Chapter 7

THE CHAMPAGNE ROUTE TO AVERMECTINS AND MILBEMYCINS

Steven V. Ley and Alan Armstrong
Department of Chemistry
Imperial College
South Kensington
London SW7 2AY, United Kingdom

I. Introduction ........................................... 237
II. The Challenge ........................................ 238
III. Initial Plans and Results ............................ 240
IV. The Next Stage ....................................... 247
V. Synthesis of Model Compounds and Model Reactions .... 253
VI. At Last, Milbemycin β1: The Real Thing .......... 263
VII. The Final Celebration: Avermectin Bla Synthesis .... 269
References .............................................. 290

I. Introduction

Much has been written on these pages of the challenge of organic synthesis and its comparison with conducting symphonies, playing chess, or creating other artistic forms. Some have remarked upon the immense intellectual challenges presented by the synthesis of complex structures and the elegance of the solution of these problems. More practical and realistic views have been expressed in terms of the frustrations, dead-ends, and even dropped flasks leading to the eventual joy of success. Others have commented that synthesis is a springboard for the discovery of new reactions and methods, as well as being the best training ground for young scientists who will go forward to make their own inventions and discoveries for the future benefit of
all. While all of this is true, there is much more to the experience of being involved with synthesis. Only those who have been intimately absorbed will understand its truly creative element.

Some have the view that organic synthesis is a mature subject with little opportunity for new developments to be made. To the extent that we have come a long way in the last thirty years, this is true. We can now prepare complex target molecules in a relatively short period of time. We are at a point where we can use the tools of synthesis to powerful effect in the study of fundamental molecular problems in the areas of biology and material science. However, we are only just beginning to achieve the levels of selectivity in bond construction that are needed for tomorrow's problems. There is still so much more to discover.

In the next few pages we present our work on the synthesis of the avermectins and milbemycins, and unveil our thoughts, plans and philosophy in a roughly chronological order. Some of our approaches proved unsuccessful, but nevertheless triggered the new ideas and methods which eventually worked and led to the consumption of much champagne!

II. The Challenge

In the mid 1970's, workers in the Sankyo laboratories and the Kitasato Institute working with Merck, Sharp, and Dohme discovered the milbemycins and avermectins as a major new class of potent antiparasitic and insecticide agents. Many new members of this series have been characterized since these early days, firmly establishing them as therapeutically and commercially important compounds. The architectural and biological novelty of these compounds soon made them popular targets for total synthesis. In this chapter we discuss our efforts towards milbemycin β₁(1) and avermectin B₁a(2), these being key representative examples of these macrolide natural products.

Although there is considerable structural diversity within the milbemycins and avermectins, there are several common features which need to be addressed in any synthetic program. Firstly, all contain a highly substituted spiroacetal fragment. This basic unit is also present in many other biologically active species, yet at the outset of our work,
methodology for its formation was rather limited. Opportunities therefore presented themselves for new synthetic chemistry towards these groupings. The preparation of the sixteen-membered macrolactone ring was considered to be straightforward using existing methods, but this was only possible due to the significant advances made in large-ring synthesis in relatively recent times. Careful synthetic planning would also be required to effect the introduction of the several stereocenters possessed by 1 and 2. This would most reasonably be achieved using a convergent approach whereby isolated fragments containing groupings of asymmetric centers are coupled. The range of substituted double bonds in the avermectins and milbemycins obviously presents many problems to the synthetic chemist, and again, attention to these details early on should avoid frustration later. The “southern” C1–C10 portion of these molecules would be expected to display a high tendency for aromatization, thus suggesting that these molecules may be susceptible to strongly acidic or basic conditions. The use of the terms “northern” and “southern”, defining
portions of the molecules based on their common structural presentations, is used in this review. Although we recognize that it is not entirely satisfactory, it has become popular in the avermectin and milbemycin area. Finally, the high level of oxygen functionality needs careful attention when planning a synthesis to avoid unnecessary tactical problems of functional group elaboration and protection. When one superimposes these details with the desire to develop new synthetic methods and to adopt a novel approach, one is confronted by a challenging problem. Despite this, syntheses of milbemycin $\beta_3$,\textsuperscript{4} milbemycin $\beta_1$,\textsuperscript{5} milbemycin $E$,\textsuperscript{6} avermectin A1a,\textsuperscript{7} avermectin B1a\textsuperscript{8} and the avermectin B1a aglycone\textsuperscript{9} have all been reported. These syntheses amply demonstrate the versatility and imagination that is possible in natural product synthesis programs.

III. Initial Plans and Results

We began our studies in this area rather late as two groups in the USA, those of Smith\textsuperscript{4c} and Williams\textsuperscript{4a}, had already reported their syntheses of milbemycin $\beta_3$, which is the simplest member of the series and possesses an aromatic southern portion. Undeterred, we set about devising some new routes to the inherent spiroacetal fragment since we believed that there was a need for improved procedures. The first method we investigated was prompted by our interest in selenium-mediated cyclization reactions of carbonyl compounds with double bonds.\textsuperscript{10} We were able to show that hydroxyalkenyl ketones underwent spiroiselenocyclization when treated with N-phenylselenophthalimide and zinc bromide (Scheme 1).\textsuperscript{11} This reaction is an intramolecular version of a process first reported by Sharpless.\textsuperscript{12}

Although this method began our interest in the area and we were able to use the route for the preparation of some simple pheromone natural products, it was hardly sophisticated enough for the project in hand. At about this time our colleague at Imperial College, Tony

\[ \text{Scheme 1. (a) } \text{N-(phenylseleno)phthalimide, ZnBr}_2, 78\%. \]
Barrett, had also begun synthetic studies on the milbemycins and avermectins, so it seemed reasonable that we should join forces and write a proposal to the Wolfson foundation to support our work. This was successful, and prompted the first champagne celebration. It also had the effect of concentrating our thoughts to improve the methods and to seriously begin the process of total synthesis. The problem of spiroacetal preparation as we saw it related to the need for a simple procedure, but one which would be versatile and permit multifunctional substitution. We believed that by controlling stereochemistry in one preformed ring, we would have advantages over any acyclic process. The well known anomic effect would be expected to allow sterecontrol at the anomic center. We thought it would be possible to make cyclic ether derivatives which would undergo a Wittig or Horner-Wittig reaction at the 2-position with aldehydes containing hydroxyl-substituted side-chains. The resulting enol ether should then close to give the spiroacetal simply on treatment with an acid.

It turned out to be an easy process to prepare both 2-triphenylphosphonium salts and 2-diphenylphosphinoxy cyclic ethers from lactols or dihydropyrans. As anticipated, these coupled well with aldehydes to give enol ethers which underwent cyclization on treatment with camphorsulfonic acid, giving spiroacetals. A few examples of this process (Scheme 2) serve to illustrate its potential. Again,

![Scheme 2](image)

Scheme 2. (a) LDA, THF, \(-78^\circ\text{C}\), then add aldehyde or lactol. (b) KOt-Bu, THF. (c) Cat. CSA, MeOH.
this sequence was used to prepare some pheromone natural products, from the olive fly *Dacus oleae* and the common wasp *Paravespula vulgaris*. Pleasingly, other groups have subsequently used our methods for spiroacetal preparation. More importantly, however, these promising reactions could be applied to a simple synthesis of the spiroacetal fragment of the milbemycins, giving us considerable encouragement (Scheme 3).

![Scheme 3](image)

Scheme 3. (a) 2 equivalents BuLi, THF, −78°C to 25°C. (b) NaOMe, MeOH. (c) 3M HCl, 36%.

This work had achieved not only a new spiroacetal preparation but also something we believed to be fundamentally more important: the formation of carbon-carbon bonds at the 2-position of cyclic ethers. Indeed, it was this realization that prompted the discovery of the final new method that we developed, one which has since proved to be extremely versatile and has opened up many new synthetic areas. This relates to the use of 2-benzenesulfonyl cyclic ethers. The phenylsulfonyl group was chosen to facilitate anion formation at the anomeric center much in the same way as we had used phosphonium salts and diphenylphosphine oxides. However, we anticipated that the anion would be more nucleophilic and might react with a wider variety of electrophiles, not only with aldehydes but also with ketones, halides and epoxides to effect carbon-carbon bond formation. Reductive desulfonylation would afford the substituted product, while elimination would give an enol ether. As before, if these enol ethers contained hydroxyl-substituted side chains, then cyclization under acidic conditions would provide spiroacetals. The crystalline and fairly stable sulfones were easily prepared from hydropryans, lactols or lactol ethers by treatment with benzenesulfonic acid or alternatively by oxidation of the corresponding anomeric sulfides. In the first experiments, we found these sulfones to be excellent precursors for spiroacetal preparation. Following deprotonation with *n*-butyllithium at low temperature, the resulting anions reacted with halides to give a product which underwent spontaneous elimination of benzenesulfonic acid on warming to room temperature. Acidic work-
up gave spiroacetals in excellent yield (Scheme 4). The method turned out to be generally useful for the preparation of dihydropyran enol ethers. It was also found that direct substitution of the phenylsulfonyl group by organometallic reagents provided a simple new method for forming carbon-carbon bonds at the position adjacent to oxygen in cyclic ethers (Scheme 5). Later work showed that we were also able to translate this substitution chemistry to cyclic amines, piperidines and pyrrolidines. These additional bonuses that come as a result of developing methodology for natural product synthesis are very satisfying and one should always be prepared to take these opportunities as they arise.
In spite of these successes, not all was going well with the other stages of the synthesis. For example, methods for introduction of an appropriate C_{10}–C_{15} alkene side chain into the previously synthesized spiroacetal fragment were proving unexpectedly difficult. Not only were attempts at displacement of C_{16}-leaving groups very sluggish owing to the β-oxygen effect of the neighboring pyran oxygen, but methods for controlling the E-geometry of the C_{14}–C_{15} double bond were also unsatisfactory (Scheme 6). Almost a year of hard work by Andrew Jackson gave very little to show for his efforts. Because of these difficulties, we were forced to rethink our strategy. In fact the solutions to these problems, which will be discussed later, greatly simplified the whole route to the northern hemisphere portion of these molecules and resulted in a unified approach to all members of the avermectin and milbemycin family. It is also interesting to note that while we were struggling with the formation of the C_{15}–C_{16} and C_{14}–C_{15} bonds, other groups\textsuperscript{c} were experiencing similar difficulties which they commented upon in subsequent publications.

In the meantime, we had begun to explore a route to milbemycin β₁ \textsuperscript{1} in which we conceived a coupling of a northern fragment as an alkenyl anion reaction with a C_{1}–C_{7} cyclohexanone southern region (Scheme 7). In this way, we would have a novel coupling approach.
combined, we hoped, with a method of controlling the important C7 angular hydroxyl configuration. This was an attractive approach but again, despite considerable effort by the student on the project, Paul Booth, we were unable to get very far, although some useful model studies were undertaken. For example, we were able to prepare protected dienol compounds such as 3 but these could never be converted to the required organometallic species for coupling. We were later able to obtain alkenyllithium reagents 4, derived from 2-butyne-1,4-diol, but while these added to simple cyclohexanones, they failed to add to more highly substituted examples necessary for this work.

![Diagram](image)

Concurrent with these early side chain and spiroacetal studies, we had also begun to address the issue of the synthesis of southern zone fragments. We planned to adopt a strategy which could be applied to both mono- and bicyclic southern units. On paper, we were most attracted by the Diels-Alder route which is shown retrosynthetically in Scheme 8. Although we eventually abandoned this approach, other groups (Ireland and more recently Uang) were much more successful, even though they have not yet used their fragments in total synthesis studies. Jung has also reported a Diels-Alder approach to the avermectin hydrobenzofuran unit. Ian O'Neil, who examined our route, did make significant progress, especially on model studies and in the preparation of appropriately substituted dienes, and these reactions are reported here. We eventually gave up this route mainly because the alternative sequence which we were developing was proving more versatile (vide infra). We were also becoming concerned about the configurational stability of the C2 stereocenter and the liability of the 3,4-double bond to move into conjugation with the ester group. Furthermore, we were worried that addition reactions to a hindered C8 carbonyl group flanked by two heteroatoms would later prove problematic. Nevertheless, the nice feature of the
approach was the concise way the cyclohexene ring could be constructed with a predictable *cis-endo* selectivity to control relative stereochemistry. We also envisaged the use of a phenylseleneenyl group in position X (Scheme 8), *via* its selenoxide and a [2,3]-sigmatropic shift, to set up the desired C₅ oxygen stereochemistry, simultaneously placing the double bond in the required 3,4-position. Crimmins has subsequently shown the viability of a related selenoxide migration process.²⁷

In model studies we were able to effect the Diels–Alder reaction of an acetoxy dienophile 5 with a substituted diene 6 to give the cycloaddition product 7 in 65% yield (Scheme 9). Disappointingly, all attempts to convert 7 to useful substrates for the synthesis by α-oxidation or direct nucleophilic addition to the C₅ ketone failed. Although we were also able to prepare a phenylseleneenyl-substituted diene 8 by a short, stereoselective sequence (Scheme 10), it failed to react with 5 to give any cycloaddition product.

![Scheme 8](image)

**Scheme 8**

![Scheme 9](image)

**Scheme 9.** (a) 115°C, toluene, 72h, 65%.
IV. The Next Stage

We now reached a stage where we had to consolidate our successes and rethink our strategy, particularly for the introduction of the diene side chain and the preparation of the southern hemisphere portion of the molecules. The next important step came when we were able to show that the anions derived from 2-benzenesulfonyl tetrahydropyrans react with epoxides. This one reaction became the heart of all the remaining hydroxy-substituted spiroacetal syntheses leading to milbemycin β1 (1) and avermectin B1a (2). In general terms, treatment of 2-benzenesulfonyl tetrahydropyrans with n-butyllithium effects formation of the anion, which then reacts with epoxides containing masked hydroxyl groups for later spirocyclization on treatment with acid (Scheme 11).

In a specific example, reaction of the anion from the sulfone 9 with the epoxide 10 gave the milbemycin spiroacetal 11 in 76% yield following treatment of the intermediate enol ether with camphorsulfonic acid (Scheme 12). Similar reactions with other substrates afforded models for the avermectin spiroacetal, or, by reversing the coupling partners, gave the spiroacetal common to the avermectin 2 series (Scheme 13). More recently, a modification of the same general method has allowed the preparation of unsaturated systems similar to those found in avermectin B1a. The basis of this
modification relates to the trapping of the intermediate enol ether with a selenium electrophile. Spirocyclization gives selenium-containing spiroacetals. Oxidation and syn-elimination then provides the unsaturated systems (Scheme 14).

The success of the epoxide ring-opening process also stimulated another idea to solve the problem of the side chain introduction, and especially for controlling the $E$-geometry of the C$_{14}$–C$_{15}$ bond. Since the configurations of the C$_{17}$ and C$_{19}$ centers are common to all avermectins and milbemycins, we conceived the idea of using the bis-epoxide 12 as a double electrophile. We had previously shown$^{31}$ that the milbemycin C$_{14}$–C$_{15}$ $E$ double bond could be constructed by opening epoxides using appropriately substituted alkenyl-metallic reagents. Indeed, when the bis-epoxide 12 was reacted with the vinyl cuprate reagent 13, we obtained the addition product 14. Reaction of 14 with the sulfone anion 9 in the presence of titanium (IV) isopropoxide, followed by an acidic work-up, gave the C$_{11}$–C$_{25}$
fragment 15 of the milbemycins (Scheme 15). Conceptually, this route represents a most expedient and enormously versatile sequence to these northern hemisphere units, being capable of affording milbemycins, avermectins or novel analogues simply by appropriate choice of the various coupling components.
Along with these studies we were formulating a route to the southern portion of the natural products based upon a stereoselective alkenyl-anion addition reaction to a cyclohexanone derivative 16, setting up the important C7 angular hydroxyl stereochemistry. The choice of 16 was deliberate in that it should be readily available in the required optically active form, and all the functionalities can be readily manipulated to the desired materials, including the later opportunity for the preparation of the bicyclic hydrobenzofuran fragment needed in the avermectin synthesis. In this way, we would have a single, coherent route to all members of the milbemycin and avermectin family. Preparation of the necessary starting materials for this phase of the synthesis proceeded smoothly, and could be carried out on a 100-gram scale. Prins reaction\(^32\) of 2,5-dihydro-4-methylanisole put together the carbon framework. Following silylation, reaction with ethylene glycol in the presence of pyridinium tosylate gave 17; hydroboration and deprotection gave 16 in racemic form (Scheme 16). The deprotection step was not straightforward owing to problems of rapid β-elimination using conventional reagents, but use of the excellent Lipshutz method,\(^33\) involving acetal exchange with acetone in the presence of Pd(II) salts, provided reproducible and high yields. Preparation of optically pure 16 will be discussed later.

**Scheme 16.** (a) Me$_2$Al, (CHO)$_2$, CH$_2$Cl$_2$, 0°C, 64%. (b) TBDPSCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, 98%. (c) Ethylene glycol, PPTS, C$_6$H$_5$OH, reflux, 16h, 88%. (d) BH$_3$, Me$_2$S, then aqueous NaOH, H$_2$O$_2$. (e) PdCl$_2$(CH$_2$CN)$_2$, acetone, 98%. (f) 2-lithio-4-phenylthio-but-1-ene, THF/ether, -78°C, 87%. (g) mCPBA, CH$_2$Cl$_2$, then Oxone®, MeOH/THF/H$_2$O, 88%.
In order to assess 16 as an eventual precursor for milbemycin $\beta_1$ synthesis, several further experiments were performed. Although we found that vinyl magnesium bromide would add to 16, other vinyl side chains were less accommodating and not at all satisfactory (vide supra). Eventually, we found that 2-lithio-4-phenylthiobut-1-ene would add in excellent yield and with high selectivity. After oxidation with potassium peroxymonosulfate (Oxone®), the sulfone 18 was obtained (Scheme 16). We had planned that the phenylsulfone group in 18 could be used to effect coupling to the northern hemisphere fragment. At first sight, the C$_8$ methylene group in 18 appears to be wrongly placed in the side chain. However, we believed this could be a very desirable feature in that it could mask the $E,E$-dienol unit of milbemycin $\beta_1$ until a late stage, when hydroxyl-directed epoxidation and allylic rearrangement should produce the correct substitution pattern. This process was shown to be viable in a model study using diethylaluminum-2,2,6,6-tetramethylpiperidine$^{34}$ to effect the rearrangement (Scheme 17).

In another important series of transformations, 18 was elaborated to a unit 19 which contains many of the structural elements found in the natural product milbemycin $\beta_1$ (Scheme 18). Oxidation of the C$_3$ hydroxyl group of 18 was followed by regioselective selenenylation and syn-elimination to give 20. C$_7$-hydroxyl-directed reduction with sodium triacetoxyborohydride and methylation with diazomethane in the presence of fluoroboric acid gave 19. These last steps gave us encouragement for using this selenoxide elimination approach for the introduction of the C$_3$–C$_4$ double bond in the total synthesis studies, possibly at a very late stage of the synthesis. This could avoid anticipated problems$^{26}$ associated with epimerization at C$_2$ or the ready

![Scheme 17](image-url)

\textit{Scheme 17.} (a) Diethylaluminum 2,2,6,6-tetramethylpiperidine, benzene, 50%.
isomerization of the double bond into conjugation on oxidation of the C1 center.

The remaining problem to be solved was how to obtain this southern zone fragment in optically pure form for the synthesis of milbemycin β1. Attempts of effect a kinetic resolution by asymmetric hydroboration35 of the dioxolane 17 to give an optically enriched alcohol were moderately successful, but the reaction was very unreliable and could not be used on a preparative scale. We therefore had to resort to an alternative sequence. This involved initial catalytic osmium tetroxide cis-hydroxylation of 17 followed by reaction with (1S)-(−)-camphoric acid chloride to give the separable diastereomeric esters 21 and 22 (Scheme 19). These could be processed to (+)- and (−)-17 by ester hydrolysis, formation of the orthoformates and conversion to the optically pure alkenes by treatment with acetic anhydride.36 Hydroboration and deprotection were then performed as described earlier, to provide either enantiomer of 16. Determination of the absolute configuration was achieved by X-ray crystallography on a derivative 23 obtained from 22 by dehydration using thionyl chloride and pyridine.
Scheme 19. (a) OsO₄, NMO, t-BuOH/THF/H₂O, 71%. (b) LS-(−)-camphoric acid chloride, Et₃N, DMAP, CH₂Cl₂. (c) K₂CO₃, MeOH, 88%; (d) (MeO)₂CH, PPTS, CH₂Cl₂, 100%; (e) Ac₂O, reflux, 64%, then as Scheme 16.

Not all was as straightforward as it seemed, however, as initially the absolute configuration was misassigned based upon the X-ray data and the reported structures for the (1S)-(−)-camphoric acid residue in the original Aldrich catalog and in the review by J. W. Scott in Morrison’s “Asymmetric Synthesis," which as reported are actually incorrect! The error only became clear to us later when we began synthesizing the model compounds reported in the next section. Coupling to an optically pure northern hemisphere fragment afforded an isomeric milbemycin β₁ compound and caused us to reassign our diastereomeric esters 21 and 22. This was a hard lesson to learn, but it points out that one should not always trust X-ray structure determinations and that not all you read in books is true!

V. Synthesis of Model Compounds and Model Reactions

At this stage we were feeling fairly confident that our plans for the synthesis were beginning to be effective. A superstitious person when it comes to structures, the senior author is usually reluctant to write these down until the actual products are in hand. It was at about this time that, at his birthday party, he was presented with a sweater
made by some members of the group, with the completed structure of milbemycin $\beta_1$ emblazoned on the front. It was a further three years before the synthesis of milbemycin $\beta_1$ was completed!

The next phase of the work required us to devise coupling strategies and functional group manipulation. This involved model studies to avoid depletion of stocks of precious materials. Many questions still needed to be answered before we felt we could embark on the journey down the final road of using the correct enantiomerically pure fragments in coupling reactions. Since only a very small sample of milbemycin $\beta_1$ was available to us, we did not have the luxury of being able to study the relay work which is common practice in natural product synthesis. De novo synthesis of a complex molecule is a much more difficult task than learning to couple degraded fragments based on an adequate natural product supply.

The problems that remained were to find a suitable method to create the side chain $E,E$-dienol portion of milbemycin $\beta_1$, and to establish a route to macrocyclic materials. We first attempted to modify the southern fragment 19 by directed epoxidation followed by allylic rearrangement to give a more suitable coupling unit 24 (Scheme 20). Surprisingly, when we used standard hydroxyl-

\[ \text{Scheme 20.} \{ (a) \text{VO(acac)}_2, \text{t-BuOOH, 66\%} \} \]
directed epoxidation with vanadyl acetylacetonate and tert-butyl hydroperoxide or m-chloroperbenzoic acid, none of the allylic epoxide 25 was obtained. Rather, we obtained the homoallylic product 26 selectively and in high yield. We therefore decided to investigate some coupling reactions in the hope that the products would undergo the selective reactions we desired. By modification of the previously described methods, gram quantities of a northern hemisphere model spiroacetal 27 were prepared in just six steps. This was coupled with the dianion generated from 19 and, after reductive desulfenylation, the E-alkene 28 was obtained. Unfortunately, this too reacted under the Sharpless conditions to give the homoallylic epoxidation product 29 (Scheme 21).

The coupled product 28 was then investigated as a model to study the macrolactonization reaction. Here too, we met with little success. Although 28 could be easily deprotected with fluoride to afford a

Scheme 21. (a) 2 equivalents BuLi, THF/HMPA, then add (27). (b) PhCOCl. (c) 6% Na/Hg, THF/McOH, Na2HPO4., 45%. (d) VO(acac)$_2$, t-BuOOH, 50%.
primary alcohol, \textit{all} attempts, with a range of oxidizing reagents, failed to give either an aldehyde or the carboxylic acid necessary for macrolactonization. We also briefly studied a novel approach to macrocyclic ring construction involving an attempt to trap a Pummerer-type intermediate. As a model for this, we synthesized the sulfide 30, and on treatment with \textit{N}-chlorosuccinimide/iodine obtained a reactive intermediate iodide 31 which could be trapped with methanol to give the thioacetal 32. Unfortunately, intramolecular cyclization to give the macrocyclic acetal 33 was never observed (Scheme 22). It could be argued that this was a poor model for the real system, so before abandoning the approach we also prepared the sulfide 34 and sulfoxide 35 as precursors. Under a variety of Pummerer conditions these suffered degradation \textit{via} fragmentation of the C$_2$-C$_7$ bond assisted by the angular hydroxyl group.\textsuperscript{40}

![Chemical structures](image)

What we had learned from these studies was that early incorporation of the C$_3$-C$_4$ double bond caused many problems, as did attempts to effect directed epoxidation and rearrangement to establish $E,E$-dienol side chain groupings. To address these issues we decided to prepare a 3,4-dihydro model compound 36 as this has considerable skeletal homology with milbemycin $\beta_1$, and we envisaged introduction of the C$_3$-C$_4$ double bond using the selenium-based methodology established earlier. In this new approach, therefore, we reasoned that incorporation of the necessary oxygenation at the C$_8$ position in the southern coupling fragment would overcome many of the difficulties encountered above. Hydroboration of 18, the previously synthesized C$_1$-C$_{10}$ unit, gave the diastereomeric alcohols 37 and 38 in a 2:9 ratio. Reaction of the major isomer 38 with benzaldehyde and pyridinium tosylate gave a separable 1:1 mixture of benzylidene acetals 39 and 40. Only one of these, 39, was carried through the synthesis, and the acetal 40 could be recycled by
re-exposure to the acetalization reaction conditions. Treatment of 39 with two equivalents of tert-butyllithium followed by quenching of the resulting α-sulfonyl carbanion with phenylselenenyl chloride, gave the intermediate selenides. Oxidation with m-chloroperbenzoic acid resulted in smooth syn-elimination of the selenoxides to give the E-vinylc sulfone 41 (Scheme 23). This was to be used as a coupling fragment in the synthesis of the model compound 36, but also turned out to be the most suitable piece for the total synthesis of milbemycin β₁.
Scheme 23. (a) BH$_3$·Me$_2$S, then aq. NaOH, H$_2$O$_2$. (b) PhCHO, PPTS, C$_6$H$_5$, reflux. (c) 2.2 eq. i-BuLi, THF, −78°C, then PhSeCl, 70%. (d) mCPBA, CH$_2$Cl$_2$/aqueous NaHCO$_3$, 99%.

For the preparation of the model compound 36, we propose to couple the previously synthesized spiroacetel 27 with the dianion derived from 41. We thought that 41 would undergo deprotonation with two equivalents of tert-butyl lithium and that due to the conformation of the system it would remain sufficiently stable to react with 27 under Julia-type coupling conditions via the deconjugated α-sulfonyl carbanion. Following benzoylation and reductive desulfonylation, the diastereoisomeric $E,E$ dienes 42 were indeed obtained (Scheme 24). None of the other possible dienes were isolated, suggesting that steric effects may be operating in our favor in the coupling to give the desired C$_8$–C$_9$ double bond geometry. While it is difficult to predict this outcome we were nevertheless pleased and felt that this vindicated the use of a very sterically hindered group on C$_1$, which additionally had given us excellent control during the vinyl-anion addition reaction to set up the C$_7$ stereochemistry. The C$_1$ oxidation state in 42 was adjusted prior to macro lactonization. Thus, deprotection with tetra-n-butyrammonium fluoride and two-stage oxidation using Swern conditions followed by immediate further oxidation with buffered sodium chlorite gave the acids 43. The
Scheme 24. (a) 2 equivalents BuLi, THF, then add (27). (b) PhCOCl, −78°C to 25°C. (c) 6% NaHg, THF/MeOH, Na2HPO4, 25%. (d) TBAF, THF, 67°C, 77%. (e) (COCl)2, DMSO, then Et3N, CH2Cl2, 100%. (f) NaClO4, KH2PO4, 100%. (g) NaOMe, MeOH. (h) 2-chloro-N-methyl pyridinium iodide, Et3N, CH2CN, reflux, 13% (44), 15% (45). (i) TFA, CH2Cl2.
benzoyl groups were removed with sodium methoxide and the crude products subjected to macrocyclization using the Mukaiyama conditions. As we were using racemic coupling partners, two diastereomeric sixteen-membered ring macroline products 44 and 45 were expected. Removal of the benzylidene acetal protection from 44 gave the model compound 36 which, among other things, showed NMR characteristics for the olefin region very similar to β1 (Scheme 24). This route established the background for the eventually successful sequence to milbemycin β1 (1).

In another model study, we coupled the trianion generated from 18 with the C11–C15 northern hemisphere fragment 46 which had been prepared previously by the 2-benzenesulfonyl tetrahydropyran technology. After benzoylation, reductive desulfonylation gave the C10–C11 E-coupled product 47. This was then processed by similar chemistry to that established in the previous model study to provide the macroline 48 (Scheme 25). Unfortunately, due

---

**Scheme 25.** (a) 3 equivalents BuLi, THF/toluene, then add (46). (b) PhCOCl. (c) 6% Na/Hg, THF/Methanol, Na2HPO4, 30%. 
to lack of material at the end of this sequence owing to a rather modest yield (30%) in the coupling, we were unable to investigate selective epoxidation and rearrangement conditions for the installation of the \( E,E \)-dienol side chain. Nevertheless, the route showed that novel structures could be produced that potentially could be applied to \( \beta_1 \) synthesis.

The final model system we studied involved coupling of enantiomerically pure fragments. In this phase of the work we believed we were proceeding towards milbemycin \( \beta_1 \) itself, but as it turned out we prepared a novel isomer 49 owing to the initial misassignment of absolute stereochemistry of the southern \( C_1-C_{10} \) unit discussed earlier! This is just the sort of story that this series of books reveals but which goes unreported in other, more formal reviews. Compound 49 contains all the structural elements of milbemycin \( \beta_1 \), but consists of the correct \( C_{11}-C_{25} \) chirality while the \( C_1-C_{10} \) southern portion is antipodal to the natural product.40

The dianion from the antipodal unit 50 was added to the optically pure northern spiroacetal aldehyde 46. Following benzylation and reductive desulfonylation the \( E,E \)-diene 51 was obtained, albeit in a rather modest 29% yield (Scheme 26). Nevertheless, since we had good supplies of materials we were able to progress these compounds through to the final structures. Not all of the peripheral chemistry to this end is discussed; rather we will describe only the successful sequence as it was this route that set the stage for the natural product preparation. Compound 51 was converted to the macrolide 52 following essentially similar steps to those in the previous model studies. Following \( \text{C}_5 \) oxidation, the \( C_4-C_5 \) tert-butylidemethylsilyl enol ether was generated regioselectively. Attempts to generate enones directly from this intermediate silyl enol ether were not successful, but reaction with phenylselenenyl chloride gave the selenide
Scheme 26. (a) 2 equivalents t-BuLi, THF, −78° C, then add (46), (b) PhCOCl, DMAP, pyridine, 25°C. (c) 6% NaHg, THF/McOH, Na2HPO4, 29%. (d) (COCI)2, DMSO, then Et3N, CH2Cl2, 100%. (e) TBDMSOTf, Et3N, CH2Cl2, then PhSeCl, −30°C, 92%. (f) TFA, CH2Cl2, −78° C. (g) 2-phenylsulfonyl-1-3-(p-nitrophenyl)oxaziridine. (h) NaBH4, CeCl3, 7H2O, MeOH, 23% (54), 13% (55), 21% (56). (i) TBDMSOTf, Et3N, 0°C, CH2Cl2, 40%. (j) CH2N2, HBF4, CH2Cl2, 70%. (k) HF/pyridine, 60%.
53. After some experimentation it was found that after deprotection of 53, oxidation to the selenoxides using an oxaziridine reagent\textsuperscript{47} and subsequent syn-elimination, followed by reduction under the Luche\textsuperscript{48} conditions (sodium borohydride and cerium(III) chloride) three products 54, 55, and 56 could be obtained in 23\%, 13\% and 21\% yields, respectively. 55 could also be recycled to 56 by oxidation and reduction. Other attempts to maximize the formation of the endo versus the exo methylene isomers in the syn-elimination step using chiral oxidizing agents or by utilizing alternative levels of hydroxyl group protection failed. Finally, 56 was converted to 49 by selective protection of the primary hydroxyl group using tert-butylidemethylsilyl chloride, methylation of the C$_5$ hydroxyl with diazomethane and fluoroboric acid as in the earlier model sequence, and finally deprotection with hydrogen fluoride. As these last steps were being completed, it became apparent from the NMR spectra that we were not producing milbemycin $\beta_1$ as we had hoped. From extensive additional NMR and molecular modeling work on 49, we tentatively believed that we were producing a conformational isomer (atropoisomer) of $\beta_1$ around the C$_7$–C$_{12}$ bonds caused by constraining this unit with the cyclic benzylidene acetal group earlier in the synthesis. We were unhappy with this explanation, as were Dick Stoodley after the Perkin Meeting in Manchester in April 1988 and Clay Heathcock later that year at the Sendai Meeting, although they were unable to suggest solutions to the problem. We continued to analyze the data until we realized the simple mistake associated with the X-ray structure determination of the absolute configuration discussed earlier. All then became clear—we had in fact coupled the antipodal southern zone. The synthesis of milbemycin $\beta_1$ should now be straightforward after paying the debt of one beer lost in the bet with Professor Stoodley.

VI. At Last, Milbemycin $\beta_1$: The Real Thing

Based upon everything we had discovered so far, we could now define a synthetic plan to milbemycin $\beta_1$ (1) which we were extremely confident would be successful. This plan utilized the new chemistry for spiroacetal preparation and it employed the use of the bis-epoxide to link the side chain to the spiroacetal, with control of geometry and
configuration. It also used the coupling and macrolactonization sequences shown to be effective in the model compound syntheses. Furthermore, the plan was consistent with a general strategy which later also proved to be applicable to avermectin B1a synthesis (*vide infra*).

This highly convergent synthetic plan is presented in Scheme 27, showing the essential building blocks for the process. The preparation of 41 was described earlier; the alkenyl iodide 57 was obtained from S-(-)-methyl-3-hydroxy-2-methylpropionate, and the bis-epoxide 12 from ribonic acid-δ-lactone. The sulfone 9 was derived from the known carboxylic acid 58 using a modified selenolactonization procedure under thermodynamic conditions with N-phenylselenophthalimide (NPSP) and tin(IV) chloride in boiling dichloromethane to give 59 as the major product. These conditions were used during our other selenium-mediated cyclization chemistry reported earlier. Reductive removal of the phenylselenenyl group from 59 gave the lactone 60 which was converted to 9 by treatment with diisobutylaluminum hydride then benzenesulfinic

![Scheme 27](image-url)
acid (Scheme 28). Efficient coupling of 57, 12, and 9 to give the C_{11}−C_{25} northern hemisphere fragment 15 was discussed earlier (Scheme 15). Compound 15 was elaborated to the aldehyde 46 by benzoylation and fluoride treatment to give the alcohol 61, which was then oxidized using tetra-n-propyl ammonium perruthenate, TPAP{superscript 49} (Scheme 29). This reagent, which is a new room temperature, catalytic oxidant for alcohols, has served us well in many of our synthetic programs.

Coupling of the northern C_{11}−C_{25} unit 46 to the southern C_{1}−C_{10} fragment 41 was examined next, following the general procedures shown to be successful in the model studies. Treatment of 41 with two equivalents of tert-butyllithium gave the dianion which again reacted with 46 through its C_{10} carbon atom to give the coupled material in good yield (84%). Reductive elimination and benzoylation afforded the \( E,E \)-diene 62 (Scheme 30). Deprotection of 62 with tetra-n-butyl-ammonium fluoride gave the \( C_{1} \) alcohol 63. This

Scheme 28. (a) \( \text{N}-(\text{phenylselene}) \)-phthalimide, SnCl\(_{4}\), CH\(_{2}\)Cl\(_{2}\), reflux, 78\%. (b) Bu\(_{3}\)SnH, AIBN, DME, 80°C, 87\%. (c) DIBAL\(_{x}\), toluene, −78°C, 94\%. (d) PhSO\(_{2}\)-H, CSA, CH\(_{2}\)Cl\(_{2}\), 91\%.

Scheme 29. (a) Ph\(_{2}\)COCl, DMAP, pyridine, 85\%. (b) TBAF, THF, 95\%. (c) TPAP, NMO, 4Å ground sieves, CH\(_{2}\)Cl\(_{2}\), 85\%.
was oxidized in two steps, using the TPAP reagent to provide the aldehyde 64 followed by reaction with sodium chlorite to give the acid, which, after removal of the benzoate groups, was subjected to macro lactonization to give 65 (Scheme 30).

For the final steps of the synthesis the C5 hydroxyl group in 65 was oxidized to the carbonyl compound 66 using TPAP. At this stage we decided to deviate from the model studies by removing the benzylicene acetel protection in the hope that we would avoid any possible conformational problem associated with this ring constraint. This was achieved by brief exposure to trifluoroacetic acid. The product diol 67 reacted with tert-butyldimethylsilyl triflate and triethylamine, followed by addition of phenylselenenyl chloride, to give the selenide 68. Thus, in this one reaction we had effected regioselective selenenylation simultaneous with protection of the primary hydroxyl group. Oxidation of 68 with the Davis oxaziridine reagent44 gave the intermediate selenoxides which underwent spontaneous syn-elimination at room temperature to give a mixture of exo and endo products in a 1:2 ratio by 1H NMR. Owing to the possibility of aromatization of these compounds, they were most conveniently handled by work-up of this mixture with cerium(III)chloride/sodium borohydride to give the alcohols 69, 70, and 71 in a 1:1:1 ratio, in excellent overall yield. The compound 70 could be recycled to 71 by oxidation (TPAP) and reduction as above. Finally, methylation of 71 with methyl iodide and silver oxide under ultrasonication50 gave 72. Treatment with HF/pyridine gave us the long sought-after natural product milbemycin B1 (I) (Scheme 31). The synthetic sample was identical by 1H NMR, 13C NMR, IR, mass spectrum, optical rotation and TLC (3 solvent systems) to an authentic sample kindly provided by the Sankyo company.51

The day was Friday, January 27, 1989, and we celebrated with three jeroboams of champagne, which were consumed by the group in as many minutes! We then spent the next two months repeating the work and bringing material through to complete all our data and to optimize yields to tidy up the work for publication. The paper was written and submitted on March 28, just after Easter. You can imagine our surprise when, shortly afterwards, we received a referee’s comment on the work: “Preliminary reporting of organic synthesis should not be allowed to degenerate into uncheckable claims to priority. I would
Scheme 30. (a) 2.2 equivalents t-BuLi, THF, −78°C, then add (46), 84%. (b) 6% Na/Hg, NaHPO₄, 3 : 1 THF:MeOH, −40°C. (c) PhCOCl, DMAP, pyridine/CH₂Cl₂, 29%. (d) TBAF, THF, reflux, 91%. (e) TPAP, NMO, 4Å ground sieves, CH₂Cl₂, 76%. (f) NaClO₃, 2-methyl-2-butene, KH₂PO₄, t-BuOH/H₂O. (g) NaOMe, MeOH. (h) 2-chloro-1-methyl-pyridinium iodide, Et₃N, CH₂CN, reflux, 9 hours, 49% from (64). (i) TPAP, NMO, 4Å ground sieves, 83%.
much rather see this work described in two notes...". The referee also commented .. "it sets a bad example in that there is entirely inadequate characterization of all new compounds."

We were obviously very angry at these comments, since it was not our policy to unduly fragment work. Details of two key compounds were provided, as was a statement to the fact that all compounds had
been fully characterized by spectroscopic and microanalytical or accurate mass data. We modified the paper\textsuperscript{52} by adding six extra words and appealed to the Editor for his sense of fair play. Our appeals were immediately accepted, but with a "revised" submission date of April 25, 1989.

VII. The Final Celebration: Avermectin B1a Synthesis

The prize of this area of synthesis must be avermectin B1a (2) as it contains all the structural challenges of the series and also plays the central biological role. Throughout our work we endeavored to formulate a general strategy to these molecules. Indeed, the highly convergent route which evolved for milbemycin \( \beta \)\( _1 \) synthesis can also be adapted broadly to encompass the synthesis of 2. Following a similar convergent plan, we envisaged coupling of five key fragments (Scheme 32).
We retained the idea of constructing the spiroacetal portion through coupling of a side chain fragment derived from 73 and a hydropyranyl sulfone 74 with the bis-epoxide 12. The reduced hydrobenzofuran C1-C10 unit 75 was chosen following our previous experience for introducing the 3,4-unsaturation at a late stage in the synthesis. The carbohydrate residue oleandrose 76 needed for the coupling differentiates the avermectins from the milbemycins, which lack the bis-saccharide at the C13 position. Synthesis of the bis-epoxide 12 was commented upon earlier, although the remaining pieces of the puzzle in Scheme 32 are new. Another important difference from the work on milbemycin β1 was the availability of generous supplies of the natural product for degradation and relay studies.53 This was an enormous advantage, giving us the opportunity to match synthetic fragments with material obtained by degradation and manipulation. The complication for some of this work was that the natural product supply additionally contains approximately 5% avermectin B1b, the C25 isopropyl avermectin, which needs to be removed by tedious HPLC prior to some studies to ensure really clean samples and spectra. While we have used some similar degradation reactions to those described in the literature, many discussed here are new and have not been reported elsewhere.

The first of our degradation studies was aimed at providing material for the southern C1-C10 fragment 75 (Scheme 33). Here avermectin B1a (2) was converted to the C2-conjugated ester 77 using the Hanessian protocol.54 The free hydroxyl groups at C9-C10, and C4' were benzyolated to give 78 prior to selective C9-C10 double bond cleavage by ozonolysis in the presence of Sudan Red 7B as an indicator to detect excess ozone. Reductive work-up with sodium borohydride afforded the two fragments 79 (92%) and 80 (78%). The southern unit 80 was converted to the required coupling fragment via conversion of the primary hydroxyl group to the sulfide 81 using diphenyldisulfide and triphenylphosphine. Oxidation of the sulfide with Oxone® gave the sulfone 82. This, on conjugate reduction with an excess of sodium borohydride, gave a 1.4:1 mixture of esters 83 and 84. However, the β-isomer 84 was readily converted to 83 by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 70% yield. Reduction of 83 with lithium aluminum hydride gave the triol 85 which could be protected selectively with tert-butyldiphenylsilyl chloride to give 86. This material was
obtained in a reasonable 10% overall yield from avermectin B1a. Silylation afforded 75, identical to material prepared later by synthesis (vide infra).

In related degradation studies, the avermectin B1a aglycone (87), obtained from 2 by acidic glycolysis,\textsuperscript{35} was hydrolyzed using potassium hydroxide to open the macrolide and effect migration of the C\textsubscript{3} double bond into conjugation (Scheme 34). Methylation with diazomethane gave 88, which was subjected to silylation with tert-butyldimethylsilyl chloride to give 89. In a similar fashion to the previous degradation study, this was selectively ozonized to provide the C\textsubscript{11}-C\textsubscript{25} northern fragment 90 (87\%) as well as a C\textsubscript{1}-C\textsubscript{10} segment 91 (85\%). Both of these could be used in relay studies. For example, oxidation of 90 with the Swern reagent followed by methylationenation with dibromomethane/zinc/titanium tetrachloride\textsuperscript{56} gave 92 in 93\% overall yield. Compound 92, after deprotection
with HF in acetonitrile, afforded 93. This was also identical to the material targeted for synthetic studies (*vide infra*).

Among many other degradation and relay studies that we investigated,\(^{57}\) one final sequence (Scheme 35) provided key compounds which, we planned, would lie on the total synthesis pathway. Here we were able to show that the aglycone 87 could be selectively oxidized at the C2 position with manganese dioxide before conjugate reduction with sodium dithionite (Na₂S₂O₄)\(^{58}\) to give 94, albeit in a rather modest 35% overall yield. Nevertheless, this sequence could be used to prepare several other important compounds in the pro-
posed synthesis pathway and could conceivably be a route to novel avermectin analogues. Reduction with sodium borohydride gave the triol 95 which could be hydrolyzed to the acid 96 using potassium hydroxide in methanol. This compound was used in the later macrocorticosterization studies. Reduction of 96 with lithium aluminum hydride afforded the pentol 97 which also featured as a pivotal compound in the total synthesis.

These degradation and relay studies played a major role in facilitating a rapid conclusion to the avermectin B1a synthesis compared to the previous de novo synthesis of milbemycin B1a. However, although the groundwork that was covered during the B1 synthesis served us well, and most of our plans towards avermectin B1a worked, as with any major synthetic program it was not easy. We first tackled the problem of the preparation of the C1–C10 sulfone 75. As it turned
out, this was one of the most difficult problems to solve. We had set our goals high in that we wished to use a consistent strategy which would be widely applicable; from a common precursor, we hoped to prepare both the monocyclic southern zone fragments of milbemycin $\beta_1$ and the bicyclic hydrobenzofuran unit which occurs in so many avermectins and milbemycins. With regard to manipulation of intermediates used in the synthesis of the milbemycin southern hemisphere, the major task to be faced was the introduction of oxygen functionality at C$_8$. The obvious possibility of $\alpha$-oxygenation of a C$_5$-carbonyl group was generally thwarted by the ready $\beta$-elimination of a protected C$_7$-hydroxyl group upon deprotonation at C$_6$. In view of this problem, a C$_3$–C$_6$ olefin appeared to be potentially the most flexible precursor to oxygenation at these two positions. In addition to the possibility of direct oxidation, the large number of methods that would allow cyclization of a C$_9$-hydroxyl group onto this double bond was appealing. The regioselective elimination of the C$_2$-hydroxyl group present in most of the milbemycin southern hemisphere intermediates prepared to date would provide the most direct route to C$_3$–C$_6$ unsaturation. Initial results were promising; it was found that the mesylate 98, prepared from the corresponding alcohol 39, gave a 6:1 mixture of the olefin 99 and its C$_4$–C$_5$ isomer 100 after stirring overnight with basic alumina in carbon tetrachloride (Scheme 36). Unfortunately, we had difficulties in removing the benzylidene acetal protecting group from 99 due to problems with elimination of the tertiary hydroxyl group. More seriously, stocks of the particular batch of Woelm basic alumina that we had been using in these elimination reactions were running low, and we were unable to repeat the good elimination ratios with other samples. We therefore decided to investigate the introduction of the C$_5$–C$_6$ double bond before addition of the C$_6$–C$_{10}$ side chain. We found that the hydroxycyclohexanone

\[ \begin{align*}
\text{Scheme 36.} & \quad \text{(a) Woelm basic alumina, CCl}_4, 12\text{h, 80\%, 6:1 (99):(100).}
\end{align*} \]
16 could easily be dehydrated using methanesulfonyl chloride and triethylamine in dichloromethane to provide the cyclohexenone 101. However, rather disappointingly, this reacted with our favorite side chain, 2-lithio-4-phenylthiobut-1-ene, with poor selectivity, giving a 1:1 mixture of addition products 102 and 103 (Scheme 37). This ratio appeared to be insensitive to changes of temperature or solvent. Oxidation of the desired sulfide 103 gave the corresponding sulfone 104. We then spent a considerable period of time trying to effect selective olefin functionalization with this compound. We were particularly interested in the possibility of selective osmium tetroxide cis-hydroxylation of the ring double bond, or selective hydroboronation of the terminal methylene. Only one of the many transformations attempted, however, gave acceptable selectivity. Hydroxyl-directed epoxidation using the Sharpless conditions of vanadyl acetylacetonate and tert-butyl hydroperoxide provided predominantly the ring epoxide 105 (69%), along with the bis-epoxide 106 (22%). This bis-epoxide proved suitable for X-ray structure determination, allowing rigorous proof of stereochemistry at C$_7$ and C$_8$.

Since the ring epoxide 105 was the only compound we were able to obtain selectively, it became the focal point for further synthetic

**Scheme 37.** (a) MsCl, Et$_3$N, CH$_2$Cl$_2$, 100%. (b) 2 equivalents 2-lithio-4-phenylthiobut-1-ene, 1:1 ether/THF, -78°C, 44% (102), 50% (103). (c) Oxone$^\text{®}$, 1:1 THF/MeOH/pH 4 aqueous buffer, 89%. (d) VO(acac)$_2$, t-BuOOH, CH$_2$Cl$_2$, 69% 105, 22% 106.
transformations. The major blemish in the synthesis of 105 was the lack of stereocontrol in the side chain addition to the enone 101. As an alternative route, it was envisaged that nucleophilic addition to the epoxy ketone 107 should occur with good stereoselectivity. Tony Barrett, by this time working at Northwestern University, had shown the utility of similar epoxy ketones in the synthesis of avermectin model systems. Unfortunately, attempts to perform direct epoxidation of our enone 101 under basic conditions resulted in facile \( \beta \)-elimination of tert-butylidiphenylsilanol. Reduction gave predominantly the \( \text{C}_7-\beta \)-alcohol, precluding the use of a hydroxyl-directed epoxidation sequence to establish the \( \text{C}_5-\text{C}_6 \) stereochemistry. At around this time, several reports began appearing in the literature describing the power of dioxiranes in organic synthesis. The observation by Murray\(^{62} \) that a dilute (ca. 0.1 M) solution of dimethyldioxirane (108) could be distilled over from a basic mixture of acetone and Oxone\(^{65} \) was particularly interesting, since this provided a powerful, anhydrous oxidant. Pleasingly, reaction of such a dioxirane solution with enone 101 gave a readily separable 5:1 mixture of epoxides in favor of the desired isomer 107 (Scheme 38). The stereoselectivity of this reaction is not easily rationalized, but, as in every multi-step synthesis, the occasional piece of hard-earned good fortune is very welcome! We were also delighted to find that addition of 2-lithio-4-phenylthio-but-1-ene to 108 occurred with excellent diastereoselectivity. Oxidation of the sulfide 110 gave the sulfone 105, identical to the compound prepared by the previous route.

![Chemical structures](107) and (108)

We considered several options for continuing the synthesis from 105. Attempts to functionalize the terminal methylene group being unsuccessful, we examined many methods for epoxide opening with an oxygen nucleophile. Unfortunately, cleavage of the tert-butylidiphenylsilyl group always preceded epoxide opening. The conditions that we settled upon for this step are shown in Scheme 39;
Scheme 38. (a) Dimethyldioxirane, acetone/CH₂Cl₂, 11% (109), 64% (107). (b) 2-lithio-4-phenylthio-but-1-ene, THF, -70°C, 95%. (c) Oxone®, 1:1:1 THF/McOH/pH 4 aqueous buffer, 88%.

Scheme 39. (a) 1:1 15% H₂SO₄:THF, 60°C, 12h, 80%. (b) TBDPSCl, imidazole, DMF, 91%. (c) TBDMSOTf, Et₃N, CH₂Cl₂, 91%. (d) (COCl)₂, DMSO, then Et₃N, 73%. (e) NaBH₄, McOH, 79%.

selective re-protection of the primary hydroxyl group of tetraol 111 was inconvenient but trivial. Surprisingly, the diequatorial product of epoxide opening was obtained rather than the expected diaxial isomer.

The triol 112 now in hand possessed the correct C₅-stereochemistry, but inversion of the C₅ alcohol was necessary. Application of an oxidation-reduction procedure to this problem would require prior protection of the C₅-hydroxyl. Fortunately, it was found
that treatment with tert-butylidimethylsilyl triflate and triethylamine in dichloromethane gave 113 in excellent yield. This selectivity suggests that the C₆-hydroxyl group is very hindered, and indeed, difficulties were experienced in oxidizing this alcohol. Best results were achieved using an excess of the Swern reagent at higher temperature (−35°C) than is usual. Sodium borohydride reduction then gave the desired C₆-epimer 114.

We then tried to effect a selenium-mediated cyclization⁶⁴ of the C₆ alcohol of 114 onto the terminal double bond, since this would not only close the furan ring, but the resulting C₆-selenide would be a precursor to a C₉–C₉ double bond. This transformation could not be achieved, although a variety of conditions were examined. Turning instead to chemistry similar to that used in the preparation of the milbemycin southern hemisphere, the methylene group in 114 was subjected to hydroboration using borane–dimethyl sulfide followed by work-up with basic hydrogen peroxide to give the alcohols 115 as a 2:1 mixture of C₆ isomers (Scheme 40). While separation was possible, and the remaining steps of the synthesis were performed initially on the separate isomers, it was more convenient to perform the reaction on the mixture since both isomers converge in the later steps of the synthesis. Formation of the tetrahydrofurans 116 proceeded in 78% yield simply using p-toluenesulfonyl chloride and pyridine at 50°C. The final steps to the required southern zone fragment 75 involved treatment of 116 with 2.2 equivalents of n-butyllithium in THF at −78°C, quenching with phenylselenenyl chloride, followed by oxidation of the selenides with m-chloroperbenzoic acid and γα-elimination of the resulting selenoxides to afford the vinylic sulfones 117. Treatment of this mixture with tert-butyllithium resulted in proton abstraction from the position α to the sulfone rather than from the γ-position. However, under thermodynamic conditions, the vinylic sulfones mixture 117 was converted cleanly and stereoselectively to the E-allylic sulfone fragment 75 using DBU in acetonitrile at room temperature.⁶⁵ The synthetic compound 75⁶⁶ was spectroscopically identical to the sample obtained by degradation and manipulation of natural avermectin B1a.⁵⁷

The next key compound required for the synthesis was the hydrobenzofuran sulfone 74. While there are many conventional routes to this material that one could use, we chose to exploit a more
interesting synthetic procedure based on \( \pi \)-allyltrimcarbonyliron lactone complexes which we had developed in our laboratories. We found that the allylic alcohol 118, readily available from \((S)\)-2-methylbutanal,\(^{67}\) underwent asymmetric epoxidation using the excellent Sharpless procedure\(^{67}\) to give 119 (Scheme 41). This was oxidized and methylated to give the vinyl epoxide 120 as the precursor for the iron carbonyl chemistry. Reaction with diiron nonacarbonyl gave the readily separated diastereomeric tricarbonyliron lactone complexes 121 and 122. These could be transformed separately to the same unsaturated \( \delta \)-lactone 123 under previously established, high pressure carbonylation conditions.\(^{69,70}\) These reactions also afforded small amounts of other unsaturated lactone isomers which had to be removed by column chromatography. The double bond in 123 was removed by hydrogenation using hydrogen and platinum(IV) oxide to give 124. This was then readily transformed to the desired sulfone 74 by diisobutylaluminum hydride reduction and treatment with benzenesulfonic acid as in the earlier work. Since we required a double bond in this ring in the
Scheme 41. (a) Ti(OiPr)$_4$, t-BuOOH, D-(-)-diethyl tartrate, $-23^\circ$C, CH$_2$Cl$_2$, 81%.
(b) (COCl)$_2$, DMSO, then $Et_3N$, 80%. (c) Ph$_3$PCHBr, KHMSD, THF, 85%. (d) Fe$_5$(CO)$_9$, THF, 74%, ca. 1:1 121:122. (e) CO, 240 atm., 140$^\circ$C, benzene, 40%. (f) CO, 250 atm., 50$^\circ$C, benzene, 65%. (g) H$_2$, Ph$_3$P$_2$, EtOAc, 100%. (h) DIBAL, $-78^\circ$C, toluene, 93%. (i) PhSO$_2$H, CaCl$_2$, CH$_2$Cl$_2$, 85%.

final product, one might question why we removed this bond by hydrogenation. This is reasonable question, and indeed we did attempt to effect coupling reactions with this bond in place, but without success. We also examined other approaches to the sulfone 74 in order to guarantee supplies and to effect correlatives for absolute configuration determination. One of these routes gave 74 in just seven steps from L-isoleucine (Scheme 42). The key reaction in this sequence involved Brown's allylidisopinocampheyborane chemistry$^{71}$ which worked extremely well to set up two of the stereocenters. The sulfone obtained by these reactions was also subjected to X-ray crystallography to confirm the relative configuration and also the absolute configuration as a result of incorporating one
known stereocenter. This is also a route which we have not previously published.

The remaining fragment of the original general plan needed before we could begin coupling studies was the side chain alkenyl bromide 73. We investigated many routes to related units based on our knowledge from the milbemycin work, but none was entirely satisfactory due to low yields or because of long, inelegant sequences. It was at about this time that Danishefsky\(^7\) reported his beautiful synthesis of avermectin A1a and we were attracted by, among other things, the way he established the C\(_{12}\) and C\(_{13}\) stereocenters. We believed that his approach, once again based on Brown’s allylborane chemistry, could be adapted to our synthesis. We found that the hydroxy vinyl-bromide 125, after oxidation with TPAP, reacted smoothly with (+)-IPC-but-2-enyl borane. Protection of the alcohol as its silyl ether in the usual way gave 73 in 51% overall yield (Scheme 43). All was now set up to study the coupling reactions. Metal exchange of 73 with tert-butyllithium and trimethylaluminum gave a presumed intermediate aluminate which once again reacted with the bis-epoxide 12 to give the product alcohol. Silylation afforded 126. Reaction of 126 with the anion derived from the 2-benzenesulfonyl pyran 74, prepared earlier, in the presence of boron trifluoride etherate, gave the rather labile enol ether 127 on work-up. Using chemistry we had established on model systems, 127 was subjected to selenenylation, spirocyclization, elimination and deprotection to provide the northern
hemisphere 93 of avermectin B1a without purification of intermediate compounds. These reactions all proceeded in good yield. We believe this to be an extremely expedient route, comparing extremely well with any existing synthesis of similar fragments.\(^{72}\) It should be remembered that 93 was also available by natural product degradation and modification from the relay studies. Finally, 93 was converted to the aldehyde 128 suitable for coupling with the southern C\(_1\)-C\(_{10}\) carbon skeleton 75 by protection and subsequent oxidative cleavage of the terminal methylene group.\(^{73}\)

The stage was now set to perform the final couplings and head towards avermectin B1a itself. Treatment of 75 with two equivalents of tert-butyllithium at \(-78^\circ\)C followed by reaction with the aldehyde
128 successfully effected the important coupling of the two major components, giving the hydroxysulfones 129. Following reductive elimination, the E, E-diene 130 was obtained (Scheme 44). We then decided to take a very bold step and remove all the protecting groups by reacting 130 with tetra-n-butylammonium fluoride to give the pentol 97. We hoped that by exploiting the reactivity differences of the various hydroxyl groups in 97 we would be able to prepare the avermectin B1a aglycone 87 without the need for further protection. This turned out to be the case and the reader will now recognize the importance of the relay and modification studies we performed earlier as these underpin the next sequence of reactions. Selective primary alcohol oxidation of 97 under the Oshima conditions\(^\text{74}\) gave an intermediate aldehyde which was immediately oxidized further to the C\(_1\)-acid 96. We believed that this would undergo intramolecular macro lactonization rather than any intermolecular coupling process and indeed, treatment with 2-chloro-1-methylpyridinium iodide gave 95. The next selective transformation which had to be achieved was the oxidation of the secondary C\(_5\) hydroxyl group in the presence of the C\(_{13}\) allylic secondary hydroxyl group. On the face of it, this task

\[ \text{Scheme 44. (a) 2.2 equivalents \text{-BuLi}, THF, \text{–78°C}, then add 128, 74%. (b) 6\% NaHg, THF/MeOH, Na\(_2\)HPO\(_4\), 34\%. (c) TBAF, THF, \text{Δ 94\%}. (d) RuCl\(_3\)(PPh\(_3\))\(_3\), benzene. (e) NaClO\(_4\), 2-methyl-2-buten, KH\(_2\)PO\(_4\), \text{-BuOH/H\(_2\)O, 29\% from 97. (f) 2-chloro-1-methyl-pyridinium iodide, Et\(_3\)N, CH\(_2\)CN, reflux, 9 hours, 47\%.} \]
appears to be a difficult one, but from molecular modeling studies and other chemistry we believed the C_{13} position to be more hindered than C_3 and therefore thought that it was worth a try. We found that by using our TPAP reagent stoichiometrically at 0°C we could achieve this transformation, giving 94 in 60% yield (Scheme 45).

Installation of the carbonyl group at the C_3 position now gave access to the chemistry discovered in the milbemycin work for introduction of the important 3,4-double bond. Once again, this was achieved by selenenylation of an intermediate, regioselectively produced enol ether, to give the α and β selenides 131 and 132 in a 1:1 ratio. Sym-elimination of the selenoxides from 131 using the Davis oxaziridine reagent gave the avermectin B1a aglycone (87).

Scheme 45. (a) TRAP, CH_2Cl_2, 60%. (b) TMSOTf, B_3N, CH_2Cl_2, 0°C, 93%. (c) PhSeCl, CH_2Cl_2, -78°C, 90%, then HF, CH_2CN, 88%, 1:1 131/132. (d) 2-phenylsulfonyl-3-([nitrrophenyl]oxaziridine, CHCl_3, 23°C. (e) NaN_3, CeCl_3, 7H_2O, MeOH, 35% 87, 23% 11. (f) CH_2COCl, pyridine, 97%.
(35%) and the \textit{exo}-methylene derivative 133 (23%) after reaction with cerium(III) chloride and sodium borohydride.\textsuperscript{76} The synthetic aglycone was, of course, identical in all respects to the material obtained from the natural product by glycolysis. The formation of the \textit{exo}-methylene isomer 133 in these eliminations is annoying and we have not yet found a method either to produce the \textit{endo}-isomer exclusively or to convert 133 to 87. Similar elimination of the \(\beta\)-selenide 132 gives only the \textit{exo}-product. We are continuing to study these reactions until we solve this step to our satisfaction.

Having prepared the aglycone we could have declared a formal total syntheses of avermectin B1a since the coupling of the \textit{bis}-oleandrosyl disaccharide unit was known,\textsuperscript{74,77,78} but we had come a long way and could not give up so easily. It seemed to us that there were still challenges left in this molecule that were worthy of study. In particular, new methods for the preparation of 2-deoxy sugars would be useful, as would alternative glycosidation reactions. These could find applications in many other areas.

Although syntheses of oleandrose have been reported,\textsuperscript{77,78,79} we chose to adopt a new approach, using \(\pi\)-allyltricarbonyliron lactone complexes. We had shown that alkenyl cyclic sulfites served as novel, non-volatile precursors for complex formation.\textsuperscript{80} We therefore prepared the cyclic sulfite 135, configurationally defined at the important \(C_4\) center (Scheme 46). This was reacted with diiron non-acarbonyl in benzene under ultrasonic conditions to give the two diastereoisomeric complexes 136 and 137. Carboxylation of these compounds in the presence of acrolein as an iron carbonyl scavenger to minimize double bond migration gave the \(\beta,\gamma\)-unsaturated lactone 138. Owing to volatility this was generally isolated in yields of around 50%, although in one run a 98% yield was recorded. The lactone 138 was then treated with dimethylidioxirane to give a mixture of unstable epoxides which were best not isolated but reacted with 2% triethylamine in pyridine to give the two hydroxy lactones 139 and 140. In fact, 140 is the natural product osmundalactone which had been prepared previously by somewhat longer synthetic sequences.\textsuperscript{81} In our original communication\textsuperscript{82} only one of these lactones, 140, had been converted to oleandrose. However, we have now devised a convergent route which also transforms the other isomer 139 to oleandrose. These unsaturated lactones are separable but because of their instability it is necessary to use silica gel columns
Scheme 46. (a) Allylmagnesium bromide, THF, −60°C to 25°C, 74%. (b) Catalytic TsOH, MeOH, 92%. (c) SOCl₂, CCl₄, 100%. (d) Fe₅(CO)₉, benzene, ii), 65%. (e) CO, Δ, acrolein, pressure, benzene, 51%. (f) Dimethylidioxirane, acetone, 0°, then 2% Et₃N/pyridine, 75%, 2:1 139:140. (g) Diethyl azodicarboxylate, PPh₃, Et₂O, PhCO₂H, 92%. (h) DIBAL, THF, −78°C. (i) Dibal, toluene, −78°C. (j) 1% DBU, MeOH.
which have been doped with pyridine. Diisobutylaluminum hydride reduction of 140 in THF gave an unstable intermediate, presumably a lactol or a ring-opened equilibrating mixture. The crude product was immediately treated with DBU in methanol at room temperature to give oleandrose 76 and cymarose 141. We believe these are produced under these conditions as an equilibrium mixture by ring opening, \(\beta\)-elimination and readdition, followed by ring closure. Indeed, re-exposure of cymarose 141 to the reaction conditions rapidly establishes the 7:3 ratio of 76 to 141 which facilitates a recycling process to permit isolation of more oleandrose via Florisil chromatography.

The other hydroxyl lactone isomer 139 required an inversion of configuration prior to its conversion to oleandrose. This was readily achieved by reaction under Mitsunobu conditions to give the benzoate 142. Similar reduction of this compound with diisobutylaluminum hydride in toluene gave entry to the same intermediate lactol which was converted to the oleandrose/cymarose mixture. As we are using a convergent route to oleandrose it is appropriate to describe a combined yield for the process from the lactone 138 of 40% following one recycle of the cymarose. This novel route further exemplifies the use of tricarbonyliron lactone complexes for synthesis.

Since these studies we have also developed a new, three-step preparation of oleandrose from \((S)\)-\((-)\)-methyl lactate 143 which employs the conjugate exchange process and gives access to multigram quantities of this useful sugar derivative (Scheme 47). The process involves addition of an excess of (3-butenylsulfanyl) benzene dianion to \((S)\)-\((-)\)-methyl lactate 143 to give the keto sulfones 144 as 1:1 mixture of diastereomers. Chelation-controlled reduction of 144 with ethereal zinc borohydride furnished the diols 145 and 146 in a 1:20 ratio. The high stereoselectivity appears to be unaffected by the mixture of stereoisomers present in 144. The final step in the synthesis involved oxidative cleavage, elimination of benzenesulfinic acid and conjugate addition of methanol in the presence of DBU to the resulting \(\alpha,\beta\)-unsaturated aldehyde, followed by ring closure. All these reactions are carried out in one pot and this leads to oleandrose 76 and cymarose 141 as in the previous sequence. Following one recycle of cymarose under the re-equilibration conditions, a total yield of 55% of oleandrose can be realized from \(S\)-\((-)\)-methyl lactate 143.
We next studied dimerization reactions of oleandrose derivatives to provide the disaccharide, using a new glycosidation method which we had developed.\textsuperscript{84} We preferred to follow this pathway rather than simply adopt existing methods. We believe our new route also has practical advantages and has proved to be both efficient and reliable.

Reaction of oleandrose 76 with acetic acid activated by carbonyl-diimidazole gives a \(1:1\) mixture of diacetate 147 and the first coupling partner, the \(C_1\) monoacetate 148, in excellent yield (Scheme 48). The mixture here was especially useful and was a designed part of the plan to afford differentiated materials for the coupling procedure. Treatment of the diacetate 147 with lithium triethylborohydride at \(-78^\circ C\) cleanly afforded the \(C_4\) monoacetate 149 which is the second coupling unit. Conversion of 149 to its imidazoylcarbonyl glycoside and coupling with the \(C_1\) monoacetate 148 activated by the addition of silver perchlorate in ether at 40° C gave the disaccharide diacetate 150 in 62% yield after separation of a small amount of the \(C_1\) \(\beta\)-anomer. Once again, selective deprotection of 150 worked extremely well at \(-78^\circ C\) using 2.5 equivalents of lithium triethylborohydride to give 151. In contrast to the previous coupling, compound 151 had to be converted to the imidazoylyl-thiocarbonyl glycoside 152 by treatment with thiocarbonyl-diimida-
Scheme 48. (a) Carbonyldiimidazole, AcOH, CH₂Cl₂, 93%, 1:1 mixture, (b) 2.5 equivalents LiBH₄, THF, -78°C, 95%. (c) Carbonyldiimidazole, THF, AgClO₄, 62%. (d) 2.5 equivalents LiBH₄, -78°C, 98%. (e) Thiocarbonyldiimidazole, THF, 97%. (f) 134, AgClO₄, K₂CO₃, THF/toluene, 64%. (g) LiBH₄, THF, -78°C, 90%.
zole in THF since the corresponding imidazooyl carbonyl derivative failed to undergo coupling with the very hindered C₁₃ hydroxyl group of the avermectin aglycone. On the other hand, reaction of avermectin B₁a aglycone C₅ monacetate 1₅₄ with 1₅₂ in the presence of silver perchlorate and potassium carbonate in THF/toluene gave 1₅₃ in 65% yield. A small amount of contaminating β-anomer always produced in these glycosidations was readily removed by chromatography. Finally, removal of the two acetate groups, from C₅ and C₆, was achieved with treatment with an excess of lithium triethylborohydride, to give the macrolide anthelmintic agent avermectin B₁a (2), identical in all respects to the natural product. Champagne time!

Acknowledgments

We thank a large number of people: N. J. Anthony, P. M. Booth, M. G. Brasca, D. S. Brown, D. Culshaw, D. Dice-Martin, M. J. Ford, C. Greck, P. Grice, I. A. O’Neill, A. Jackson, A. B. Jones, J. G. Knight, H. C. Kolb, B. Lygo, A. Madin, S. Mukherjee, A. N. Shaw, G. Strange, S. Vile, A. D. White, A. Wonnacott and M. Woods, all of whom have contributed so much to the success of this project. Not all have been rewarded with publications although their names are mentioned in the text and their efforts are duly acknowledged. We also thank the SERC, Ministerio de Educacion y Ciencia (Spain), the British Council, SmithKline Beecham for a CASE award, Farmitalia Carlo-Erba, and NATO for their support of this work. Finally, little of this work would have been possible had it not been for the generous financial contributions from ICI Strategic Research Fund, Merck, Sharp and Dohme and, especially, Pfizer Central Research.

References

THE CHAMPAGNE ROUTE TO AVERMECTINS AND MILBEMYCINS

7