Chapter 7

PROBLEM SOLVING IN ORGANIC SYNTHESIS: THE FALSE STEPS, FAILED PATHWAYS, AND ULTIMATELY SUCCESSFUL ROUTE TO THE BOTTOM HALF OF IVERMECTIN

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I. Introduction

Many metaphors have been used to describe the total synthesis of natural products—the intricacies of a chess match; the theme and variations of a musical composition; a long, tortuous, and unpredictable journey; the creation of a work of art. The title of this series uses a military analogy in its description of the practice of organic synthesis, with the implied use of well-developed tactics in an overall sound strategic plan. While all of these are certainly appropriate, to me it has always seemed a problem-solving contest. Nature presents us with the basic problem in the form of a novel

molecular structure. We then further define the problem by adding certain artificial parameters. For example, we might limit the maximum number of steps or try to heighten the efficiency of bond construction. But most importantly, in each synthesis we try to guarantee the development of new and hopefully general synthetic methods along the way, because a synthesis which uses all known chemistry does not contribute greatly to the overall knowledge of the field. Once the problem is defined, we look for a solution, or rather several solutions, since in the abstract we can't be sure that the first, or indeed any, will work. This continuing contest with nature, this attempt at solving a particular problem, is what generates, for me, the intellectual excitement and fervor of research in organic synthesis. Lastly, at least in the best of all worlds, the final solution should fulfill one additional require-ment, one that is really a matter of taste: the synthesis should be elegant, or beautiful, or clever. Just as masterpieces of art or music have a certain undefinable quality that sets them apart, so should the truly great achieve-ments of organic synthesis. This eminent goal, though often unattainable, is nonetheless worth striving for.

I wish to thank the editor and publisher for producing this series of books in which the story of a synthetic effort can be explained in full. I agree completely with the thoughts expressed in the preface to the first volume, that students and chemists who want to learn about synthesis must see more than just the positive results that appear in brief communications. They must be made aware of the whole picture—why certain routes were chosen, why some failed, and why new and different approaches were selected. Otherwise, the magnitude of the challenge can be misunderstood and the real accom-plishments of the synthesis underestimated. The student or chemist is often left with the wholly incorrect impression that organic synthesis is already such a mature, well-developed field that no further studies in synthesis are necessary. However, there are still numerous unsolved major problems in the synthesis of important molecules. I hope those who read this account will enter this richly stimulating field of science and join in the problem solving.

II. The Problem

In 1981 I became aware of the structures of a group of strongly antiparasitic compounds, namely the avermectins and milbemycins.[1] Of particular interest both biologically and synthetically was the commercial anthelmintic agent 22,23-dihydroavermectin B_{1a}, also called ivermectin (1). After several years of letting various "paper" synthetic routes simmer, we finally began a synthetic effort in this area in earnest in early 1984. Our original synthetic plan involved the fairly obvious disconnection of the

1 R=sBu, iPr

2

3
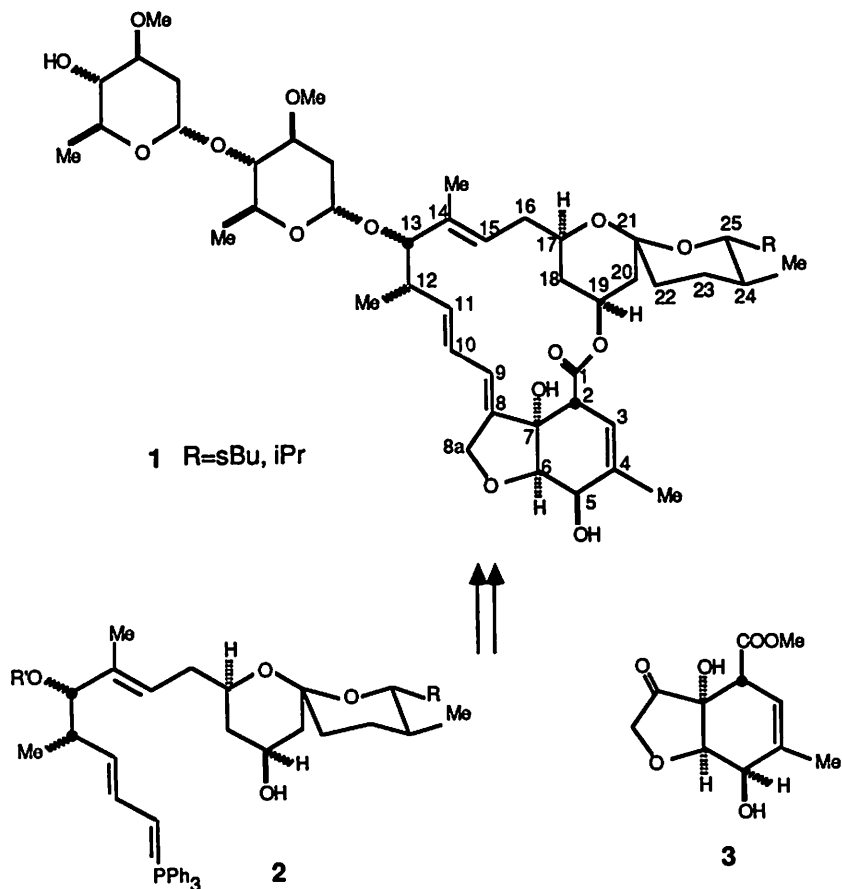
molecule into two smaller portions, e.g., **2** and **3**, which could be reconnected by a sequence of some type of Wittig reaction and macrocyclic lactonization, or the alternative route of esterification and intramolecular Wittig-type olefination. Several other groups already had synthetic programs under way aimed at the total synthesis of these molecules using a similar type of disconnection. Quite often the two compounds **2** and **3** or their analogs were described as "northern" and "southern" "hemispheres," "segments," or "subunits." Being somewhat more laid back in Los Angeles, we refer to **2** and **3** as the top and bottom halves, respectively. Since I had funds[2] and space for only one co-worker on this project, we decided to attempt to synthesize what for us was the more interesting of the two halves, namely the bottom half **3**. This compound is a highly functionalized small molecule (6 oxygen atoms for only 11 carbons) in which there are four contiguous

asymmetic centers and each carbon atom (with the exception of the allylic methyl group at C-4) is functionalized. It would be expected to be relatively unstable since it could lose 2 moles of water fairly easily (being both a β-hydroxy ester and a vinylogous β-hydroxy ester) to give an aromatic ring (a benzofuranone). Thus we thought this highly functionalized, potentially quite labile small molecule would be a quite attractive synthetic target.

We examined various possible disconnections of 3 and initially zeroed in on the following approach (Scheme 1). We hoped that 3 might be available from a diol such as 4 by base-catalyzed cyclization with loss of a leaving group (X = OTs, halide, etc.) and eventual deprotection where necessary. One would expect to obtain the fused five-membered ring system rather than the alternative bridged six-membered ring. It should be pointed out in passing that our "paper" synthetic musings were put on a firm basis when Fraser-Reid published the first synthesis of a bottom half component similiar to 3 in which just such a cyclization of a molecule very similar to 4 was successfully carried out.[3] An alternative approach to 3 would be via the C-5 epimer (in its protected form) 5, which could be oxidized to the enone and reduced from the α face to give the required 5β-alcohol and thereby, after deprotection, 3. A very similar inversion of the 5α-alcohol to the 5β-alcohol via an analogous oxidation–reduction sequence had already been reported in the milbemycin D series,[4] and thus the conversion of 5 to 3 had literature precedent. As we will see much later, this transformation turned out to be more difficult than we had been led to expect from the literature results. We hoped that 5 would be available by the acid-catalyzed cyclization of the epoxy alcohol 6. Again in this case, recent results have shown that our early hypothesis was sound, since Barrett has reported the acid-catalyzed cyclization of a slightly less functionalized epoxy alcohol to give a product analogous to 5.[5] The cyclization of 6 to 5 would still be worth testing since there is the possibility that the 3,4-olefin might promote attack at C-5 (which is now allylic) to give the bridged six-membered system rather than attack at C-6 to give the desired fused five-membered system.

A potential common precursor to both 4 and 6 would be the corresponding 5,6-olefin, which would clearly be too unstable toward aromatization (via loss of the 7-alkoxy function) to be useful in a synthetic approach. Therefore we chose in our synthetic strategy to protect the 3,4-olefin and the 7-hydroxyl group jointly as a cyclic trans-chloro ether, e.g., 7. This compound should be much more stable to acid and base and should be convertible into 4 and 6 by a sequence of stereospecific hydroxylation or epoxidation, respectively, followed by reductive elimination of the trans-chloro ether. An obvious synthetic route to this substituted oxanorbornene 7, namely an intermolecular Diels–Alder reaction between the substituted furan 8 and methyl
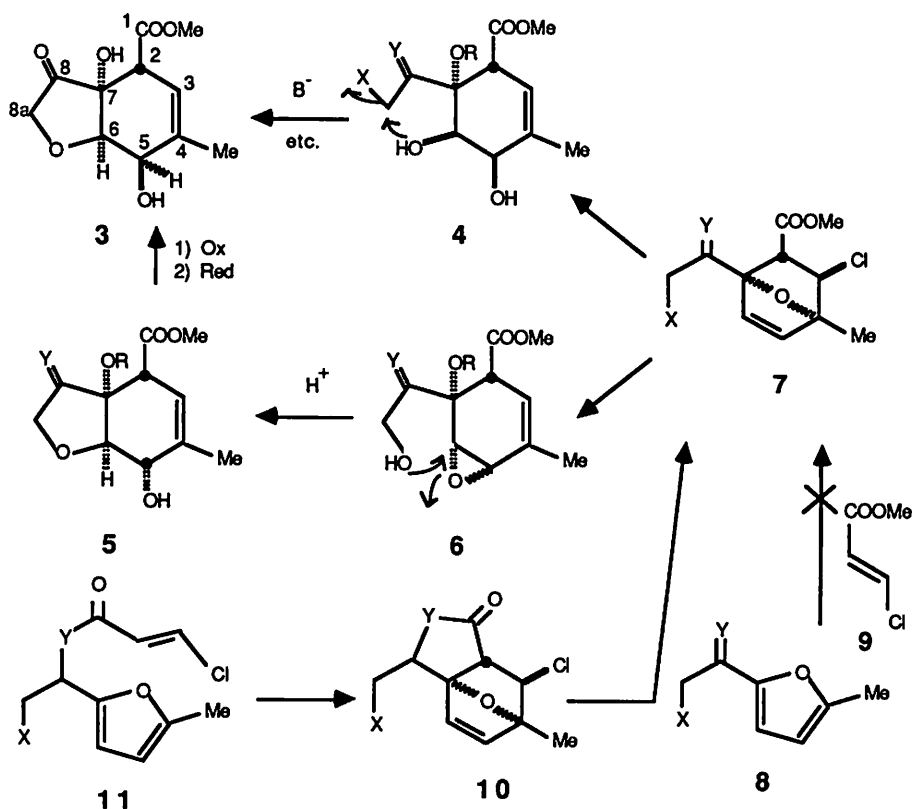
SCHEME 1

β-chloroacrylate **9**, was quickly eliminated from consideration, since a mix-ture of four compounds (both regio- and stereoisomers) would be expected. Indeed, in the desired isomer **7** the ester group has the less favorable exo stereochemistry (cis to the bridging oxygen) and thus would probably be a very minor component. This potentially thorny problem of regio- and stereochemistry could be neatly solved by tying together the ester of the dienophile to the Y function of the diene, namely by choosing **10** as the im-mediate precursor of **7**. Now the key Diels–Alder reaction has been made intramolecular, which (if it can be made to work) guarantees both the desired regiochemistry (only one isomer is now possible) and stereochemistry (the five-membered ring can only be bridged via an exo substituent)! Thus our ultimate precursor in this route to **3** was the simple β-chloroacryloyl

derivative of the furfuryl system, **11**, in which X could be a hydrogen or, better, a protected hydroxyl group and Y, at least theoretically, could be any heteroatom (O,NR,S), easily convertible to a ketone function. With this initial synthetic design, then, we began our efforts toward a synthesis of **3**.

III. Intramolecular *N*-Furfurylacrylamide Diels–Alder Approach[6]

Initially we decided to prepare compounds **11** with X = H for three reasons: they were easier to make, they would serve as good models for the desired cycloaddition, and the adducts derived from them might be hydroxy-lated at a later stage. The choice for Y in **11** was more limited since Parker had reported that compounds with an ester linkage (Y = O) or a secondary amide linkage (Y = NH) would not cyclize to give the desired adducts.[7] For this reason we originally chose Y = NR in **11** and began with the highly activating *o*-hydroxyphenyl substituent which Mukaiyama had used (as the magnesium salt) to force even quite hindered acrylamides to cyclize.[8] 2-Acetyl-5-methylfuran **12a** was reductively aminated with *o*-hydroxyaniline and sodium cyanoborohydride to give the amine **13a**, which was acylated with β-chloroacryloyl chloride to give the *N*-furfurylacrylamide **14a**. Heating **14a** at 110°C in toluene for 12 hours gave a 74% yield of a 5:1 mixture of diastereomers **15a** and **16a**. Thus we were able to carry out this key cycloaddition in good yield without having to use the magnesium salt. Because of the difficulties associated with the removal of the *o*-hydroxyphenyl

TABLE I

INTRAMOLECULAR DIELS–ALDER REACTION OF **14** to Give **15** and **16**[a]

Compound	R_1	R_2	R_3	R_4	R_5	Time (h)	Yield (%)	**15:16**
a	Me	H	Me	*o*-HOC$_6$H$_4$	Cl	12	74	5:1
b	Me	H	Me	CH$_2$Ph	Cl	1.1[b]	100	>95:<5
c	Me	H	Me	CH$_2$Ph	H	1	100	>95:<5
d	H	H	Me	CH$_2$Ph	Cl	1	100	>95:<5
e	Me	H	H	CH$_2$Ph	Cl	8	67	
f	Me	OMe	Me	CH$_2$Ph	Cl	<10 min[c]	100	1:1
g	Me	H	Me	H	Cl	48[d]	0	
h	Me	H	Me	Ac	Cl	(4)[e]	100	>95:<5

[a] All reactions were carried out at 100°C in toluene solution.

[b] This reaction could also be run at 25°C proceeding in 65% yield in 6 days.

[c] This reaction was complete in 12 hours at 25°C, also providing a 1:1 diastereomer mixture.

[d] Starting material was recovered unchanged.

[e] This reaction was carried out at 153°C by heating **14g** in acetic anhydride for 4 hours, effecting both acetylation and cyclization.

group from the nitrogen, we decided to investigate the cyclization of other N-substituted derivatives of **14**, as well as other structurally modified analogs. All of the *N*-furfurylacrylamides **14** were prepared by the analogous sequence of reductive amination and acylation. The results of their thermal cycloadditions are shown in Table I.

A large amount of interesting information concerning these cycloadditions can be derived from a close scrutiny of Table I, as follows. (1) The *N*-benzyl compounds are much more reactive than the corresponding *N*-(*o*-hydroxyphenyl) compound (**14b** versus **14a**) and are more diastereoselective. The structures of the diastereomers were assigned by analogy to **15b**, which was analyzed by X-ray crystallography. (2) The methyl on the chain linking the diene and dienophile greatly accelerates the reaction (reaction of **14b** is complete in 1.1 hours while **14e** is only 67% reacted after 8 hours). This acceleration is probably a special case of the *gem*-dimethyl effect.[9] (3) By raising the electron density of the furan system, one can greatly speed up cyclization (**14f**). Now, however, a 1:1 mixture of diastereomers is formed since the normally favored endo isomer now suffers strong steric interaction with the adjacent methoxy group. (4) Finally, the secondary amide **14g** does not give the desired cycloadduct **15g** (or **16g**) under these conditions, thus confirming Parker's results.[7]

Three interesting points should be made regarding these data. First, the diastereoselectivity is probably due to steric hindrance between the alkyl group R^3 on the chain and the N-substituent (R^4) in the transition state **17x**


12   13

14   15   16

17x   **17n**
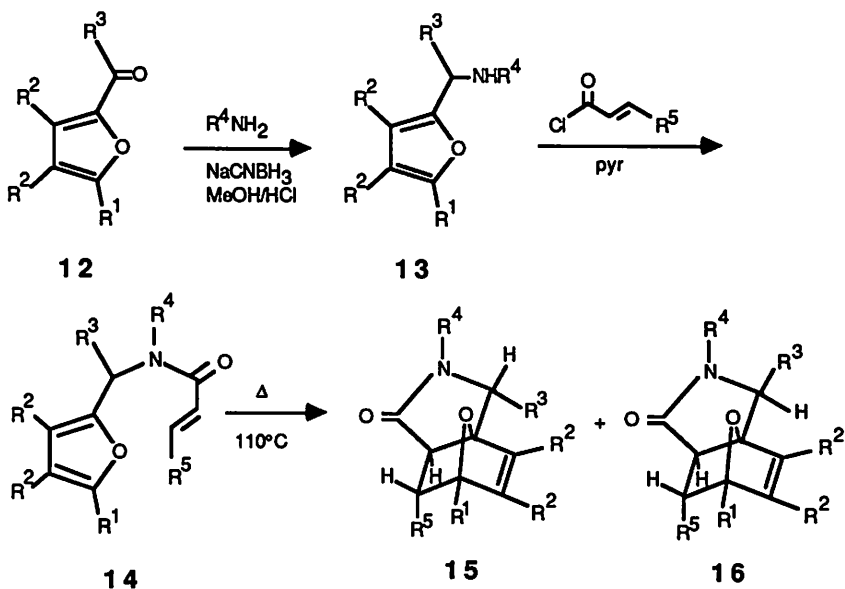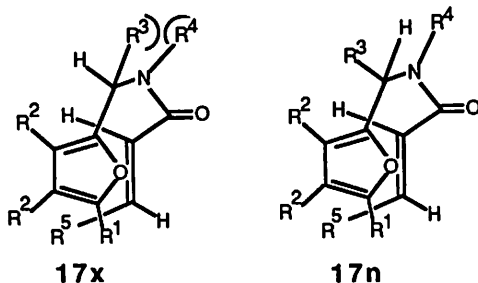
leading to **16**, which is not present in the transition state **17n** leading to **15**. Only when $R^2 = OMe$ does the interaction of R^2 and R^3 in **17n** become sufficient to offset the R^3, R^4 interaction in **17x** and a 1 : 1 mixture results. This diastereoselectivity is of no value in this synthesis since that center of chirality is destined to be destroyed (by reconversion to a ketone), but this could prove useful in other natural product syntheses.

Second, the reason given most often for the reluctance of secondary amides to cyclize is a kinetic one, namely that the ground state greatly prefers the s-trans conformation about the N—CO partial double bond, which cannot cyclize, rather than the s-cis conformation required for cyclization. While this may well be the case, we have now shown that there is also a thermodynamic bias against cyclization of secondary amides. Heating of **14g** gives none of the product **15g**. However, by heating **14g** in acetic anhydride, we can prepare the adduct **15h**, which on hydrolysis (HCl/EtOH) gives **15g**. When **15g** is heated in toluene, it slowly reverts back to **14g**, thus indicating that **14g** is more stable thermodynamically than **15g** and that the reaction is reversible at this temperature. The surprising fact is that the N-substituted cases lie totally on the side of the adducts, while the N-unsubstituted case lies far on the side of the starting furan! The reasons for this difference in stability have not yet been clarified.

Finally, the acceleration of cyclization due to substituents on the connecting chain, while not of great value here, might find significant use in other systems, especially ones which are slow to cyclize. In these cases, a thioalkyl group or dithioacetal unit could be placed on the chain connecting the diene and dienophile to facilitate cycloaddition due to the *gem*-dimethyl effect and then removed after after serving its purpose to regenerate the unsubstituted connecting chain.

To return to the synthesis, we decided to test our key reductive elimination step.[10] The olefin of **15b** was hydroxylated to give **18**, which could be cleaved with sodium in liquid ammonia and THF to give the triol lactam **19** in good yield. Thus we felt that we had a chance of carrying out this important step in later, more functionalized derivatives.
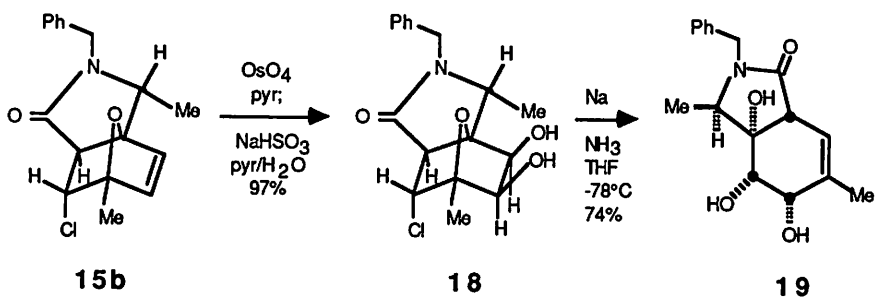
Although **19** has the correct functionality for eventual conversion to our target intermediate **4**, the stereochemistry of the 5,6-diol is opposite to that needed, namely it must be trans to the oxygen at C-7. In order to use this approach for the preparation of a molecule which could lead to **4**, we required a cis hydroxylation of the oxanorbornene system from the more hindered endo direction, an unknown transformation in this system. We attempted to use the Woodward method for cis hydroxylation from the more sterically hindered direction.[11] However, we could only isolate the products of a novel structural rearrangement. Treatment of **15bd** under Woodward's conditions (I_2, AgOAc, aq. AcOH) gave the rearranged products **20bd** in 60% yield, while treatment of **15b** with NBS in aqueous DMSO gave the similar structurally rearranged product **21**, also in 60% yield.[12] The proposed mechanism involves migration of the C-1—C-2 bond to the halonium ion derived from addition of the positive halogen species (I^+ or
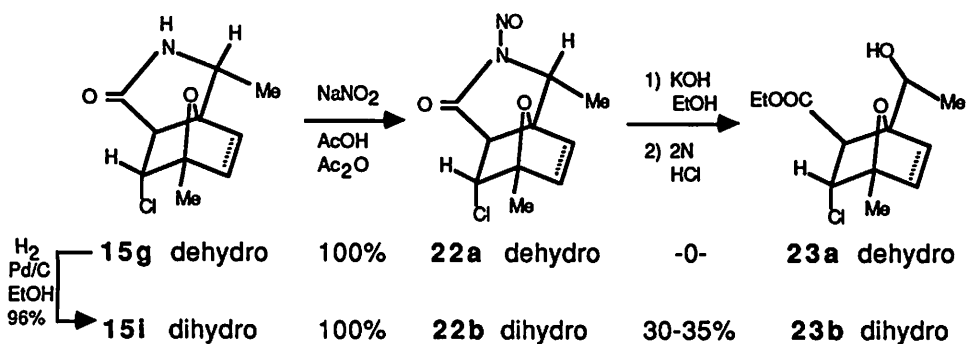
15b R=Me
15d R=H

20bd

20bd

21
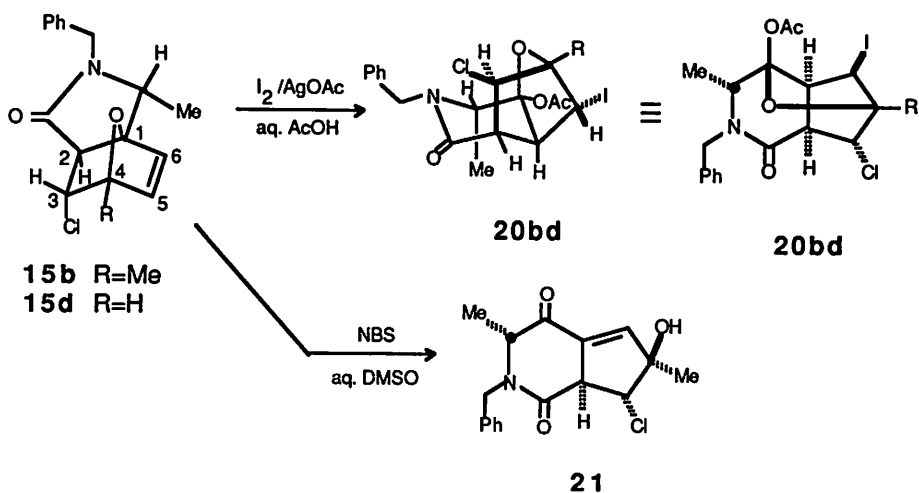
Br$^+$) to the exo face of the olefin, **A**, followed by trapping of the cation of **B** with solvent (AcOH or H$_2$O) to give **20bd** (R' = Ac) or **C** (R' = H). Opening of the hemiketal **C** to **D** and base-catalyzed elimination of HBr would give **21**.[12]
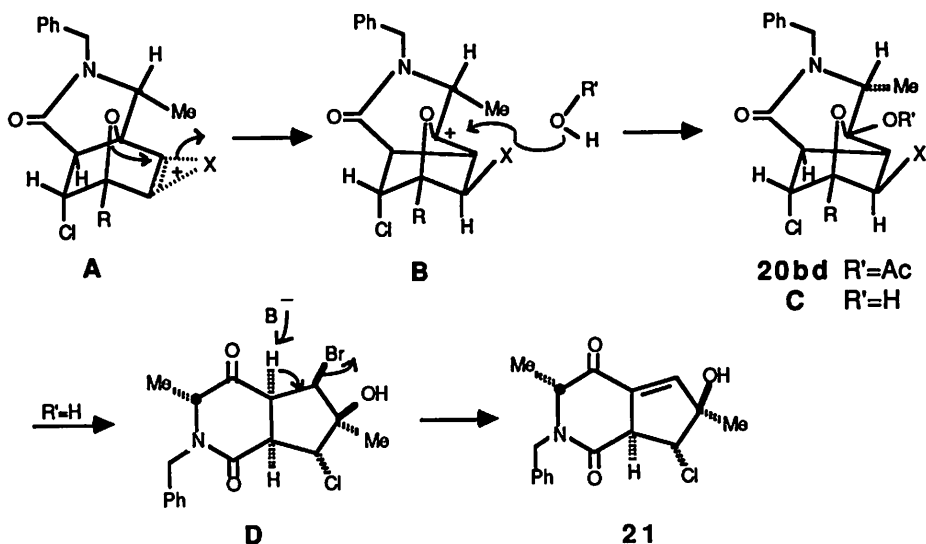

Although these compounds might be of value in the synthesis of other natural products, they were clearly of no use in the construction of intermediates such as **4** for the synthesis of the ivermectin bottom half **3**. There are other potential routes to cis-endo-hydroxylated oxanorbornenes— for example, hydride reduction of the α-diketone derived from oxidation of the diol **18**, from the less hindered exo direction, or perhaps catalytic hydrogenation of the dibenzyloxy analog of **15f** from the exo face. However, we decided to abandon, at least temporarily, all routes to **3** which passed via **4** and to concentrate our efforts on the epoxide route via **6**.

We also examined in this series methods for regeneration of the ketone functionality at what becomes C-8 in the final product. Nitrosation of **15g** and its hydrogenated analog **15i** gave the N-nitroso lactams **22ab** in good yield. Cleavage of these compounds under Mukaiyama's conditions[8b] gave essentially no product in the case of **23a** and only 30–35% of **23b**. Clearly, a better method of ketone regeneration would have to be developed in order to use this approach.

We thought that perhaps the accelerating effect of the methyl on the chain might make it possible to use the ester linkage in the cyclization.

15g dehydro	100%	**22a** dehydro	-0-	**23a** dehydro
15i dihydro	100%	**22b** dihydro	30-35%	**23b** dihydro

Clearly, the lactone of the cycloadducts would be readily hydrolyzed under base-catalyzed conditions to give the hydroxy ester and thence the desired keto ester. However, all attempts at cyclizing the furfuryl β-chloroacrylates **24ab** under thermal or Lewis acid conditions afforded none of the desired cycloadducts **25ab**, giving back only starting materials in the absence of Lewis acids and decomposition in their presence.


24a R=H
24b R=OMe

25a
25b
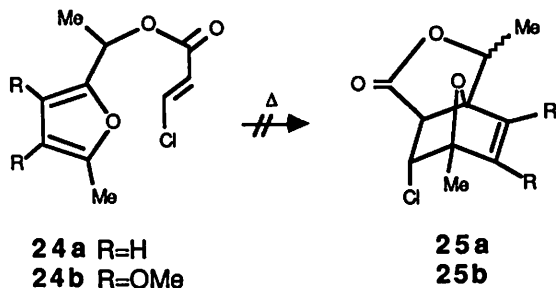
During any total synthesis, you have to step back from time to time and look at the overall sequence to see if, by pushing hard on one tack, you've allowed any foolish or uneconomical procedures or assumptions to slip in. We now did this here and decided that we had, and right at the very beginning too! The first step of the synthesis was the reductive amination of the furyl ketone **12a** to give the amine **15b**. In the first step we had taken the correct oxidation state and reduced it, thereby necessitating a reoxidation step later in the synthesis. It's true that we needed a nitrogen atom to append the acryloyl group to effect the cyclization, but perhaps this nitrogen could be part of an aminal, so that the oxidation state is retained. The aminal **26** was prepared and acylated to give **27ab**, which could be readily cyclized to the tetracyclic adducts **28ab** in excellent yield. Thus we could keep this carbon

12a   **15b**

26   **27a** R = H   1.5 h   **28a**
                27b R = Cl   3.5 h   **28b**
   90%
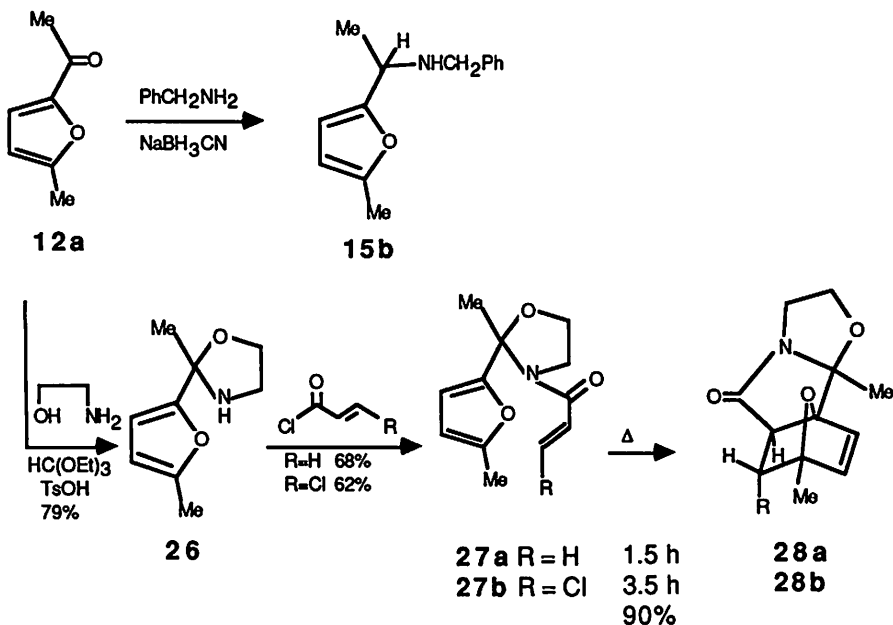
at the ketone oxidation state and still effect the intramolecular Diels–Alder reaction, thereby eliminating the problem of oxidation of the secondary amine to ketone mentioned above.

To continue the approach, epoxidation of **28b** occurred as expected completely from the exo face to give the epoxide **29** in good yield. Hydrolysis–methanolysis of the lactam aminal of **29** proved quite difficult. Although the C—O bond of the aminal was readily cleaved, the lactam was quite resistant to hydrolytic opening, due presumably to a Thorpe-Ingold-like effect (the intermediate amino carboxylic ester would be expected to cyclize very readily since the groups are held very close together). However, under forcing conditions—10% sulfuric acid in methanol at 65°C

28b   **29**   **30**
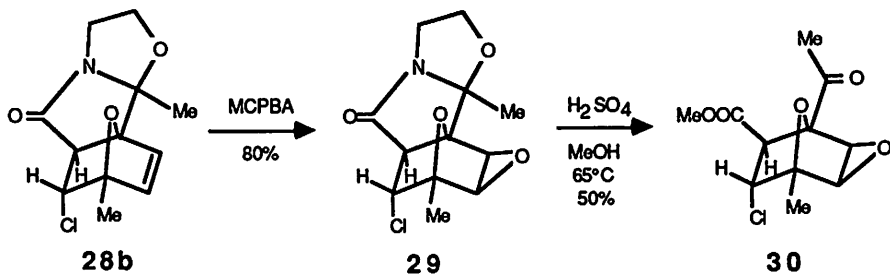
for 14 hours—a 50% yield of the desired ester **30** was obtained. It is somewhat surprising that the strongly acidic conditions do not cause skeletal rearrangement of the epoxide similar to that seen for the halonium ions derived from **15bd**. Perhaps the protonation of the epoxide oxygen occurs syn to the bridging oxygen so that a strong internal hydrogen bond can occur, e.g., **E**. This species would be much less prone to rearrangement since migration of the C—C bond is made somewhat unfavorable due to both resonance and inductive effects.[12]
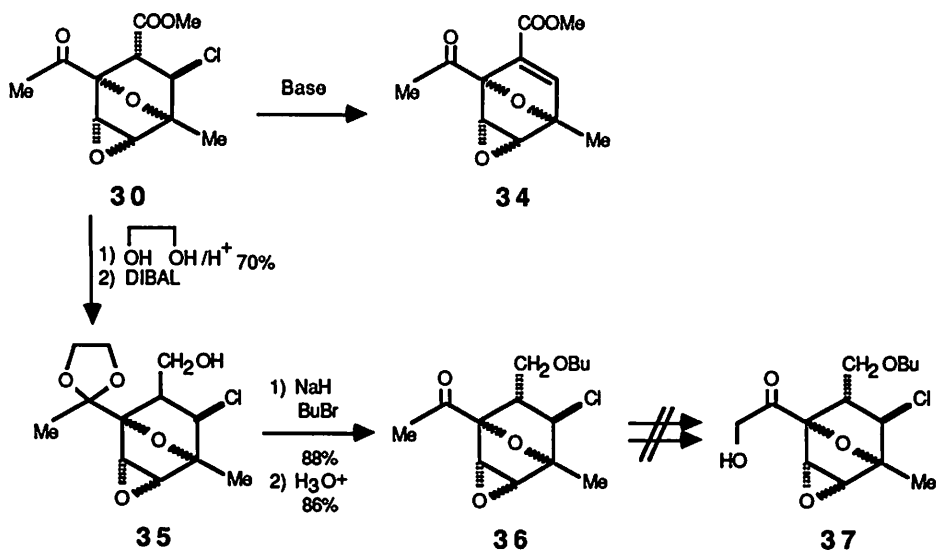

E
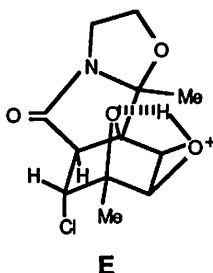
The successful use of simple aminals derived from 2-aminoethanol prompted us to investigate the possibility of preparing optically active material by use of the readily available amino alcohols derived from natural amino acids. The use of L-valinol **31** illustrates this approach. Reaction of **12a** with L-valinol **31** followed by acylation with β-chloroacryloyl chloride furnished a 1.5:1 mixture of diastereomers **32ab** which could be separated chromatographically only with difficulty. The structures of these compounds were assigned on the basis that under the equilibrating conditions, the more stable diastereomer (**32a** with isopropyl cis to methyl and trans to furan) should be the major product.[13] However, thermolysis of the mixture produced a 90% yield of the adducts **33ab**, which could be very easily separated by flash chromatography to give 54% of **33a** and 36% of **33b**. These compounds were then separately converted into the two enantiomers of **30** (**30′** and **30″**) by epoxidation and hydrolysis as described above. The L-valinol can be easily isolated in the workup of the hydrolysis step. Thus L-valinol serves as a recyclable resolving agent for the chromatographic separation of diastereomers. The enantiomer required for the synthesis of the natural products is the minor isomer **30″**, although it could be made the major component by using the unnatural D-amino alcohol in the first step. However, the facility of this resolution and the fact that the undesired cycloadduct **33a** can be reconverted into **12a** and L-valinol **31** by hydrolysis and thermolysis (retro Diels–Alder reaction) make it quite useful for preparing the optically pure material **30″**.
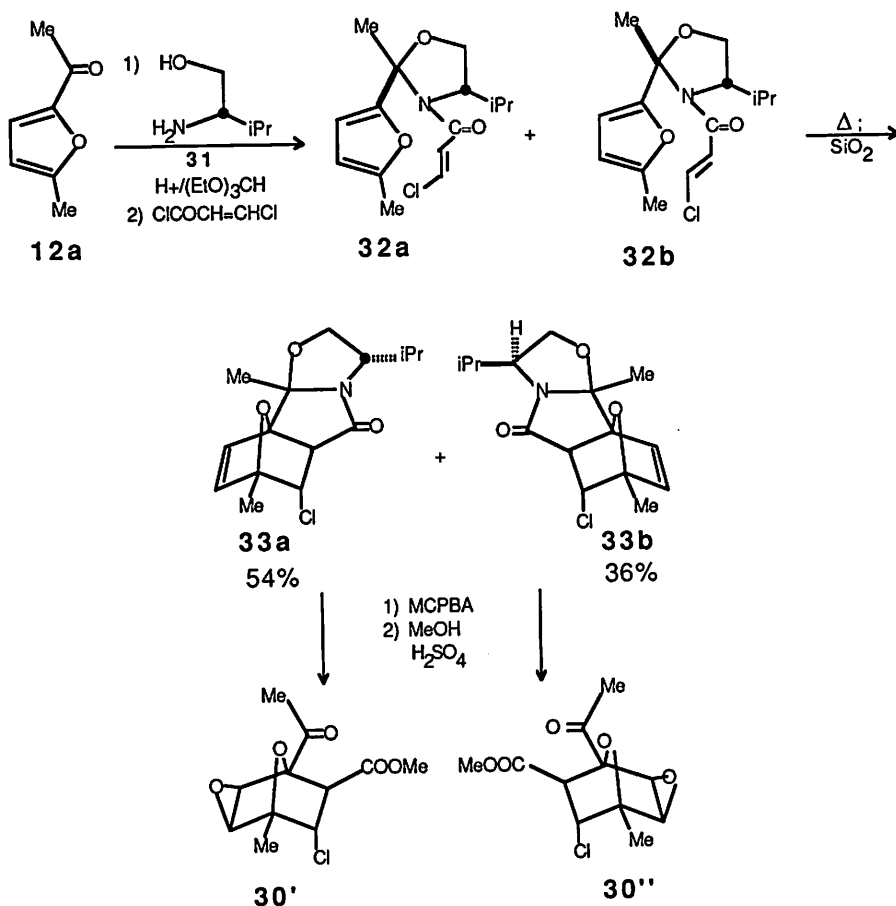
To return to the synthesis, attempts to hydroxylate the methyl ketone of **30** under basic conditions were unsuccessful due to rapid elimination of HCl from the β-chloroester leading to the α,β-unsaturated ester **34**. Therefore the ester was reduced to the primary alcohol, which was protected as its benzyl ether **36** in four steps via the hydroxy ketal **35**. However all attempts to α-hydroxylate **36** via its enolate or silyl enol ether failed to afford the desired α-hydroxy ketone **37**, giving either recovered **36** or decomposition, depending on the conditions. The reasons for our failure to produce **37** in this matter are not well understood and perhaps with more investigation might be overcome. But at this juncture we were left with no choice but to abandon this particular route in favor of the following alternative.

Since there were difficulties associated with α-hydroxylation of the acetyl group at a late stage in the synthesis, we pursued the alternative of per-

forming this functionalization at the very outset of the synthesis. Treatment of **12a** with 1 equivalent of LDA in THF followed by trapping of the enolate with trimethylsilyl chloride produced the silyl enol ether **38**, which was oxidized with MCPBA to produce after hydrolysis in 90% yield the α-hydroxy ketone **39**. Ketalization with ethylene glycol afforded **40**, which was then benzylated under the normal conditions to give **41** in 54% yield for the two steps. A final acidic hydrolysis (95%) furnished the desired α-benzyloxy ketone **12b**, thus making it available in 46% overall yield from **12a**.[13]
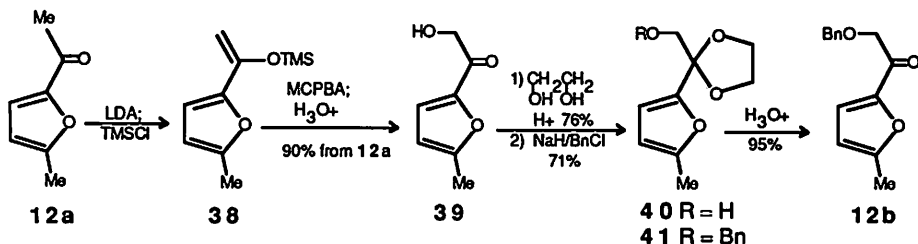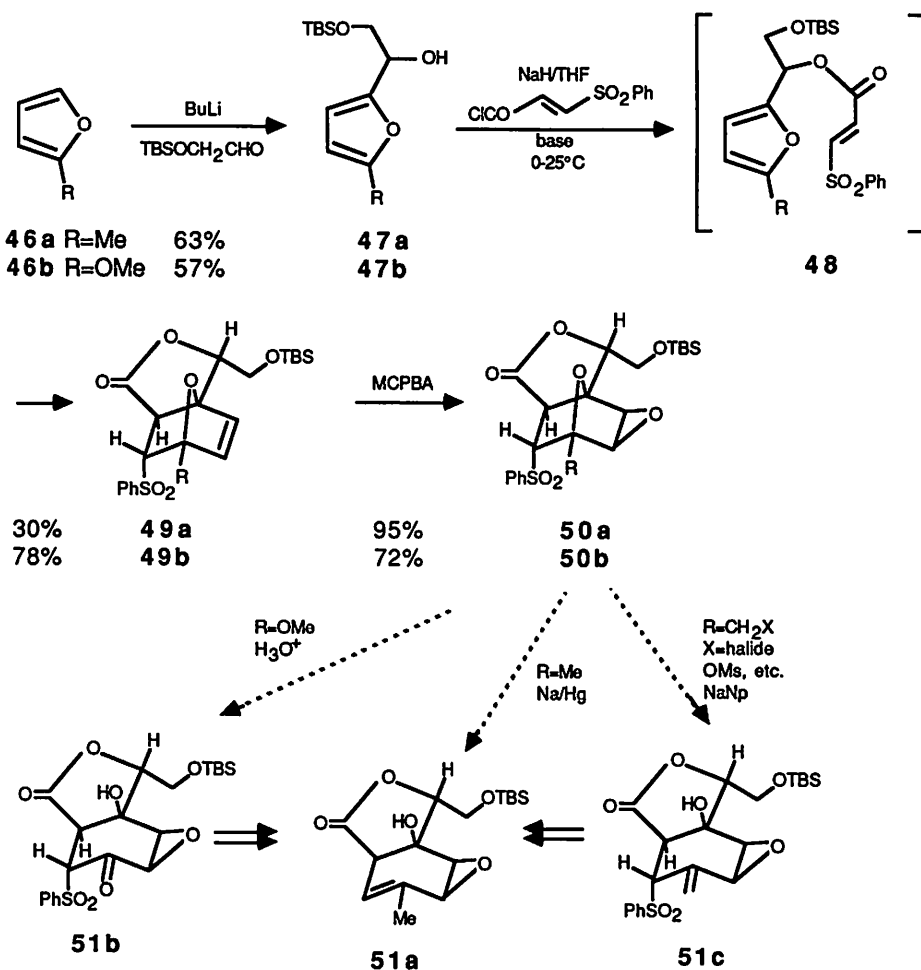

Reaction of **12b** with 2-aminoethanol, triethyl orthoformate, and *p*-toluenesulfonic acid produced in 97% yield the aminal, which was immediately acylated with β-chloroacryloyl chloride to furnish **42** in 60% yield. Refluxing a solution of **42** in toluene for 3 hours produced a 90% yield of the cycloadduct **43** as a single stereoisomer. Epoxidation of the olefin of **43** with
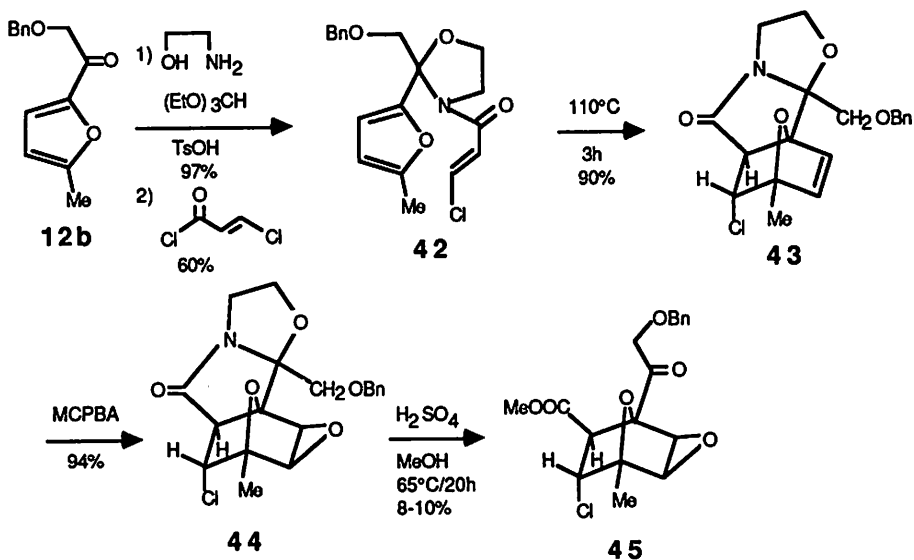
1 equivalent of MCPBA in dichloromethane at 0°C furnished in 94% yield the epoxide **44**, which was then subjected to acidic methanolysis (10% H_2SO_4 in MeOH, reflux, 20 hours) to afford the desired epoxy ester **45** in a yield of only 8–10%, although occasionally higher yields (~35%) were obtained. Our inability to carry out this hydrolysis consistently in reasonable yield was the death for all routes proceeding via intramolecular N-furfurylacrylamide cycloaddition and prompted us to seek totally different approaches.

Before leaving this area completely, I want to point out some interesting preliminary results which may permit the resurrection of this approach.[14] Metalation of the 2-substituted furans **46ab** with n-butyllithium followed by trapping with the silyloxy acetaldehyde produces the alcohols **47ab**. Reaction of the anion of these alcohols with E-β-phenylsulfonylacryloyl chloride afforded the intramolecular Diels–Alder adducts **49ab** directly via the esters **48ab**. Thus if one activates sufficiently the β-carbon atom of the acrylate system, then ester linkages can be utilized successfully in these internal cycloadditions. In both cases a mixture of diastereomers is obtained with the endo silyloxymethyl isomer shown as the major component (structure again assigned by X-ray crystallographic analysis of **49a**). These can be easily separated by flash chromatography and the more abundant endo isomer epoxidized to give **50ab**. We are attempting to utilize these sulfones to produce the hydroxylactone **51a** as follows: reductive elimination of **50a** should give directly **51a**, while hydrolysis of **50b** should produce **51b**, which could potentially be used to prepare **51a**. Finally, the analog of **50** with

46a R=Me 63%
46b R=OMe 57%

47a
47b

48

30% 49a
78% 49b

95% 50a
72% 50b

R=OMe
H₃O⁺

R=Me
Na/Hg

R=CH₂X
X=halide
OMs, etc.
NaNp

51b

51a

51c

R = CH₂X, where X is an easily reduced group, might also be reductively eliminated to give the exocyclic olefin **51c**, which might be convertible to **51a**. Results in this area will be reported in due course.[14]

## IV. Background for Choosing Alternative Approach

From the very first time I examined the structure of the ivermectin bottom half **3**, I had always tried to come up with the simple disconnection shown, namely in the formal sense, a Diels–Alder cycloaddition between the dienophile **52** and the diene **53**. As drawn, this would give the epimer at C-5

but, as discussed earlier, we felt that this stereochemistry could be inverted late in the synthesis. However, this disconnection always seemed quite problematic for the following reasons. Through the work of many synthetic chemists (Danishefsky, Suzuki, Normant, Negishi, Trost, Zweifel, Kishi, and others), we can now prepare almost any diene one can imagine and therefore the preparation of **53** should present no great difficulty. The problem arises with the dienophile for this cycloaddition, the furanone **52**. Although the electron-withdrawing carbonyl group lowers the electron density of the double bond, the two ethereal oxygen atoms make the olefin electron-rich and therefore presumably much less reactive in the normal electron demand Diels–Alder reactions. There are several examples with α-acyloxy or α-silyloxy enones reacting in normal cycloadditions but very few with β-alkoxy enones and none to my knowledge with both α and β-alkoxy substituents. In effect, the furanone **52** is too electron-rich for the cycloaddition with the diene **53**. Because of this fact, we chose to shelve this approach at the beginning of our studies.

   **3**   **5 2**   **5 3**   **5 4**
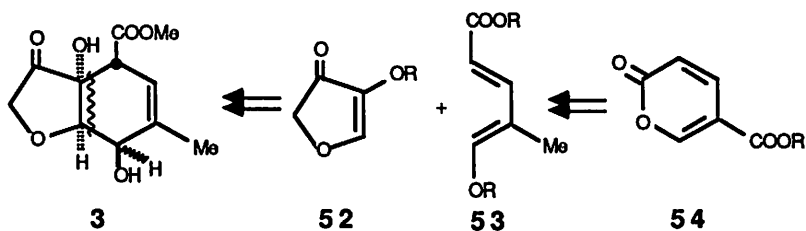
As often happens in a large research group where students are working on widely different projects, another ongoing project aimed at a totally different molecule gave us, at least theoretically, a solution to the problem of the use of the electron-rich dienophile **52** in this approach to **3**. The real trick was in getting the cross-fertilization of research ideas to occur, to realize that by making fairly small changes, we could apply the chemistry involved in a completely different project to this approach to the ivermectin bottom half **3**. I want to briefly summarize the work we had been doing on the cycloaddition of coumalates **54** with electron-rich olefins to give the reader an indication of why we chose this molecule as a replacement for the diene **53** in our successful approach to **3**.

Sometime earlier we had carried out cycloadditions with electron-rich 6-alkoxy pyrones[15] in approaches to the anthracycline antitumor agents. More recently[16] we had investigated the cycloadditions of benzopyrones with electron-rich olefins as a route to AB-ring analogs of the same natural products. However, the project ongoing in the group at the time of the
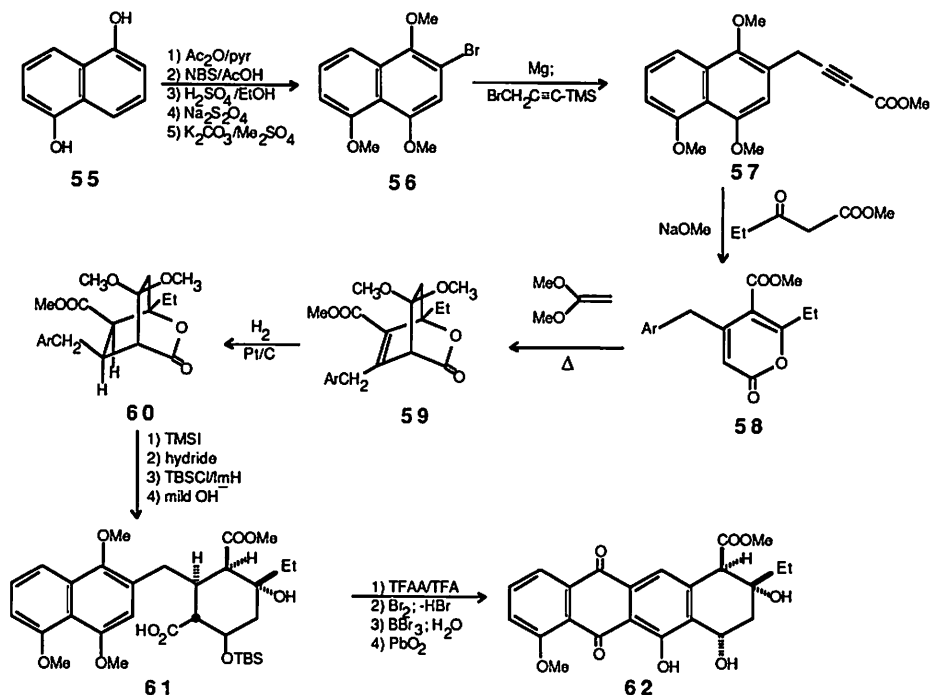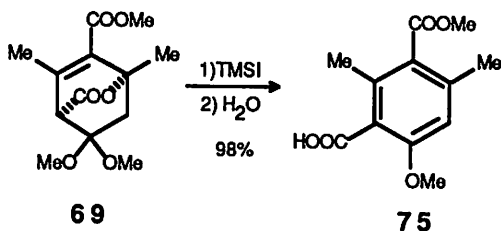
SCHEME 2

ivermectin work involved the approach to aklavinone **62** outlined in Scheme 2.[17] The key step of this sequence involved the cycloaddition of the 4,6-disubstituted coumalate **58** (prepared from **55** as shown) with dimethyl ketene acetal to give the bicyclic lactone **59**, which would then be reduced to give **60** (and thence **62**). Before beginning chemistry on the real system, we carried out some model studies.[18] Behringer and Heckmaier[19] had reported in 1969 that methyl coumalate (**63**) reacted with dimethyl ketene acetal to give the bicyclic lactone **64**. However, the corresponding lactone **66** could not be isolated from the cycloaddition of the 4,6-dimethyl derivative **65** with diethyl ketene acetal; rather it lost carbon dioxide and ethanol to give the aromatic product **67**. By carefully controlling the temperature of this reaction, we were able to isolate good yields of the corresponding lactone **69** from the reaction of the corresponding methyl coumalate **68** with dimethyl ketene acetal. However, if the temperature is raised slightly, the aromatic ester **70** becomes the major product. This lactone **69** could be hydrogenated to give the saturated lactone **71** in fair yield under vigorous conditions. This
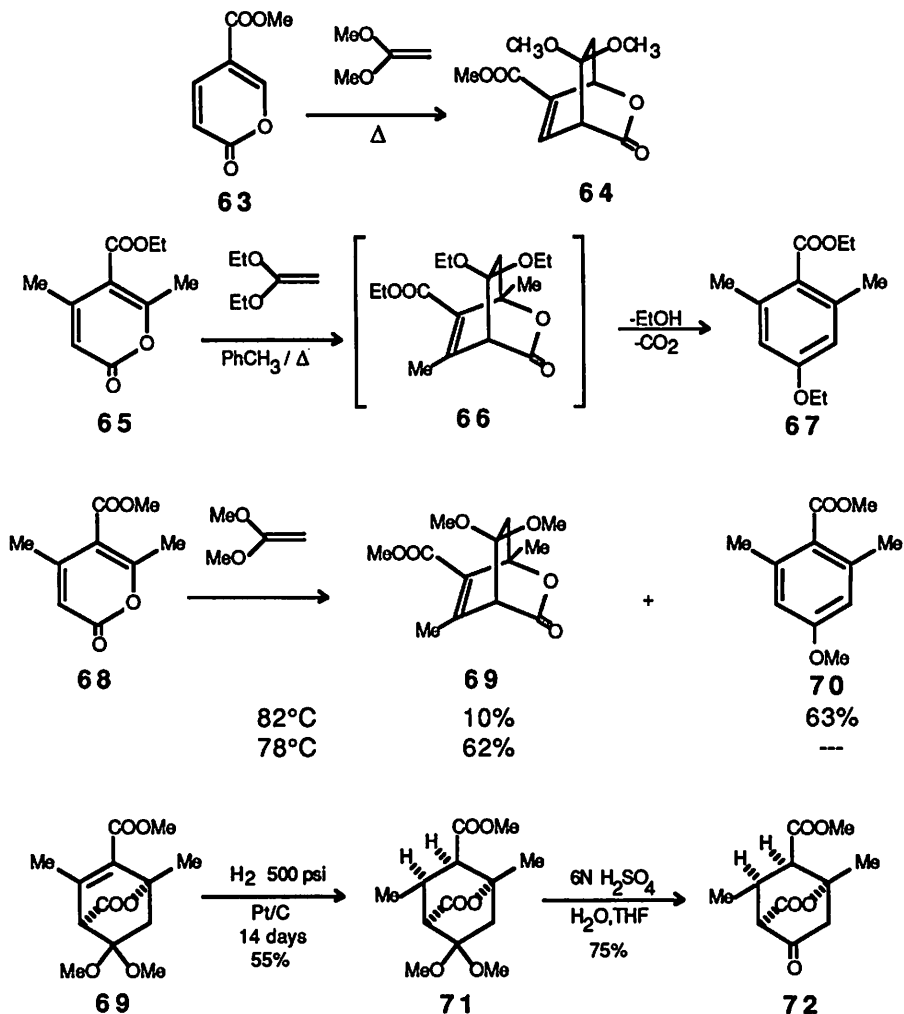
hydrogenation is difficult due to severe steric hindrance of the tetrasubsti-
tuted olefin (although the strain of the bicyclic system should increase its
reactivity) and the electron-withdrawing ester on the double bond. But
reaction at 500 psi over 14 days gave a reasonable yield of **71**. The ketal of
the lactone **71** could then be hydrolyzed to produce the keto lactone **72**.
Attempted hydrolysis of olefinic lactone **69** gave predominately the *p*-
hydroxybenzoate **73** with some of the *p*-methoxybenzoate **70** also being
formed, indicating that hydrolysis to the desired ketone **74** is probably
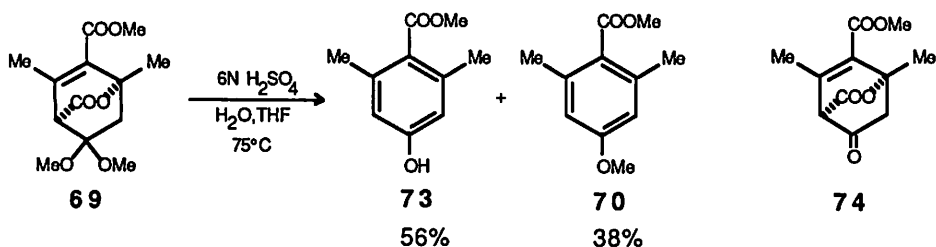
occurring but that it is too unstable with respect to enolization and loss of carbon dioxide to be isolated. It is interesting that the use of trimethylsilyl iodide for this hydrolysis produced, in nearly quantitative yield, the penta-substituted aromatic ester **75**, presumably by preferential reaction with the lactone, cleavage of the tertiary allylic C—O bond, deprotonation, and loss of methanol. This may prove to be a useful method for the synthesis of pentasubstituted aromatic compounds and potentially (by the use of 1,1-dimethoxyalkenes in place of the ketene acetal) even hexasubstituted aroma-tics.


This approach to aklavinone **62** eventually foundered on our inability to reduce the double bond in a very closely related bicyclic lactone. Thus the cycloaddition of **76** (a close analog of **58**, prepared as outlined in Scheme 2) with dimethyl ketene acetal afforded a 54% yield of the bicyclic lactone **77** (with 28% of the aromatic ester **78** also being produced). However, all attempts to reduce the olefin of **77** furnished only the debenzylated phenol **79** with no evidence for double-bond hydrogenation. Presumably the extra steric hindrance of an ethyl group (versus a methyl in **69**) and a naphthyl-methyl group in **77** (also versus a methyl in **69**) causes the double bond to be too unreactive to hydrogenate under these conditions. But this unsuccessful foray into aklavinone synthesis via coumalate–ketene acetal cycloadditions suggested a potentially useful alternative in the ivermectin series.

To return to the synthesis of the ivermectin bottom half **3**, we now
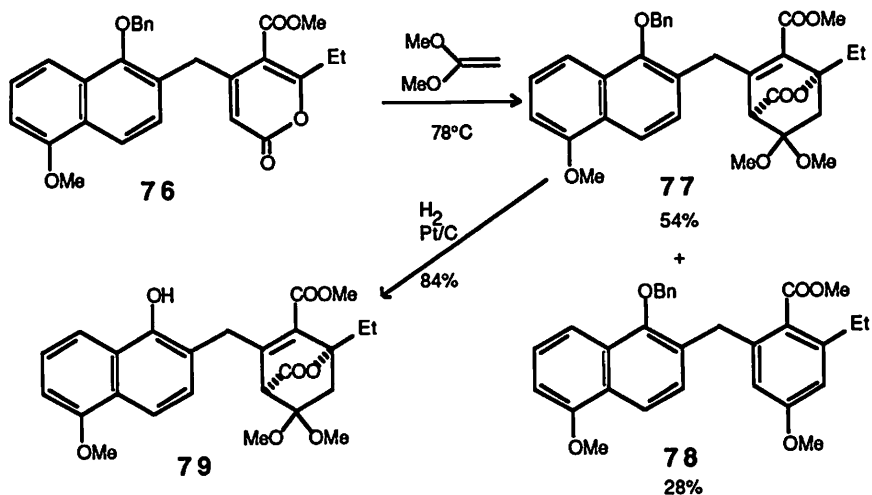
proposed that reaction of a coumalate **54** with the electron-rich olefin **52** might be expected to proceed based on the analogies given above. However, the furanone **52** is not a ketene acetal (as our earlier dienophiles were) and thus might be expected to be somewhat less reactive. More serious, however, was the fact that it was a 1,2-dioxygenated olefin rather than a 1,1-dioxygenated olefin and thus could lead to a mixture of regioisomers. Behringer proposed that the ketene acetal–coumalate cycloaddition was a
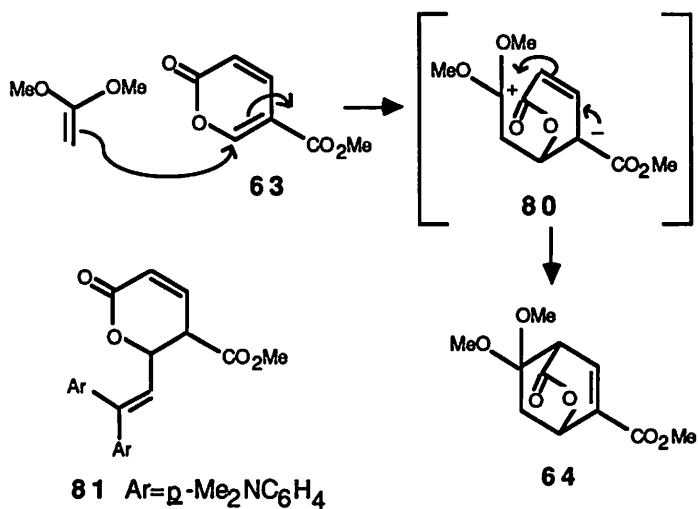
two-step process (rather than a concerted cycloaddition) proceeding via a zwitterionic intermediate, e.g., **80**, which then closes to the bicyclo[2.2.2] octane system **64**. The nonsynchronous mechanism was supported by the isolation of **81** in 92% yield from the reaction of the corresponding 1,1-diarylethylene with **63**.[19] In the reaction of **52** with **54**, two intermediates **82ab** are possible. An unbiased observer would clearly predict the latter, **82b**, to be the more stable since although both **82ab** are α-oxygenated carbonium ions, the former, **82a**, has the destabilization of a carbonyl group (with δ+ on the carbon atom) α to the positive charge. Therefore this route seemed destined to lead to the regioisomer of **3** via **83b** rather than the correct natural subunit via **83a**. Even if the cycloaddition is concerted (rather than proceeding via a zwitterionic intermediate), one would make the same prediction based on partial formation of bonds in the transition state. Thus wherever we have invoked a zwitterionic intermediate, one could equally well substitute an asymmetric transition state with nonsynchronous bond formation.
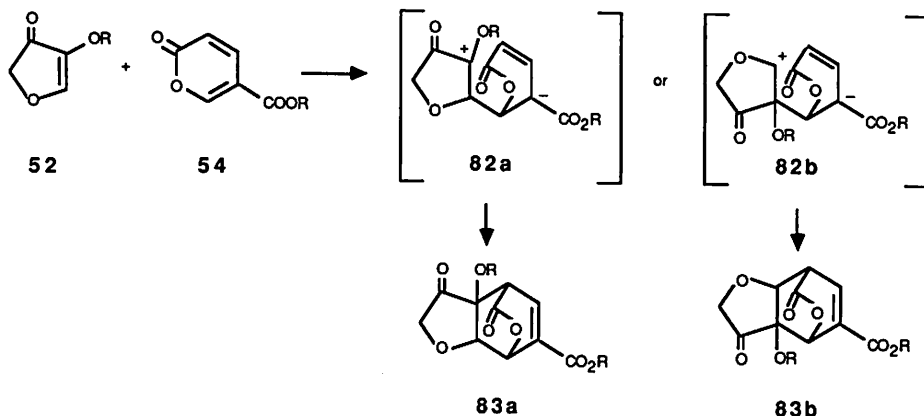

Faced with this regiochemical difficulty, we suggested a small alteration in the dienophile which might alleviate the problem. It is true that we eventually need a carbonyl at what becomes C-8 of **3** but it doesn't have to start out life that way. For example, it could be any type of protected carbonyl and, in particular, an enol ether, e.g., the 3,4-dialkoxyfuran **84**. Now an analysis of the proposed zwitterionic intermediates **85ab** of the cycloaddition of **84** with **54** suggests that the desired regioisomer **85a** would be the more stable due to the increased resonance stability of the carbonium ion. One would then expect **86a** to be the major regioisomer formed. Thus was born our alternative, ultimately successful, approach to the synthesis of **3**.
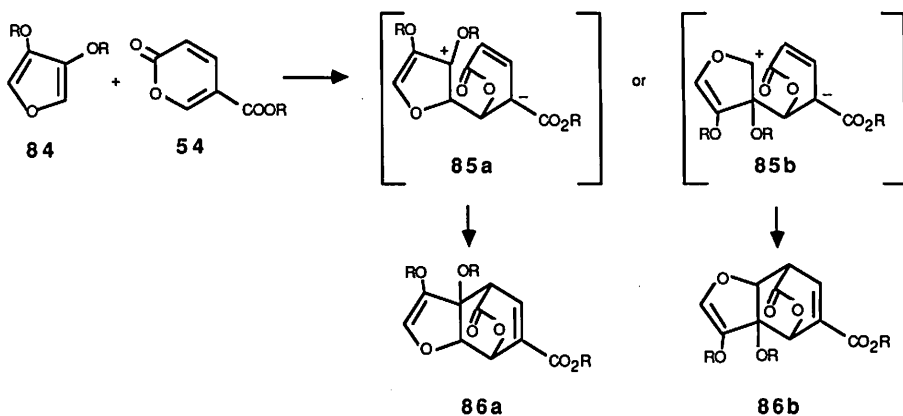
V. Furan–Coumalate Diels–Alder Approach[20]

There are times when you hope that your co-worker has read everything the literature has to offer concerning a certain key reaction to learn not only the directly related but also any ancillary information. And there are times when you hope that your co-worker will take your prediction of sure success for a certain reaction on faith and will not hunt up discouraging or contradictory counterexamples in the literature (which might weaken his resolve to force the reaction to work). The furan–coumalate cycloaddition was a clear example of the latter. Although there was good precedence in our own work for the reaction to occur in the desired manner, e.g., **84** acting as dienophile and **54** serving as diene to give **86a**, there was equally good precedence for the alternative reaction mode, namely **84** as diene and **54** as dienophile to give a completely different cycloadduct, the 7-oxabicyclo [2.2.1]heptene **87**. Several groups [21] had carried out cycloadditions of the
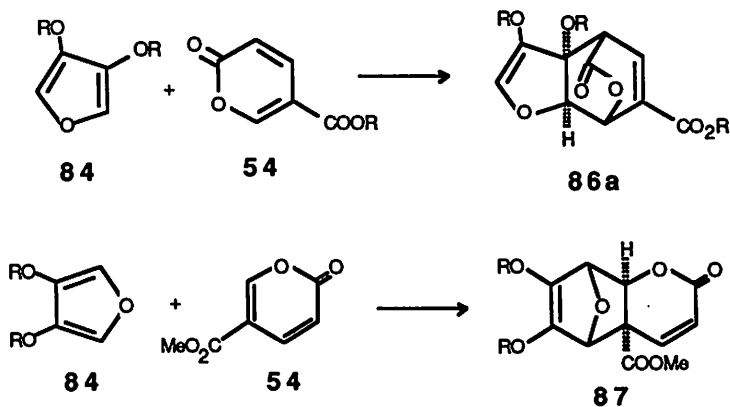
latter type with coumalates **54** and several simple dienes, e.g., butadiene, isoprene, and 2-ethoxybutadiene **88abc**, to give the adducts **89abc**. Thus a strong argument could be made, based on literature precedent, that the 3,4-dialkoxyfuran would serve as diene rather than dienophile versus coumalate and lead to **87** rather than the desired **86a**. Only experiment could settle this question of chemoselectivity.

88a X = H	**54**	**89a X = H**
88b X = Me		**89b X = Me**
88c X = OEt		**89c X = OEt**
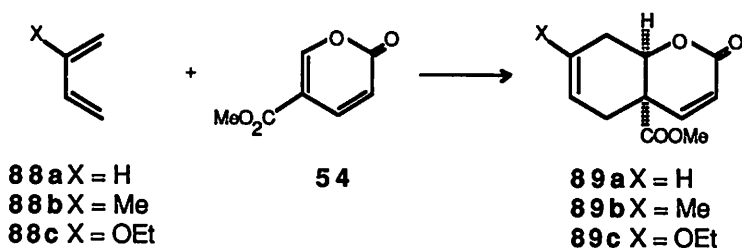
Therefore, there were four possible problems with the reaction of **84** with **54**: (1) chemoselectivity: would **86a** or **87** be favored? (2) regioselectivity: would **86a** or **86b** be favored? (3) stereoselectivity: we have not even discussed endo versus exo selectivity of the desired mode of cycloaddition; and finally (4) the crucial question of reactivity, namely, would **84** and **54** react at all? Consider that in this reaction the aromaticity of two nonbenzenoid aromatic systems must be broken in a single thermal reaction under mild conditions. It might well have been the case that the loss of resonance energy in the transition state was too great to permit the reaction to occur at all.

As it turned out, we won on three of the four possible problems and tied on the last one. The two components *reacted*, with the right *chemoselectivity* and complete *regioselectivity* but with no *stereocontrol*. We tested the reaction first on a model system, namely the reaction of 3,4-dimethoxyfuran **90**[22] with methyl

90   **63**   MeOH
                            Δ /2h
                            52%
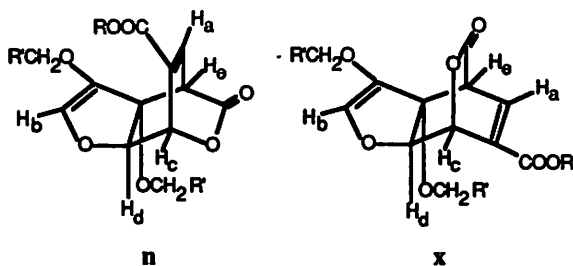

91n   **91x**
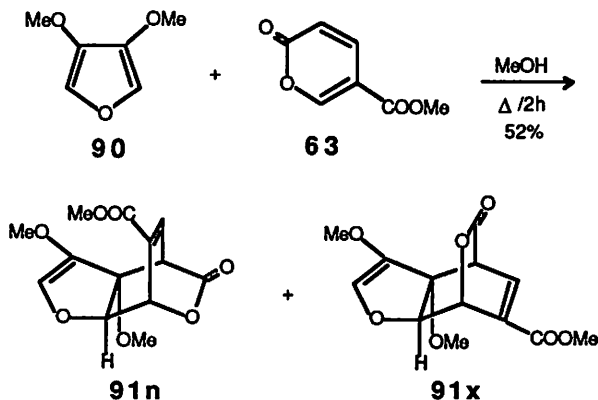
coumalate **63**.[23] Refluxing a solution of these two components in methanol gave, after silica gel chromatography, the two pure stereoisomers **91nx** in approximately equal amounts in a combined yield of 52%.

The high-field ^{1}H NMR spectra of the isolated isomers (Table II) clearly indicated that the isomers possessed the same regiochemistry and differed only in their stereochemistry. This was obvious from the splitting patterns of H_c and H_e, the protons α to the oxygen and carbonyl of the lactone, respectively. H_c appeared as a doublet of doublets, coupled both to H_d and via allylic coupling to H_a, while H_e appeared as a simple doublet in each isomer. This could be the case only if the cycloadditions had occurred with the expected regiochemistry as shown. The stereochemistry of the adducts could not be determined simply from their NMR spectra. However, the less polar fraction from the chromatography, the exo isomer **91x**, proved to be nicely crystalline, so its structure could be assigned as exo by a single-crystal X-ray crystallographic analysis.

The reasons for the chemoselectivity are not obvious. One reasonable
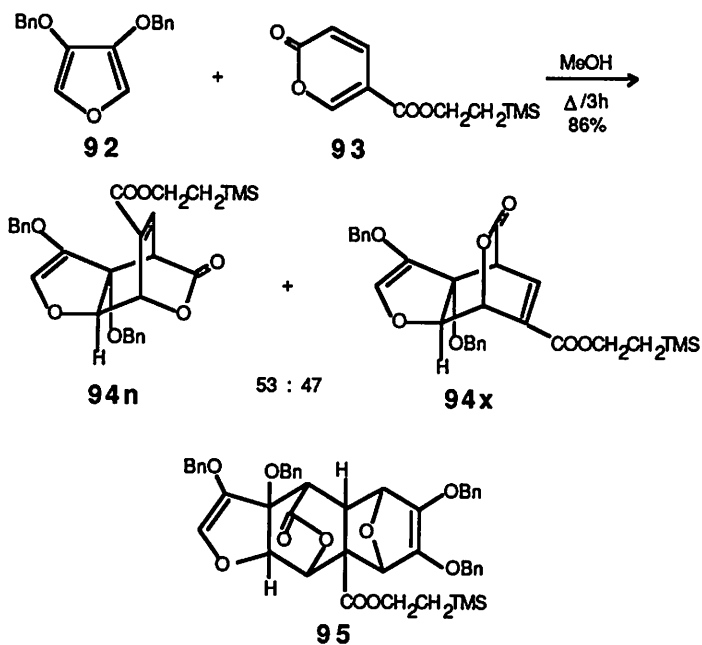
TABLE II

SELECTED ^{1}H NMR DATA FOR CYCLOADDUCTS[25]

n   x

	Compound			
	91n	**91x**	**94n**	**94x**
R	Me	Me	$(CH_2)_2$TMS	$(CH_2)_2$TMS
R'	H	H	Ph	Ph
H_a	7.26	7.35	7.17	7.30
H_b	5.95	6.20	6.01	6.25
H_c	5.79	5.84	5.78	5.84
H_d	4.77	4.33	4.81	4.39
H_e	4.00	4.12	4.17	4.27
J_{ae}	6.75	6.1	6.85	6.2
J_{cd}	4.7	2.0	4.7	2.2
J_{ac}	2.4	1.75	2.3	~1.0

hypothesis is that with these particular reagents, both cycloaddition reactions are not concerted but rather proceed via the same zwitterionic intermediate **85a**, which can then close reversibly to either **86a** or **87**. The ratio of products would then be determined by thermodynamics, namely the difference in the stability of the two structural isomers. One would predict that the bicyclo[2.2.2]octene system of **86a** would be much more stable than the bicyclo[2.2.1]heptene system of **87**, and thus **86a** would be expected to predominate in the thermodynamic equilibrium.[24]
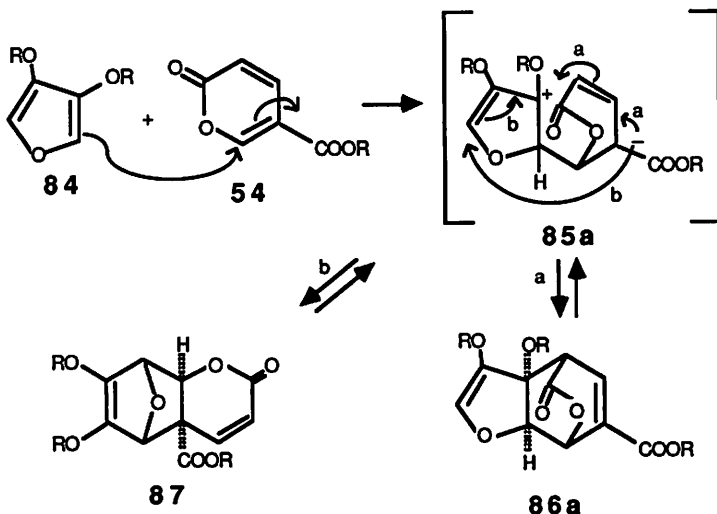

The isolation of only the desired regioisomers implies that our original proposal concerning the stability of the zwitterionic intermediates **85ab** (or the corresponding asymmetric transition states) must have some validity. The fact that a 1 : 1 mixture of stereoisomers is obtained is not surprising, since there is reasonable secondary orbital overlap in both the endo and exo transition states.

Now that the key step of the synthesis had been carried out successfully in a model series, we turned to preparing the starting materials for the real system, choosing 3,4-bis(benzyloxy)furan **92** and 2-(trimethylsilyl)ethyl coumalate **93** as the two components. The furan **92** was prepared in five steps from diglycolic acid by a slight modification of the literature route,[22] while the coumalate **93** was made in three steps from inexpensive DL-malic acid via coumalic acid and its acid chloride.[23] Reaction of **92** and **93** in refluxing methanol for 3 hours gave a 1 : 1 mixture of **94n** : **94x** in 38% yield with approximately 20% of a 2 : 1 furan : pyrone adduct being formed for

BnO OBn

+

COOCH$_2$CH$_2$TMS

MeOH
Δ/3h
86%

92   **93**

COOCH$_2$CH$_2$TMS

BnO

O

+

BnO

O

O

O

OBn

H

COOCH$_2$CH$_2$TMS

OBn

H

94n   53 : 47   **94x**

BnO OBn H

OBn

OBn

H

COOCH$_2$CH$_2$TMS

95

which the structure **95** (mixture of stereoisomers) has been assigned. This latter compound **95** is presumably formed by a Diels–Alder addition of the electron-rich furan **92** to the strained acrylate unit of the initial cycloadducts **94nx**. However, a simple modification of the reaction conditions as follows permitted us to overcome this obstacle. Refluxing a methanol solution containing 10 equivalents of **93** and 1 equivalent of **92** for 3 hours followed by silica gel chromatography afforded an 86% yield of **94n** and **94x** in a ratio of 53 : 47 with only a trace of **95** being produced. In addition, this simple chromatography returned 86% of the unreacted coumalate **93** in pure form for use in further cycloadditions. The structures of the endo and exo adducts **94n** and **94x** were assigned by the close similarity of their ^{1}H NMR spectra to those of **91n** and **91x**, respectively, especially the coupling constants of H$_c$ and H$_e$ (Table II).

Although both stereoisomeric adducts **94nx** are potentially useful intermediates for the synthesis of **3**, the possible difficulties associated with isomerization at C-2[26] led us to initially examine only the conversion of the endo adduct **94n** to **3**. It should be pointed out that this readily available compound **94n** possesses the entire molecular skeleton of the desired target **3** with functionality at all the necessary positions but with two major problems, namely an ester at C-4 instead of a methyl group and the incorrect stereochemistry at C-5.
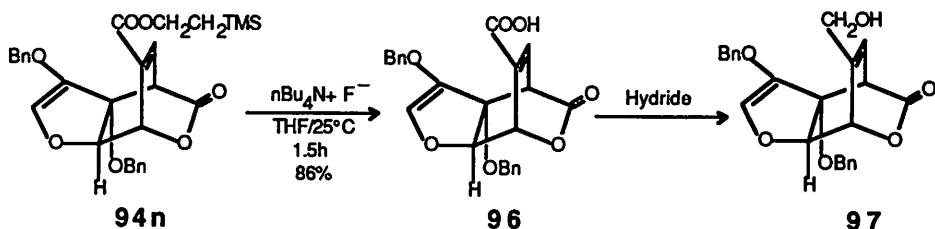
We first corrected the functionality at C-4 as follows. Fluoride-promoted hydrolysis of the silylethyl ester of **94n** furnished the crystalline acid **96** in 86% yield. Many methods were attempted to reduce this acid or the corresponding silylethyl and methyl esters to the desired allylic alcohol **97**, including the following: borane (and several complexed boranes) on the acid **96**; sodium and zinc borohydride on the derived mixed anhydride **98**; lithium ethoxyaluminum hydride on the ester **94n**; DIBAL on the methyl ester; and lithium triethylborohydride on various esters. Although in a few cases (e.g., the first two mentioned above) we could obtain low yields of **97** (20–25%), the preferred reaction pathway generally involved 1,4-addition of hydride to the acrylate moiety to produce an intermediate carbanion **99**, which then opened the strained lactone via β-elimination to give ring-opened allylic alcohols such as **101**, with either an acid or hydroxymethyl function at
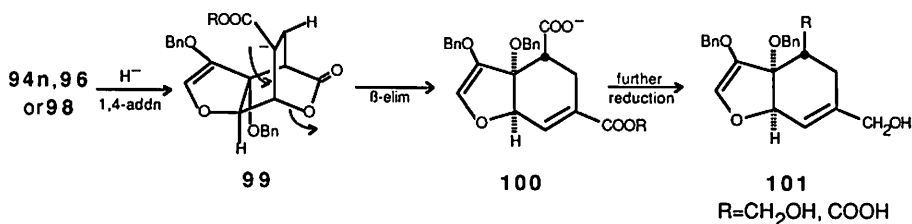
C-2. While attempting to find other reduction methods to overcome this difficulty, we decided to try a different approach. Since we eventually wanted a methyl group at C-4 of **3**, we wondered if we could use a pyrone in the initial cycloaddition which already had a methyl group at C-5 of the pyrone. For this reason we prepared several 5-methylpyrones **102a–e**, the parent and several analogs with electron-withdrawing substituents at C-3 (in order to stabilize the full or partial negative charge of the zwitterionic intermediate such as **85a**). The preparation of these compounds is shown in Scheme 3. However, reaction of **102a–e** with **92** in methanol or toluene at various temperatures up to reflux with or without Lewis acids gave none of the desired cycloadduct **103**. Without Lewis acid, starting materials were recovered; with Lewis acids, the pyrone was recovered but the furan was
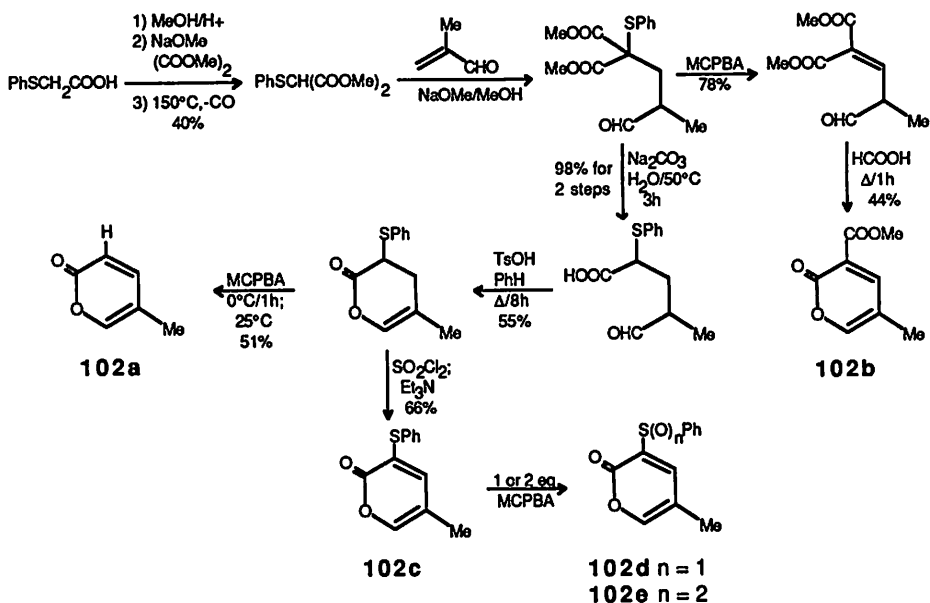
SCHEME 3
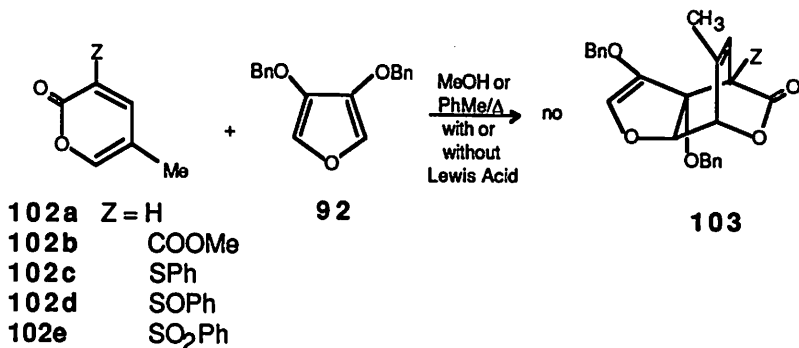
decomposed. Thus it seems that if C-5 of the pyrone bears an electron-donating group, even a methyl group, production of the desired cycloadduct, e.g., **103,** is totally suppressed.

It should be pointed out that even if this alternative approach had worked, the overall savings, in terms of the total number of steps in the synthesis, would really have been small. The silylethyl coumalate **93** is available in three steps from malic acid, while the 5-methylpyrones **102a–e** require anywhere from six to nine steps to prepare. Thus the benefit of not having to

96 → **98** → **97 10%**

+

104 50%
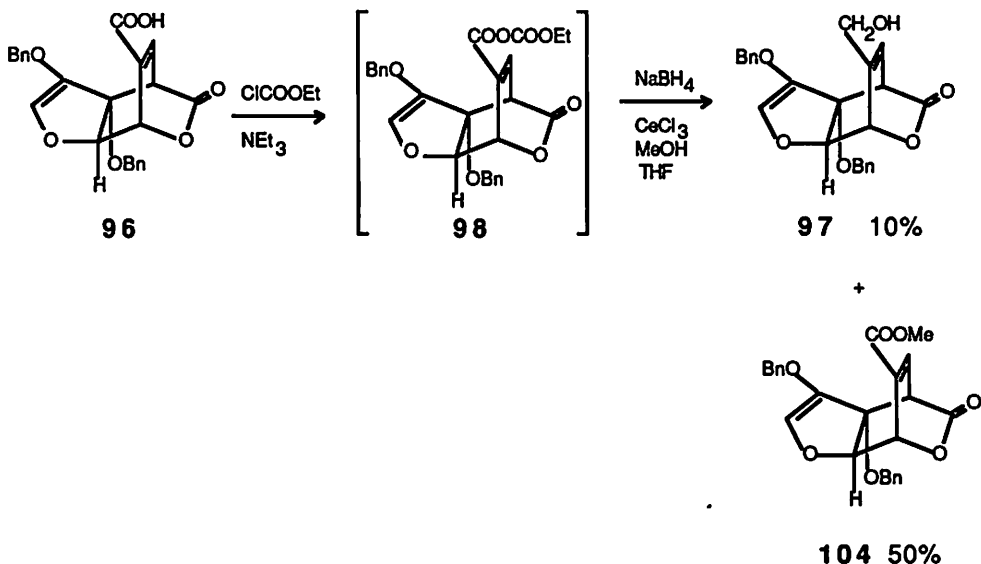
convert ester to methyl would have been offset by a longer sequence in making the starting materials.

The solution to our problem of selective reduction came from a modification of the work of Luche[28] on the 1,2-reduction of enones using sodium borohydride in the presence of trivalent lanthanide salts. Although Luche has not looked extensively at other functionalities, we thought that the principle of modifying the borohydride reagent to favor 1,2- over 1,4-reduction might apply as well to other α,β-unsaturated carbonyl or carboxyl groups. Therefore we treated the mixed anhydride **98**, prepared *in situ* from **96**, with methanolic sodium borohydride in the presence of dissolved $CeCl_3$. Although about 10% of the desired alcohol **97** was produced, the major product was the corresponding methyl ester **104**, the not-unexpected product of methanolysis of the mixed anhydride **98**. Clearly it was necessary to find a trivalent lanthanide salt which was soluble in aprotic solvents. At this point, we began a tour of the lanthanide series of the periodic table. After several unsuccessful attempts to use various erbium and cerium salts, we finally succeeded by using samarium triiodide, which is partially soluble in THF. Thus, addition of the anhydride **98**, prepared *in situ* from **96**, to a suspension of samarium triiodide in THF at 0°C followed by slow addition of sodium borohydride at 5–15°C produced the desired alcohol **97** in 71% yield. Thus, by using an organic-soluble trivalent lanthanide salt, we could induce sodium borohydride to effect 1,2-reduction rather than 1,4-reduction of the reactive mixed anhydride. We are currently attempting to use this

96   **97**
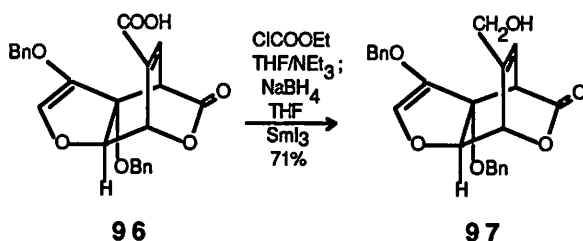
alcohol **97** for the preparation of the bottom halves of the milbemycins (α_9, α_{10}, and F), which have an acyloxymethyl group at C-4. Conversion of the hydroxymethyl group of **97** to methyl was attempted by several different methods, including various hydride reductions of the corresponding primary bromide, chloride, or sulfonate; tributyltin hydride/AIBN reduction of the primary bromide or chloride; and cupric sulfate/DMF reduction of the bromide. All of these met with somewhat mixed results, generally giving only fair yields of the desired methyl compound. The best method proved to be reduction of the chloride **105** (prepared in 98% yield from the alcohol **97** by treatment with triphenylphosphine and carbon tetrachloride) with sodium (trimethoxy)borohydride in warm HMPA to give an 82:18 mixture (^{1}H NMR integration) of the desired endocyclic olefin **106** and its exocyclic isomer **107** in 84% yield. We were unable initially to separate these isomers and thus used the mixture in separate steps. Later we found that **106** could be crystallized from the mixture. We have not yet been successful in isomerizing the exocyclic isomer **107** into the endocyclic **106** via various metal-catalyzed processes.

97   **105**   **106**   **107**
                                                                        82:18
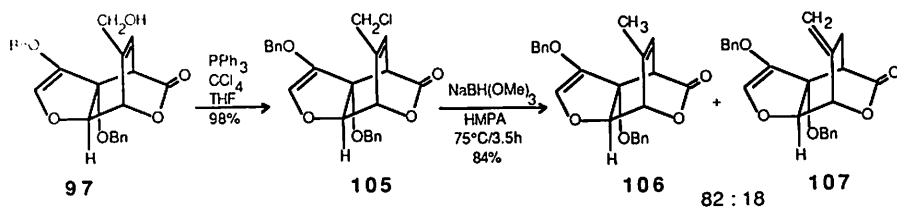
Having surmounted one of the two major synthetic hurdles, namely the conversion of the ester at C-4 into the desired methyl group, we turned our attention to the final synthetic challenge, namely the inversion of the alcohol stereochemistry at C-5. All along, from the very beginning of our synthetic planning, we had assumed that the sequence of allylic alcohol oxidation to the enone followed by sodium borohydride reduction would give the desired

5β-alcohol, as in the natural series.[4] Therefore we attempted to put this planning into practice.

The first step involved hydrolysis of the mixture of lactones to give the opened hydroxy acid. We initially tried to carry out this transformation under very mild conditions in order to avoid any potential problems associated with C-2 epimerization or conjugation of the resulting β,γ-unsaturated acid to the α,β-unsaturated acid. This type of epimerization and conjugation in base has been seen often in both the natural series[27a] and simpler bottom half analogs.[27b] However, our inability to open the lactone of our system under mild conditions forced us to use more vigorous conditions. Hydrolysis of the 82:18 mixture of lactones 106 and 107 with potassium hydroxide in refluxing aqueous ethanol for 1 hour produced the hydroxy acid, which was immediately esterified with diazomethane to give the hydroxy ester 108 in 80% overall yield. We don't know if the undesired isomer 107 is converted into 108 or if the product is derived solely from 106, although we suspect the latter to be true (with any products derived from 107 being destroyed under these conditions). We observe none of the corresponding α,β-unsaturated ester 109 in this reaction. The β,γ-unsaturated ester 108 is stable indefinitely at 25°C and can be purified by silica gel chromatography without conjugation to the α,β-unsaturated isomer 109. We could also show that no epimerization at C-2 had occurred by recyclization of 108 to give back the lactone 106 during an attempted reduction of the benzyl groups by treatment with calcium in ammonia. For this to occur, the hydroxyl and ester groups must both still have the α-stereochemistry. Thus our system differs significantly with regard to
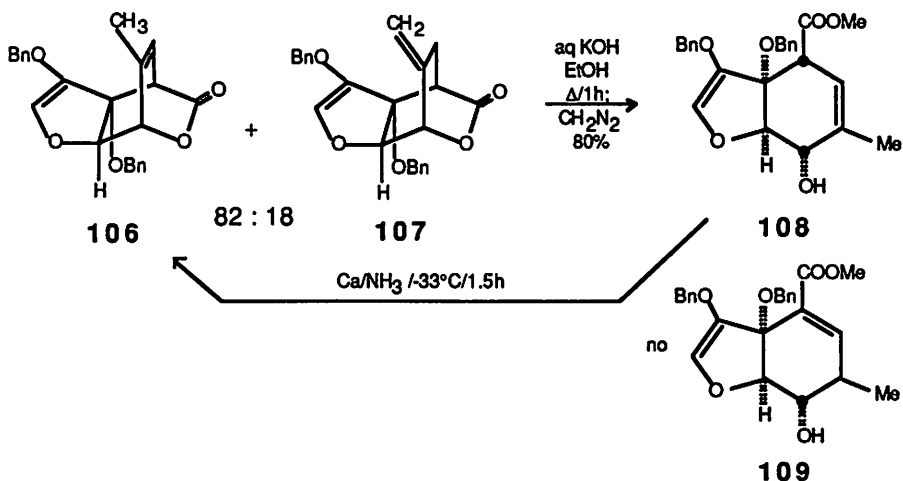
epimerization and conjugation from the natural material and the structurally similar one of Fraser-Reid,[27b] presumably because of differences in the relative energies of the isomers due to the presence of the benzyl enol ether and benzyl ether.

We next attempted to correct the C-5 stereochemistry. Oxidation of the allylic alcohol **108** under modified Swern conditions, using trifluoroacetic anhydride, DMSO, and triethylamine in dichloromethane at −65°C, afforded the enone **110** in 96% yield. However, disaster struck when we reduced this enone **110** with sodium borohydride in methanol at 0°C to 25°C, the conditions used for the conversion of 5-oxomilbemycin D to milbemycin D.[4] Only the starting 5α-alcohol **108** was obtained, with none of the desired, and expected, 5β-alcohol **111** being produced! Thus it appears that the free hydroxyl group at C-7 is required to direct this simple reduction from the α face of the molecule. The reaction that we had been depending on from the start, based on reasonable literature precedent, had completely failed us in the end!
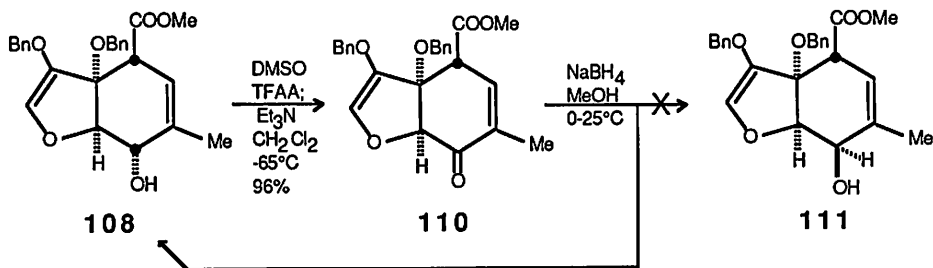

We originally tried to get around this difficulty by trying other totally different approaches, namely inversion of stereochemistry by the Mitsunobu reaction or by displacement of the corresponding mesylate of **108** by various nucleophiles, including cesium acetate and formate and potassium acetate in the presence of crown ethers. None of these methods proved satisfactory. We then decided to try to free the hydroxyl at C-7 by removing the benzyl protecting groups so that our enone would be even closer to the natural system and perhaps would reduce correctly. Many methods for benzyl ether removal proved unsuccessful (lithium or calcium in ammonia, chromate oxidation to benzoate and hydrolysis, benzylic bromination and hydrolysis, triarylaminium radical oxidation–hydrolysis, simple catalytic hydrogenation). However, palladium-catalyzed transfer hydrogenation of the benzyl ethers could be successfully carried out. Treatment of **108** with 1,4-cyclohexadiene and palladium on carbon in ethanol gave an excellent yield of the ketone **112**, in which the more sterically accessible benzyl enol ether has

108   **112**   **113**
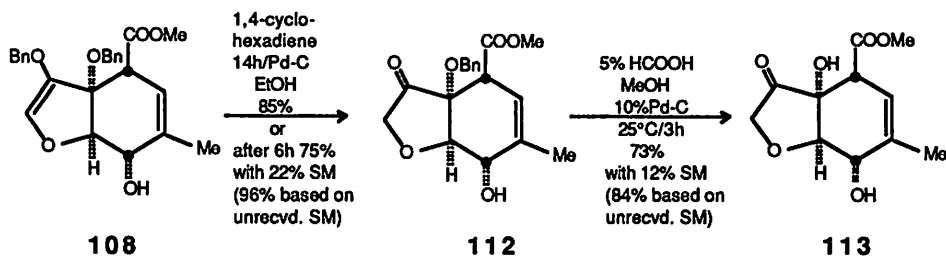
been cleaved. Further treatment under these conditions did not remove the more hindered tertiary benzyl ether. But switching to the more reactive hydrogen source, formic acid, effected the desired removal of the tertiary benzyl ether to give the ketodiol 113 in good yield. However, the coupling constants of the H-5 and H-6 protons in the ^{1}H NMR of 113 gave us a real shock and convinced us initially that maybe we had isomerized the alcohol at C-5 by solvolysis under the acidic conditions! In all of these compounds, the six-membered ring is forced to adopt a boatlike conformation (as shown by both simple Dreiding models and more sophisticated MM2 calculations). In 112, $J_{5,6}$ was 12 Hz, indicating that the molecule probably exists predominately in the conformation 112a rather than 112b (with the alcohol and ester groups occupying the flagpole–bowsprit positions). However, in 113, $J_{5,6}$ was only 1.75 Hz! Thus, either the change from benzyl ether to alcohol forced the molecule to now exist in a totally different conformation (113b rather than 113a) or the stereochemistry at C-5 had been inverted to give the desired final product 3! We originally could not see any strong reason for the molecule 113 to adopt a different conformation from that of 112 and thus initially favored the idea that inversion at C-5 occurred via the allylic cation (our critical faculties were clearly clouded by a lot of wishful thinking at this point). We soon realized that this was not the case. First, one could argue that in 113b the C-7 hydroxyl could now form a strong internal hydrogen bond to the ester, which was not possible in 113a or indeed in the benzyl ether 112. Thus it was very likely, on this basis alone, that epimerization had not occurred. Second, a coupling constant of 1.75 Hz was inconsistent for the expected $J_{5,6}$ for 3 since in most of the known natural avermectins and milbemycins and their close synthetic analogs, $J_{5,6}$ was about 5–6 Hz. The final evidence for the structure of 113 came from comparison of its ^{1}H NMR with that of the known 5-epi avermectins prepared by Mishima and co-workers,[4] which had $J_{5,6}$ = 1.5 Hz. Thus it was clear that the ketodiol had the structure 113. However, we had obviously developed a mild method for the selective removal of the benzyl groups in good yield and had prepared the bottom half synthon 113 for the 5-epi avermectins. All that remained was the nagging problem of correcting the C-5 stereochemistry.

112   **112a**   **112b** $J_{5,6} = 12\,Hz$

113   **113a**   **113b** $J_{5,6} = 1.75\,Hz$
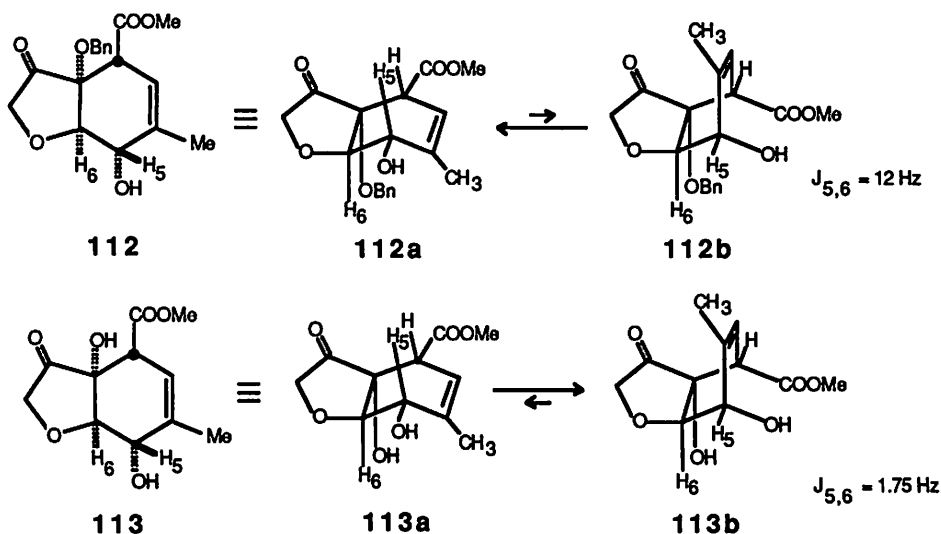
The solution to this problem had been before our eyes for some time but we hadn't looked closely enough. In fact, this synthesis is essentially a paean to the value of lanthanide salts in organic chemistry. Luche[28] had shown that added lanthanide salts not only favor 1,2- over 1,4-reduction of enones but also have an effect on the stereoselectivity of the reduction. In cyclohexenones one generally favors the equatorial alcohol by the use of lanthanide-modified hydride reagents, although there are some notable exceptions (with piperitone the axial alcohol is favored). We hoped that the presence of lanthanide salts would help promote complexation of the 7α-benzyl ether with the borohydride reagent to internally deliver hydride from the α face. This turned out to be the case. Reduction of the enone **110** with sodium borohydride and CeCl$_3$ in methanol at 0°C furnished a 9:1 mixture of the desired 5β-alcohol **111** and the starting 5α-alcohol **108** in 84% yield. The stereoselectivity is greatly lowered by trace amounts of DMSO left over from


110   **111**   9:1   **108**

$J_{5,6} = 5.8\,Hz$ $J_{5,6} = 12\,Hz$
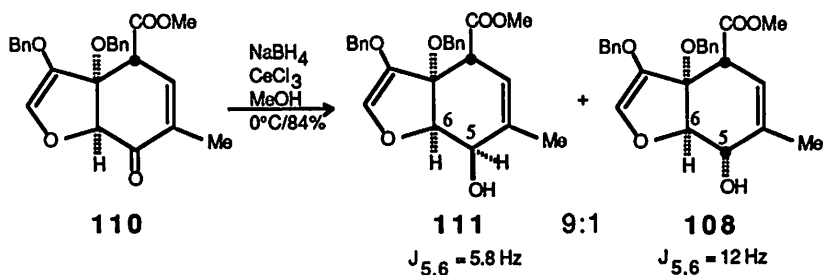
the preparation of **110** from **108**. That the 5β-alcohol **111** had indeed been formed was inferred from the 500-MHz ^{1}H NMR, in which the coupling constant between the hydrogens at C-5 and C-6, $J_{5,6}$, was calculated to be 5.8 Hz; in the starting alcohol **108** $J_{5,6}$ is 12 Hz. Thus by the simple expedient of adding CeCl$_3$ and carrying out the reduction at 0°C, we were able to completely invert the stereoselectivity of the reduction from producing totally **108** to giving a 9:1 mixture favoring **111**.

The synthesis of **3** was completed in two steps of transfer hydrogenation, analogous to those carried out earlier for the C-5 epimer **108**. Reduction of the sterically more accessible benzyl enol ether of **111** with 1,4-cyclohexadiene and palladium on carbon in ethanol at 25°C for 2 hours furnished the cyclopentanone **114** in 72% yield. Removal of the more hindered tertiary benzyl ether of **114** required a more reactive hydrogen source. Treatment of **114** with 18% formic acid and palladium on carbon in methanol at 25°C for 3.5 hours afforded the desired target molecule **3** in 78% yield (based on unrecovered starting material). Carrying out this final transfer hydrogenation until all of the starting material disappeared resulted in the formation of a substantial amount of the overreduced product in which the 3,4-double bond has also been reduced. The structure assignment of **3** is again based on spectroscopic data—IR, MS, and especially 500-MHz ^{1}H NMR, which indicates that the $J_{5,6}$ is 5.6 Hz, a value that corresponds well with those of the natural product and its derivatives.[4]
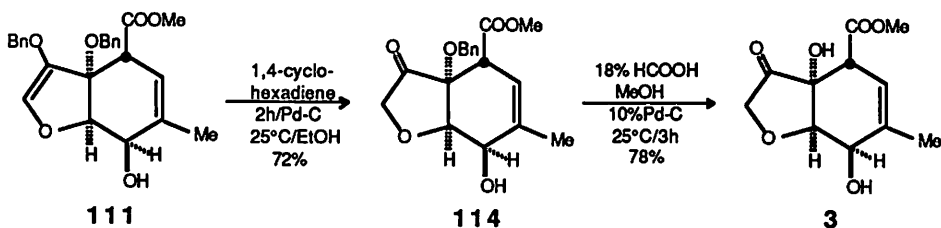
Thus we have finally reached our goal of a rapid and efficient total synthesis of the bottom half of ivermectin **3**. Although this account of the synthesis has necessarily rambled a bit to examine all of the false steps and failed pathways on the way to **3**, the overall synthesis is in fact quite concise, as is shown in Scheme 4. The synthesis of **3** requires only 10 steps from **92** and **93** and proceeds in an overall yield of 9%. The 5-epimer **113** is available in only eight steps and 17% overall yield.[29] We believe this represents a really excellent construction of a very functionalized and oxygenated substructure of a complex natural product and hope that others will view it as somehow elegant, beautiful, or clever.
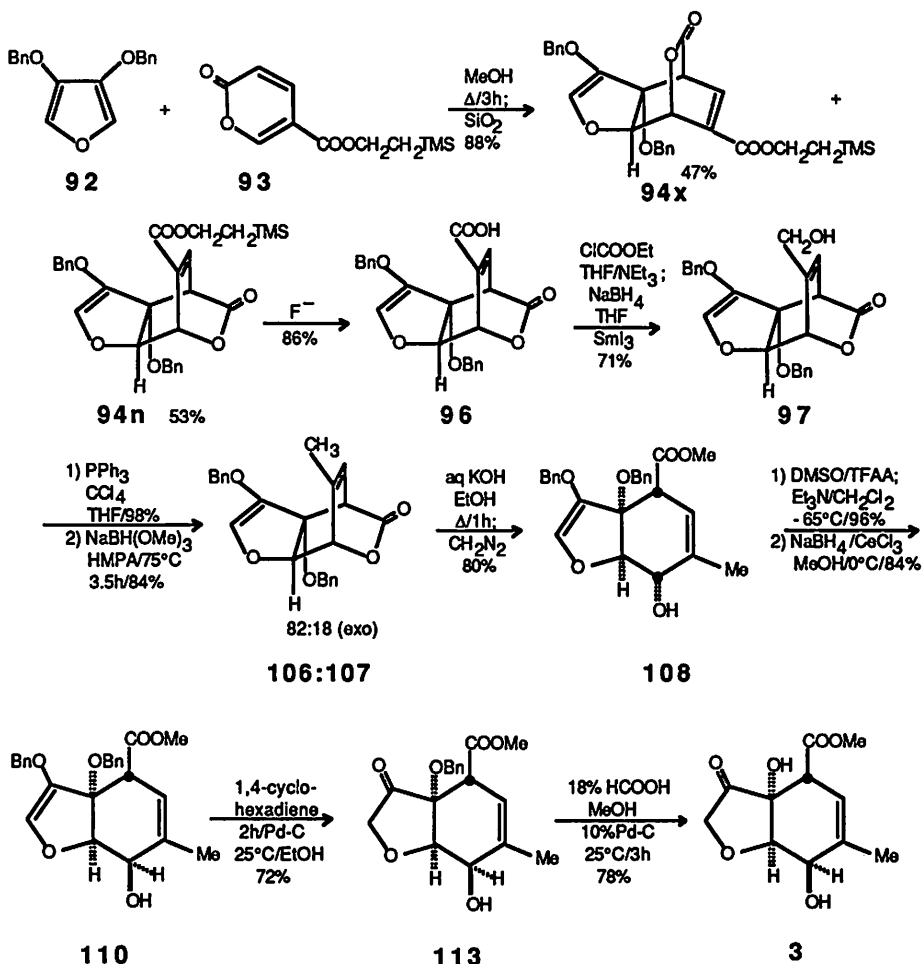
SCHEME 4

VI. Conclusion

With the completion of the synthesis of **3**, the descriptive part of this account is finished. However, it is instructive to review briefly what new synthetic methods or principles have come forth from this work and to consider what our further goals are. We have (1) provided new information on intramolecular Diels–Alder cycloadditions of furfuryl systems (especially amides and esters); (2) determined that there is a thermodynamic bias against cycloaddition of secondary *N*-furfurylacrylamides and for tertiary *N*-furfuryl

acrylamides; (3) exposed a novel and perhaps useful *gem*-dimethyl effect in these intramolecular cyclizations; (4) discovered and explained the reasons for the diastereoselectivity of side-chain substituents in these cycloadditions; (5) developed a new method for the conversion of these furan cycloadducts into cyclohexenol derivatives; (6) discovered new, interesting rearrangements in the reactions of 7-oxanorbornene systems with electrophiles; (7) developed a useful method for the easy introduction of asymmetry into the cycloadducts by the use of L-valinol as a chiral auxiliary; (8) explored in detail the preparation of unsymmetrical 4,6-disubstituted pyrones and their cycloadditions with electron-rich olefins; (9) developed a good method for the synthesis of highly functionalized bridged olefinic lactones and showed that they are good precursors of tetra-, penta-, and perhaps even hexasubstituted aromatic systems; (10) produced the first example of the cycloaddition of two nonbenzenoid aromatic systems (furan and pyrone) in which the aromaticity of both is lost in one step under mild conditions; (11) developed a new method for the 1,2-reduction of acids to allylic alcohols using a samarium triiodide-modified borohydride reagent; (12) provided an additional example of the utility of lanthanide salts in controlling the stereoselectivity of the 1,2-reduction of enones; and (13) determined the preferred conformation of close analogs of **3** by ^{1}H NMR measurements—all in addition to accomplishing the primary goal of synthesizing **3**. For the future, we hope to (1) investigate the use of compounds such as **97** for the preparation of the natural materials (milbemycins α_9, α_{10}, and F) with a (2-pyrroloyl)oxymethyl group at C-4;[30] (2) develop a method for transforming the exo adduct **94x** into the ivermectin bottom half **3**; (3) study the reaction of the 7-keto derivatives of **3** (with the alcohols protected) with various nucleophiles; (4) extend this synthesis to the preparation of the natural products themselves and several simpler macrocyclic analogs; and (5) further study the use of the furfuryl acrylate cycloadducts for the preparation of these and other natural products.

Acknowledgments

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24. Molecular mechanics calculation (MM2) predict that **86a** (R = Me) is much more stable than **87**.

25. Chemical shift data are given in parts per million downfield from internal tetramethylsilane and coupling constants are in hertz. The spectra were recorded at 500 MHz. Other resonances in the spectra are as follows: **91n**, 3.82 (3 H, s), 3.57 (3, H, s), 3.35 (3 H, s); **91x**, 3.83 (3 H, s) 3.61 (3 H, s), 3.24 (3 H, s); **94n**, 7.40–7.26 (10 H, m), 4.69 (2 H, AB, q, J = 11.2 Hz), 4.65 (2 H, s), 4.30 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s); **94x**, 7.40–7.24 (10 H, m), 4.74 (2 H, s), 4.55 (2 H, d, J = 11.5 Hz), 4.46 (2 H, d, J = 11.5 Hz), 4.31 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s).

26. Pivnichny and co-workers [27a] report that the avermectins (2β-H) isomerize first to the 2-epimer (2α-H) and then to the conjugated isomer (Δ^2) on treatment with hydroxide in aqueous methanol. Fraser-Reid[27b] has questioned Hanessian's early work[27c] on the deconjugation of the Δ^2-olefin to give the Δ^3-olefin with the correct stereochemistry at C-2 under kinetic protonation, although Hanessian's latest paper[27d] contains ^{1}H NMR data that seem consistent with his claim.[31]

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30. We have just recently been able to convert **97** into the hydroxymethyl analog of **3** by an adaptation of the route described using a benzyl ether as a protecting group with its eventual removal by transfer hydrogenation. M. E. Jung and D. B. Head, unpublished results.

31. Since this manuscript was submitted, Hanessian has published an article which clears up this controversy. He showed that Δ^2-avermectin B_{1a} can be converted into 2-epiavermectin B_{1a} and then by partial isomerization in the presence of imidazole into a 1:1 mixture of avermectin B_{1a} and its 2-epimer, along with 10–20% of the Δ^2 isomer. S. Hanessian, D. Dubé, and P. J. Hodges, *J. Am. Chem. Soc.*, **109**, 7063 (1987).