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New ventures in the chemistry of avermectins

Thomas Pitterna *, Jérôme Cassayre, Ottmar Franz Hüter, Pierre M. J. Jung, Peter Maienfisch, Fiona Murphy Kessabi, Laura Quaranta, Hans Tobler

Syngenta Crop Protection Münchwilen AG, Crop Protection Research, Chemistry, Schaffhauserstr. 101, CH-4332 Stein, Switzerland

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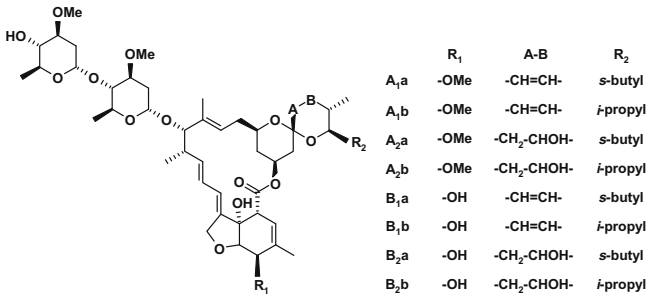
ABSTRACT

An overview is given on recent work towards new avermectin derivatives of extremely high insecticidal and acaricidal activity. These compounds were prepared from commercially available abamectin (avermectin B1) **1**. For the synthesis, many novel entries have been opened up, making use of modern synthetic methods and applying them, for the first time, to the chemistry of avermectins. Several types of avermectin derivatives can be regarded as key innovations in the field. These are, in particular, 4″-deoxy-4″-(*S*)-amino avermectins **3**, 4′-*O*-alkoxyalkyl avermectin monosaccharides **5**, 4″-deoxy-4″-C-substituted 4″-amino avermectins **6** and 2″-substituted avermectins **7**. 4″-Deoxy-4″-(*S*)-amino avermectins **3** were obtained by the consecutive application of the Staudinger and Aza-Wittig reaction. 4′-*O*-Alkoxyalkyl avermectin monosaccharides **5** were prepared by alkoxyalkylation of 5-O-protected avermectin monosaccharide. For the synthesis of 4″-deoxy-4″-C-substituted 4″-amino avermectins **6**, several methods were used to construct the fully substituted 4″-carbon centre, such as a modified Strecker synthesis, the addition of organometallics to a 4″-sulfinimine and a modified Ugi approach. In order to prepare 2″-substituted avermectins **7**, 5-O-protected avermectin monosaccharide was coupled with carbohydrate building blocks. An alternative synthesis involved the hitherto unknown enol ether chemistry of 4″-oxo-avermectin and the conjugate addition of a cuprate to an avermectin 2″,3″-en-4″-one. In addition, a number of other highly potent derivatives were synthesised. Examples are 4″-*O*-amino avermectins **8**, as well as products arising from intramolecular rhodium catalysed amidations and carbene insertions. A radical cyclisation led to an intriguing rearrangement of the avermectin skeleton. Many of the new avermectins surpassed the activity of abamectin **1** against insects and mites.

1. Introduction

To date, two avermectins (abamectin **1** and emamectin benzoate **2**) have been commercialised in crop protection. Their properties, such as mode of action, chemistry, insecticidal activity, safety, agronomic use and importance in crop protection have been the subject of a recent review.[1] In this introduction, only a brief background is given of this chemical class, which was discovered and pioneered by Merck scientists. It will be followed by an overview of recent innovations that originated from Syngenta researchers. Their major contributions will be discussed in detail in the following sections, synthetic chemistry work in particular. The last chapter will highlight he biological activity of the new avermectins.

The naturally occurring avermectins, a group of 16-membered macrocyclic lactones, are fermentation products from *Streptomyces avermitilis*, a naturally occurring soil Actinomycete. They possess anthelmintic, insecticidal and acaricidal activity. From the fermentation, eight different avermectins were isolated (Fig. 1), which comprise four pairs of homologues. Each pair contains a major component (the a-component) and a minor one (b-component). They are usually produced in a ratio between 80:20 and 90:10. One of these pairs, avermectin B_1, that is the mixture of avermectins B_1a (>80%) and B_1b (<20%), is commonly referred to as avermectin B_1 or abamectin **1** (Fig. 2).



	R_1	A-B	R_2
A_1a	-OMe	-CH=CH-	*s*-butyl
A_1b	-OMe	-CH=CH-	*i*-propyl
A_2a	-OMe	-CH_2-CHOH-	*s*-butyl
A_2b	-OMe	-CH_2-CHOH-	*i*-propyl
B_1a	-OH	-CH=CH-	*s*-butyl
B_1b	-OH	-CH=CH-	*i*-propyl
B_2a	-OH	-CH_2-CHOH-	*s*-butyl
B_2b	-OH	-CH_2-CHOH-	*i*-propyl

Figure 1. Structures of the naturally occurring avermectins.

* Corresponding author. Tel.: +41 61 323 84 88.
E-mail address: thomas.pitterna@syngenta.com (T. Pitterna).

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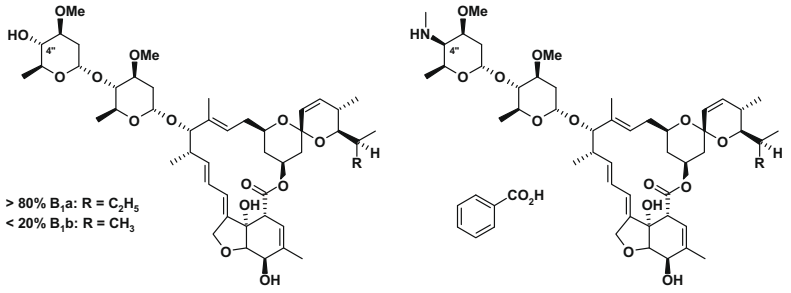


Figure 2. Commercialised Avermectins in crop protection.

Abamectin **1** was introduced as an acaricide and insecticide by Merck Sharp & Dohme Agvet (now Syngenta Crop Protection AG) in 1985 under the trade names Vertimec® and Agrimec®. Subsequently, Merck scientists performed a targeted analoging program around abamectin. They mainly focused on the identification of a compound active against a broad spectrum of Lepidoptera. The program culminated in the discovery of emamectin, which was developed as the benzoate salt (MK-244) for the control of Lepidoptera. Emamectin benzoate **2** was introduced to the market by Novartis (now Syngenta Crop Protection AG) in 1997 under the trade names Proclaim® and Affirm®. Recently, Syngenta scientists have published biocatalytic approaches to the synthesis of emamectin, a topic that will not be covered in this review.[2–4]

The goal of avermectin research at Syngenta was to identify compounds with properties such as higher activity, a different activity spectrum and improved safety, as compared with the existing products. Table 1 shows an overview of the new types of avermectins that were the result of this venture. The structures of the most important ones (**3–8**) are shown in the schemes of the following chapters, as indicated in Table 1. The other structures (**9–17**), which will not be further discussed in detail, are shown in Figure 3.

2. 4″-Deoxy-4″-(*S*)-amino avermectins

Our objective was to find a process for the specific formation of 4″-*(S)*-amines **3**, and to compare their pesticidal activity with that of 4″-*(R)*-amines such as emamectin **2**.[5–7] Access to 4″-amino avermectins has been commonly achieved by the reductive amination of 4″-oxo-avermectin. This process results in the predominant generation of the axially disposed 4″-*(R)*-configured amine.[34] Amines with the equatorial 4″-(*S*) configuration occur as by-products, which are difficult to separate. Our strategy involved 4″-(*S*)-azide **19** as a key intermediate. This compound was readily available by S_N2 displacement of 4″-*(R)*-triflate **18** with NaN_3. The 5-O TBDMS protected triflate **18** is accessible from abamectin in four steps.[30]

The consecutive application of the Staudinger- and the aza-Wittig reaction, followed by reduction of the intermediate imines **22** and deprotection, led to 4″-*(S)*-alkylamines **3** in good yields. Basic hydrolysis of phosphorane **20** and deprotection afforded the primary 4″-*(S)*-amine **21**. It is interesting to note that the Staudinger reaction did not proceed with triphenyl phosphine, but required the use of the less bulky and more reactive $(CH_3)_3P$.[31] Thus, 4″-*(S)*-amines **3** and their derivatives **4** were made readily accessible for the study of their properties for the first time. In this group, amine **23** and amide **24** are among the most active avermectins. In fact, they are among the most potent insecticides and acaricides known so far.

3. 4′-*O*-Alkoxyalkyl avermectin monosaccharides

The synthesis and biological activity of alkoxyalkyl derivatives of avermectin and of avermectin mono-saccharide have been described in the patent literature.[8] Scheme 2 illustrates the synthesis of monosaccharide derivatives. Avermectin B_1 monosaccharide **25** is protected as 5-O TBDMS ether **26**. This compound can react with α-chloro ethers to give **27**. Deprotection yields alkoxyalkyl ethers **5**. Among many highly active derivatives of this kind, methoxymethyl ether **28** showed the most favourable balance of pesticidal activity and safety.

4. 4″-Deoxy-4″-C-substituted 4″-amino avermectins

With the development of emamectin **2**, it was demonstrated that a 4″-amino substituent can dramatically influence the activity

Table 1
New avermectins from Syngenta

Compound type	Structure shown in	General structural type	Patent application	Publication year	Ref.
3	Scheme 1	4″-(*S*)-Amino avermectins and salts thereof	WO2003020738	2003	5
4	Scheme 1	Derivatives of 4″-(*S*)-amino avermectins	WO2003095468	2003	6
5	Scheme 2	4′/4″-*O*-Alkoxyalkyl avermectins or avermectin monosaccharides	WO2004056844	2004	8
6	Schemes 3–5	4′/4″-C-Substituted 4′/4″-amino avermectins or monosaccharides	WO2005097816	2005	9
7	Schemes 6 and 7	13/4′/4″-Glycosides, includes 2″-substituted avermectins	WO2006024405	2006	13
8	Scheme 8	4′/4″-*O*-Amino avermectins or monosaccharides	WO2004069852	2004	16
9	Figure 3	4′/4″-Alkyl avermectins or monosaccharides	WO2004069853	2004	21
10	Figure 3	4″-*O*-Sulfamoyl avermectins	WO2003053988	2003	22
11	Figure 3	4′-*O*-Sulfamoyl avermectin monosaccharides	WO2004111070	2004	23
12	Figure 3	4′/4″-*O*-Carbamoyl avermectins or monosaccharides	WO2005021569	2005	24
13	Figure 3	4″-(*R*)-Amino avermectins	WO2002068441	2002	25
14	Figure 3	Salts of 4″-(*R*)-amino avermectins	WO2002068442	2002	26
15	Figure 3	Derivatives of 4′-amino avermectin monosaccharides	WO2004067534	2004	27
16	Figure 3	4′/4″-Hydroxylamino avermectins or monosaccharides, and nitrones	WO2004067543	2004	28
17	Figure 3	4′/4″-Oximes and hydrazones, avermectins or monosaccharides	WO2004066725	2004	29

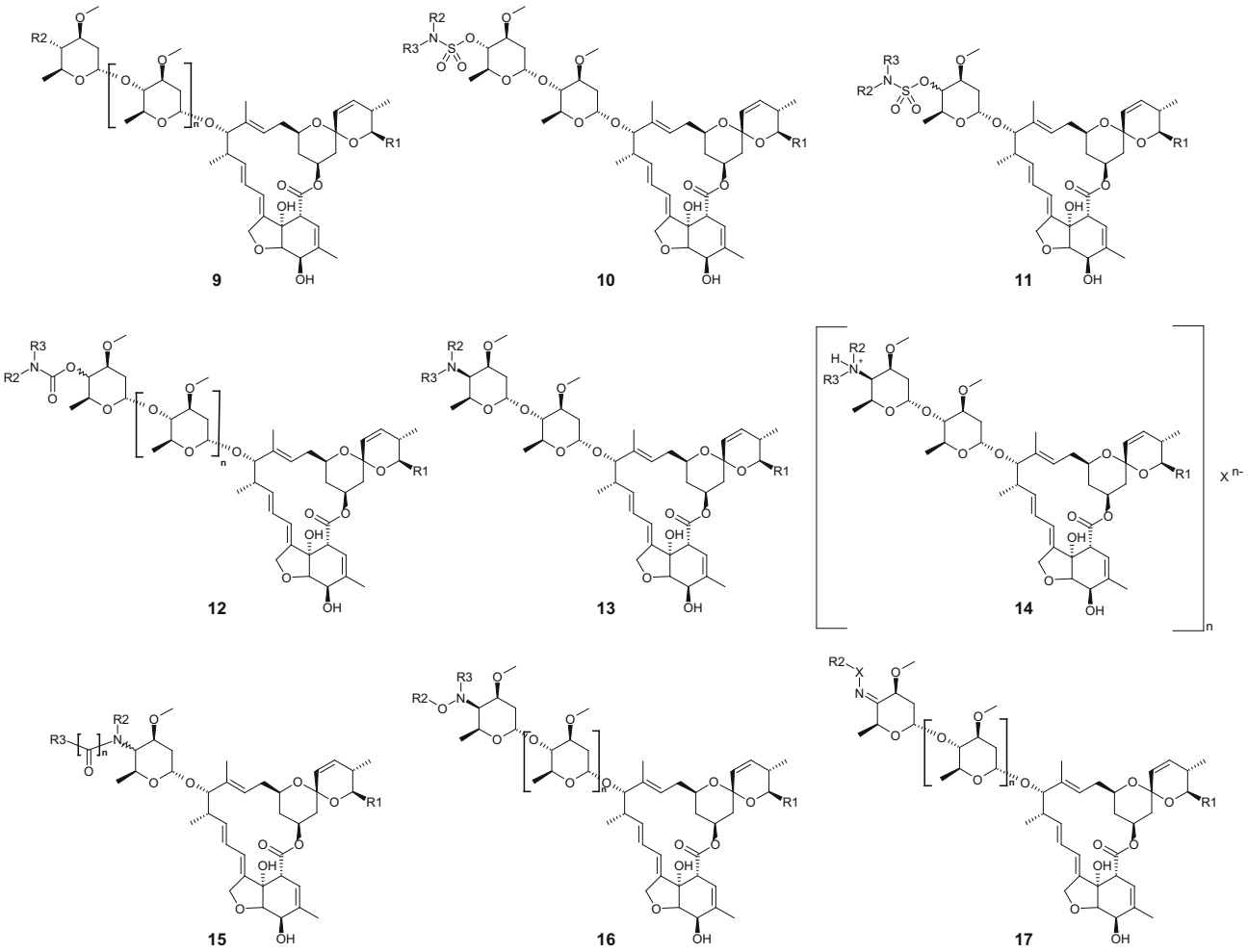


Figure 3. General structures from the patent literature.

spectrum of avermectin derivatives.[1] Further evidence for this was observed, when we investigated 4″-(*S*)-amines **3** and their derivatives **4** (Section 2). In addition, we have described the excellent activity of 4″-alkyl avermectins.[21] Therefore, we set out to investigate the synthesis of 4″-deoxy-4″-C-substituted 4″-amines. As a result of our studies, we have identified a diverse range of such compounds that possess excellent activity against insects and mites.[9] For their synthesis, we developed three different approaches, as described in the following.

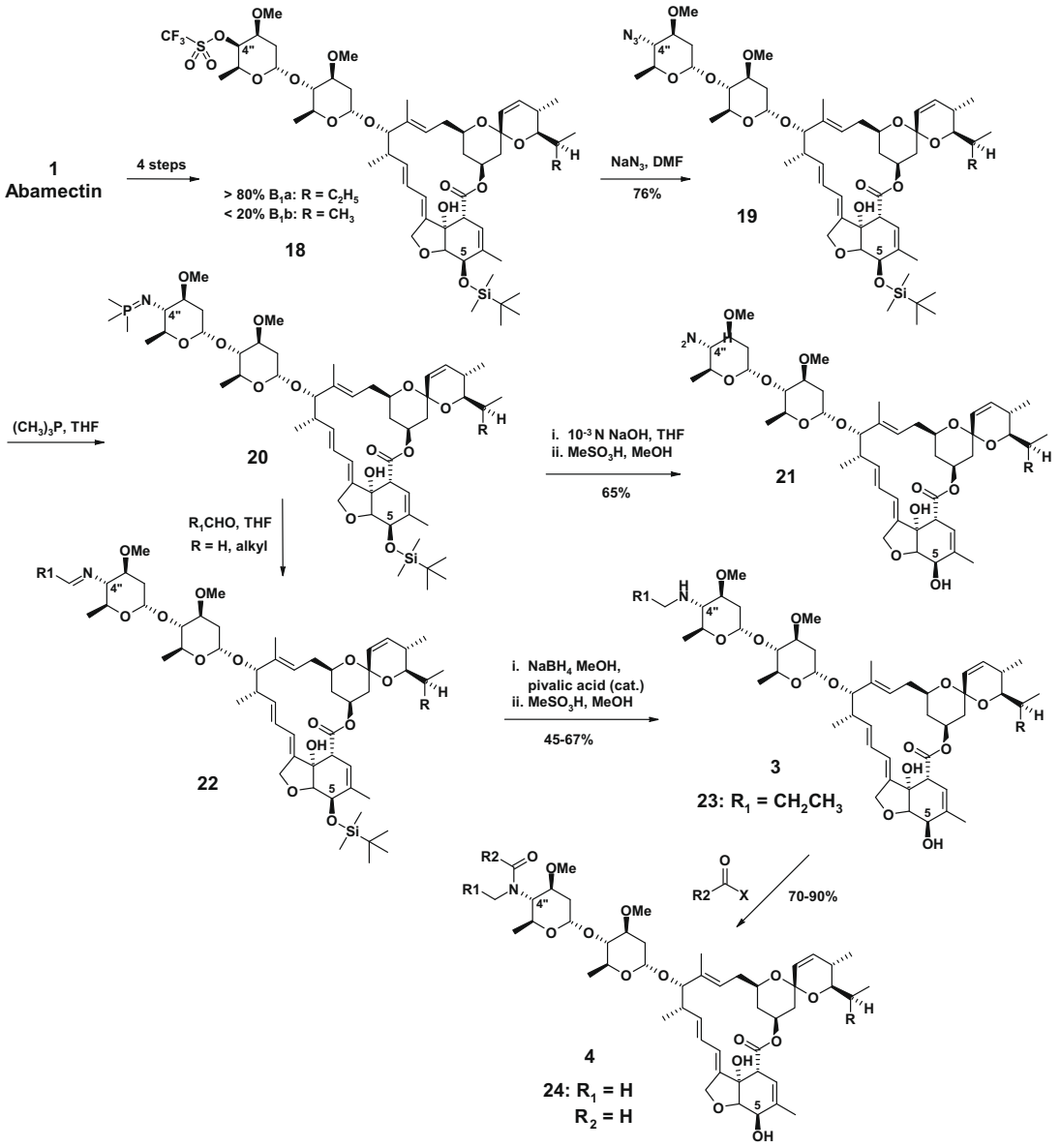
Our first approach involved the chemistry shown in Scheme 3.[10] Oxime **29** is available from abamectin in three steps.[32] Treatment of **29** with diphenyl disulfide and tributylphosphine gave the S-phenylsulfinimine **30**.[33] Oxidation of **30** with MCPBA gave **31** as a mixture of two diastereoisomers. Addition of Grignard reagents to **31**, followed by deprotection, gave us access to a range of 4″-deoxy-4″-C-substituted 4″-amino avermectins **6**. Addition of methylmagnesium bromide, followed by deprotection and acylation yielded acetamide **33**, one of the best compounds of the series.

We designed another synthetic approach using a modification of the Ugi reaction with the intermediate **31**.[11] Thus, treatment of this compound with an isonitrile in the presence of trifluoroacetic acid and pyridine, followed by deprotection, yielded the α-trifluoroacetylamino carboxylic acid amides **6**. In this manner, various isocyanides could be readily converted to the corresponding Ugi product in low to moderate yields. It should be pointed out that the reaction of **31** with isonitriles is the first example of an Ugi reaction of a sulfinimine which was described in the literature so far. In addition, it is interesting to note that earlier attempts to use ketone **34** directly in an Ugi reaction with ammonium acetate and isopropylisonitrile failed.

The development of this procedure was inspired by a method described by Merck chemists, who used the combination $ZnCl_2$/hexamethyldisilazane for a synthesis of emamectin **2**.[12] By this method, the 4″-imine intermediate is formed in solution under essentially water free conditions, and subsequently reducted with $NaBH_4$ in the presence of ethanol.[34] In our work, we treated the solution containing the 4″-imine with TMS-CN. This reagent is frequently used as a lipophilic cyanide source for Strecker reactions of aldehydes or ketones in combination with amines, but not so far with imines generated with the combination of $ZnCl_2$ and hexamethyldisilazane.[35] For the synthesis of methylamine **35** we used heptamethyl-disilazane instead. Compound **35** was the most active insecticide and acaricide of the series. In lieu of hexa- or heptamethyldisilazane, we also generated N-silylated amines in situ from primary amines and TMS-Cl, in order to obtain N-substituted derivatives **6** directly. Such a one-pot procedure involving in situ generated N-silylated amines, $ZnCl_2$ and TMS-CN represents a new variation of the Strecker reaction, and it is unprecedented in the literature to the best of our knowledge.

5. 2″-Substituted avermectins

Up until our own work, there were no avermectin derivatives reported that would provide an understanding of the influence of



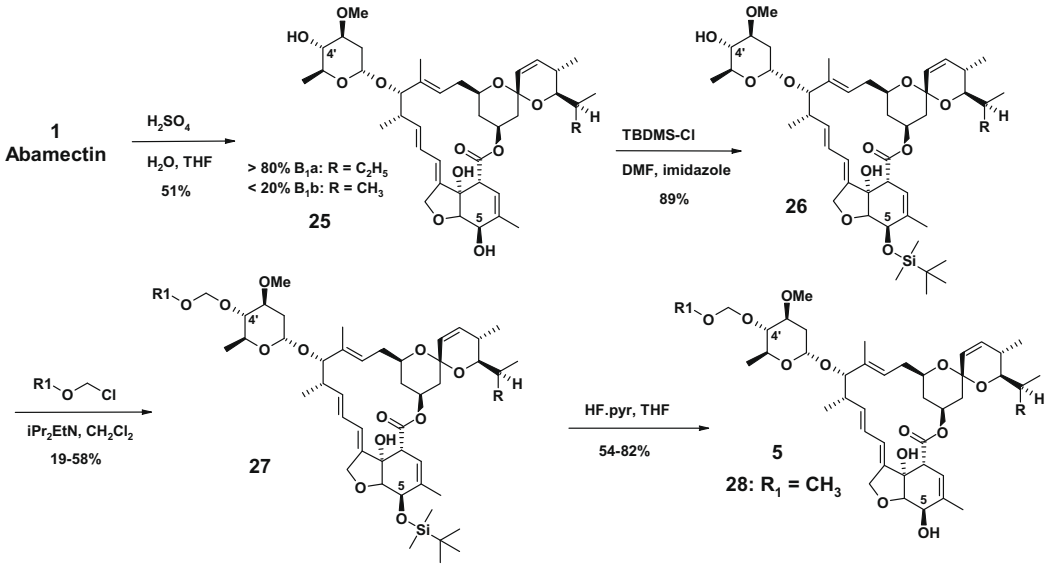
Scheme 1. Synthesis of 4″-deoxy-4″-(*S*)-amino avermectins.

substituents on C-2″ on activity.[13] The oleandrose unit in natural avermectins is unfunctionalised on this carbon atom. In addition, due to the vicinity of the anomeric centre, C-2″ is not an obvious position for derivatisation either. In this chapter, two very different approaches towards such targets are summarised.

In our first, somewhat systematic approach, we replaced a whole oleandrose unit by glycosidation of 5-O protected avermectin monosaccharide **26**.[14] The thioglycoside method for glycosidation, followed by deprotection of the 5-hydroxy group, gave good results for the coupling of **26** with many different glycosyl donors.[36] The reaction temperature was adjusted to the reactivity of the glycosyl precursors. For 'armed' glycosyl donors (saccharides with methyl or alkoxy groups) the reaction was carried out between −70 °C and −50 °C. For 'disarmed' glycosyl donors (saccharides with electron withdrawing substituents, such as acyl, carbonate, or carbamate groups) the reaction was carried out between −40 °C and −10 °C. Usually, a mixture of isomers (α and β on the anomeric centre) was obtained in this step, which could be separated. Interestingly, the β-linked L-rhamnopyranosyl derivative **36**, containing a 2″-methoxy group, was the most active compound in this series.

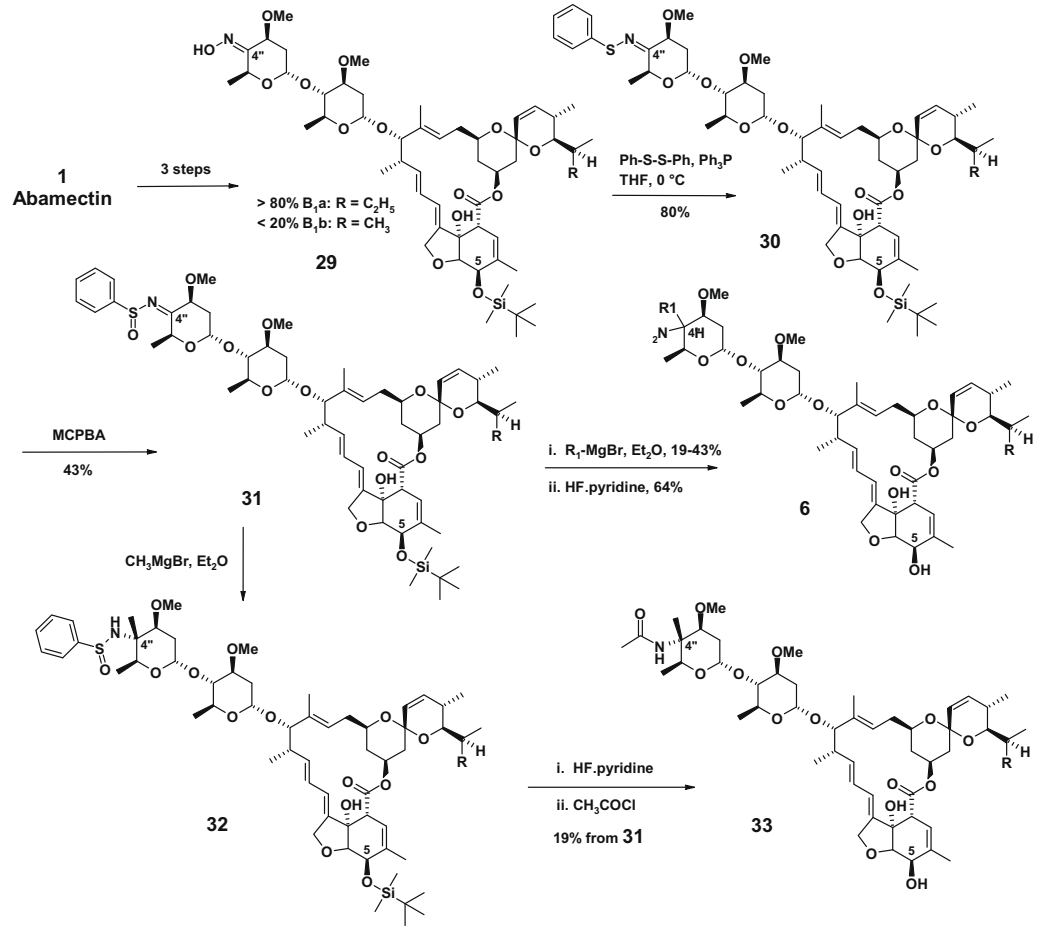
We arrived at the second approach in a more serendipidous manner, but it allowed us, for the first time, to functionalise C-2″ of avermectin directly.[15] Starting with 4″-ketone **34**, we decided to investigate the hitherto unknown enol ether chemistry of avermectins. We envisaged that 4″-silyl enol ethers should be feasible synthetic targets, as long as we choose a stable enough silyl group. Therefore, we treated **34** with triisopropyl-silyl triflate and Hünig's base in toluene. Upon heating to 80 °C for 2 days, we observed the formation of silyl 3″,4″-enol ether **37** along with equal amounts of its regioisomer (4″,5″-enol ether). Based on the closest example from the literature, one would expect that oxidation of **37** with MCPBA would give an α-diketone derivative.[37] However, we observed the exclusive formation of enone **38**.

Because C-2″ is functionalised in this compound, we now had the opportunity to introduce a substituent by 1,4-addition chemistry. Cuprate addition to **38** gave ketone **39**. The stereochemical orientation of the 3″-methoxy group has been reversed, presumably as a result of thermodynamic control. Reduction of **39** with $NaBH_4$, followed by deprotection, gave 4″-alcohol **40**, reductive amination and deprotection gave 4″-amine **41**. In both cases, the C-4″-(*S*) products are formed. As indicated in earlier chapters, ketone **34**

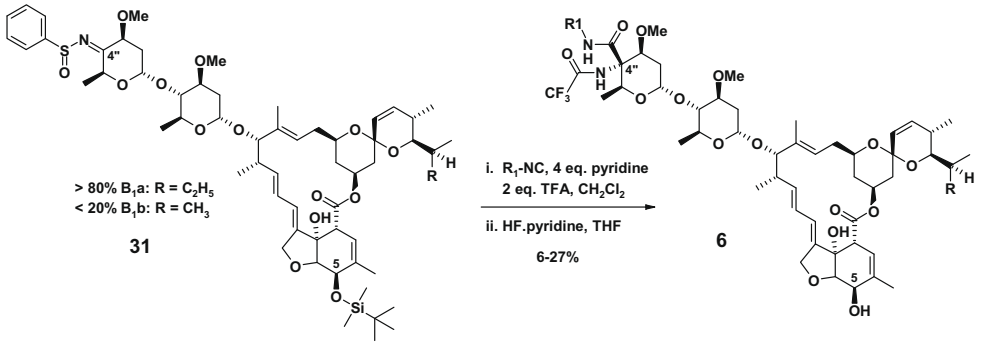


Scheme 2. Synthesis of 4′-*O*-alkoxyalkyl avermectin monosaccharides.

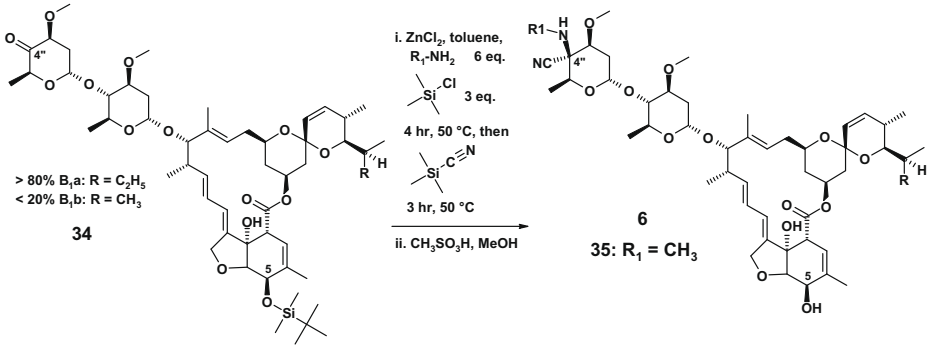
forms the C-4″-(*R*) products in these reactions.[34] The difference in stereochemical outcome is probably due to the different preferred conformations of **34** and **39**, which are apparent from their NMR spectra. In both cases, preferred equatorial attack of hydride gives rise to the observed product distribution. In contrast, the addition of Grignard reagents to **39** is not very selective, and usually yielded mixtures of diastereoisomers **42** and **43**. Treatment of **39** with methylmagnesium bromide, separation of the isomers and deprotection yielded tertiary alcohol **44**, the most active analogue of this series.



Scheme 3. 4″-Deoxy-4″-C-substituted 4″-amino avermectins from sulfinimines.



Scheme 4. 4″-Deoxy-4″-C-substituted 4″-amino avermectins from Ugi type reactions.

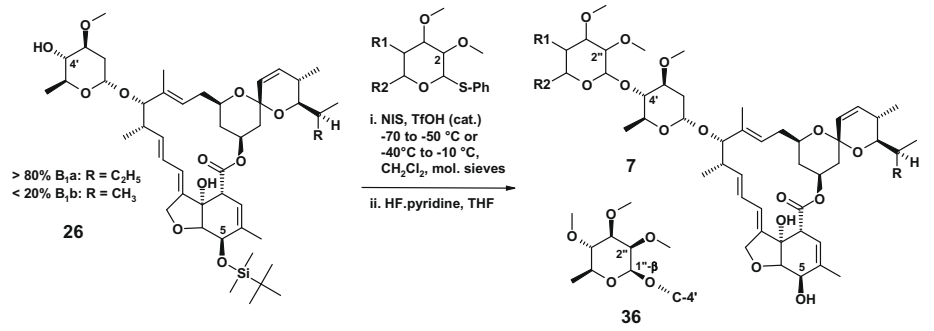


Scheme 5. 4″-Deoxy-4″-C-substituted 4″-amino avermectins from Strecker reactions.

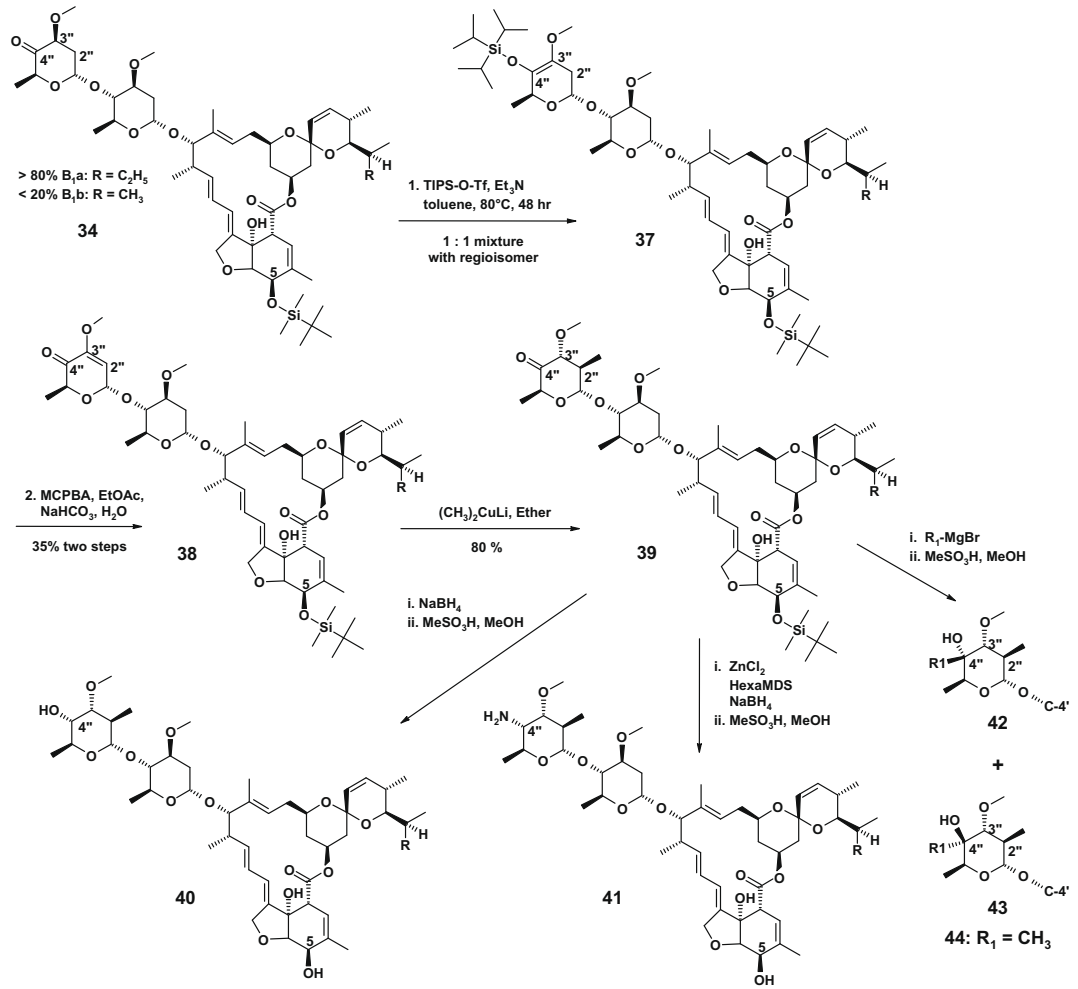
6. Other new chemistry

Considering the different activity spectrum of abamectin **1** and emamectin **2**, we became interested in 4″-O-amino-avermectins **8**, which might combine the insecticidal properties of both.[16,17] Triflate **18** became the key intermediate in our synthetic plan.[30] Upon treatment with *N*-hydroxyphtalimide, 4″-(*R*)-triflate **18** was cleanly converted into the 4″-(*S*)-O-phthalimido derivative **45**.[38] Deprotection of both the 5-*O*-silyl ether and the phthalimido group yielded 4″-O-amino avermectin B_1 **46** in good yield. This compound was used for the synthesis of derivatives **8**. Among these, oxime **47** showed the best activity profile.

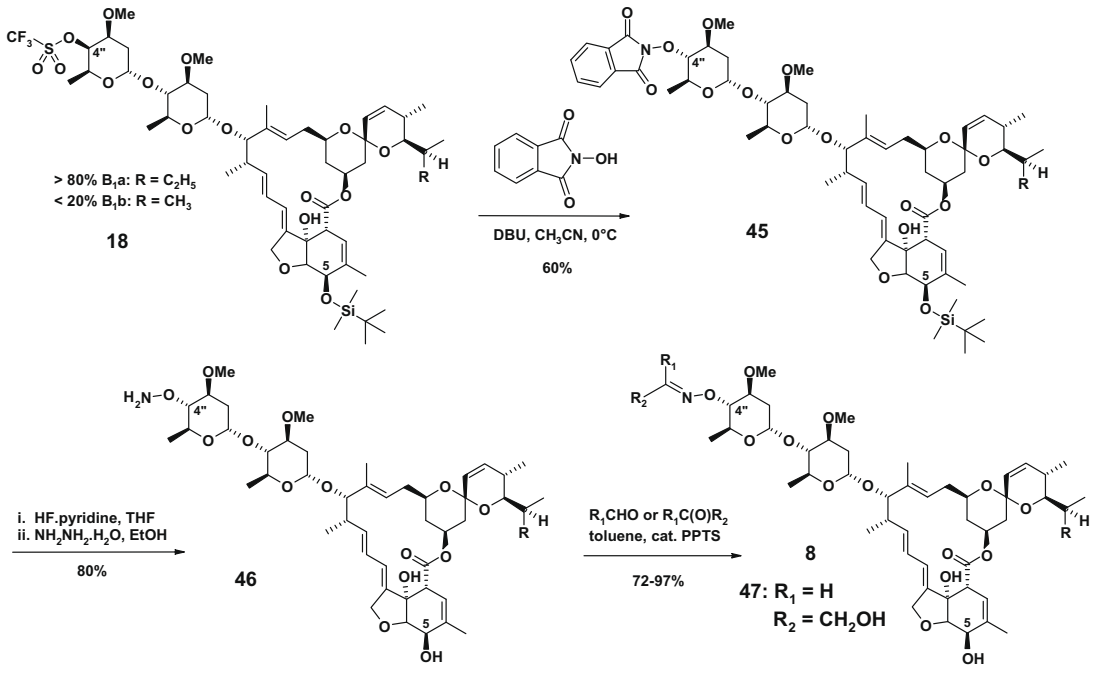
Recently, Du Bois and co-workers reported a simple and efficient intramolecular Rh(II)-catalysed amination reaction of sulfamate derivatives.[39] We became interested in this chemistry, because it offered an opportunity for modifications at the otherwise not very accessible region of the C-3″-methoxy area of avermectins. In addition, 4″-O-sulfamates **10** (cf. Table 1 and Fig. 3) showed very attractive biological activity.[22] For these reasons, we prepared sulfamate **48** from abamectin **1** in two steps.[18] Treatment of **48** under the conditions of Du Bois led to the unprecedented 3″-modified avermectins **49** and **50** with 7- and 5-membered rings fused via nitrene insertion into the primary C–H bond of the C-3″-methoxy group and into the tertiary C–H bond of C-3″, respectively. No traces of insertion into the C–H bond of C-5″ have been observed, probably because of a directing effect induced by coordination of the 3″-O-atom to the metallo nitrene intermediate. Reduction and Grignard addition on the activated 5-membered cyclic imine **49** allowed to prepare *cis*-fused cyclic sulfamates.[18] However, product **50**, in particular, turned out to be a very versatile intermediate. Deprotection of **50** gave **51**, one of the most active analogues of this series. Benzoylation of **50** gave **52**, which we used to cleave the 7-membered ring in a radical desulfonylation reaction that gave, after deprotection, the 3″,4″-diol **53.**[40] Thus, we found a simple sequence to selectively remove the 3″-*O* methyl group of avermectins. Potentially, diol **53** could be a valuable intermediate to further explore structure–activity relationships in the C-3″-methoxy area of avermectins (Scheme 9).



Scheme 6. 2″-Substituted avermectins from glycosidation of monosaccharides.



Scheme 7. 2″-Substituted avermectins from a 4″-enol ether.



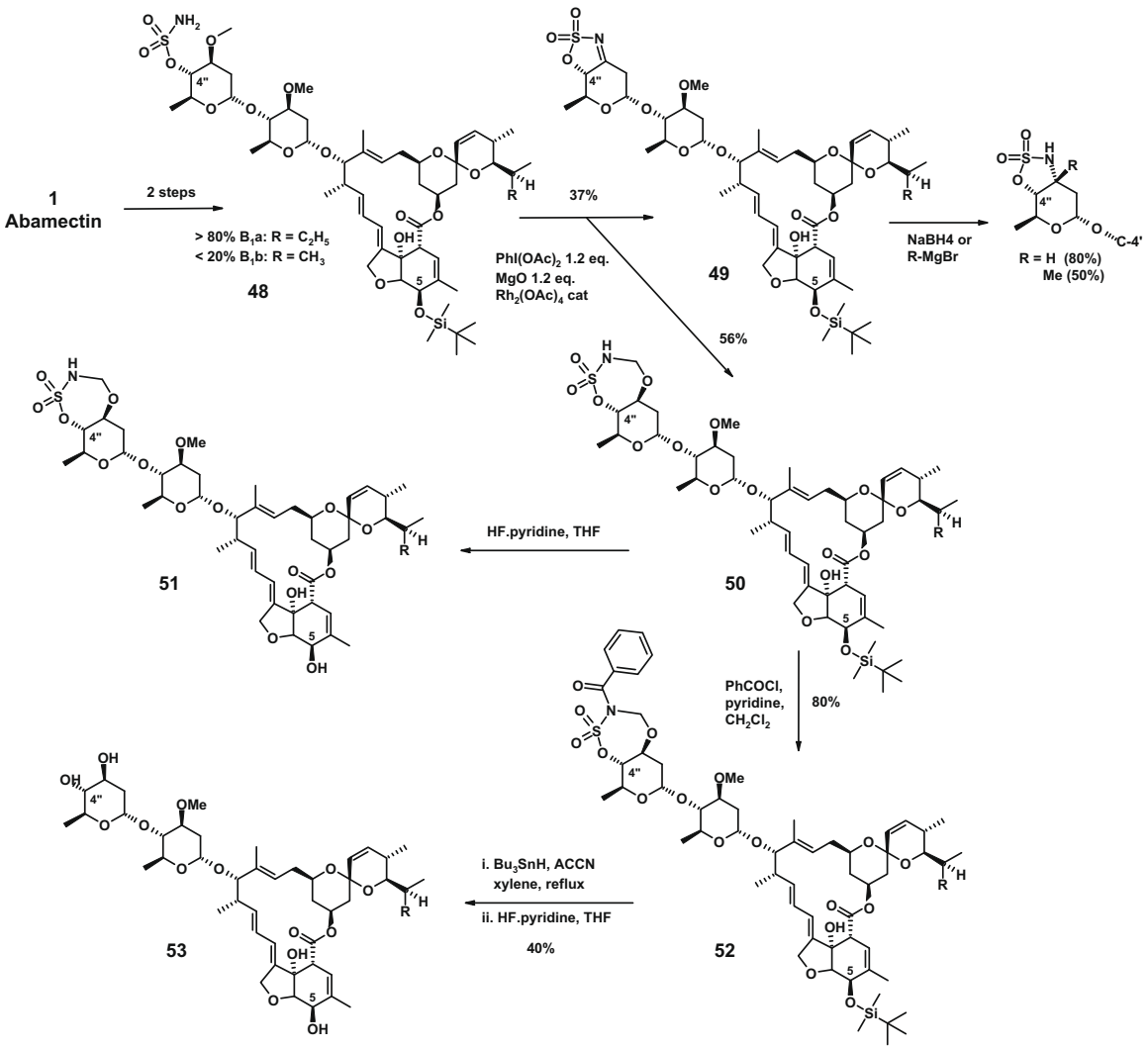
Scheme 8. Synthesis of 4″-*O*-amino avermectins.

Our interest in the carbene insertion chemistry of avermectins originated in the high insecticidal potency of 4″-amino derivatives **4** (Section 2).[19] We intended to prepare conformationally restricted analogues by rhodium catalysed carbenoid insertions, that would be expected to occur preferentially into the primary C–H bond of the C-3″-methoxy group and into the tertiary C–H bond of C-3″ of **56**, respectively.[41] We prepared diazoamide **56** in three simple steps from emamectin **2**, via bromide **54** and amine **55**. Although in low to medium yields, the rhodium catalysed insertion worked according to expectations. Depending on the rhodium catalyst used, we observed different ratios of the insertion products **59** (the most potent analogue) and **60** (Scheme 10).

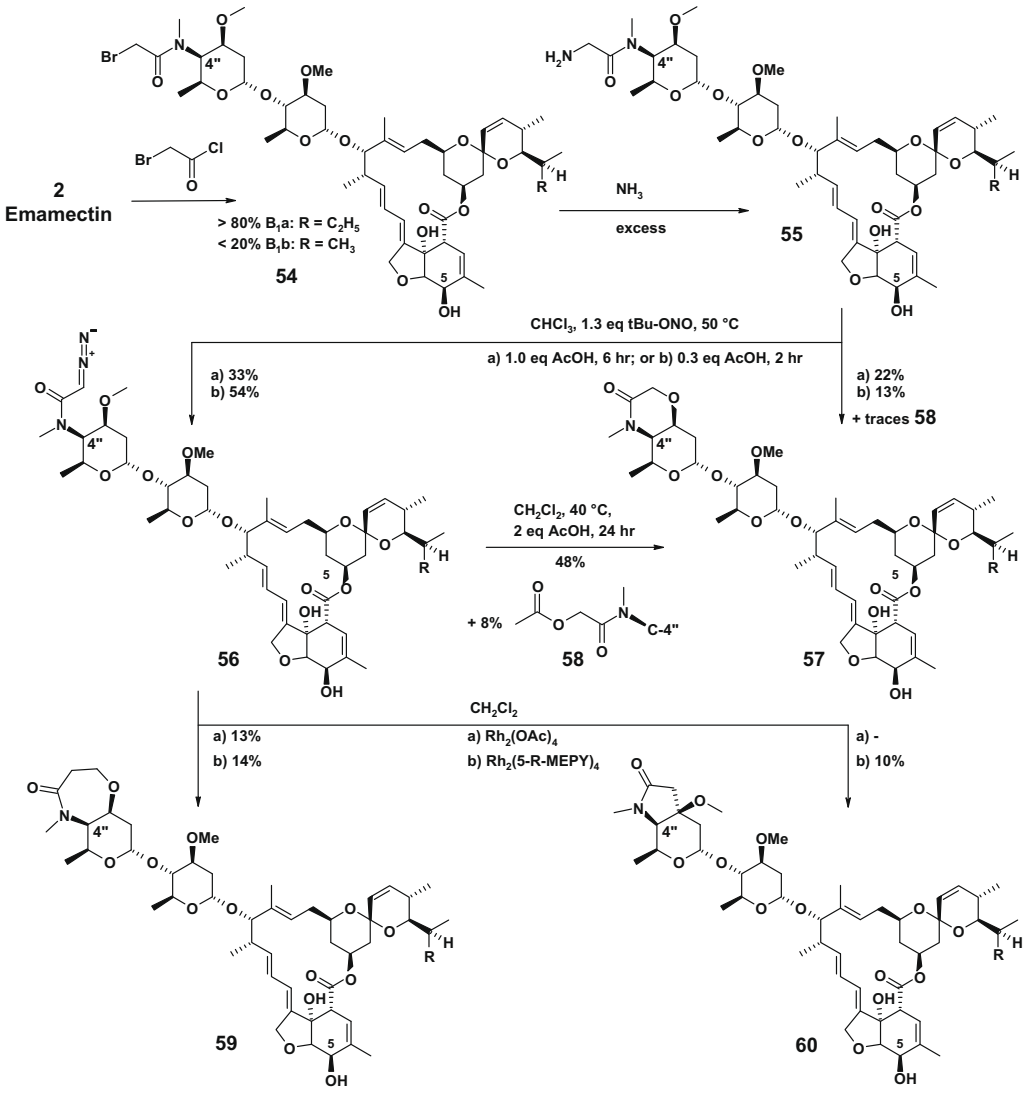
When we prepared diazoamide **56** from amine **55**, however, we made a quite interesting observation. Careful analysis of the reaction mixture revealed, beside 33% of **56**, the presence of side products **57** (22%) and **58** (traces). Reduction of the amounts of acetic acid (from 1.0 to 0.3 equiv) and shorter reaction time (2 instead of 6 h) caused the formation of more **56** (54%) and less **57** (13%). From this we could conclude, that the 6-membered lactam ring of **57** is probably formed in an acid catalysed reaction. Subsequently, we have shown that diazoamide **56** can be transformed into **57** by treatment with acetic acid in dichloromethane (48%). In this reaction, acetate **58** appears as a side product (8%). Use of formic acid favours the cyclisation product, as we found in the transformation of **61** to **62**, which represent the 4″-(*S*)-series.

There is no precedence for this reaction in the literature. We propose the following mechanism for the formation of **57** (Scheme 11). It involves protonation of the diazo amide **56** and intramolecular nucleophilic replacement of dinitrogen by the oxygen of the 3″-methoxy group, followed by methylation of acetate by an intermediate oxonium cation. We have not observed the build-up of such an oxonium species during the reaction. Therefore, the loss of methyl appears to be fast, the cyclisation step would be rate limiting. Alternatively, both steps could be concerted. Acetate side product **58** could be formed from either intermediate. If this mechanism is operating, then the less basic diazomalonate **63** should not undergo this cyclisation, as it cannot be protonated by a weak acid. Indeed, we observed that **63** remained unchanged for several days upon heating with formic acid, and no traces of **64** could be detected.

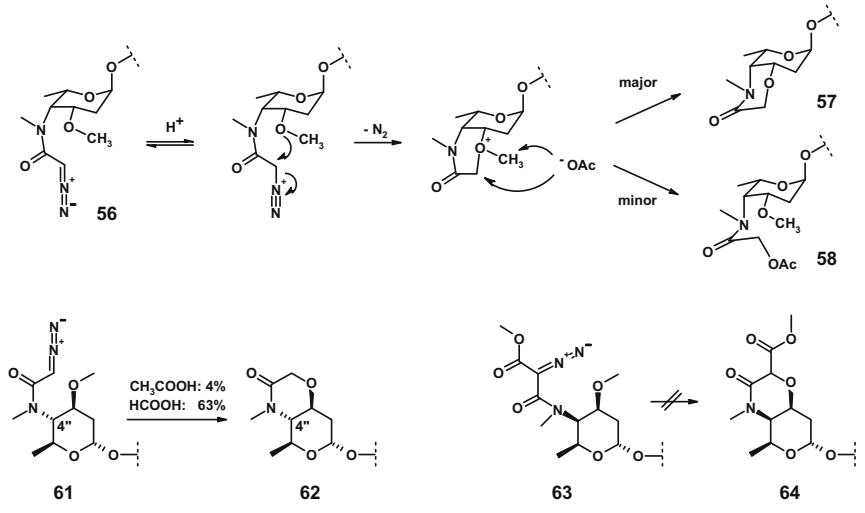
During our optimisation program towards more active and safer avermectins, we have made many interesting observations of the chemistry of this intriguing class of macrolactones. In the above, we have described several reactions that were both surprising and lacked literature precedence. As another example, an unexpected radical rearrangement of the avermectin skeleton was reported recently.[20] It was discovered during our efforts directed towards the preparation of the C-4-hydroxymethylated derivative **67** shown in Scheme 12. For the introduction of the hydroxymethyl group, it was envisaged to use a Nishiyama radical cyclisation followed by a Tamao oxidation.[42,43]



Scheme 9. Rhodium catalysed amidations.

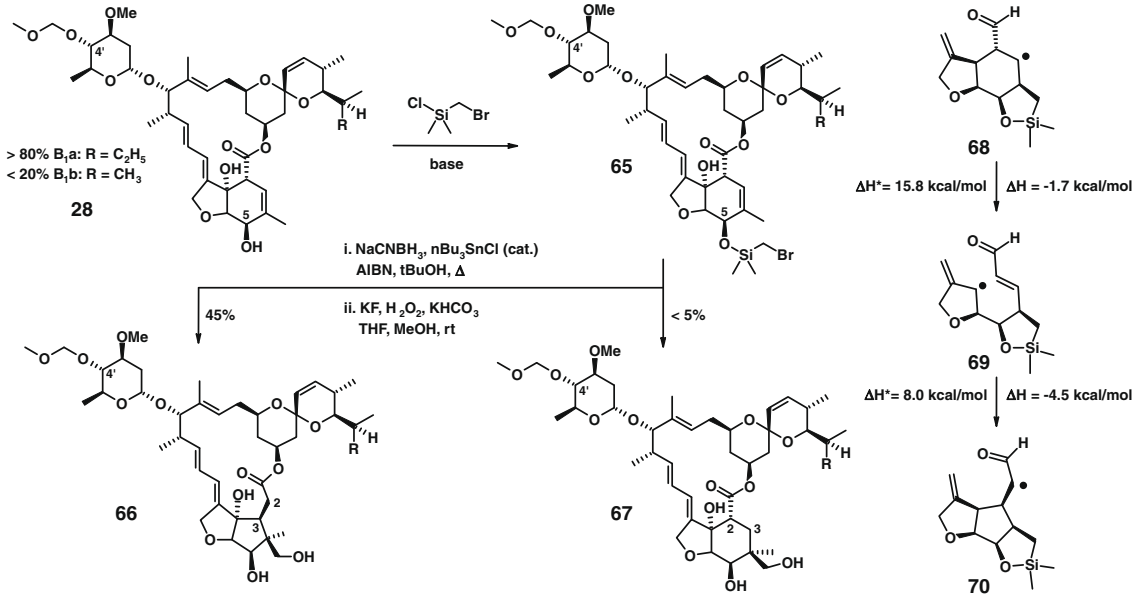


Scheme 10. Rhodium catalysed carbene insertions and acid catalysed cyclisations.



Scheme 11. Proposed mechanism of acid catalysed cyclisations.

We have mentioned 4″-*O*-methoxymethyl ether **28** earlier in this review. This compound was chosen as a starting material for the present studies. It was transformed into the 5-*O*-silyl ether **65**, which in turn was subjected to the radical cyclisation–Tamao



Scheme 12. Radical rearrangement of the avermectin skeleton.

oxidation sequence. Surprisingly, hydroxymethyl addition product **67** was formed in less than 5% yield. The major product from this sequence of transformations was **66**, originating from a skeleton rearrangement. This rearrangement shed a new light on the chemistry of radicals such as the model structures **68**, **69** and **70**. Houk and co-workers investigated this simplified model system by computational methods, and they demonstrated that the pathway of rearrangement shown in Scheme 12 is energetically feasable.[20]

7. Biological activity and safety

All avermectin derivatives mentioned herein have been evaluated in biological screens against many agronomically important pests, such as mites and insects. In Table 2, the most interesting compounds are listed, which were obtained in the synthetic programs discussed in the previous chapters. For the illustration of the pesticidal spectrum, we have chosen tests against *Spodoptera littoralis*, a Lepidoteran species, *Frankliniella occidentalis*, a Thrips species and *Tetranychus urticae* as a representative spider mite.

The data reveal the following trends in structure–activity relationships. 4″-Amines and their derivatives of the (*S*)-series (**23** and **24**) are better acaricides than those of the (*R*)-series (**2**). 4′-*O*-Alkoxymethyl avermectin mono-saccharides (**28**) are not only better acaricides than abamectin (**1**), but are more active against *Spodoptera* and Thrips as well. The 4″-C-substituted 4″-amines (**33** and **35**) are comparable to **1** as acaricides, and sometimes better activity against Thrips can be seen. The same can be said of 2″-substituted derivatives (**36** and **44**). The 4″-*O*-amino derivatives (**47**) showed the same activity against mites and Thrips as **1**, but weaker activity against *Spodoptera*. The 7-membered cyclic sulfamate (**51**) and the 7-membered lactams (**59**) were generally somewhat weaker than **1** over the whole pest spectrum, except for the excellent acaricidal activity of **59**.

A selection of the new avermectins was evaluated in toxicological tests (rat) and in ecotoxicological studies (Daphnia). It was found, that enhanced activity against insects and mites, does not generally result in less favourable safety properties. On the contrary, 4″-*O*-methoxymethyl ether **28**, in particular, surpassed even the commercial products **1** and **2** with respect to their safety-performance ratio (Table 3).

8. Conclusion

In summary, our recent venture into the rich chemistry of avermectin macrocyclic lacton has resulted in a wealth of novel, extraordinary potent insecticides and acaricides, some of which were found to show an even better safety profile to mammals and the environment than the commercial products from this chemical class. In our studies, we have demonstrated the use of many novel synthetic methods for the modification of avermectin derivatives. In several instances we have encountered completely novel transformations. Thus, with our approaches we have

Table 2
Insecticidal and acaricidal activity of new avermectins

Compound	Structure	S.l.[a]	F.o.[b]	T.u.[c]	Ref.
1	Abamectin	0.8	3	0.01	1
2	Emamectin benzoate	0.05	3	0.2	1
23	4″-Deoxy-4″-(*S*)-propylamino avermectin B_1	0.2	3	0.05	5
24	*N*-Formyl-4″-deoxy-4″-(*S*)-methylamino avermectin B_1	0.8	0.8	0.01	6
28	4′-*O*-Methoxymethyl avermectin B_1 monosaccharide	0.05	0.8	0.003	8
33	4″-Deoxy-4″-(*S*)-4″-methyl-4″-acetylamino avermectin B_1	3	0.8	0.01	9
35	4″-Deoxy-4″-(*R*)-4″-cyano-4″-methylamino avermectin B_1	>3	3	0.01	9
36	2″-*O*,3″-*O*,4″-*O*-Trimethyl-4′-*O*-β-L-rhamnopyranosyl avermectin B_1 monosaccharide	3	0.8	0.01	13
44	4″-(*R*)-2″-(*R*)-Methyl-3″-*epi*-4″-methyl avermectin B_1	0.8	3	0.01	13
47	4″-*O*-(2-Hydroxy-ethylideneamino) avermectin B_1	>0.8	3	0.01	16
51	4′-*O*-(1-Methyl-8,8-dioxo-hexahydro-2,5,9-trioxa-8-thia-7-aza-benzocyclo-hepten-3-yl) avermectin B_1 monosaccharide	>0.8	>3	0.2	18
59	4′-*O*-(1,9-Dimethyl-8-oxo-octahydro-2,5-dioxa-9-aza-benzocyclohepten-3-yl) avermectin B_1 monosaccharide	3	12.5	0.01	19

Biological activities in the table are given as EC_{80} in ppm.
[a] *Spodoptera littoralis* feeding/contact activity against L1 larvae.
[b] *Frankliniella occidentalis* mixed population activity.
[c] *Tetranychus urticae* contact activity against adults.

Table 3
Safety data of selected new avermectins

Compound	Structure	Rat[a]	Daphnia[b]	Ref.
1	Abamectin	18.4[c]/ 221[d]	0.34	1
2	Emamectin benzoate	76–89	0.99	1
24	*N*-Formyl-4″-deoxy-4″-(*S*)-methylamino avermectin B_1	<50	1.7	6
28	4′-*O*-Methoxymethyl avermectin B_1 monosaccharide	>200	2.7	8
33	4″-Deoxy-4″-(*S*)-4″-methyl-4″-acetylamino avermectin B_1	>50	0.8	9
35	4″-Deoxy-4″-(*R*)-4″-cyano-4″-methylamino avermectin B_1	>50	n.t.[e]	9
36	2″-*O*,3″-*O*,4″-*O*-Trimethyl-4′-*O*-β-L-rhamnopyranosyl avermectin B_1 monosaccharide	>50	5	13
44	4″-(*R*)-2″-(*R*)-Methyl-3″-*epi*-4″-methyl avermectin B_1	50	n.t.[e]	13

[a] Acute oral LD_{50} in the rat, mg/kg body weight.
[b] EC_{50} (48 h) against *Daphnia magna*, μg/l.
[c] In sesame oil.
[d] In water.
[e] Not tested.

revealed new aspects of avermectin chemistry and, sometimes, of synthetic organic chemistry in general.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.12.069.

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