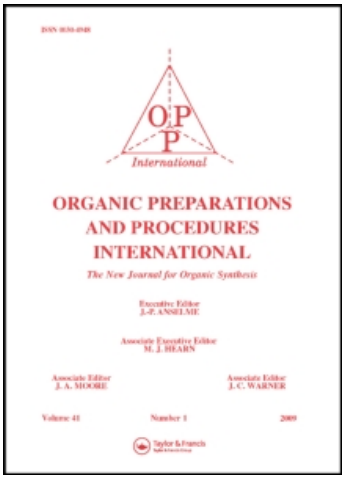

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RECENT PROGRESS IN THE SYNTHESIS OF AVERMECTINS AND MILBEMYCINS. A REVIEW

Timothy A. Blizzard[a]
[a] Merck Research Laboratories, Rahway, NJ

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Timothy A. Blizzard

Merck Research Laboratories, R50G-231
P. O. Box 2000, Rahway, NJ 07065

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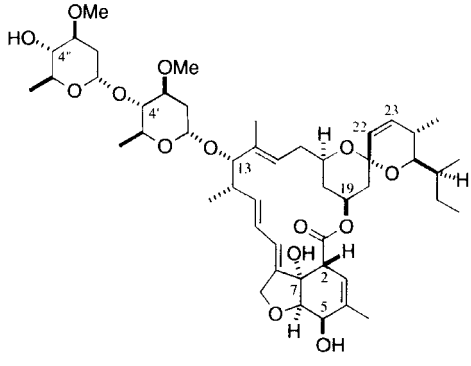
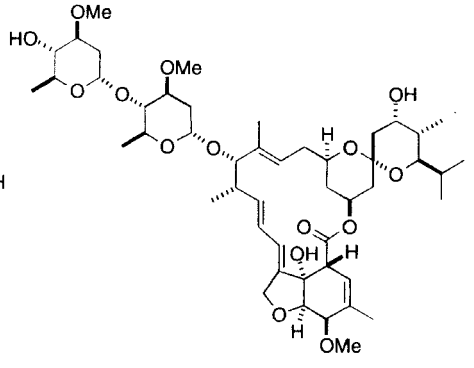
INTRODUCTION

The avermectins and milbemycins are related families of natural products characterized by the presence of a macrocyclic lactone with a fused spiroketal and a fused mono- or bi-cyclic ring of varying degrees of complexity. In addition, the avermectins also incorporate a disaccharide (oleandrosyl-oleandrose) attached *via* an oxygen to C-13 of the macrocycle. The avermectins can be subdivided into groups based on the structural features present in the aglycone. For example, the avermectin "A" series is characterized by the presence of a methoxy group at C-5 whereas the "B" series has a hydroxy group at this position. Each series is further subdivided based on the presence of a double bond ("1" series) or a single bond with a C-23 hydroxy group ("2" series) at C-22,23 of the macrocycle and by the nature of the C-25 substituent (isopropyl for the "b" series or *sec*-butyl for the "a" series). Thus, avermectin B_{1a} (**1**), which is the major component isolated from fermentation of *S. avermitilis*, has a C-5 hydroxy group ("B"), a C-22,23 double bond ("1"), and a *sec*-butyl group at C-25 ("a"). Similarly, avermectin A_{2b} (**2**), contains a C-5 methoxy group ("A"), a C-22,23 single bond with a C-23 hydroxyl group ("2"), and an isopropyl group at C-25 ("b") (*Fig.* 1). The avermectins are



Avermectin B_{1a} (**1**)



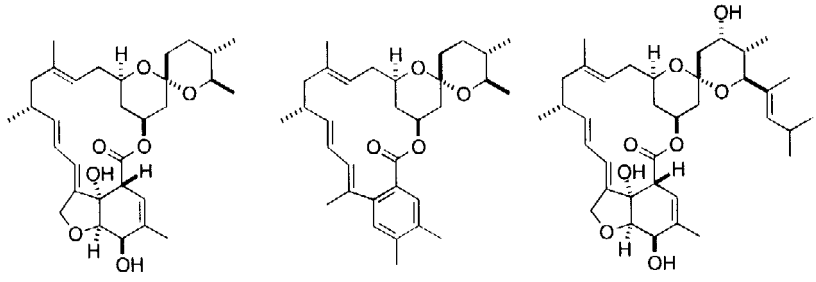
Avermectin A_{2b} (**2**)

Fig. 1

generally isolated from the fermentation as mixtures of "a" and "b" isomers. These isomers are difficult to separate on large scale (although they can be readily separated on a small scale by reverse-phase HPLC) and their biological activities are virtually identical so they are generally handled as mixtures of "a" and "b" components. The presence of a mixture is indicated by simply dropping the "a" or "b" suffix from the name and the "a" structure is used to represent the mixture graphically.

Thus, avermectin B_1 refers to a mixture of avermectin B_{1a} (>80%) and avermectin B_{1b} (<20%).

The milbemycins are structurally simpler than the avermectins. They lack both the disaccharide and the C-13 oxygen substituent found in the avermectins. Some milbemycins also lack the complex hexahydro-benzofuran moiety of the avermectins. As with the avermectins, the milbemycins can be subdivided into groups based on the structural features present; milbemycin nomenclature, however, is not as straightforward as avermectin nomenclature due to the milbemycins wider variety of structural features. Milbemycins which contain the hexahydro-benzofuran unit are referred to as the "alpha" series while milbemycins without this structural feature are classified as belonging to the "beta" series. The milbemycins can be further subdivided based on the substituents present in the spiroketal moiety. For example, milbemycin α_1 (**3**) contains the fused hexahydro-benzofuran with a hydroxy group at C-5 and a methyl group at C-25. By contrast, milbemycin β_3 (**4**) has a simplified aromatic "southern half" while the more recently discovered nemadectin (**5**) is an alpha-series milbemycin with a more highly functionalized spiroketal unit (*Fig.* 2).



Milbemycin α_1 (**3**) Milbemycin β_3 (**4**) Nemadectin (**5**)

Fig. 2

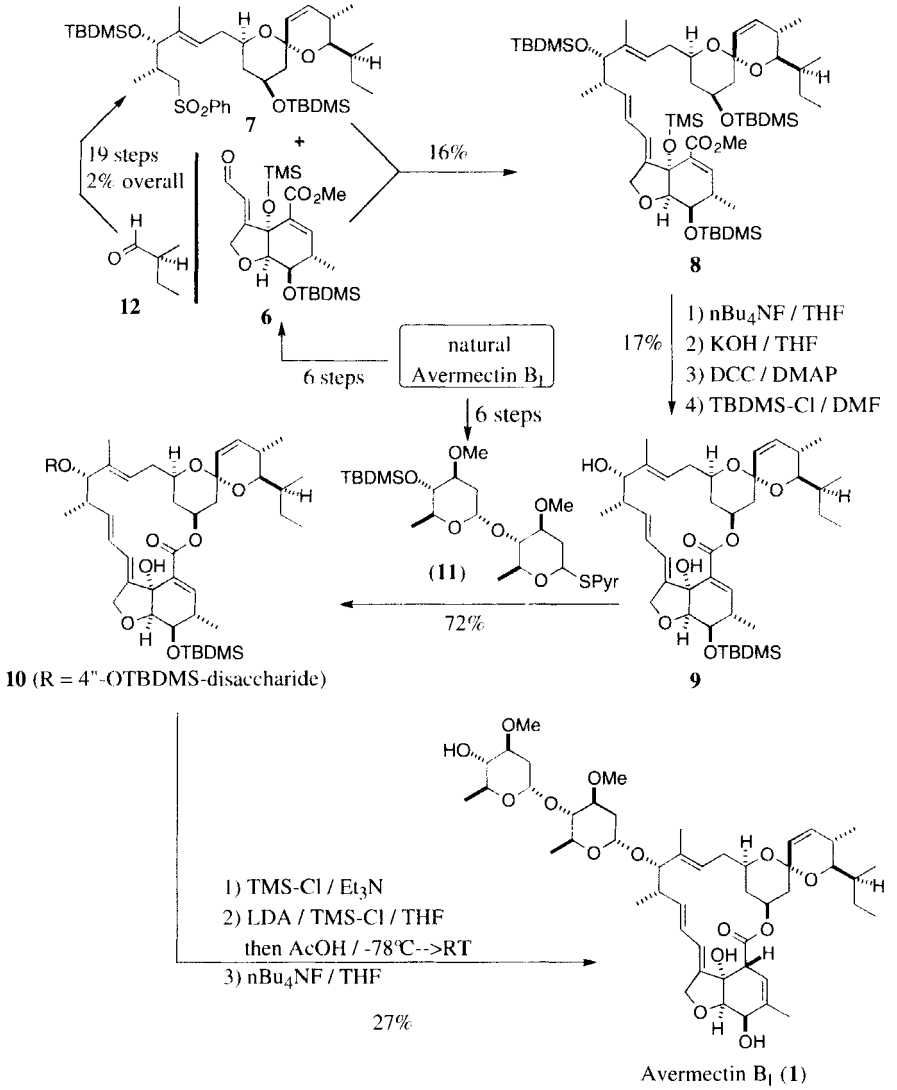
The avermectins and milbemycins are among the most potent anti-parasitic and anti-insecticidal agents known. Avermectin B_1 (abamectin) is a useful agricultural insecticide and miticide. Ivermectin (22,23-dihydro-avermectin B_1) is a semi-synthetic derivative of natural avermectin B_1 that has been widely used for the treatment and prevention of parasitic diseases in domestic animals. More recently, ivermectin has also been found to be useful for the treatment of onchocerciasis (river blindness).

The combination of the complex and interesting chemical structures of these natural products with their potent biological activities has made the avermectins and milbemycins the subjects of much chemical research since their discovery in the 1970s. This article will review the most recent results in the synthesis and reactions of the avermectins and milbemycins. Since this topic has been reviewed several times,[1] the present article will address research reported in the last three years (1991-1993), although some historically significant earlier work will also be included.

I. SYNTHESIS OF AVERMECTINS

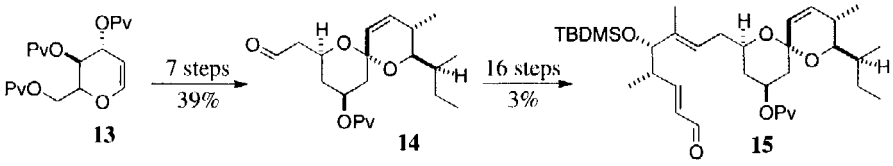
1. Naturally Occurring Avermectins

The complex highly functionalized structure of avermectins offers a significant challenge to the synthetic chemist. Numerous chemists have responded to the challenge, and substantial progress has been reported. The earlier synthetic efforts have been extensively reviewed elsewhere[1] and will not be discussed here. However, two of these early syntheses are especially noteworthy and will be reviewed briefly. The synthesis of avermectin B_{1a} (**1**), reported by Hanessian *et al* in 1986, was an early milestone in avermectin chemistry.[2a,b] Although a total synthesis was not achieved, this effort defined the key issues in an avermectin synthesis. The Hanessian synthesis (*Scheme* 1) utilized



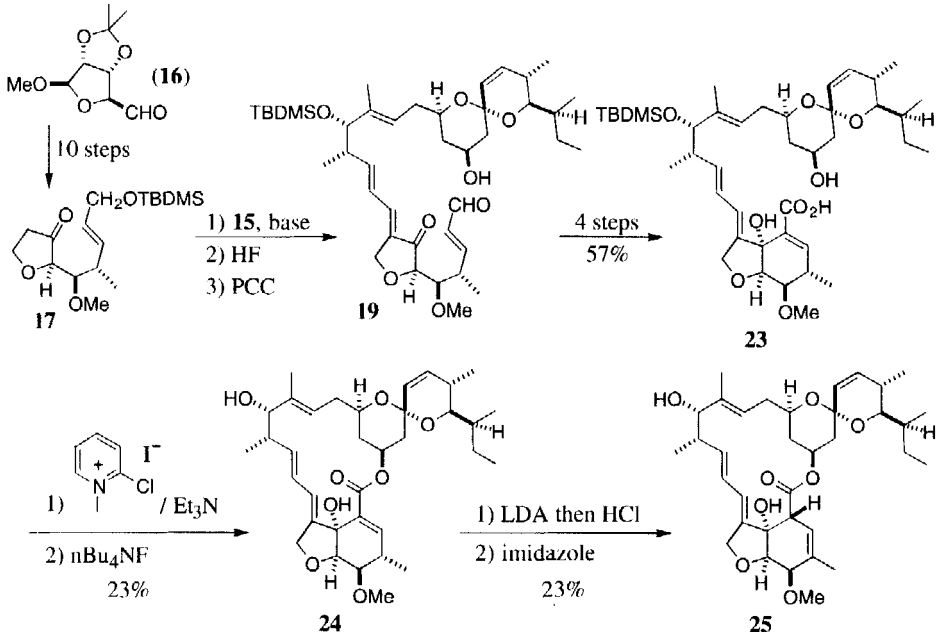
Scheme 1

a "southern half" (**6**) and a disaccharide (**11**) derived from natural avermectin B_1 (the authors also reported a total synthesis of a close analog of **6**). Synthetic "northern half" (**7**) was combined with **6** to afford intermediate **8**, which was further elaborated to the conjugated aglycone **9**. Glycosylation with **11** was followed by the critical deconjugation procedure and deprotection to afford semi-synthetic avermectin B_1. Due to the great propensity of the C-3,4-double bond of an avermectin to move into conjugation with the C-1 ester, a successful method for deconjugation of a C-2,3-double bond (or a means of avoiding the conjugation) is essential for successful completion of an avermectin synthesis. The original Hanessian process proved to be irreproducible,[2c] so a revised sequence (deconjugation to the 2-*epi* isomer followed by partial epimerization) was developed by Hanessian *et al.*[2d] The revised deconjugation method was later successfully utilized by Danishefsky *et al.* in their total synthesis of avermectin A_1 (*vide infra*).[3]



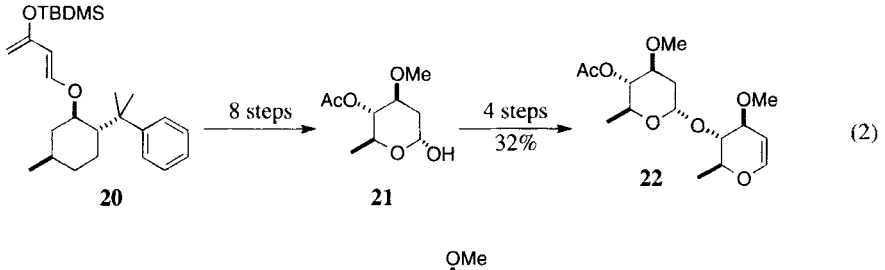
(1)

The first total synthesis of a natural avermectin (A_{1a}) was reported by Danishefsky *et al* in 1987.[3] Although this synthesis has been reviewed previously,[1] it is included here because of its historical significance. In the Danishefsky synthesis, a "northern half" (**15**) synthesized (*Eq.* 1) from D-glucal tripivalate (**13**) was coupled with a "southern half" precursor (**17**) which was synthesized

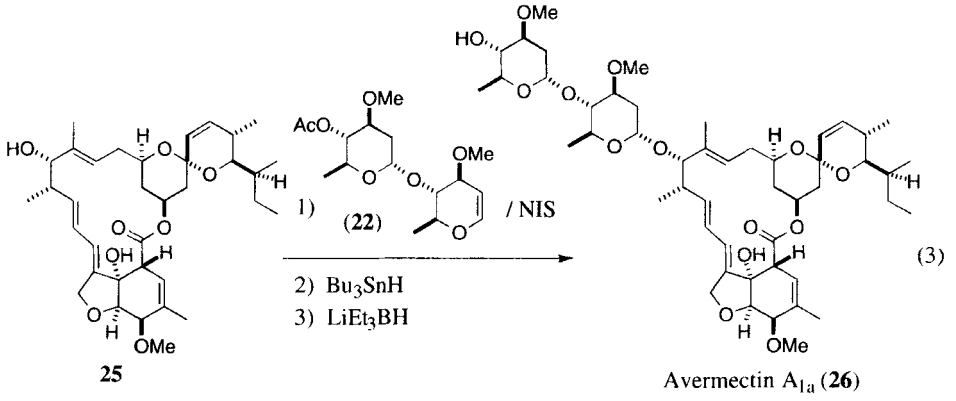


Scheme 2

from chiral aldehyde **16** (derived from D-ribose) (*Scheme* 2). The construction of the "southern half" was then completed by Michael addition of an aluminum thiophenoxide to the α,β-unsaturated aldehyde in **19** with concomitant cyclization of the resulting carbanion onto the C-7 ketone. Functional group adjustments afforded the key seco-acid intermediate **23**, which was subjected to Mukaiyama macrocyclization to afford, after desilylation, the conjugated aglycone **24**. Deconjugation of **24** using the modified Hanessian protocol provided avermectin A_{1a} aglycone **25**. Glycosylation of **25** with disaccharide **22**, prepared in several steps from chiral dienol ether **20** (*Eq.* 2) followed by deprotection, completed the total synthesis of avermectin A_{1a} (**26**) (*Eq.* 3).

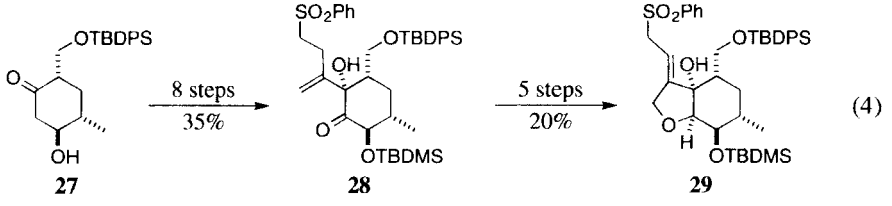


(2)



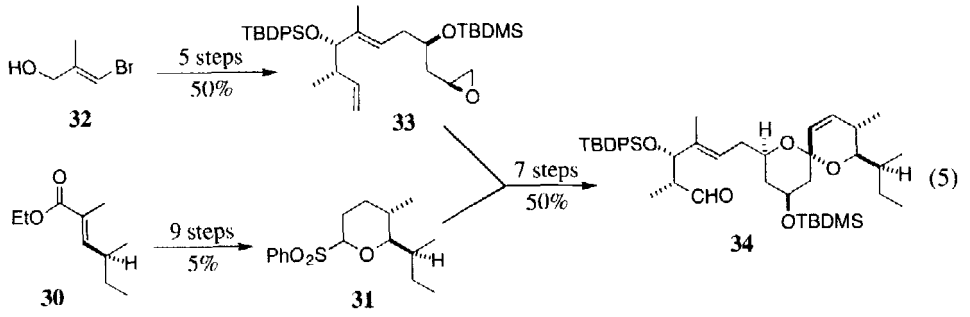
(3)

An alternative solution to the deconjugation problem is provided by the recent total synthesis of avermectin B_{1a} (**1**) by Ley *et al.*[4] In the Ley total synthesis ketone **27**, an intermediate in Ley's earlier total synthesis of milbemycin β_1, was converted to "southern half" **29** (*Eq.* 4). This was

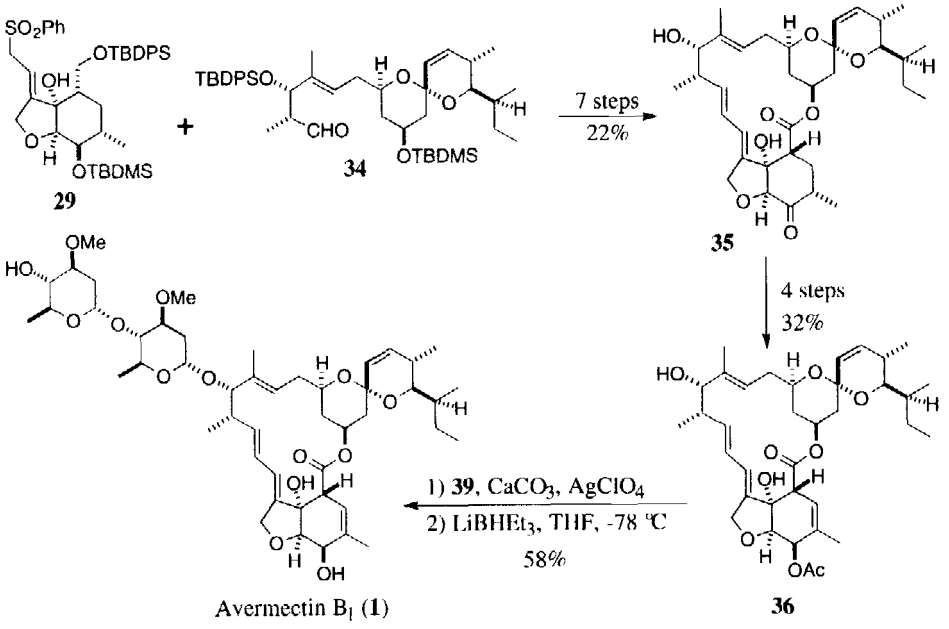


(4)

condensed with "northern half" **34** which was synthesized from α,β-unsaturated ester **30** and allylic alcohol **32** (*Eq.* 5). The resulting intermediate was ultimately converted to aglycone **35** which has the correct stereochemistry at C-2 but lacks the troublesome 3,4-double bond. Introduction of the $\Delta^{3,4}$-double bond and reduction of the C-5-ketone completed the synthesis of protected (5-OAc)

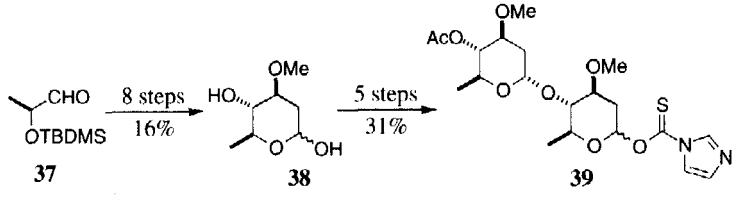


avermectin B_{1a} aglycone **36** (*Scheme* 3). By introducing the double bond at the end of the aglycone



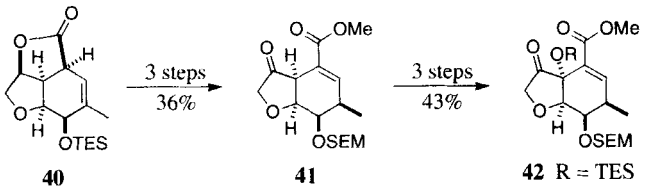
Scheme 3

synthesis Ley thus avoided the deconjugation problem altogether. Aglycone **36** was coupled with disaccharide **39**, synthesized from chiral aldehyde **37** (*Eq.* 6), to complete, after deprotection, the total synthesis of avermectin B_{1a} (**1**).



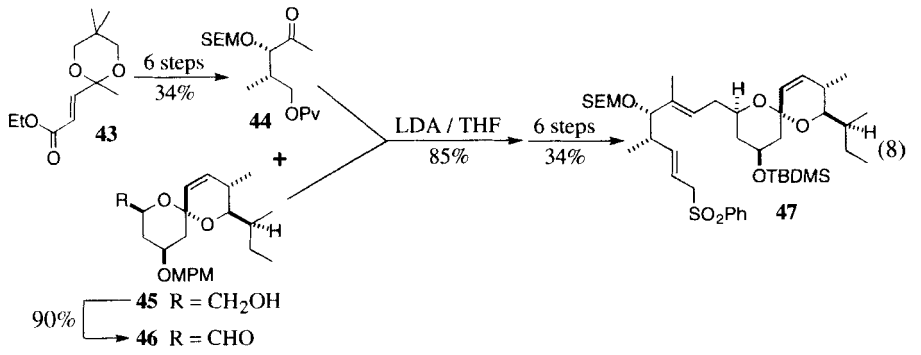
A total synthesis of avermectin B_{1a} aglycone (**50**) has recently been reported by White and co-workers.[5] The synthesis builds on their earlier syntheses of "southern half" precursor **40**[5h] and

spiroketal **45**[5c] (reviewed previously[1c] and therefore not included here). "Southern half" **42** was synthesized in six steps from lactone **40** (*Eq.* 7). "Northern half" **47** was synthesized by condensing



40 **41** **42** R = TES (7)

spiroketal **46** with ketone **44**, prepared from ester **43**, and elaborating the resulting aldol adduct to **47** (*Eq.* 8). Julia coupling of **47** with **42** afforded a hydroxy sulfone which resisted all attempts at

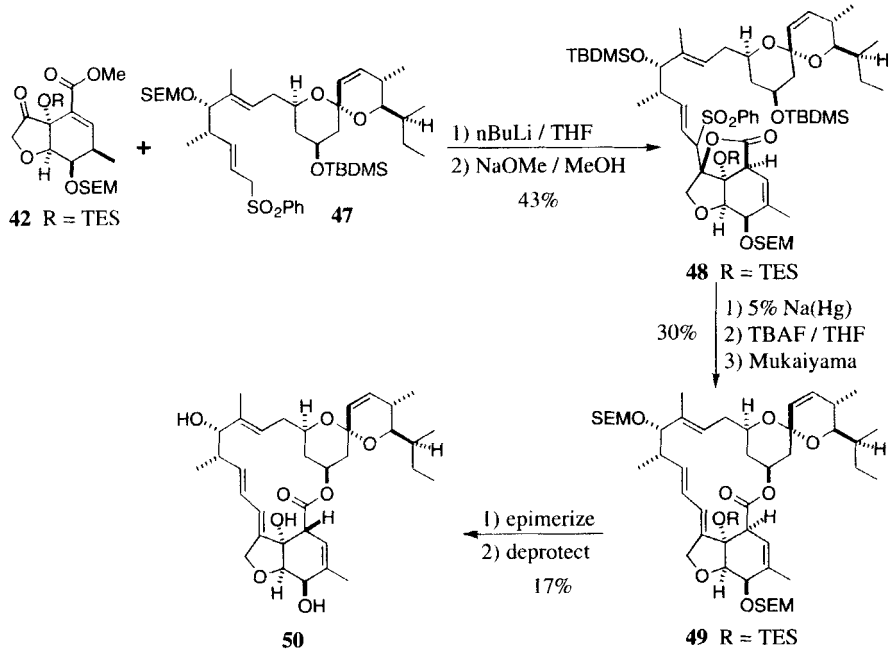


43 **44** **47** (8)

45 R = CH_2OH

46 R = CHO

conversion to the desired olefin although lactone **48** could be isolated in excellent yield (*Scheme* 4).

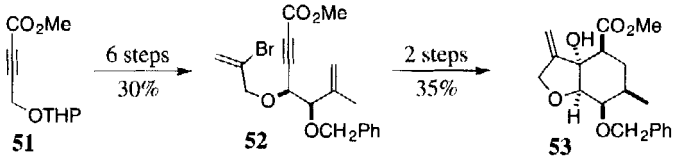


42 R = TES **47** **48** R = TES **49** R = TES **50**

Scheme 4

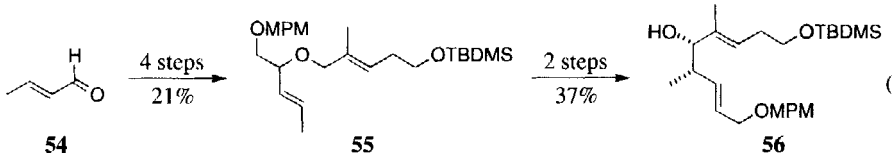
Sodium amalgam reduction of **48**, followed by deprotection and Mukaiyama lactonization, afforded protected 2-*epi*-avermectin B_{1a} aglycone **49**. Application of the second step (epimerization) of the Hanessian avermectin B_1 deconjugation procedure (*vide supra*), followed by chromatography and deprotection completed the synthesis of avermectin B_{1a} aglycone **50**.

A model study directed towards the synthesis of the "southern half" of the avermectins has recently been reported by Parsons and co-workers.[6a,b] The key step in their approach to hexahydrobenzofuran **53** is a tandem radical cyclization of acetylenic diene **52** which is in turn prepared from protected propargylic alcohol **51** (*Eq.* 9). The same group has also reported a synthesis of the



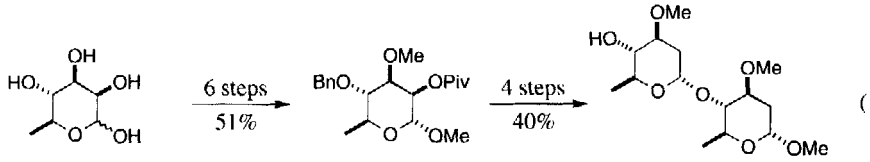
51 **52** **53** (9)

avermectin C-9 to C-17 fragment **56** from crotonaldehyde which utilizes a [2,3]-sigmatropic rearrangement of an allylic ether as a key step (*Eq.* 10).[6c]



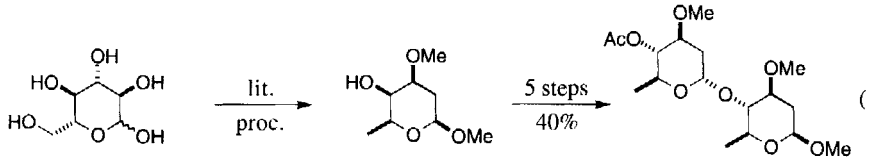
54 **55** **56** (10)

Considerable progress has been reported in the past few years in the synthesis of the disaccharide portion of the avermectins. A gram-scale synthesis of disaccharide **59** from L-rhamnose (**57**) has been accomplished by Rainer and co-workers (*Eq.* 11).[7a] The epimeric methyl glycoside **62** has



57 **58** **59** (11)

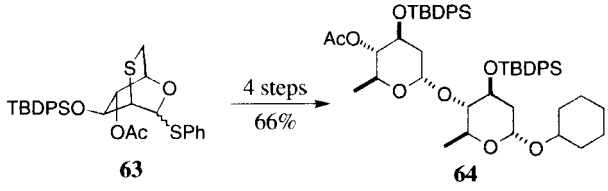
been synthesized by Mereyala *et al.*[7b] from oleandroside **61**, derived from D-glucose (**60**) by a literature procedure (*Eq.* 12). A somewhat different approach to glycosides of the avermectin disaccharide



60 **61** **62** (12)

was adopted by Toshima and co-workers,[7c] who synthesized cyclohexyl glycoside **64** from bicyclic

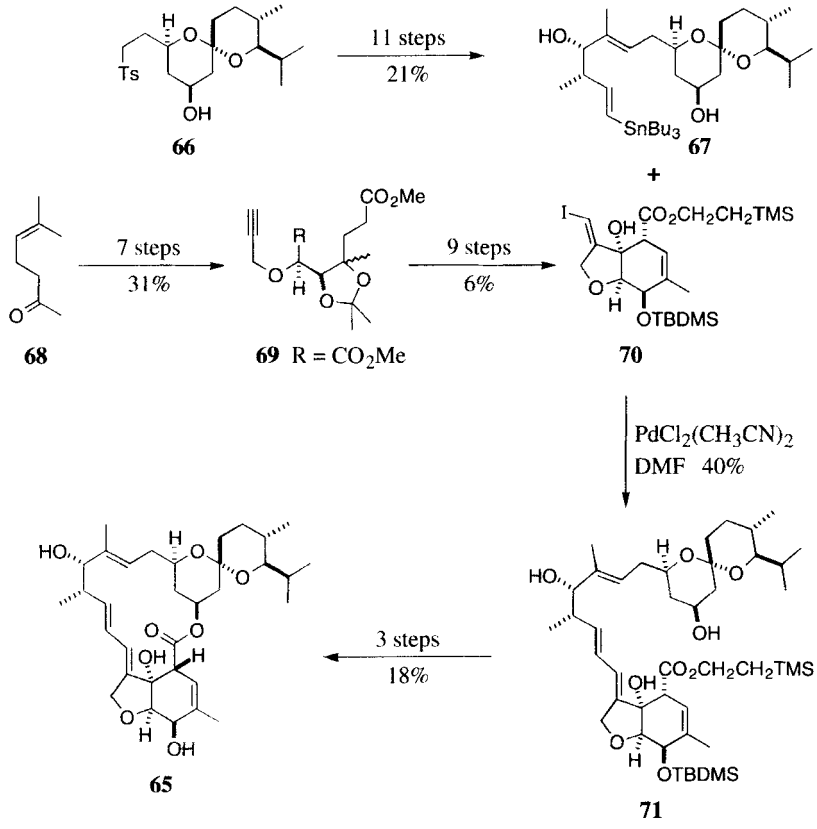
anhydro thiosugar **63** (*Eq.* 13). Several earlier total syntheses[8a-d] and two preparations[8e,f] of the disaccharide from natural avermectin B_1 have been reviewed[1] previously and are not discussed here.



63 **64** (13)

2. Unnatural Avermectins

In addition to the extensive research effort directed toward total synthesis of naturally occurring avermectins described in the previous section, much research has been directed toward synthesis of avermectins which do not occur in nature. Most of these syntheses begin with a natural avermectin, most commonly avermectin B_1 (**1**), although some total syntheses have been reported. For example, Julia *et al.*[9] have reported a total synthesis of **65**, the "b" component of ivermectin aglycone (*Scheme* 5).

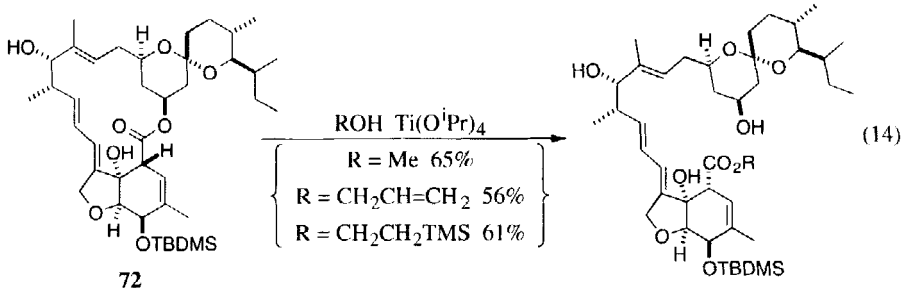


68 **69** R = CO_2Me **70** **65** **71**

Scheme 5

The Julia synthesis of **65** features a Stille coupling of "northern half" **67**, synthesized from spiroketal **66**,[9c] with "southern half" **70**, prepared from ketone **68**,[9d] to afford the key seco-acid ester **71**.

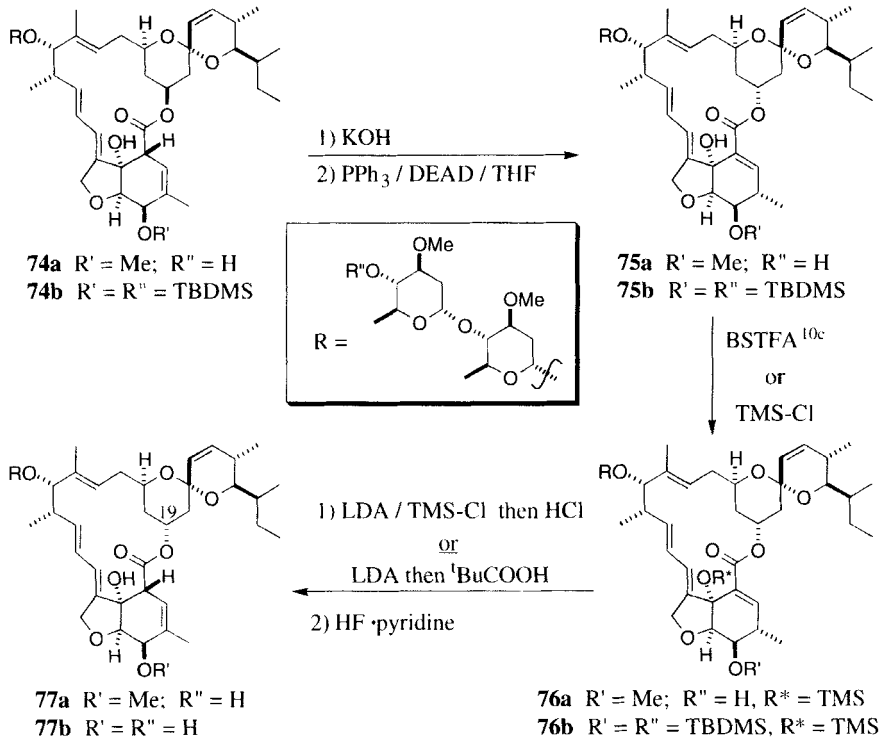
Removal of the ester protecting group, followed by macrolactonization and final deprotection, completed the synthesis of **65**.[9a,b] The coupling strategy used minimizes the need for hydroxyl protecting groups, thus improving the efficiency of the synthesis. The incorporation of a seco-acid intermediate with the correct stereochemistry at C-2 is another significant feature of the synthesis, as this avoids the deconjugation problems associated with earlier syntheses (*vide supra*). The Julia group has also reported the preparation of such seco-acids by reaction of protected aglycone **72** with a variety of alcohols in the presence of titanium isopropoxide to afford the corresponding seco-acid esters (**73**) with *retention* of the C-2 stereochemistry (*Eq.* 14).[9c] This is the only reported example of successful



72 **73** (14)

hydrolysis of an avermectin to afford a seco-acid ester without compromising the C-2 stereocenter; all previously reported hydrolysis conditions resulted in epimerization at C-2 or conjugation of the 3,4-double bond to the more stable 2,3-isomer. The ability to successfully hydrolyze and then re-lactonize an avermectin derivative without losing and subsequently restoring the C-2 stereochemistry is a major advance in avermectin chemistry, and will greatly facilitate the preparation of certain types of avermectin analogs. The preparations of 19-epi-avermectins (*vide infra*), for example, which were carried out without the benefit of this technology, would have been much more straightforward had it been available.

Two 19-epi-avermectins were prepared independently from natural avermectin B_1 (**1**) by Hanessian *et al.*[10a] and Blizzard *et al.*[10b] (*Scheme* 6). Hanessian's synthesis of 19-epi-avermectin A_1 (**77a**) and Blizzard's synthesis of 19-epi-avermectin B_1 (**77b**) proceed *via* parallel pathways from **74a**, prepared in one step (92% yield) from natural avermectin B_1, and **74b**, prepared in one step (91% yield) from natural avermectin B_1, respectively. In both cases, basic hydrolysis of the macrolactone afforded a conjugated seco-acid which was then relactonized, with inversion of configuration at C-19, under Mitsunobu conditions to afford lactones **75a** and **75b**. Completion of the syntheses required isomerization of the $\Delta^{2,3}$-double bond to $\Delta^{3,4}$ and re-establishment of the C-2 stereochemistry (note that this would have been unnecessary if the lactone hydrolysis could have been accomplished without loss of C-2 stereochemistry). Interestingly, deconjugation conditions which had previously been successful in the 19-natural series (*vide supra*) failed when applied to the 19-epi lactones **75a** and **75b**, affording instead the corresponding 2-epi derivatives. Nevertheless, the syntheses were successfully completed by using a different set of deconjugation conditions based on Hanessian's original avermectin B_1 synthesis.



74a R' = Me; R" = H
74b R' = R" = TBDMS

75a R' = Me; R" = H
75b R' = R" = TBDMS

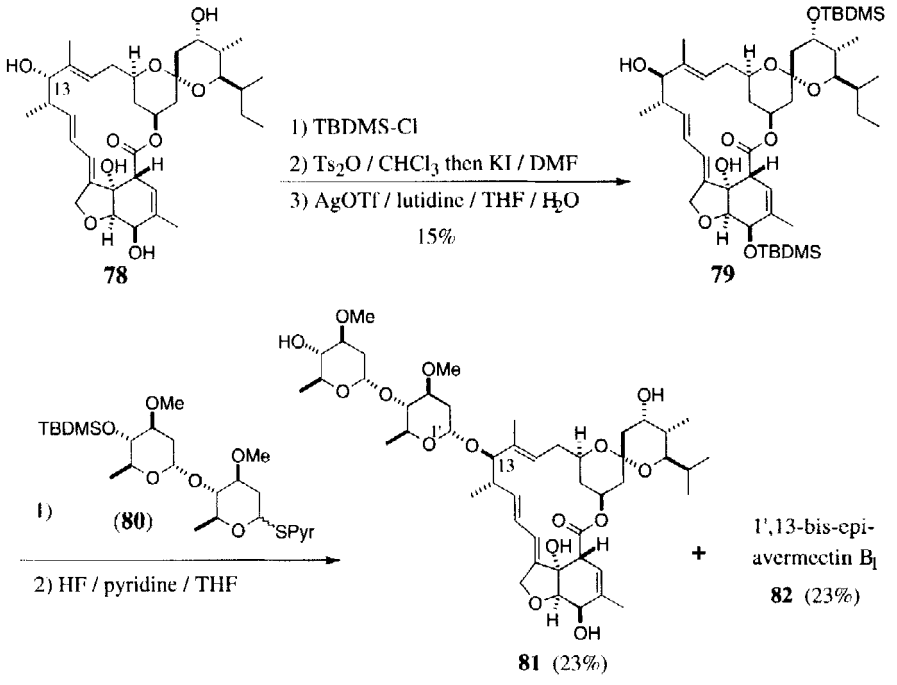
77a R' = Me; R" = H
77b R' = R" = H

76a R' = Me; R" = H, R* = TMS
76b R' = R" = TBDMS, R* = TMS

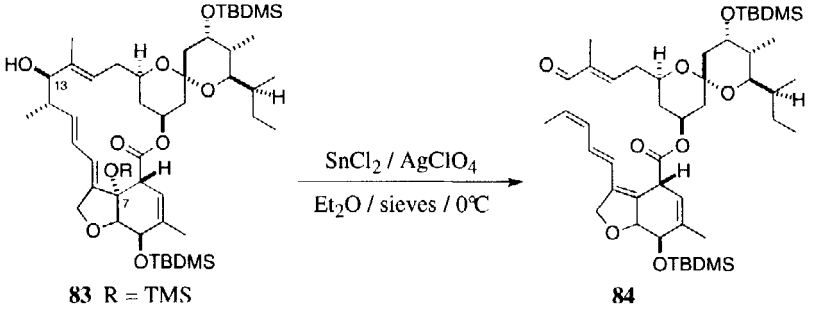
Scheme 6

Two 13-epi-avermectins, 13-epi-avermectin B_2 (**81**) and 13-epi-avermectin B_1 have also been reported recently.[11a] As with the 19-epi-avermectins, the 13-epi-avermectins were prepared by chemical modification of the corresponding natural avermectins. Thus, avermectin B_2 was converted to the known aglycone **78**, the stereochemistry at C-13 was inverted, and disaccharide **80** (also derived from natural avermectin)[8f] was reattached (*Scheme* 7). Removal of the silyl protecting groups afforded 13-epi-avermectin B_2 (**81**) and the corresponding 1'-epimer (**82**). Interestingly, the 13-epi-avermectins retained the full biological activity of the natural avermectins, unlike the 19-epi-avermectins which were essentially inactive.

A novel fragmentation reaction of avermectin aglycones was discovered during the course of studies on the synthesis of 13-epi-avermectins.[11b] Problems associated with the glycosylation of partially protected avermectin aglycones such as **79** prompted the preparation of the 7-O-trimethylsilyl derivative (**83**), with the expectation that glycosylation would proceed more cleanly with the C-7 hydroxyl group blocked. However, **83** underwent an unexpected fragmentation reaction under the glycosylation conditions to afford triene-aldehyde **84** as the major product (*Eq.* 15). Aldehyde **84** is probably derived from **83** by a vinylogous fragmentation-elimination reaction similar to the Grob fragmentation. This interesting fragmentation process could conceivably provide convenient access to avermectin intermediates for synthetic studies.

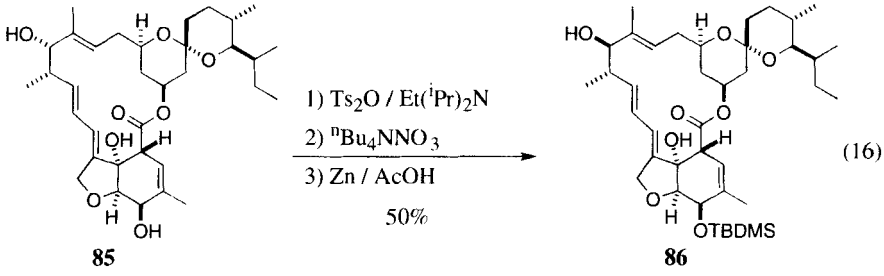


Scheme 7



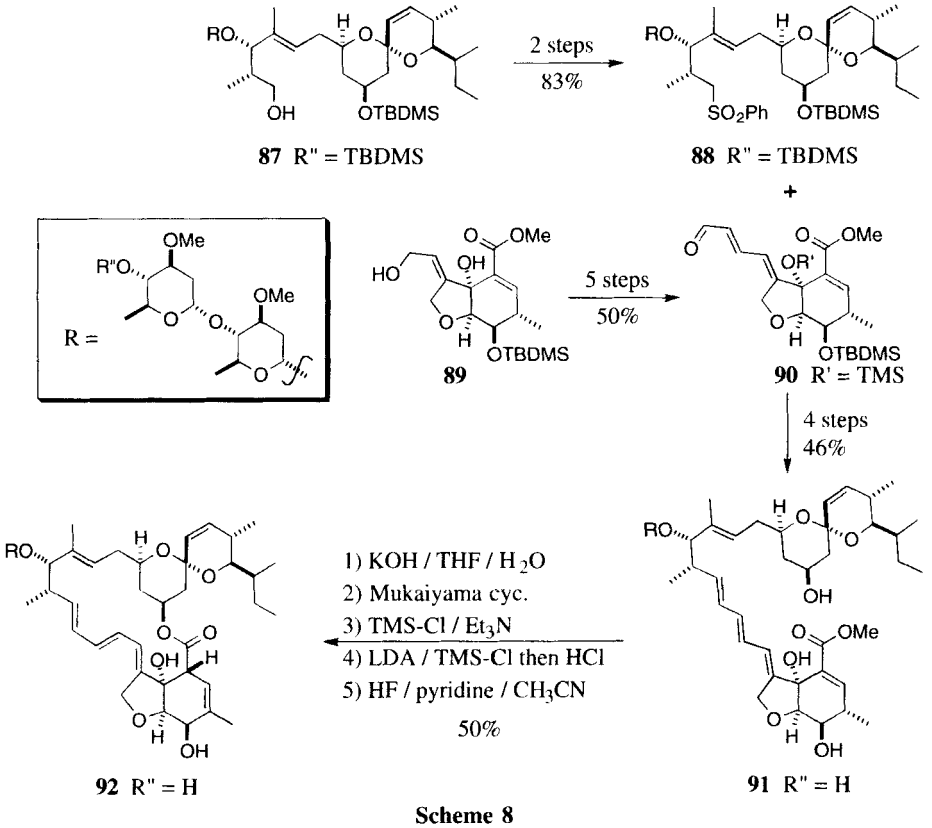
(15)

One of the major difficulties associated with the synthesis of 13-epi-avermectins is the inversion of configuration at C-13. A significant advance in this area was recently reported by Jones *et al.*[11c] who found that conversion of protected ivermectin aglycone **85** to the 13-tosylate, followed by displacement of the tosylate with nitrate provided, after cleavage of the resulting nitrate ester with zinc/acetic acid, the desired 13-epi aglycone **86** in 50% overall yield (*Eq.* 16). This straightforward reaction sequence provides a substantial improvement over the previous method involving iodide displacement followed by solvolysis (*vide supra*). An additional improvement using a slightly different process (*i. e.* displacement of a 13-mesylate with cesium acetate followed by de-acetylation) has recently been reported.[11d]



(16)

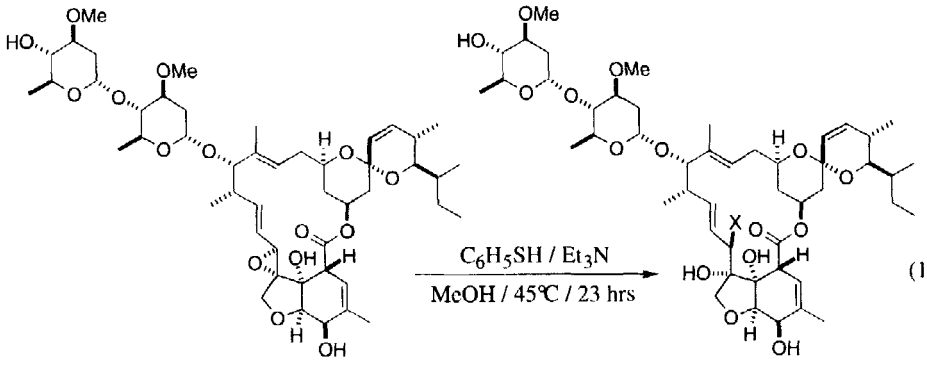
Another active area in the synthesis of unnatural avermectins has been the preparation of analogs with modified double bonds. An especially interesting achievement in this area is Hanessian's synthesis of bis-homo-avermectin B_{1a} (**92**),[12a] an analog in which the diene of avermectin B_{1a} (**1**) has been replaced with a triene. The synthesis began with "northern half" **87** and "southern half" **89**, both derived from natural **1**,[8e] which were elaborated and combined to form homologated seco-acid **91** (*Scheme* 8). Hydrolysis of the methyl ester of **91**, followed by macrolactonization, deconjugation, and deprotection then completed the synthesis of **92**.



Scheme 8

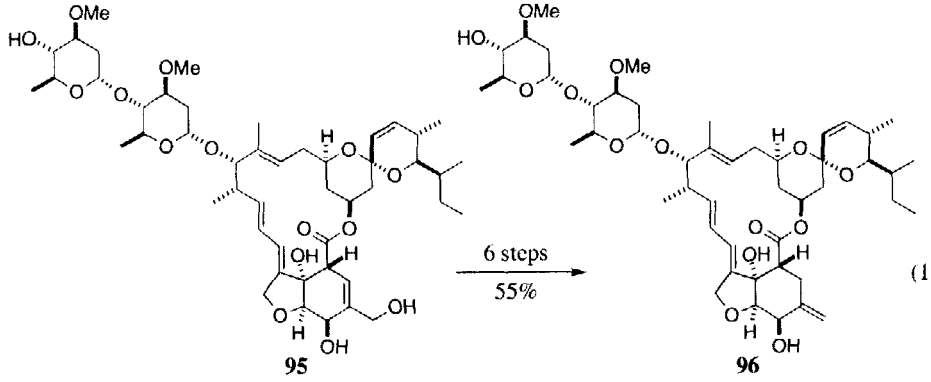
Another recent paper[12b] in this area described the reactions and stereochemistry of the previously reported avermectin B_1-8,9-oxide (**93**). Epoxide **93** was found to react readily with aromatic

thiols, affording adduct **94** (*Eq.* 17), but not with amines or alcohols (under mild conditions; more forcing conditions led to loss of the C-2 stereochemistry). An X-ray crystal structure of **94** allowed unambiguous assignment of the epoxide stereochemistry of **93** for the first time.



93 **94** (17)

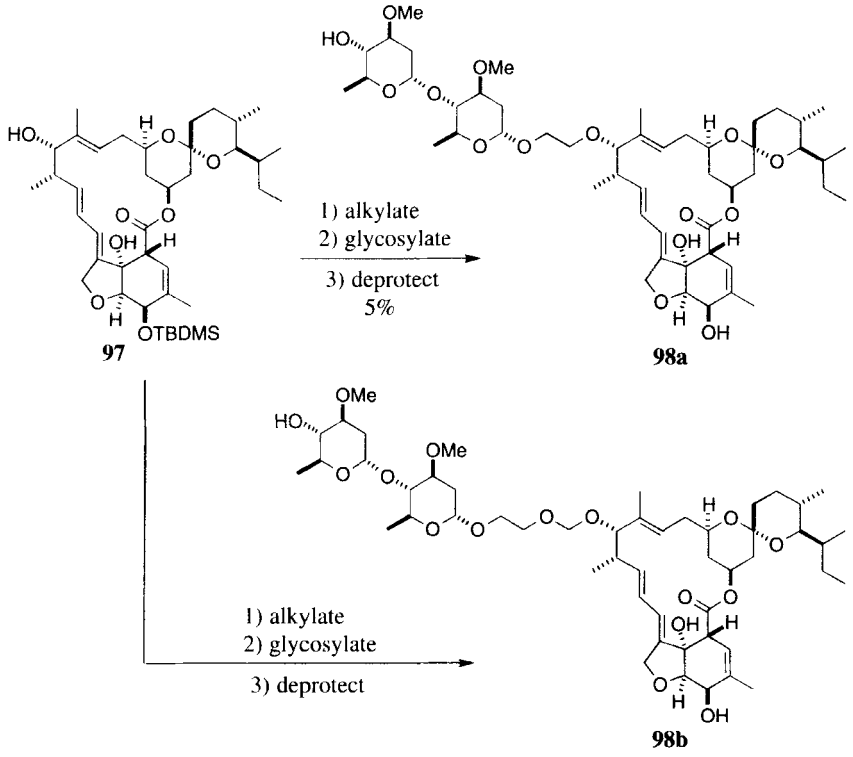
An interesting avermectin derivative (**96**) in which the 3,4-double bond has been moved to the 4,4a-position has recently been reported by Fraser-Reid *et al.*[12c] Synthesized in six steps (*Eq.* 18)



95 **96** (18)

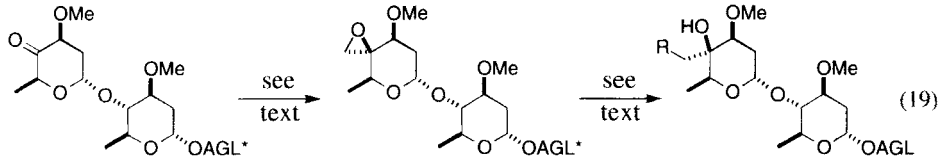
from the known 4a-hydroxy derivative **95** (from natural avermectin B_{1a}), the *exo*-methylene isomer **96** surprisingly retains the full antiparasitic activity of the natural product.

A different series of avermectin derivatives, in which various spacers have been inserted between the aglycone and the disaccharide, has also been reported recently.[13] Synthesized in three steps (*Scheme* 9) from protected aglycone **97**, derived from ivermectin, these analogs (*e. g.* **98a** and **98b**) were designed to probe the effect of varying the aglycone-disaccharide linkage on biological activity.



Scheme 9

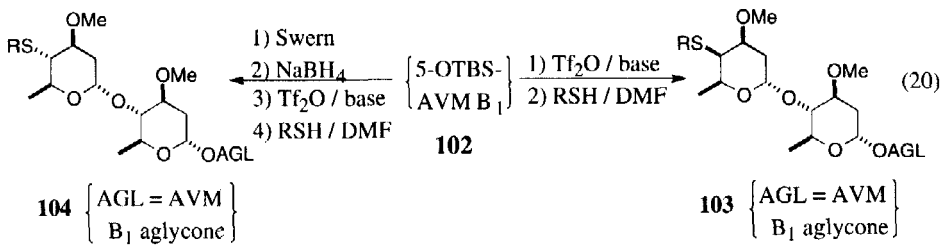
Modification of the disaccharide has also been an active research area recently. A 4"-*exo* epoxide analog (**100**) of avermectin B_1 has been prepared by reaction of the corresponding ketone (**99**) with TMS-diazomethane (a ring expanded *exo*-epoxide was also isolated).[14a] Reaction of epoxide **100** with a variety of nucleophiles (*e. g.* CN^-, RS^-, RNH_2) afforded several novel 4"-substituted avermectin derivatives (**101**) (*Eq.* 19).



(19)

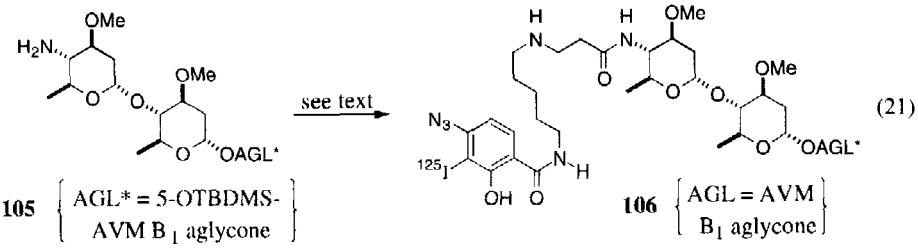
99 { AGL* = 5-OTBDMS-AVM B_1 aglycone } **100** **101** { AGL = AVM B_1 aglycone }

A series of 4"-alkythio avermectins (**103**) was prepared by activation and displacement of the 4"-hydroxyl group of avermectin B_1 (after protection of the C-5 OH). Analogs with the natural (α) stereochemistry at C-4" (**104**) were similarly obtained by sequentiallyl inverting, activating, and displacing the 4"-hydroxyl group (*Eq.* 20).



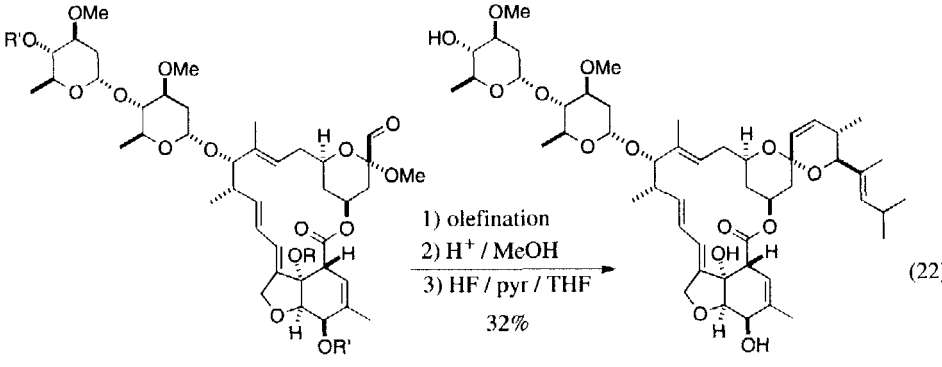
(20)

Several avermectin affinity probes (*e. g.* **106**) have also been prepared by modification of the disaccharide *via* the previously reported 4"-amino-avermectin **105** (*Eq.* 21).[14c] Analog **106** subsequently proved to be useful for photoaffinity labeling of avermectin binding proteins.[14d]



(21)

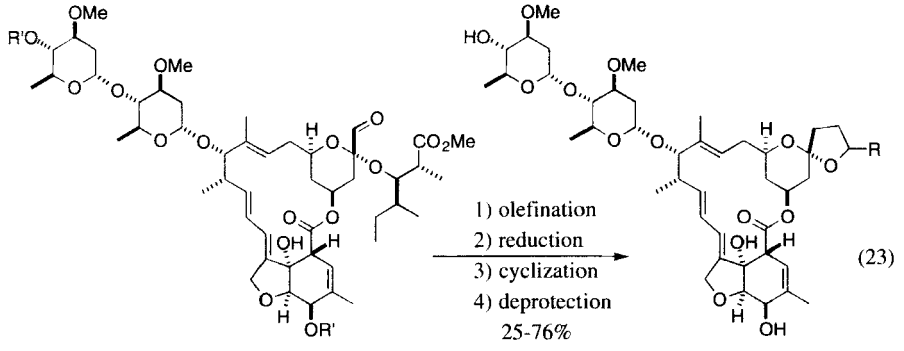
Perhaps the most active area of research in derivatization of natural avermectins in the last few years has been modification of the spiroketal portion. The discovery of an efficient method for excision of carbons 23-28 of avermectin B_2 to afford aldehyde **107**[15a] and a method for subsequent reconstruction of the spiroketal[15b] has provided access to a wide variety of avermectins with modified spiroketals. The power of this methodology was vividly demonstrated by Shih *et al* with their synthesis of an avermectin-nemadectin hybrid (**108**) (*Eq.* 22).[15c] Olefination of **107** with an appropriately



(22)

substituted Wittig reagent, followed sequentially by spiroketalization and deprotection afforded an avermectin analog (**108**) in which the *sec*-butyl side-chain at C-25 has been replaced with the isohexenyl side chain characteristic of nemadectin (**5**).

A similar strategy has been employed by Meinke *et al* to prepare analogs (*e. g.* **110**) in which the 6,6-spiroketal of avermectin B_1 has been replaced with a 6,5-spiroketal.[15d] Starting with aldehyde **109**, which was prepared on a multi-gram scale *via* a modified procedure, more than a dozen 6,5-spiroketal analogs with a wide variety of substituents at C-24 were prepared by this route (*Eq.* 23).

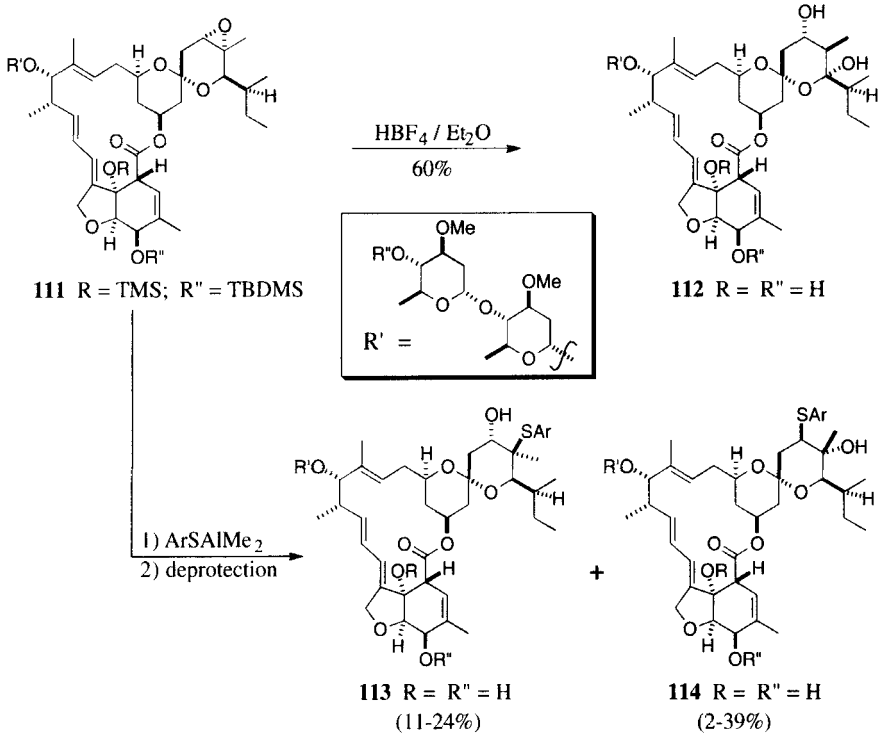


(23)

109 R' = TBDMS

110 R = H, Me, Ph, etc.

An alternative intermediate for the synthesis of spiroketal-modified avermectins, also developed by Shih *et al.*, is epoxide **111**,[15e] which was prepared in 32% yield from bis-protected avermectin B_2 *via* DAST mediated elimination of the C-23 hydroxyl group, followed by MCPBA oxidation of the resulting olefin (*Scheme* 10). Hydrolysis of **111** afforded 1,3-diol **112** *via* an



111 R = TMS; R" = TBDMS

112 R = R" = H

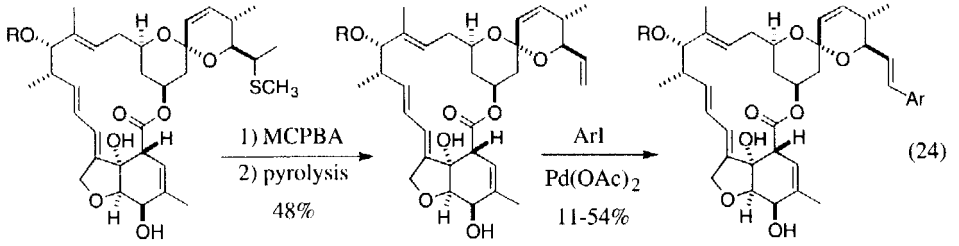
113 R = R" = H
(11-24%)

114 R = R" = H
(2-39%)

Scheme 10

unexpected 1,2-hydride shift.[15c] The epoxide could also be opened by a variety of thiols to afford thioethers **113** and **114**.[15f]

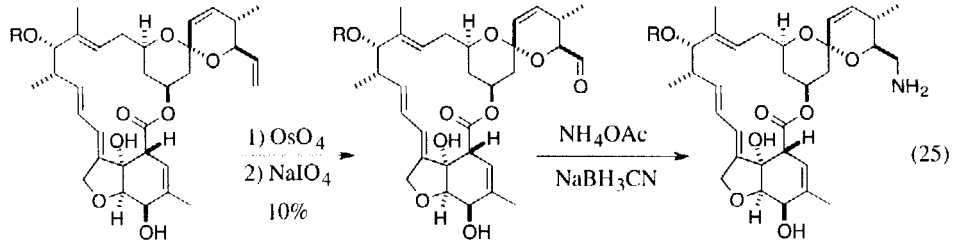
Spiroketal-modified avermectins can also be accessed biosynthetically using a mutant strain of *S. avermitilis* which is incapable of synthesizing the branched-chain carboxylic acids needed to initiate avermectin biosynthesis.[16a] The mutant strain can produce avermectins from added branched-chain carboxylic acids, however, thus providing access to a wide variety of interesting avermectins. The novel avermectins produced by this method can be used as starting materials to prepare other spiroketal-modified avermectins. Thioether **115**, for example, was prepared by adding 2-methylthio-propanoic acid to a fermentation of the blocked mutant *S. avermitilis* strain. Oxidation of **115** to the sulfoxide, followed by pyrolysis, afforded C-25-vinyl derivative **116**,[16b] which could not be prepared directly by the biosynthetic procedure since only branched-chain substitutents can be incorporated at C-25 by biosynthesis (*Eq.* 24). Analog **116** was further elaborated to extended analog **117** by Heck



(24)

115 R = oleandrosyl-oleandrose **116** **117**

coupling of various aryl iodides to the terminal olefin. The vinyl group of **116** could also be oxidatively cleaved to the aldehyde (**118**) which was converted by reductive amination to the amino-methyl derivative **119** (*Eq.* 25).[16c] A number of additional derivatives with a wide variety of substituents at C-25 were also described.[16b,c]



(25)

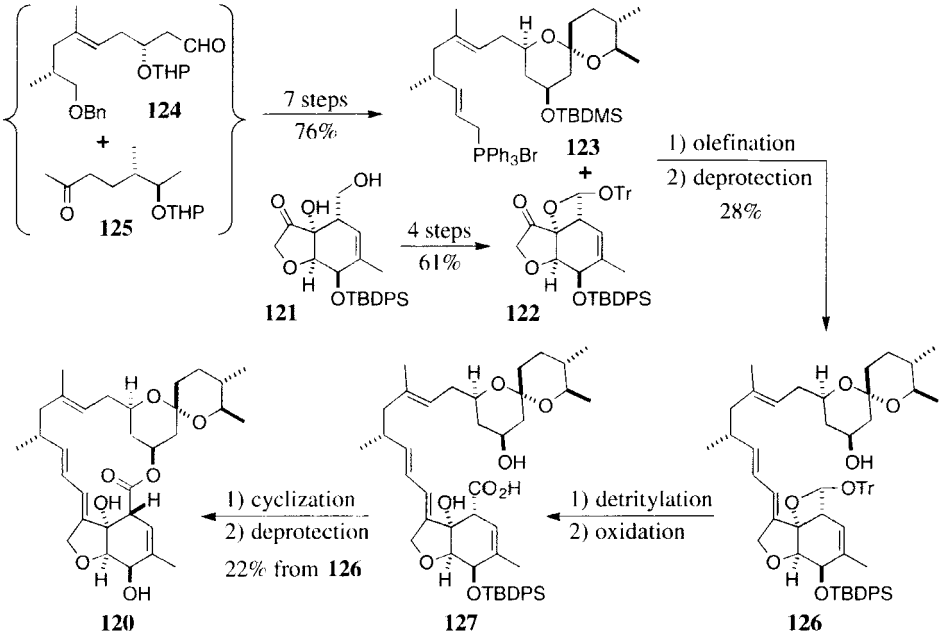
116 R = oleandrosyl-oleandrose **118** **119**

II. SYNTHESIS OF MILBEMYCINS

1. Naturally Occurring Milbemycins

Numerous total syntheses of milbemycins have been reported in the literature but most of these have previously been reviewed[1] and will not be covered here. Two new total syntheses of a naturally occurring milbemycin [milbemycin α_1 (**120**)] have been reported in the last three years.[17]

Hirama *et al*[17a] have reported a synthesis of **120** which begins with "southern half" **121**, the preparation of which had been described by Hirama and co-workers a few years earlier (*Scheme* 11). Conversion of **121** to acetal **122**, followed by coupling to "northern half" **123**, prepared from ketone **124** and aldehyde **125**, afforded **126**. Deprotection and oxidation of **126** led to seco-acid **127**, which underwent macrocyclization and deprotection to complete the synthesis. The Hirama synthesis of **120** is notable for the cyclization of a seco-acid intermediate with the correct C-2 stereochemistry in place thus avoiding the need for a deconjugation-epimerization protocol (*vide supra*).

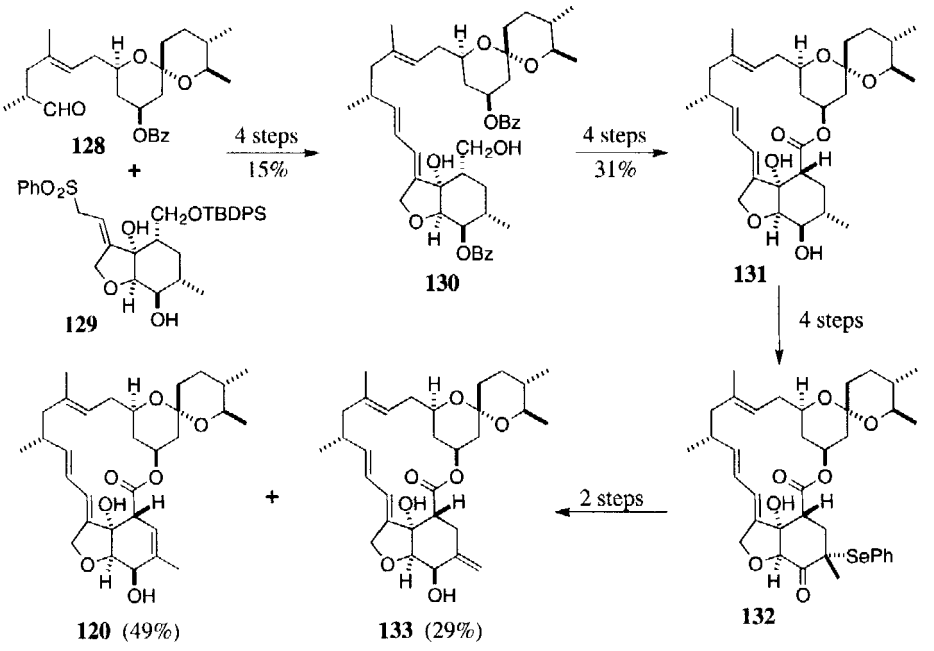


Scheme 11

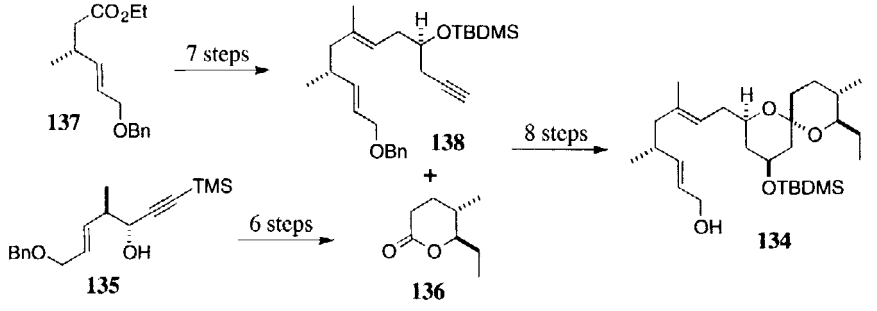
A deconjugation-epimerization protocol was also avoided by Ley *et al.* in their recently reported total synthesis of **120** (*Scheme* 12).[17b] Their synthesis began with aldehyde **128**, an intermediate in Ley's earlier synthesis of milbemycin β_1, and allylic sulfone **129**, an intermediate in Ley's synthesis of avermectin B_1 (*vide supra*). Julia coupling of **128** and **129**, followed sequentially by protection of the C-5-hydroxyl group and deprotection of the C-1-hydroxyl group afforded advanced intermediate **130**. Oxidation and macrolactonization of **130** provided 3,4-dihydro-milbemycin α_1 (**131**). The $\Delta^{3,4}$-double bond was subsequently introduced using methodology developed by the Ley group during the course of their synthesis of avermectin B_1 (*vide supra*) thus completing the synthesis of milbemycin α_1 (**120**). The isomeric *exo*-methylene analog **133** was also obtained as a by-product of the olefin introduction sequence.

Several syntheses of fragments of natural milbemycins have been reported recently.[18] Takano *et al*[18a] described a long synthesis of the "northern half" (**134**) of milbemycin K from acetylenic alcohol **135**, prepared in 7 steps from (R)-epichlorohydrin, and ester **137**, prepared in 5

steps from (S)-epichlorohydrin (*Eq.* 26).



Scheme 12



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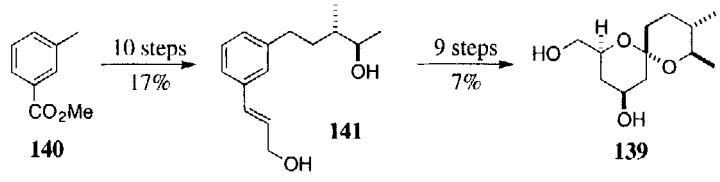
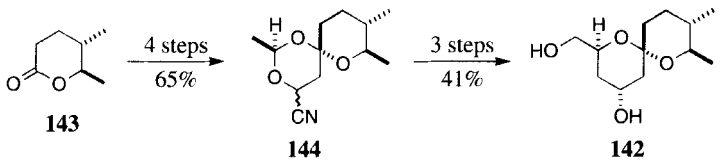
The synthesis of spiroketal fragment **139**[18b] from benzoic ester **140** *via* the intermediate allylic alcohol **141** has also been reported recently by *Holoboski et al.* (*Eq.* 27). In addition, a



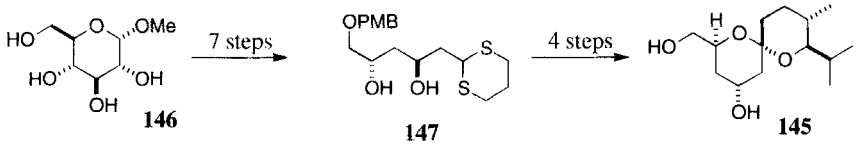
(27)

synthesis of the C-19-epimeric spiroketal fragment **142** from lactone **143** (*via* spiroketal intermediate **144**) has recently been described by Rychnovsky *et al* (*Eq.* 28).[18c] A general synthesis of several



(28)

milbemycin spiroketals (*e. g.* **145**) from glucose has also been reported recently (*Eq.* 29).[18d] Note that the spiroketal syntheses discussed here are merely the most recent entries in this active area of

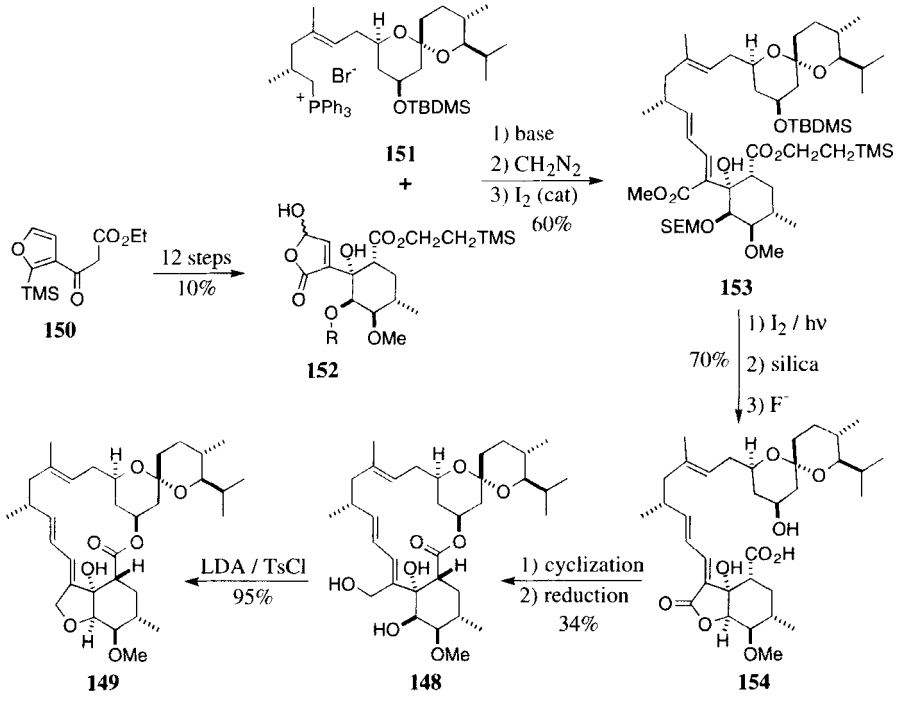


(29)

research. The numerous earlier syntheses of milbemycin and avermectin spiroketals have been extensively reviewed[1] and are therefore not included in this discussion.

2. Unnatural Milbemycins

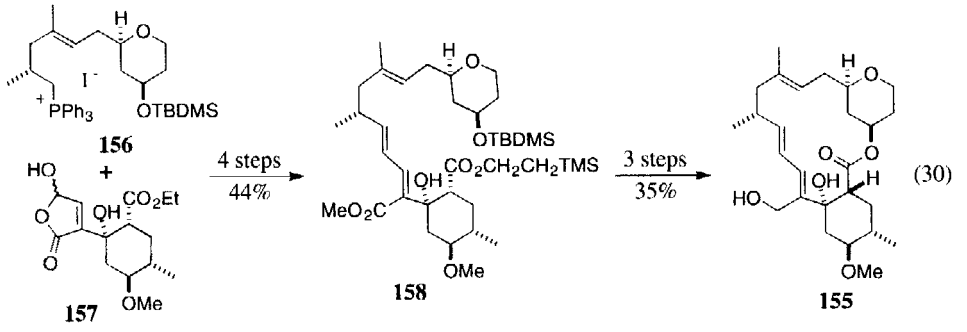
In the last three years, much effort has been directed toward the synthesis of milbemycins which do not occur in nature. Building on their previously reported synthesis of milbemycin E, the Thomas group has recently described a synthesis of 6-hydroxy-3,4-dihydro-milbemycin E (**148**)[19a] and the subsequent conversion of **148** to a dihydro-milbemycin G derivative (**149**) (*Scheme* 13).[19b]



Scheme 13

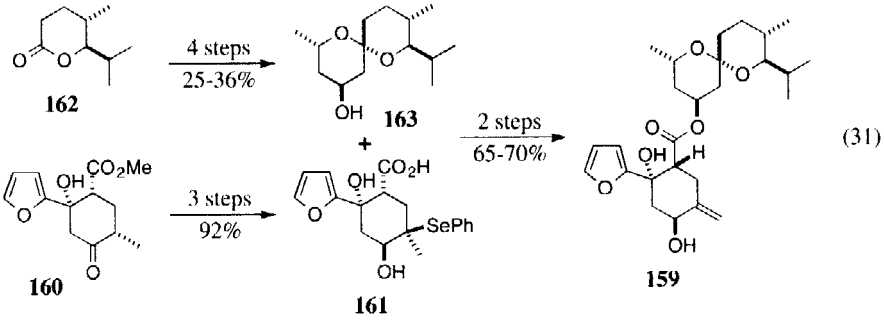
Furan **150** was elaborated to "southern half" **152** which was combined with "northern half" **151** (an intermediate in the authors' earlier synthesis of milbemycin E) to afford intermediate **153**. Conversion of **153** to seco-acid **154**, followed sequentially by cyclization and reduction completed the synthesis of **148**. The authors also described their initial efforts to extend this work to the synthesis of milbemycin G by incorporating the missing $\Delta^{3,4}$-double bond.[19b]

The Thomas group has also reported the synthesis of a simplified milbemycin analog (**155**) which lacks the spiroketal portion as well as the $\Delta^{3,4}$ double bond (*Eq.* 30).[20a] "Northern half" **156**,

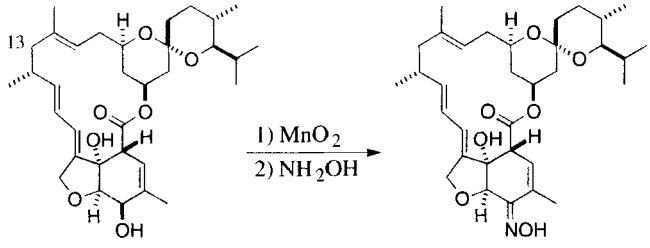


synthesized in nine steps (31% overall yield) from a bicyclic lactone, was combined with "southern half" **157**, which was prepared in 8 steps (23% overall yield) from a furan derivative, in a four step sequence which afforded protected seco-acid **158**. Deprotection, cyclization, and reduction of **158** then completed the synthesis of milbemycin analog **155**.

An even simpler milbemcyin analog (**159**), which has the spiroketal but not the macrocycle, has also been described recently (*Eq.* 31).[20b] Synthesized in a relatively short sequence from ester **160** and lactone **162**, **159** surprisingly retains weak insecticidal activity.



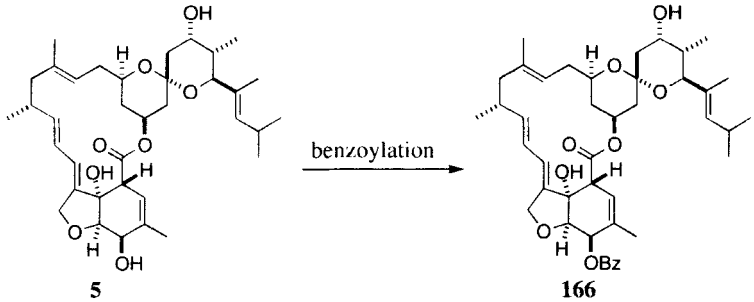
In addition to the unnatural milbemycins described above, which were prepared by total synthesis, there have been several reports, in the last three years, of the preparation of milbemycin analogs by chemical modification of natural milbemycins. Milbemycin-5-oxime derivatives (*e. g.* **164**) have been prepared by derivatization of several natural milbemycins (*e. g.* milbemycin D (**165**)) (*Eq.* 32).[21a] Derivatization at C-5 of nemadectin (**5**) has also been used to determine the absolute stereochemistry of this class of natural products. Application of the exciton chirality method to



(32)

165 **164**

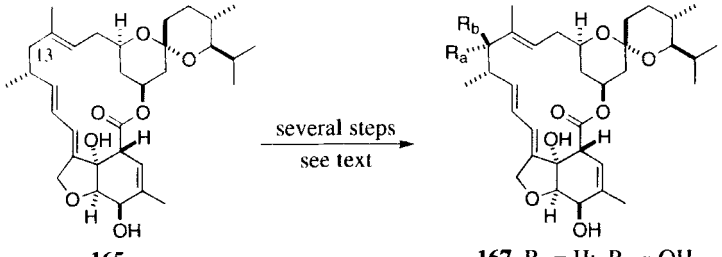
benzoate **166** allowed assignment of the absolute stereochemistry of nemadectin (*Eq.* 33).[21b] Not surprisingly, the nemadectins were found to have the same absolute stereochemistry as the avermectins and milbemycins, but this example provides an excellent demonstration of the method.



(33)

5 **166**

There has also been considerable interest in funtionalization of milbemycins at C-13, particularly oxidation which converts a milbemycin into the corresponding avermectin aglycone. Two alternative approaches to C-13 oxidation of a milbemycin have recently been reported.[22] Epoxidation of the C-14,15-olefin of milbemycin D (**165**) with MCPBA affords the α-epoxide which, upon treatment with an acidic reagent, opens to afford a 15-hydroxy-13,14-olefin which can undergo rearrangement under certain conditions to give the desired 13-β-hydroxy derivative (**167**) (*Eq.* 34).[22a] The stereochemistry at C-13 can be inverted by an oxidation-reduction sequence to afford the 13-α-hydroxy analog (**168**), which is the aglycone of the "b" component of ivermectin.[22a] An alternative approach to **167** is direct oxidation (with SeO_2) at C-13 after protection of the C-5 hydroxyl group as a ketone (which is reduced after the C-13 oxidation is complete to regenerate the essential hydroxyl group at C-5).[22b]

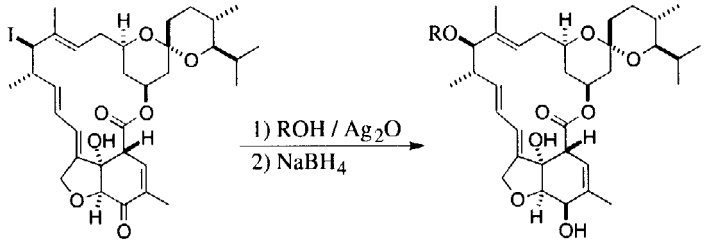


(34)

165

167 $R_a = H$; $R_b = OH$
168 $R_a = OH$; $R_b = H$

The availability of 13-hydroxy-milbemycins has enabled the synthesis of 13-alkoxy-milbemycins *via* the 13-iodo-derivative (**169**). Solvolysis of the iodide with a variety of alcohols (ROH) afforded the corresponding 13-alkoxy-milbemycin (**170**) (*Eq.* 35).[22c] Although similar chemistry had



169 **170** (35)

been described several years earlier by Merck chemists using an avermectin-derived C-13-iodide to prepare a 13-epi-avermectin aglycone which could subsequently be alkylated, this was the first report of direct alkoxy substitution at C-13 of a milbemycin. Several of the analogs prepared by this method showed improved anti-parasitic activity.

III. CONCLUSION

Substantial progress in the synthesis of avermectins and milbemycins has been accomplished over the years. The numerous total syntheses of both classes of compounds which have now been reported in combination with extensive studies on chemical modification of the natural products, have given today's chemist a broad understanding of avermectin-milbemycin chemistry. Of course, there are still problems which remain to be solved, and we can confidently look forward to many more years of interesting chemistry in this area.

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