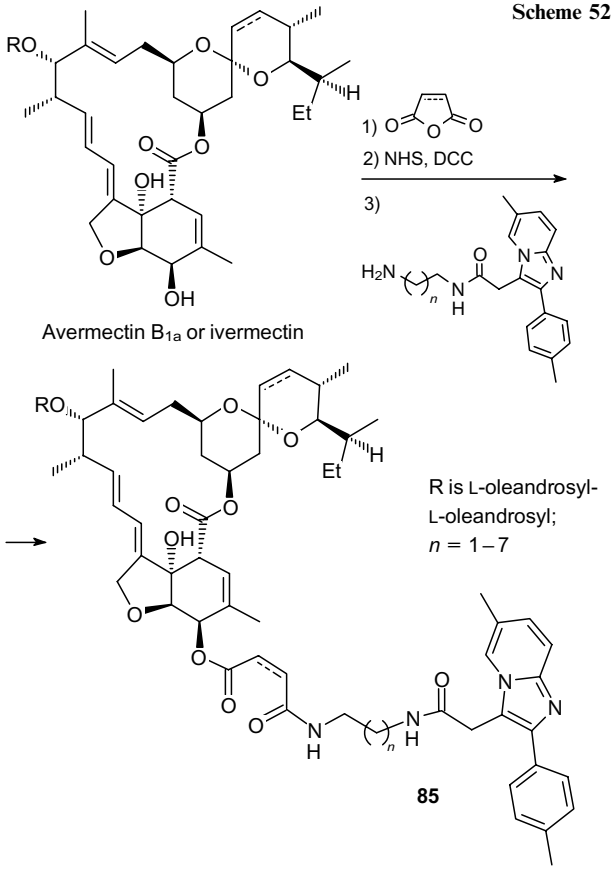
The data on the antitumour activity of ivermectin against different types of cancer are summarized in reviews.[210, 225–232] It is worth noting that antitumour activity of ivermectin is achieved at concentrations that can be clinically reachable based on human pharmacokinetic studies. Therefore, the available data on ivermectin make it possible to rapidly move into clinical trials for cancer patients.[225]

Avermectins can also be used as antibacterial agents. Thus, ivermectin and its derivatives proved to be active against methicillin-resistant *Staphylococcus aureus* (golden staph) and its biofilm infections.[145] Avermectins also kill tuberculosis mycobacteria, including multidrug-resistant clinical strains.[233–236]

Besides, ivermectin was found to have an inhibitory effect on allergic asthma symptoms[237] and be effective in patients with neurological disorders.[238] Avermectin derivatives were proposed for the treatment of FXR-mediated diseases or conditions (FXR is the bile acid receptor, also referred to as the farnesoid X receptor or NR1H4), including liver diseases, obesity, cardiovascular and gastrointestinal diseases, atherosclerosis and kidney diseases.[239] The prospects of the application of ivermectin for the treatment of other diseases are summarized in the review.[210]

The avermectins have various biological functions, which are poorly known. Thus, avermectins exhibit high $GABA_A$-modulating activity ($GABA_A$ are GABA-gated

Scheme 52



receptors).[240] Glutamate-gated chloride channels are the main targets of avermectins; however, it was recently demonstrated that these compounds exhibit high $GABA_A$-modulating activity.[240] Hybrid compounds containing the avermectin and imidazo[1,2-*a*]pyridine pharmacophores were synthesized for the first time and evaluated *in vitro* and *in vivo*.[241] Compounds **85** were synthesized based on avermectin B_{1a} and ivermectin using a linkers of variable length and showed properties of hybrid allosteric $GABA_A$ receptor modulators, which can independently bind to the benzodiazepine and avermectin binding sites of the target (Scheme 52).[241]

The data on new types of biological activity of avermectins published in the literature will be thoroughly verified and studied in detail. There is no doubt that effective avermectin-based drugs for the treatment of new diseases will be designed in the near future.

7. Conclusion

Avermectins are currently the most commonly used and effective tool against endo- and ectoparasites of humans, animals and plants. Evidently, their role as antiparasitic drugs will increase with time. Therefore, this area of research is extensively developed.

Natural avermectins are most commonly produced in industry by microbiological synthesis. The available strategies for chemical synthesis of these compounds involve many steps and afford target products in low overall yields. In the past years, efforts were made to improve these strategies.

Semisynthetic avermectin derivatives, which proved to be more active than natural products and are devoid of a number of their drawbacks, have attracted the most interest. The discovery of highly active derivatives and the presence of several reactive sites in these molecules have provided impetus to comprehensive studies of chemical modifications of avermectins in order to increase their biological activity and stability, expand the area of their application and reduce toxicity for warm-blooded animals. These studies showed the most success. A series of avermectin derivatives with high biological activity were synthesized. They have broader-spectrum activity and other improved important characteristics. It should be noted that the detailed structure – biological activity relationship analysis using mathematical modeling methods and the evaluation of the activity of natural avermectins at the molecular and cellular levels are required for the targeted modification of natural avermectins.

8. List of abbreviations and designations

AIBN — azobis(isobutyronitrile),
AVM — avermectin,
cat — catalyst,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCC — *N*,*N*′-di(cyclohexyl)carbodiimide,
DEAD — diethyl azodicarboxylate,
DIBAL — diisobutylaluminium hydride,
DMAP — 4-(dimethylamino)pyridine,
DME — dimethoxyethane,
dpm — dipivaloylmethanate,
DTBMP — 2,6-di-*tert*-butyl-4-methylpyridine,
EDCI — *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide,
EPM — eprinomectin,
FXR — farnesoid X receptor (bile acid receptor),
GABA — γ-aminobutyric acid,
$GABA_A$ — GABA-gated receptors,
HOBt — 1-hydroxybenzotriazole,
IVM — ivermectin,
LD_{90} — dose required to kill 90% of the exposed population,
LHMDS — lithium bis(trimethylsilyl)amide,
m-CPBA — 3-chloroperoxybenzoic acid,
MNBA —methyl-6-nitrobenzoic anhydride,
Naph — naphthyl,
NBA — *N*-bromoacetamide,
NBHA — *O*-(4-nitrobenzyl)hydroxylamine hydrochloride,
NIS — *N*-iodosuccinimide,
NMP — *N*-methylpyrrolidone,
NPSP — *N*-phenylselenophthalimide,
PA — phenoxyacetyl,
PG — protecting group,
PEG — polyethylene glycol,
Piv — pivaloyl,
Py — pyridyl,
rt — room temperature,
TBAF — tetra-n-butylammonium fluoride,
TBDMS — *tert*-butyldimethylsilyl,
TBDPS — *tert*-butyldiphenylsilyl,
TFA — trifluoroacetic acid,
Tf — trifluoromethanesulfonyl (triflyl),
Th — thienyl,
TMS — trimethylsilyl,
TMU — 1,1,3,3-tetramethylthiourea,
TPPMS —3-(diphenylphosphino)benzenesulfonic acid,
Tr — trityl,
p-Ts — *p*-toluenesulfonyl (tosyl).

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