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

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.

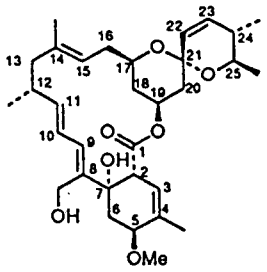
Some have the view that organic synthesis is a mature subject with little opportunity for new developments to be made. To the extent that we have come a long way in the last thirty years, this is true. We can now prepare complex target molecules in a relatively short period of time. We are at a point 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!

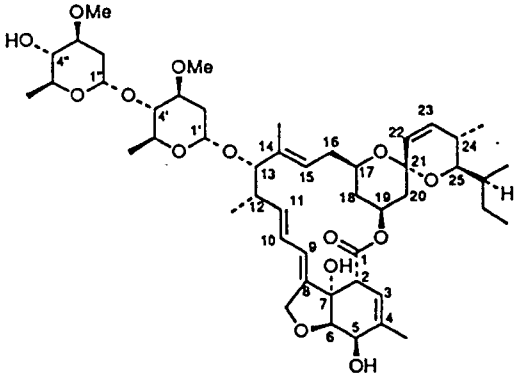
II. The Challenge

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.[1] 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.[2] In this chapter we discuss our efforts towards milbemycin β_1(**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,



Milbemycin β_1 (1)



Avermectin B1a (2)

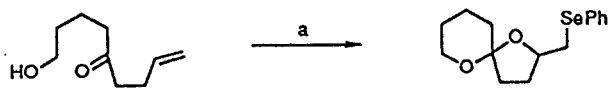
methodology for its formation was rather limited. Opportunities therefore presented themselves for new synthetic chemistry towards these groupings. The preparation of the sixteen-membered macrolactone ring was considered to be straightforward using existing methods, but this was only possible due to the significant advances made in large-ring synthesis in relatively recent times.[3] 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" C_1–C_{10} 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 β_3,[4] milbemycin β_1,[5] milbemycin E,[6] avermectin A1a,[7] avermectin B1a[8] and the avermectin B1a aglycone[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[4c] and Williams[4a], had already reported their syntheses of milbemycin β_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.[10] We were able to show that hydroxyalkenyl ketones underwent spiroselenocyclization when treated with N-phenylselenophthalimide and zinc bromide (Scheme 1).[11] This reaction is an intramolecular version of a process first reported by Sharpless.[12]

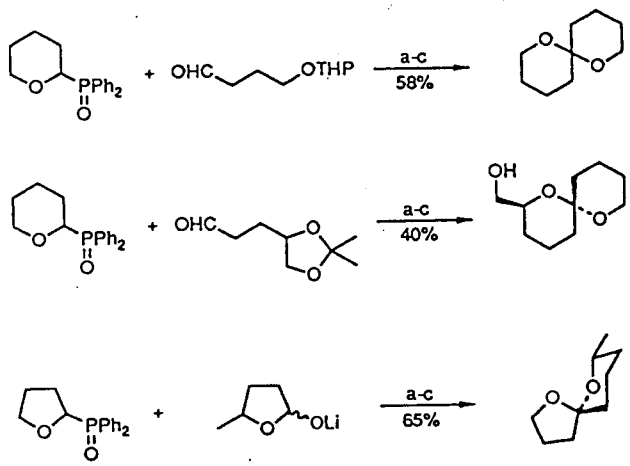
Although this method began our interest in the area and we were able to use the route for the preparation of some simple pheromone natural products, it was hardly sophisticated enough for the project in hand. At about this time our colleague at Imperial College, Tony



SCHEME 1. (a) *N*-(phenylseleno)phthalimide, $ZnBr_2$, 78%.

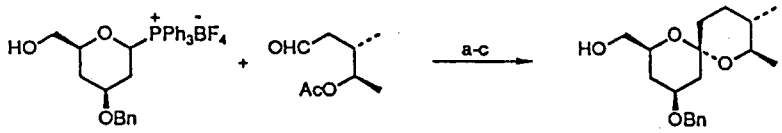
Barrett, had also begun synthetic studies on the milbemycins and avermectins, so it seemed reasonable that we should join forces and write a proposal to the Wolfson foundation to support our work. This was successful, and prompted the first champagne celebration. It also had the effect of concentrating our thoughts to improve the methods and to seriously begin the process of total synthesis. The problem of spiroacetal preparation[13] 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 anomeric effect[14] would be expected to allow stereocontrol at the anomeric 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.[15] A few examples of this process (Scheme 2) serve to illustrate its potential. Again,



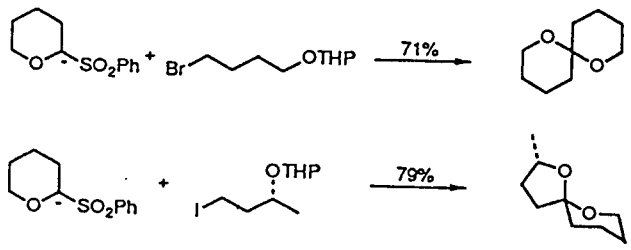
SCHEME 2. (a) LDA, THF, −78°C, then add aldehyde or lactol. (b) KO*t*-Bu, THF. (c) Cat. CSA, MeOH.

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.[16] More importantly, however, these promising reactions could be applied to a simple synthesis of the spiroacetal fragment of the milbemycins,[17] giving us considerable encouragement (Scheme 3).



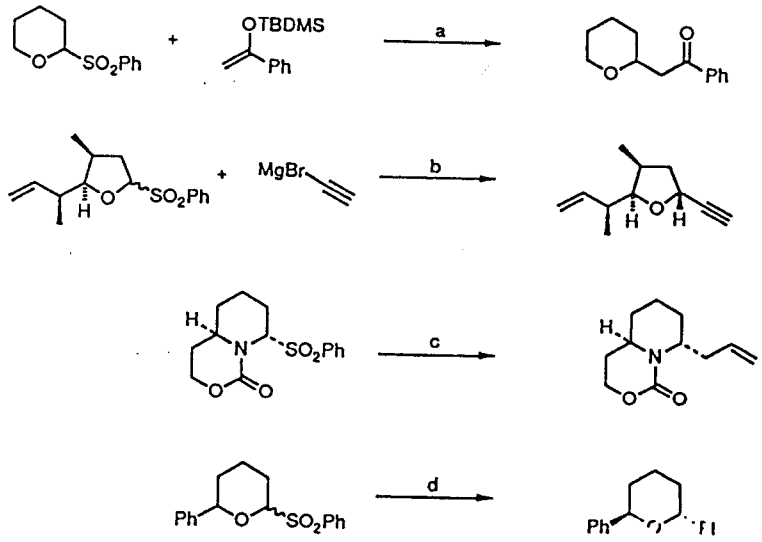
SCHEME 3. (a) 2 equivalents BuLi, THF, −78°C to 25°C. (b) NaOMe, MeOH. (c) 3M HCl, 36%.

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 phenylsulfone 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 hydropyrans, lactols or lactol ethers by treatment with benzenesulfinic acid,[18] or alternatively by oxidation of the corresponding anomeric sulfides.[19] In the first experiments, we found these sulfones to be excellent precursors for spiroacetal preparation.[18] Following deprotonation with *n*-butyllithium at low temperature, the resulting anions reacted with halides to give a product which underwent spontaneous elimination of benzenesulfinic acid on warming to room temperature. Acidic work-



SCHEME 4

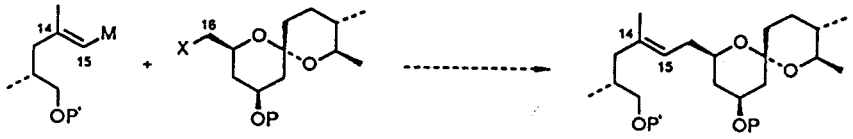
up gave spiroacetals in excellent yield (Scheme 4). The method turned out to be generally useful for the preparation of dihydropyran enol ethers. It was also found that direct substitution of the phenylsulfonyl group by organometallic reagents provided a simple new method for forming carbon-carbon bonds at the position adjacent to oxygen in cyclic ethers (Scheme 5).[20] Later work showed that we were also able to translate this substitution chemistry to cyclic amines, piperidines and pyrrolidines.[21] 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.



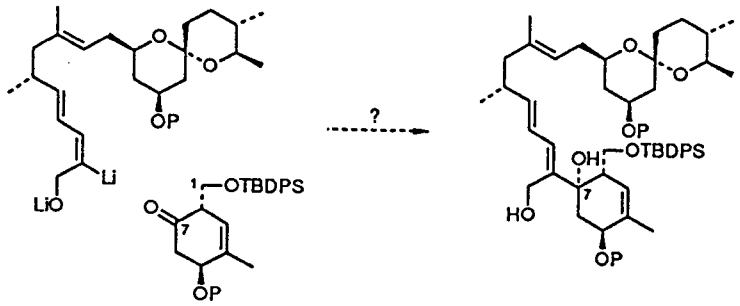
SCHEME 5. (a) $AlCl_3$, 90%. (b) $ZnBr_2$, THF, >95:5 *trans:cis*. (c) Allyltrimethylsilane, $AlCl_3$, 93%. (d) Et_2Zn, CH_2Cl_2, 25°C, 90%.

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[4d] were experiencing similar difficulties which they commented upon in subsequent publications.

In the meantime, we had begun to explore a route to milbemycin β_1 **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

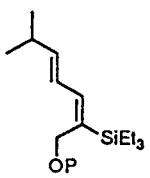


SCHEME 6



SCHEME 7

combined, we hoped, with a method of controlling the important C_7 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.



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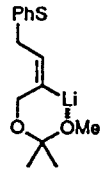
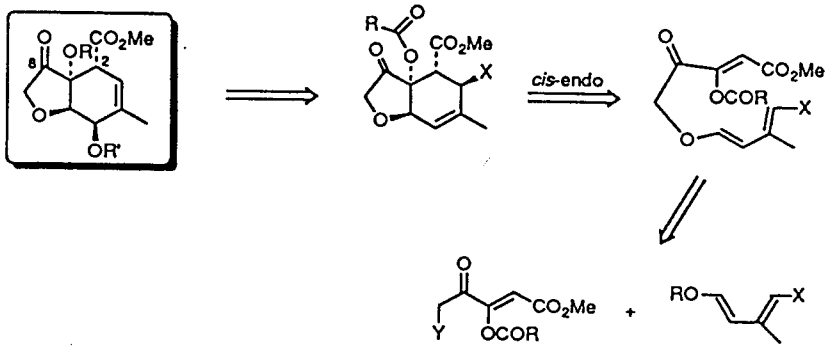


(4)

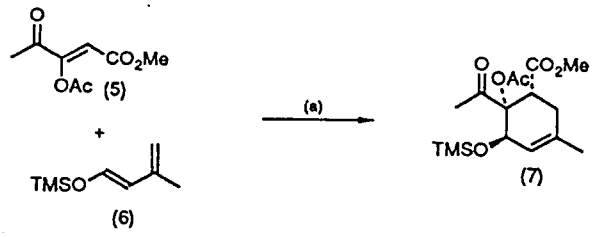
Concurrent with these early side chain and spiroacetal studies, we had also begun to address the issue of the synthesis of southern zone fragments. We planned to adopt a strategy which could be applied to both mono- and bicyclic southern units. On paper, we were most attracted by the Diels-Alder route which is shown retrosynthetically in Scheme 8. Although we eventually abandoned this approach, other groups (Ireland[22] and more recently Uang[23]) were much more successful, even though they have not yet used their fragments in total synthesis studies. Jung[24] has also reported a Diels-Alder approach to the avermectin hydrobenzofuran unit. Ian O'Neil, who examined our route,[25] 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 C_2 stereocenter and the liability of the 3,4-double bond to move into conjugation with the ester group.[26] Furthermore, we were worried that addition reactions to a hindered C_8 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 phenylselenenyl group in position X (Scheme 8), *via* its selenoxide and a [2,3]-sigmatropic shift, to set up the desired C_5 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]

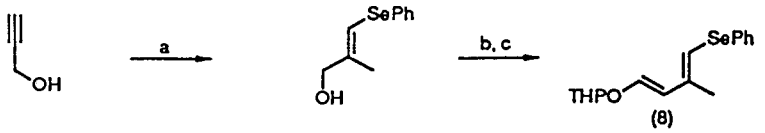
In model studies we were able to effect the Diels–Alder reaction of an acetoxy dienophile **5** with a substituted diene **6** to give the cycloaddition product **7** in 65% yield (Scheme 9). Disappointingly, all attempts to convert **7** to useful substrates for the synthesis by α-oxidation or direct nucleophilic addition to the C_8 ketone failed. Although we were also able to prepare a phenylselenenyl- substituted diene **8** by a short, stereoselective sequence (Scheme 10), it failed to react with **5** to give any cycloaddition product.



SCHEME 8



SCHEME 9. (a) 115°C, toluene, 72h, 65%.

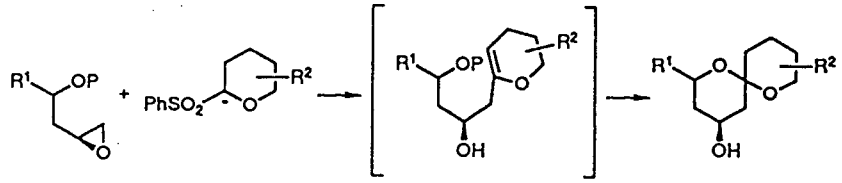


SCHEME 10. (a) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, then PhScCl, 32%. (b) MnO_2, 95%. (c) (Tetrahydropyranyl)methylenediethylphosphonate, 48%.

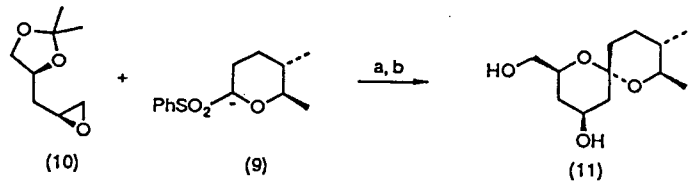
IV. The Next Stage

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.[28] This one reaction became the heart of all the remaining hydroxy-substituted spiroacetal syntheses leading to milbemycin β_1 (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).

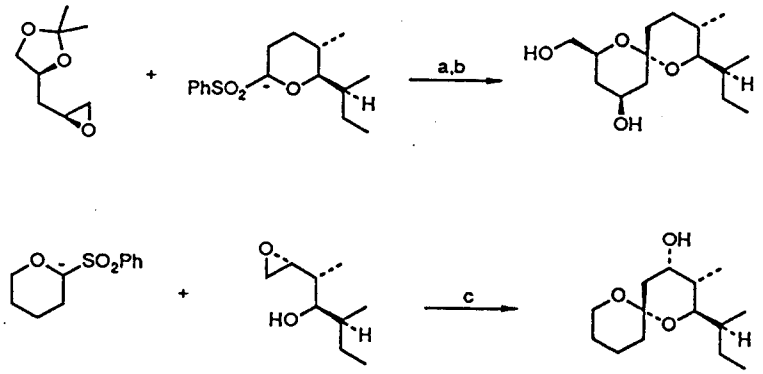
In a specific example, reaction of the anion from the sulfone **9** with the epoxide **10** gave the milbemycin spiroacetal **11** in 76% yield following treatment of the intermediate enol ether with camphorsulfonic acid[28] (Scheme 12). Similar reactions with other substrates afforded models for the avermectin spiroacetal, or, by reversing the coupling partners, gave the spiroacetal common to the avermectin 2 series (Scheme 13).[29] More recently, a modification of the same general method has allowed the preparation of unsaturated systems similar to those found in avermectin B1a.[30] The basis of this



SCHEME 11



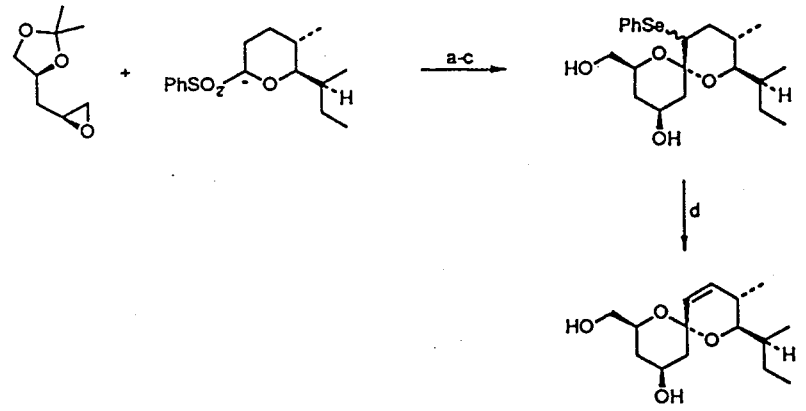
SCHEME 12. (a) BuLi, THF, −78°C. (b) CSA, MeOH, 25°C, 76%.



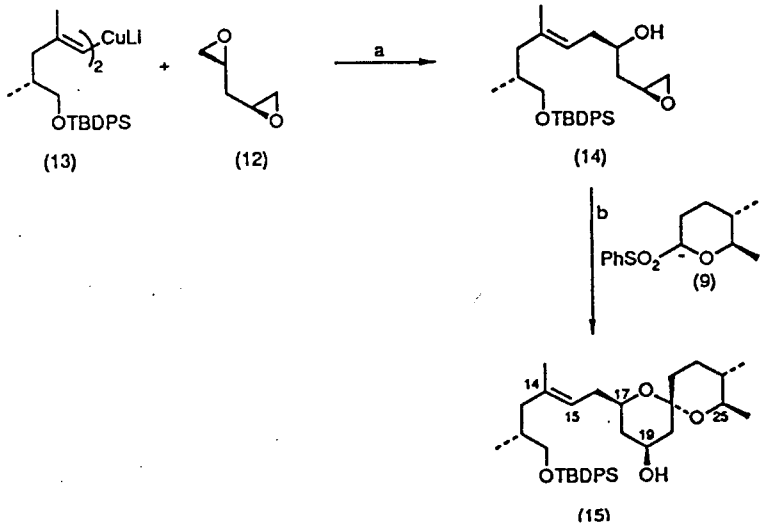
SCHEME 13. (a) BuLi, THF, −78°C, then add epoxide. (b) TsOH, 28%. (c) BuLi, THF, −78°C to 25°C, add epoxide, $Ti(OiPr)_4$, 56%.

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}



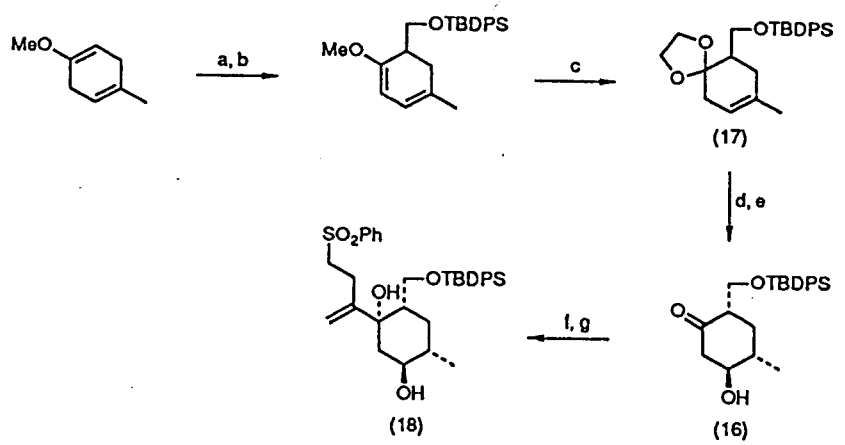
SCHEME 14. (a) BuLi, THF, −78°C to −50°C, then add epoxide. (b) PhSeCl, MeOH, Et_3N. (c) TsOH (cat.), CH_2Cl_2, 31%. (d) Camphor sulfonyl oxaziridine, CH_2Cl_2, 59%.



SCHEME 15. (a) −65°C, 4 hours, 53%. (b) Sulfone anion, $Ti(OiPr)_4$, THF, −78°C, then 5% aqueous H_2SO_4, 80%.

fragment **15** of the milbemycins (Scheme 15).[28] 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.

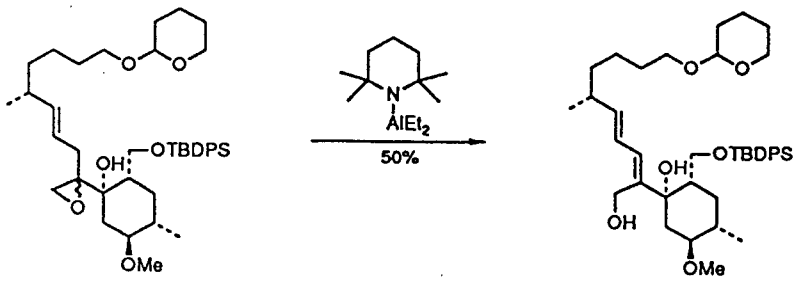
Along with these studies we were formulating a route to the southern portion of the natural products based upon a stereoselective alkenyl-anion addition reaction to a cyclohexanone derivative **16**, setting up the important C_7 angular hydroxyl stereochemistry. The choice of **16** was deliberate in 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.



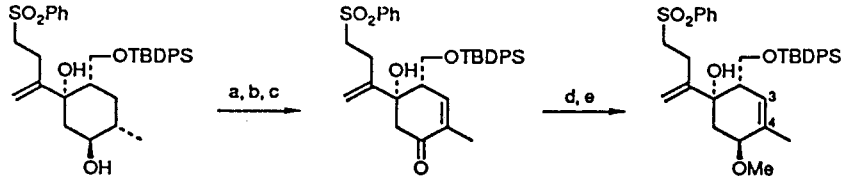
SCHEME 16. (a) Me_3Al, $(CHO)_n$, CH_2Cl_2, 0°C, 64%. (b) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 98%. (c) Ethylene glycol, PPTS, C_6H_6, reflux, 16h, 88%. (d) $BH_3 \cdot Me_2S$, then aqueous NaOH, H_2O_2. (e) $PdCl_2(CH_3CN)_2$, acetone, 98%. (f) 2-lithio-4-phenylthio-but-1-ene, THF/ether, −78°C, 87%. (g) *m*CPBA, CH_2Cl_2, then Oxone®, MeOH/THF/H_2O, 88%.

In order to assess **16** as an eventual precursor for milbemycin β_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 β_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-tetramethylpiperidide[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 β_1 (Scheme 18). Oxidation of the C_5 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. (a) Diethylaluminum 2,2,6,6-tetramethylpiperidine, benzene, 50%.

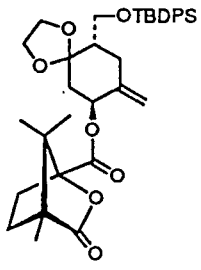


(18) (20) (19)

SCHEME 18. (a) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, 100% (b) PhSeCl, EtOAc, 25°C. (c) *m*CPBA, aqueous $NaHCO_3$, CH_2Cl_2, 96%. (d) $NaBH(OAc)_3$, AcOH, 25°C, 92%. (e) CH_2N_2, HBF_4, CH_2Cl_2, −78°C to 25°C, 94%.

isomerization of the double bond into conjugation on oxidation of the C_1 center.

The remaining problem to be solved was how to obtain this southern zone fragment in optically pure form for the synthesis of milbemycin β_1. Attempts of effect a kinetic resolution by asymmetric hydroboration[35] 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)-(−)-camphanic 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.



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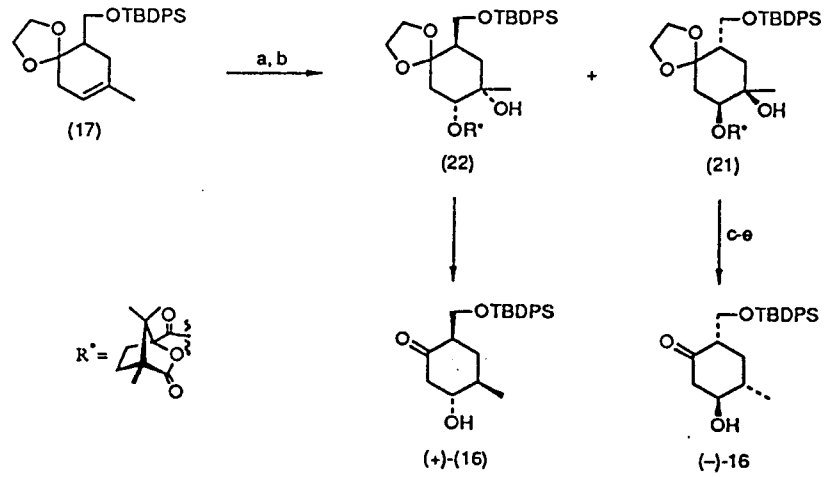


SCHEME 19. (a) OsO_4, NMO, *t*-BuOH/THF/H_2O, 71%. (b) 1S-(−)-camphanic acid chloride, Et_3N, DMAP, CH_2Cl_2. (c) K_2CO_3, MeOH, 88%; (d) $(MeO)_3CH$, PPTS, CH_2Cl_2, 100%; (e) Ac_2O, reflux, 64%, then as Scheme 16.

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)-(−)-camphanic acid residue in the original Aldrich catalog[37] and in the review by J. W. Scott in Morrison's "Asymmetric Synthesis",[38] 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 β_1 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!

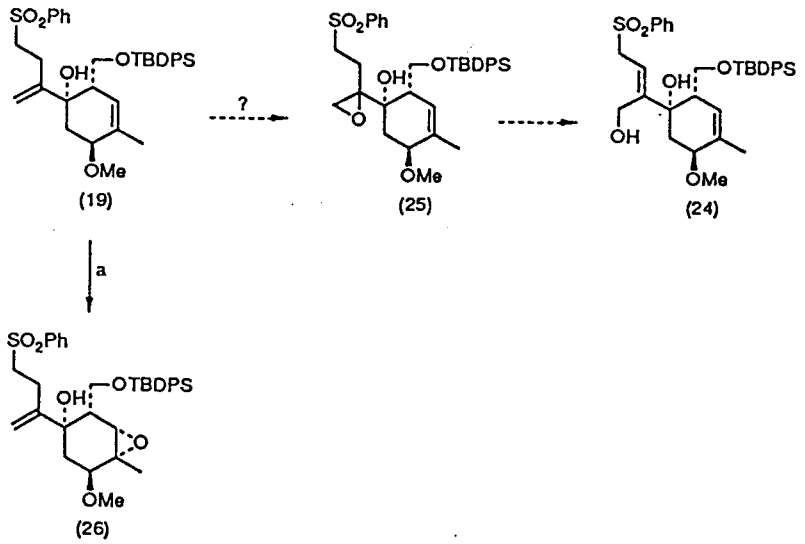
V. Synthesis of Model Compounds and Model Reactions

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 β_1 emblazoned on the front. It was a further three years before the synthesis of milbemycin β_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 β_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.

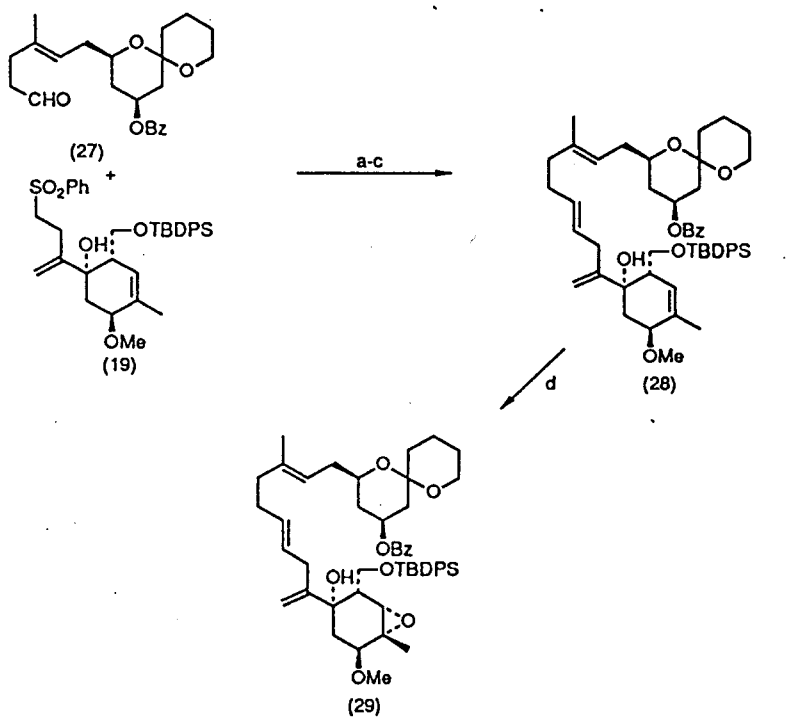
The problems that remained were to find a suitable method to create the side chain *E,E*-dienol portion of milbemycin β_1, and to establish a route to macrocyclic materials. We first attempted to modify the southern fragment **19** by directed epoxidation followed by allylic rearrangement to give a more suitable coupling unit **24** (Scheme 20). Surprisingly, when we used standard hydroxyl-



SCHEME 20. (a) $VO(acac)_2$, *t*-BuOOH, 66%.

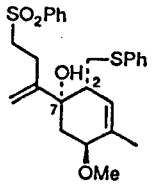
directed epoxidation with vanadyl acetylacetonate and *tert*-butyl hydroperoxide[39] or *m*-chloroperbenzoic acid, none of the allylic epoxide **25** was obtained. Rather, we obtained the homoallylic product **26** selectively and in high yield. We therefore decided to investigate some coupling reactions 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 desulfonylation, the *E*-alkene **28** was obtained. Unfortunately, this too reacted under the Sharpless conditions to give the homoallylic epoxidation product **29** (Scheme 21).[40]

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/MeOH, Na_2HPO_4, 45%. (d) $VO(acac)_2$, *t*-BuOOH, 50%.

primary alcohol, *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 *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 *via* fragmentation of the C_2–C_7 bond assisted by the angular hydroxyl group.[40]



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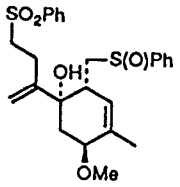
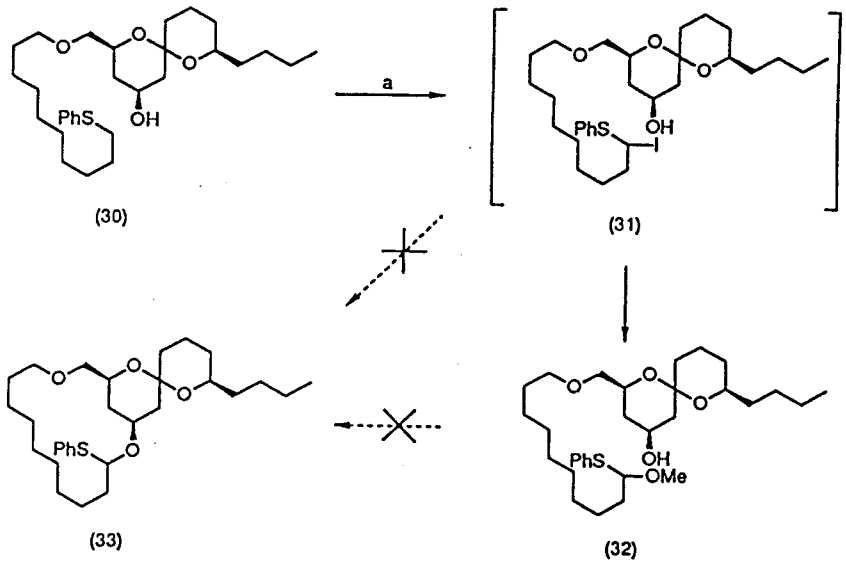


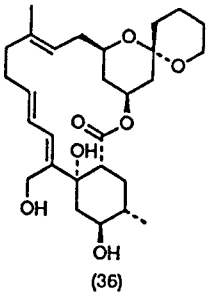
(35)

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 β_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



SCHEME 22. (a) *N*-Chlorosuccinimide, NaI, K_2CO_3, CCl_4, then MeOH, 33%.

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*-vinylic 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 β_1.



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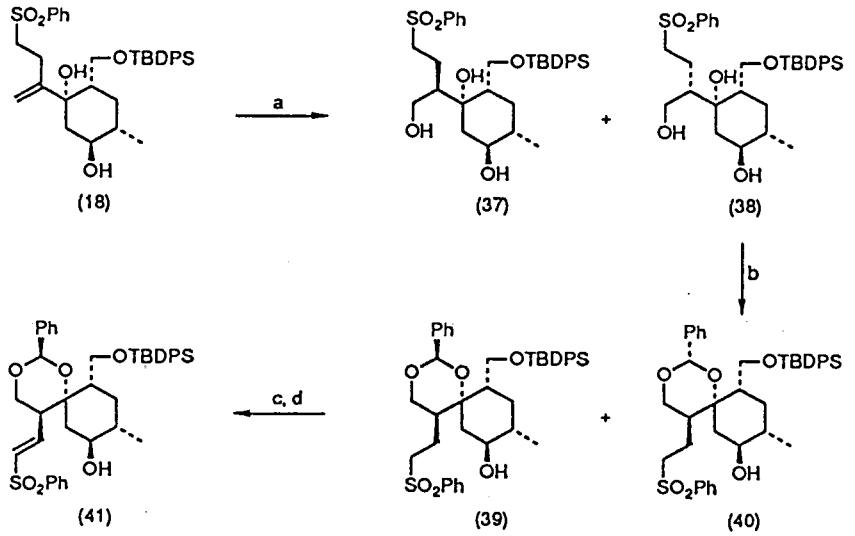
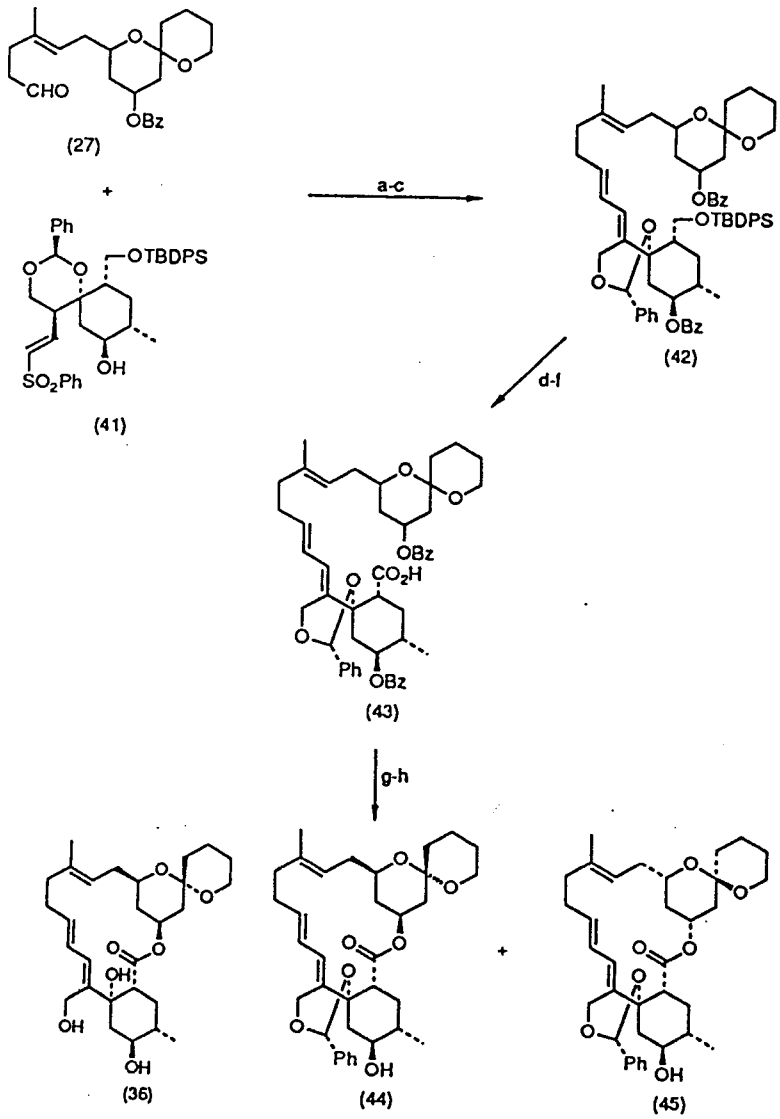


SCHEME 23. (a) $BH_3 \cdot Me_2S$, then aq. NaOH, H_2O_2. (b) PhCHO, PPTS, C_6H_6, reflux. (c) 2.2 eq. *t*-BuLi, THF, −78°C, then PhSeCl, 79%. (d) *m*CPBA, CH_2Cl_2/aqueous $NaHCO_3$, 99%.

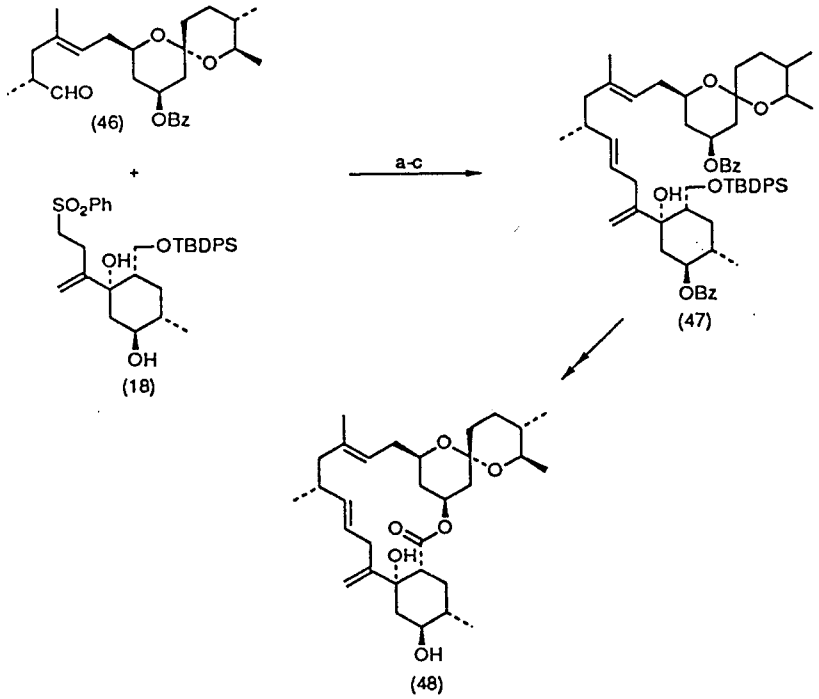
For the preparation of the model compound **36**, we proposed to couple the previously synthesized spiroacetal **27** with the dianion derived from **41**. We thought that **41** would undergo deprotonation with two equivalents of *tert*-butyllithium and that due to the conformation of the system it would remain sufficiently stable to react with **27** under Julia-type coupling conditions[41] *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 macrolactonization. Thus, deprotection with tetra-n-butylammonium fluoride and two-stage oxidation using Swern conditions followed by immediate further oxidation with buffered sodium chlorite[42] gave the acids **43**. The



SCHEME 24. (a) 2 equivalents BuLi, THF, then add (27). (b) PhCOCl, −78°C to 25°C. (c) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 25%. (d) TBAF, THF, 67°C, 77%. (e) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, 100%. (f) $NaClO_2$, KH_2PO_4, 100%. (g) NaOMe, MeOH. (h) 2-chloro-*N*-methyl pyridinium iodide, Et_3N, CH_3CN, reflux, 13% (44), 15% (45). (i) TFA, CH_2Cl_2.

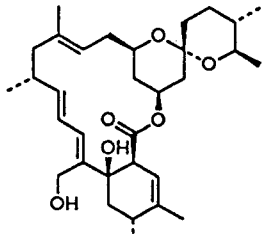
benzoyl groups were removed with sodium methoxide and the crude products subjected to macrolactonization using the Mukaiyama conditions.[43] As we were using racemic coupling partners, two diastereomeric sixteen-membered ring macrolide products **44** and **45** were expected. Removal of the benzylidene acetal protection from **44** gave the model compound **36** which, among other things, showed NMR characteristics for the olefin region very similar to β_1 (Scheme 24).[40,44] This route established the background for the eventually successful sequence to milbemycin β_1 (**1**).

In another model study,[45,46] we coupled the trianion generated from **18** with the C_{11}–C_{15} northern hemisphere fragment **46** which had been prepared previously by the 2-benzenesulfonyl tetrahydropyran technology. After benzoylation, reductive desulfonylation gave the C_{10}–C_{11} *E*-coupled product **47**. This was then processed by similar chemistry to that established in the previous model study to provide the macrolide **48** (Scheme 25). Unfortunately, due



SCHEME 25. (a) 3 equivalents BuLi, THF/toluene, then add (46). (b) PhCOCl. (c) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 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 β_1 synthesis.



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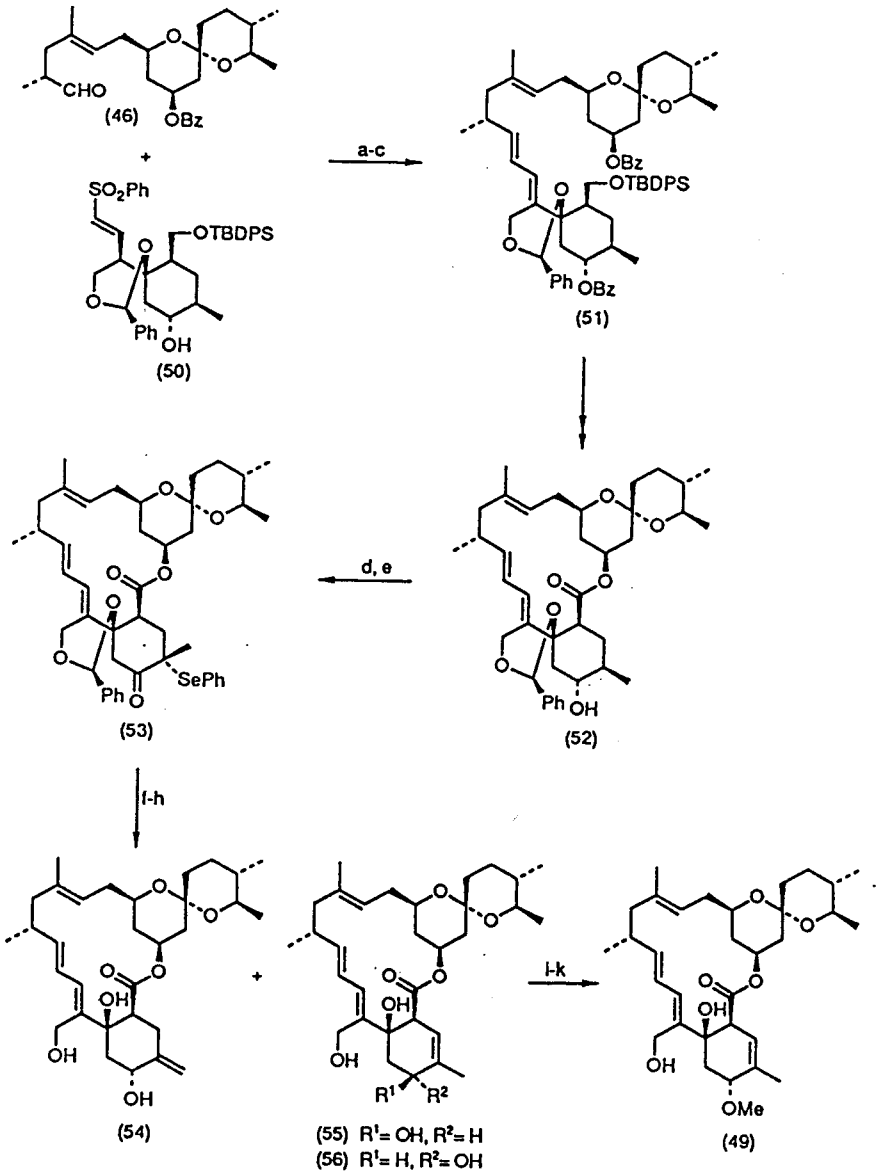
The final model system we studied involved coupling of enantiomerically pure fragments. In this phase of the work we believed we were proceeding towards milbemycin β_1 itself, but as it turned out we prepared a novel isomer **49** owing to the initial misassignment of absolute stereochemistry of the 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 β_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 benzoylation 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 C_5 oxidation, the C_4–C_5 *tert*-butyldimethylsilyl 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% Na/Hg, THF/MeOH, Na_2HPO_4, 29%. (d) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, 100%. (e) TBDMSOTf, Et_3N, CH_2Cl_2, then PhSeCl, −30°C, 92%. (f) TFA, CH_2Cl_2, −78C. (g) 2-phenylsulfonyl-1-3-(p-nitrophenyl)oxaziridine. (h) $NaBH_4$, $CeCl_3$. $7H_2O$, MeOH, 23% (54), 13% (55), 21% (56). (i) TBDMSCl, Et_3N, 0°C, CH_2Cl_2, 40%. (j) CH_2N_2, HBF_4, CH_2Cl_2, 70%. (k) HF/pyridine, 60%.

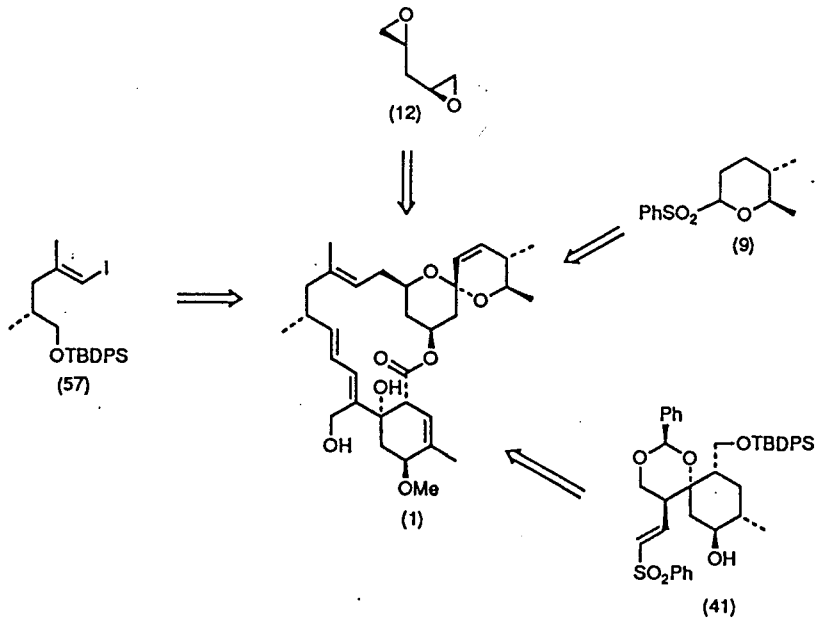
53. After some experimentation it was found that after deprotection of **53**, oxidation to the selenoxides using an oxaziridine reagent[47] and subsequent *syn*-elimination, followed by reduction under the Luche[48] conditions (sodium borohydride and cerium(III) chloride) three products **54**, **55**, 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*-butyldimethylsilyl 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 β_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 β_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 β_1 should now be straightforward after paying the debt of one beer lost in the bet with Professor Stoodley.

VI. At Last, Milbemycin β_1: The Real Thing

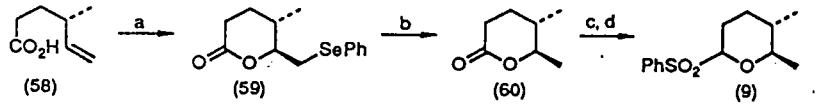
Based upon everything we had discovered so far, we could now define a synthetic plan to milbemycin β_1 (**1**) which we were extremely confident would be successful. This plan utilized the new chemistry for spiroacetal preparation and it employed the use of the *bis*-epoxide to link the side chain to 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.[5] The sulfone **9** was derived from the known carboxylic acid **58**[4b] 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.[11] Reductive removal of the phenylselenenyl group from **59** gave the lactone **60** which was converted to **9** by treatment with diisobutylaluminum hydride then benzenesulfinic



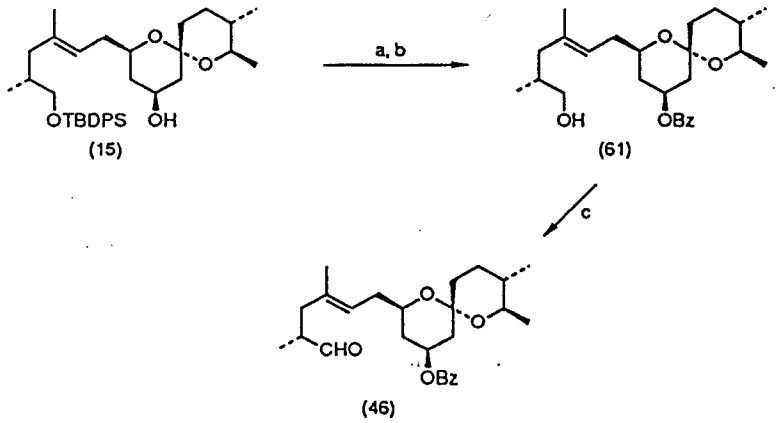
SCHEME 27



SCHEME 28. (a) *N*-(phenylseleno)phthalimide, $SnCl_4$, CH_2Cl_2, reflux, 78%. (b) Bu_3SnH, AIBN, DME, 80°C, 87%. (c) DIBAL, toluene, −78°C, 94%. (d) $PhSO_2H$, CSA, CH_2Cl_2, 91%.

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[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

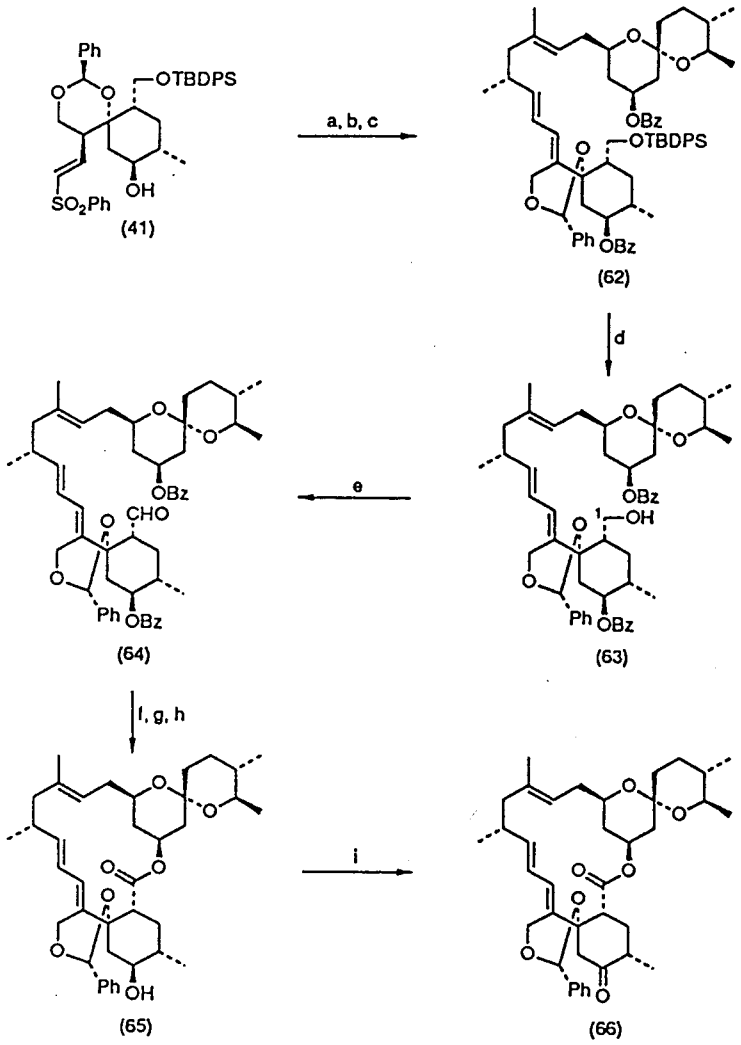


SCHEME 29. (a) PhCOCl, DMAP, pyridine, 85%. (b) TBAF, THF, 95%. (c) TPAP, NMO, 4Å ground sieves, CH_2Cl_2, 85%.

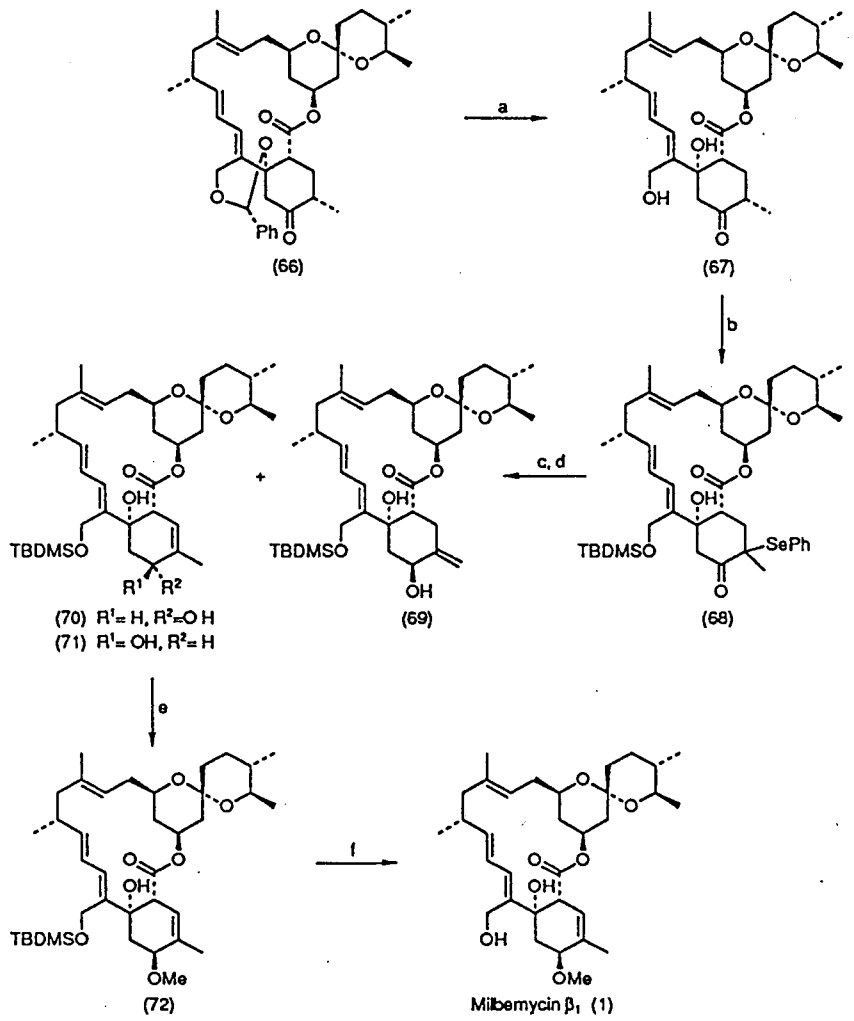
was oxidized in two steps, using the TPAP reagent to provide the aldehyde **64** followed by reaction with sodium chlorite to give the acid, which, after removal of the benzoate groups, was subjected to macrolactonization to give **65** (Scheme 30).

For the final steps of the synthesis the C_5 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 benzylidene acetal 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 reagent[47] 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 ^{1}H 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 ultrasonication[50] gave **72**. Treatment with HF/pyridine gave us the long sought-after natural product milbemycin β_1 (**1**) (Scheme 31). The synthetic sample was identical by ^{1}H NMR, ^{13}C 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, Na_2HPO_4, 3 : 1 THF:MeOH, −40°C. (c) PhCOCl, DMAP, pyridine/CH_2Cl_2, 29% (d) TBAF, THF, reflux, 91%; (e) TPAP, NMO, 4Å ground sieves, CH_2Cl_2, 76%. (f) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH/H_2O. (g) NaOMe, MeOH. (h) 2-chloro-1-methyl-pyridinium iodide, Et_3N, CH_3CN, reflux, 9 hours, 49% from (64). (i) TPAP, NMO, 4Å ground sieves, 83%.



SCHEME 31. (a) TFA, CH_2Cl_2, 92%. (b) TBDMSOTf, Et_3N, CH_2Cl, then PhSeCl, CH_2Cl_2, 50%. (c) 2-(Phenylsulfonyl)-3-(*p*-nitrophenyl) oxaziridine, $CDCl_3$, r.t. (d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH. (e) MeI, Ag_2O,))), 73%. (f) HF, pyridine, CH_3CN, 75%.

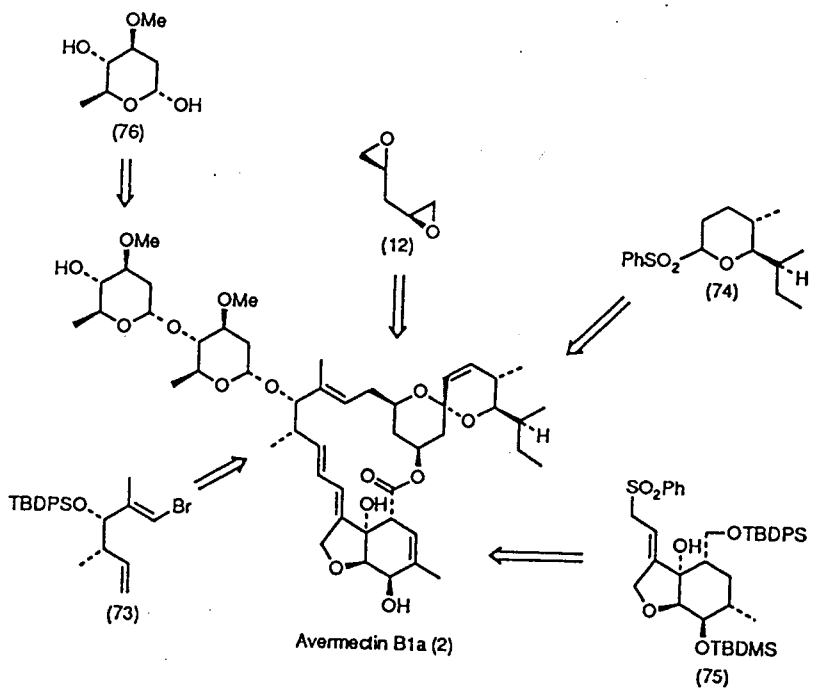
much rather see this work described in two notes...". The referee also commented .. "it sets a bad example in that there is entirely inadequate characterization of all new compounds."

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[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

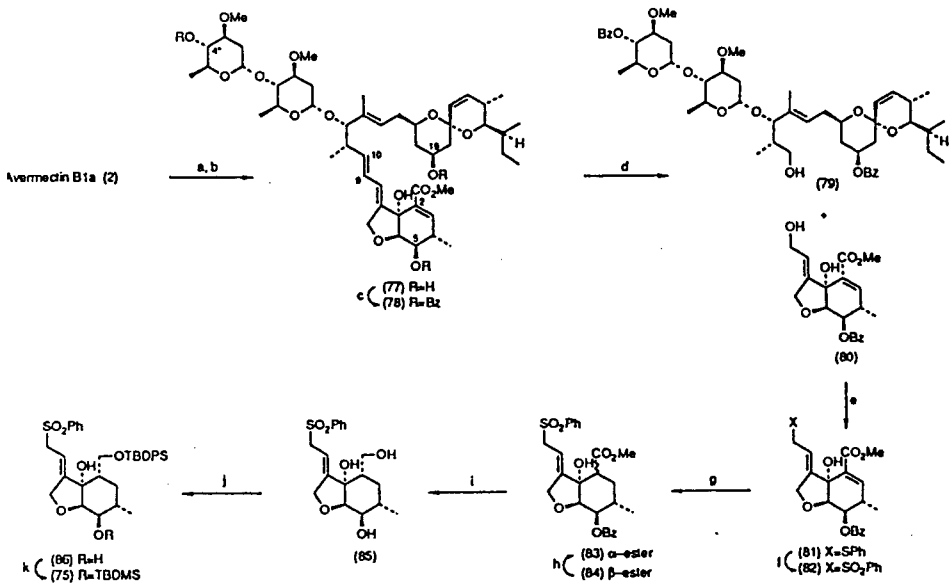
The prize of this area of synthesis must be avermectin B1a (2) as it contains all the structural challenges of the series and also plays the central biological role. Throughout our work we endeavored to formulate a general strategy to these molecules. Indeed, the highly convergent route which evolved for milbemycin β_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).



SCHEME 32

We retained the idea of constructing the spiroacetal portion through coupling of a side chain fragment derived from **73** and a hydropyran sulfone **74** with the *bis*-epoxide **12**. The reduced hydrobenzofuran C_1–C_{10} 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 C_{13} 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 β_1 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 C_{25} 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.

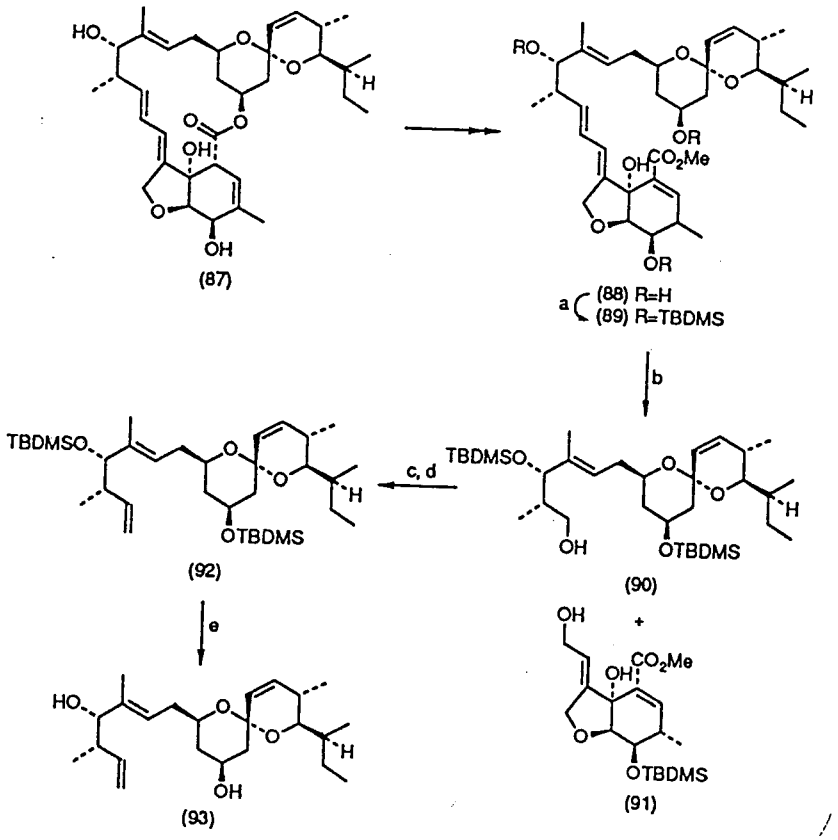
The first of our degradation studies was aimed at providing material for the southern C_1–C_{10} fragment **75** (Scheme 33). Here avermectin B1a (**2**) was converted to the C_2-conjugated ester **77** using the Hanessian protocol.[54] The free hydroxyl groups at C_5–C_{19}, and $C_{4''}$ were benzoylated to give **78** prior to selective C_9–C_{10} 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



SCHEME 33. (a) Aqueous KOH, DME. (b) CH_2N_2. (c) PhCOCl, DMAP, pyridine, 80% from (2). (d) O_3, −78°C, CH_2Cl_2/EtOH, then $NaBH_4$, 92% (79), 78% (80). (e) PhSSPh, Bu_3P, THF, 95%. (f) Oxone®, MeOH/aqueous pH 4 buffer, 99%. (g) $NaBH_4$, MeOH, 73%. (h) DBU, CH_2Cl_2, 3 days, 70%. (i) $LiAlH_4$, THF, 0°C, 70%. (j) TBDPSCl, Et_3N, CH_2Cl_2, 72%. (k) TBDMSOTf, Et_3N, CH_2Cl_2, 100%.

obtained in a reasonable 10% overall yield from avermectin B1a. Silylation afforded **75**, identical to material prepared later by synthesis (*vide infra*).

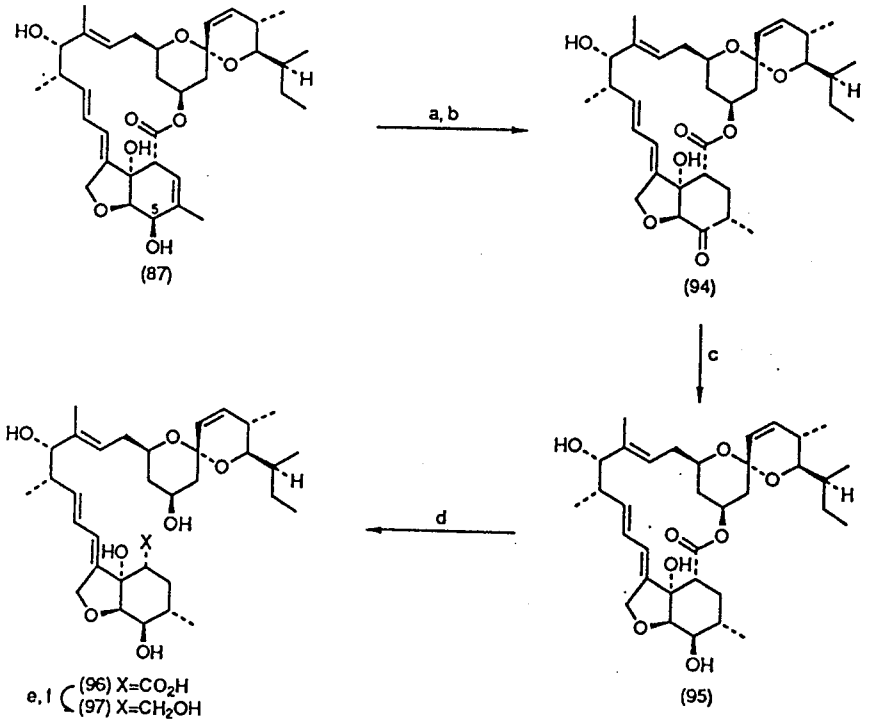
In related degradation studies, the avermectin B1a aglycone (**87**), obtained from **2** by acidic glycolysis,[55] was hydrolyzed using potassium hydroxide to open the macrolide and effect migration of the C_3 double bond into conjugation (Scheme 34). Methylation with diazomethane gave **88**, which 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_{11}–C_{25} northern fragment **90** (87%) as well as a C_1–C_{10} segment **91** (85%). Both of these could be used in relay studies. For example, oxidation of **90** with the Swern reagent followed by methylenation with dibromomethane/zinc/titanium tetrachloride[56] gave **92** in 93% overall yield. Compound **92**, after deprotection



SCHEME 34. (a) TBDMSCl, imidazole, DMAP, DMF, 75%. (b) O_3, −78°C, CH_2Cl_2–EtOH, then $NaBH_4$, 87% (90), 85% (91). (c) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2. (d) CH_2Br_2, Zn, $TiCl_4$, 93% from (90). (e) HF/CH_3CN, 90%.

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 C_5 position with manganese dioxide before conjugate reduction with sodium dithionite ($Na_2S_2O_4$)[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-

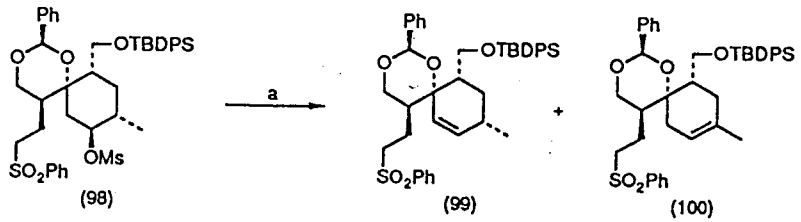


SCHEME 35. (a) MnO_2. (b) $Na_2S_2O_4$. (c) $NaBH_4$, MeOH, 30% from (87). (d) KOH, DME, Δ. (e) CH_2N_2, 88%. (f) $LiAlH_4$, Et_2O, 68%.

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 macrolactonization 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 β_1. However, although the groundwork that was covered during the β_1 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 C_1–C_{10} sulfone **75**. As it turned

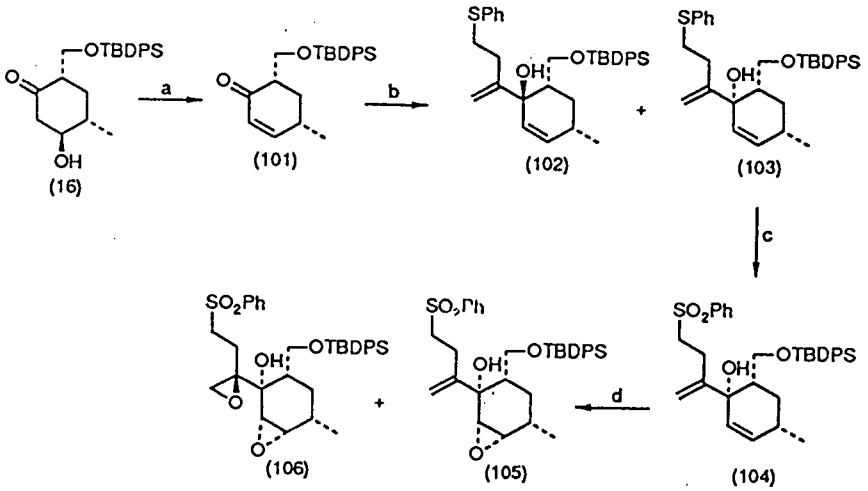
out, this was one of the most difficult problems to solve. We had set our goals high in that we wished to use a consistent strategy which would be widely applicable; from a common precursor, we hoped to prepare both the monocyclic southern zone fragments of milbemycin β_1 and the bicyclic hydrobenzofuran 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_6. The obvious possibility of α-oxygenation of a C_5-carbonyl group was generally thwarted by the ready β-elimination of a protected C_7-hydroxyl group upon deprotonation at C_6. In view of this problem, a C_5–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_8-hydroxyl group onto this double bond was appealing. The regioselective elimination of the C_5-hydroxyl group present in most of the milbemycin southern hemisphere intermediates prepared to date would provide the most direct route to C_5–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).[59] 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_8–C_{10} side chain. We found that the hydroxycyclohexanone



SCHEME 36. (a) Woelm basic alumina, CCl_4, 12h, 80%, 6:1 (99):(100).

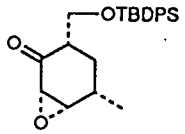
16 could easily be dehydrated using methanesulfonyl chloride and triethylamine in dichloromethane to provide the cyclohexenone **101**. However, rather disappointingly, this reacted with our favorite side chain, 2-lithio-4-phenylthiobut-1-ene,with poor selectivity, giving a 1 : 1 mixture of addition 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 hydroboration 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_5.

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_3N, CH_2Cl_2, 100%. (b) 2 equivalents 2-lithio-4-phenylthio-but-1-ene, 1 : 1 ether/THF, −78°C, 44% (102), 50% (103). (c) Oxone®, 1 : 1 : 1 THF/MeOH/pH 4 aqueous buffer, 89%. (d) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 69% **105**, 22% **106**.

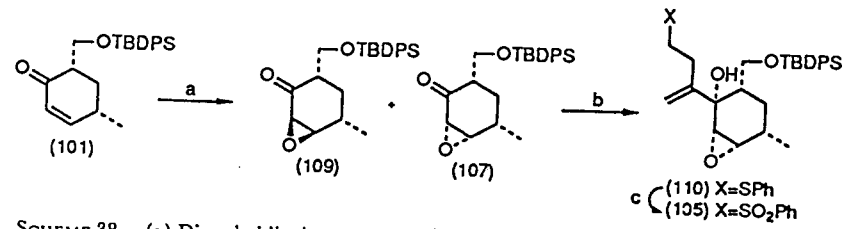
transformations. The major blemish in the synthesis of **105** was the lack of stereocontrol in the side chain addition to the enone **101**. As an alternative route, it was envisaged that nucleophilic addition to the epoxy ketone **107** should occur with good stereoselectivity. Tony Barrett, by this time working at Northwestern University, had shown the utility of similar epoxy ketones in the synthesis of avermectin model systems.[60] Unfortunately, attempts to perform direct epoxidation of our enone **101** under basic conditions resulted in facile β-elimination of *tert*-butyldiphenylsilanol. Reduction gave predominantly the C_7-β-alcohol, precluding the use of a hydroxyl-directed epoxidation sequence to establish the C_5–C_6 stereochemistry. At around this time, several reports began appearing in the literature describing the power of dioxiranes in organic synthesis.[61] 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® was particularly interesting, since this provided a powerful, anhydrous oxidant.[63] 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.



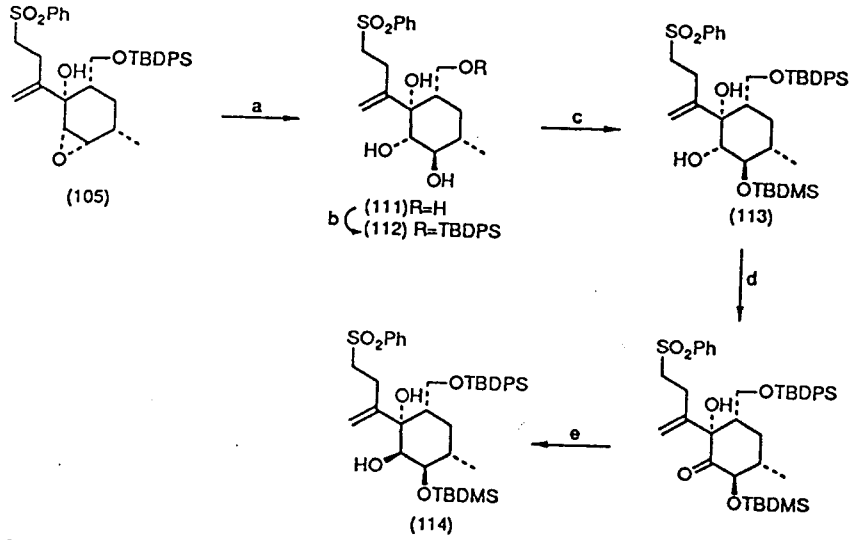
(107)

(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*-butyldiphenylsilyl group always preceded epoxide opening. The conditions that we settled upon for this step are shown in Scheme 39;



SCHEME 38. (a) Dimethyldioxirane, acetone/CH_2Cl_2, 11% (109), 64% (107). (b) 2-lithio-4-phenylthio-but-1-ene, THF, −78°C, 95%. (c) Oxone®, 1:1:1 THF/MeOH/pH 4 aqueous buffer, 88%.



SCHEME 39. (a) 1:1 15% H_2SO_4:THF, 60°C, 12h, 80%. (b) TBDPSCl, imidazole, DMF, 91%. (c) TBDMSOTf, Et_3N, CH_2Cl_2, 91%. (d) $(COCl)_2$, DMSO, then Et_3N, 73%. (e) $NaBH_4$, MeOH, 79%.

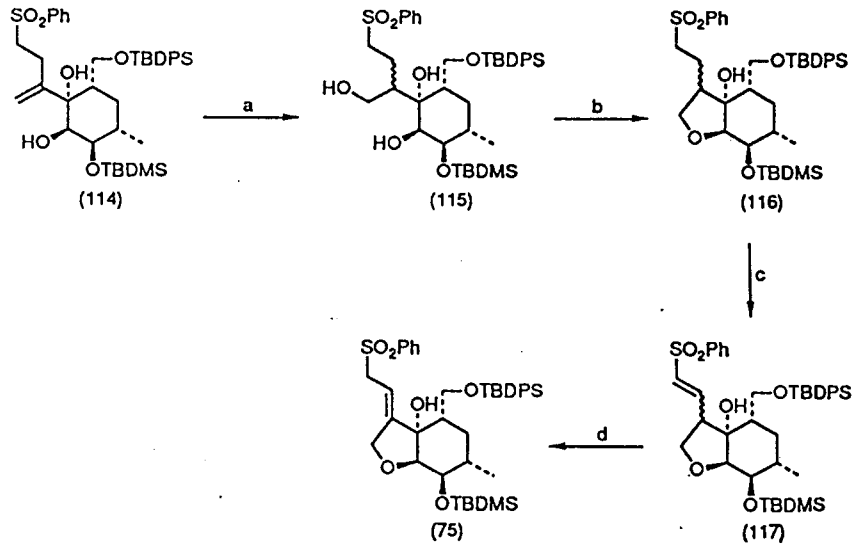
selective re-protection of the primary hydroxyl group of tetraol **111** was inconvenient but trivial. Surprisingly, the diequatorial product of epoxide opening was obtained rather than the expected diaxial isomer.

The triol **112** now in hand possessed the correct C_5-stereochemistry, but inversion of the C_6 alcohol was necessary. Application of an oxidation-reduction procedure to this problem would require prior protection of the C_5-hydroxyl. Fortunately, it was found

that treatment with *tert*-butyldimethylsilyl triflate and triethylamine in dichloromethane gave **113** in excellent yield. This selectivity suggests that the C_6-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 C_6-epimer **114**.

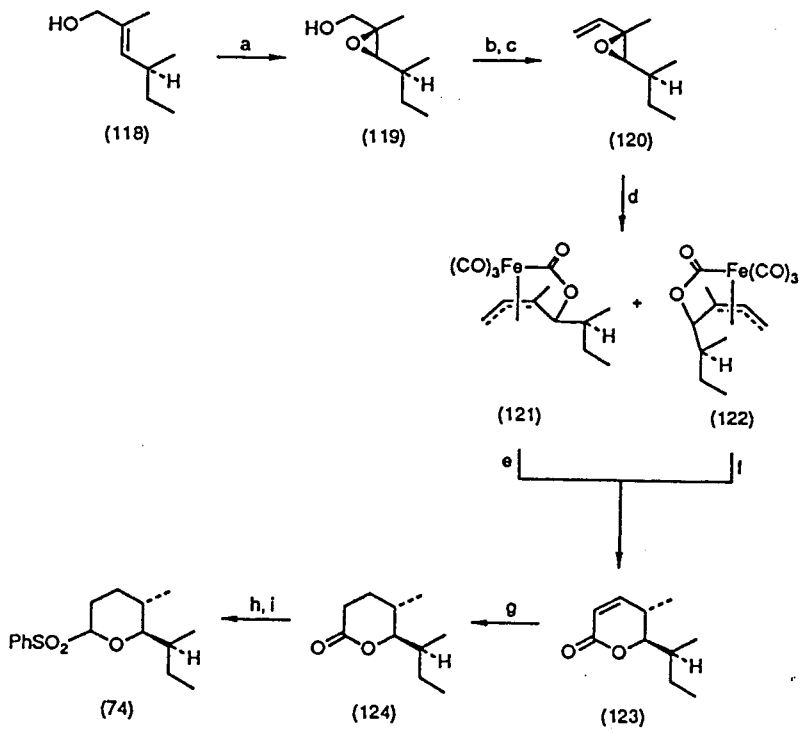
We then tried to effect a selenium-mediated cyclization[64] of the C_6 alcohol of **114** onto the terminal double bond, since this would not only close the furan ring, but the resulting C_8-selenide would be a precursor to a C_8–C_9 double bond. This transformation could not be achieved, although a 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 C_8 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 *syn*-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 **75**[66] 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



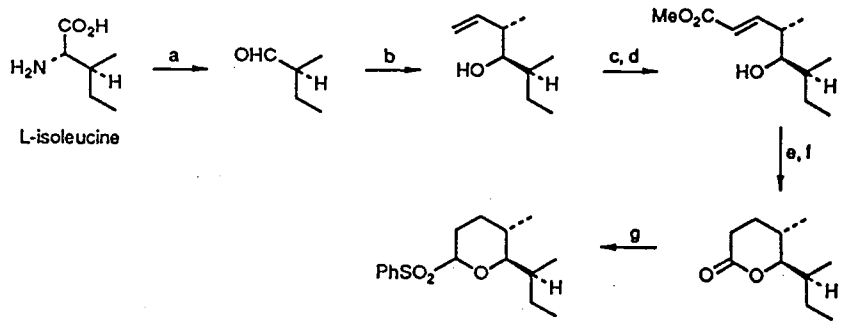
SCHEME 40. (a) $BH_3{\cdot}Me_2S$, THF, then NaOH, H_2O_2, 66%. (b) pTsCl, py, 16h, r.t., 20h, 60°C, 78%. (c) BuLi, THF, then PhSeCl, 65% (+30% starting material). (d) DBU, CH_3CN, 3.5h, 77%.

interesting synthetic procedure based on π-allyltricarbonyliron 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 methylenated 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 δ-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 benzenesulfinic 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°C, CH_2Cl_2, 81%. (b) $(COCl)_2$, DMSO, then Et_3N, 80%. (c) Ph_3PCHBr, KHMDS, THF, 85%. (d) $Fe_2(CO)_9$, THF, 74%, *ca.* 1:1 **121**:**122**. (e) CO, 240 atm., 140°C, benzene, 40%. (f) CO, 250 atm., 50°C, benzene, 65%. (g) H_2, PtO_2, EtOAc, 100%. (h) DIBAL, −78°C, toluene, 93%. (i) $PhSO_2H$, $CaCl_2$, CH_2Cl_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 correlations 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 allyldiisopinocampheyl borane 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

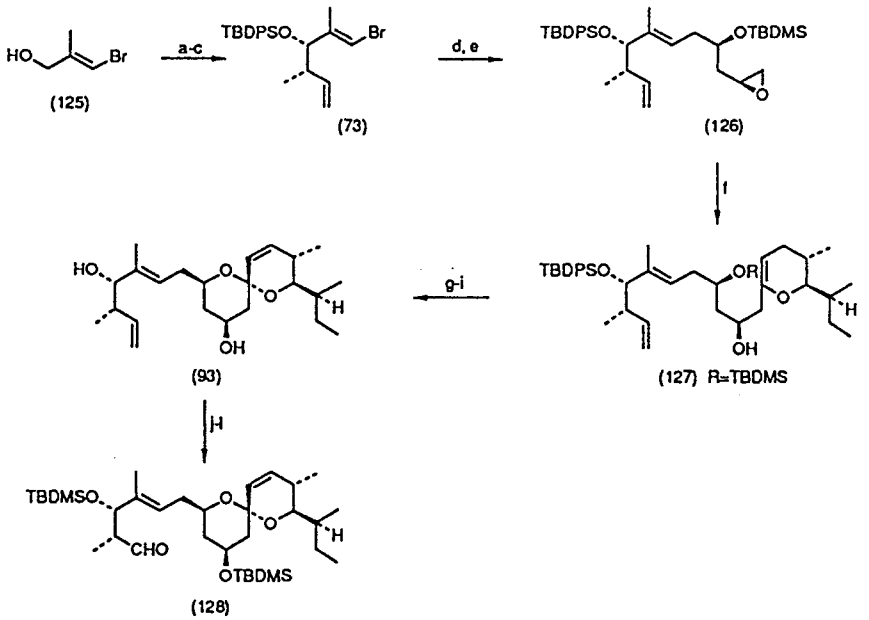


(74)

SCHEME 42. (a) Ninhydrin, 65%. (b) *E*-Crotyldi-(+)-isopinocampheyl borane, −90°C to −78°C, then NaOH, H_2O_2. (c) O_3, −78°C, then PPh_3. (d) Ph_3PCHCO_2Me, 72%. (e) H_2, Pd/C. (f) Amberlyst 15 resin, 83%. (g) As Scheme 41.

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 vinylbromide **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

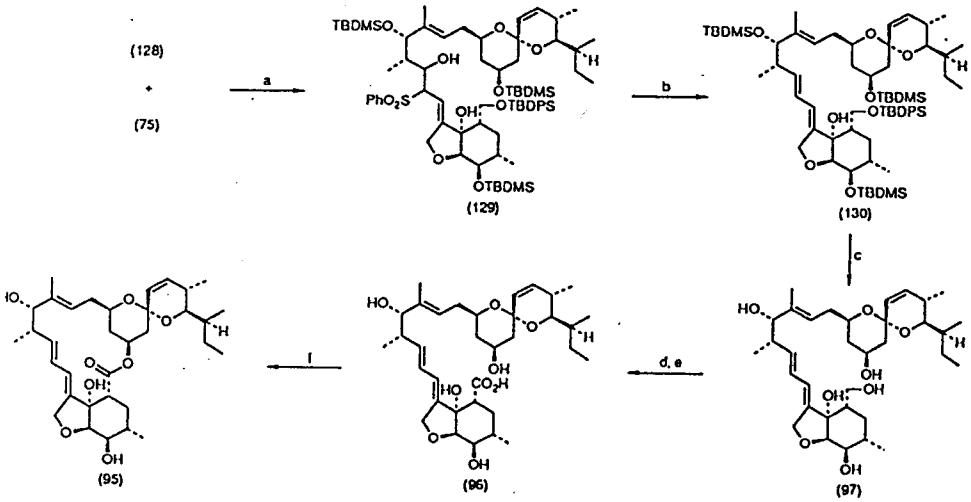


SCHEME 43. (a) TPAP, NMO, 4Å ground sieves, CH_2Cl_2, 74%. (b) *E*-Crotyldi-(+)-isopinocampheyl borane, THF-Et_2O, −90°C, 75%. (c) TBDPSCl, imidazole, DMAP, DMF, 50°C, 92%. (d) *t*-BuLi, Me_3Al, −78°C to 0°C, then add (12), −30°C to 0°C, 82%. (e) TBDMSCl, DMAP, Et_3N, DMF, 94%. (f) Sulfone anion, $BF_3{\cdot}OEt_2$, 45%. (g) PhSeCl, MeOH, Et_3N, CH_2Cl_2, then CSA, MeOH/CH_2Cl_2, 66%. (h) 2-(Phenylsulfonyl)-3-(*p*-nitrophenyl) oxaziridine, $CHCl_3$, 50°C, 77%. (i) TBAF, THF, Δ, 91%. (j) TBDMSCl, imidazole, DMF, 95%. (k) OsO_4, NMO, *t*-BuOH/THF/H_2O, 71%. (l) $NaIO_4$, KH_4PO_4, H_2O/MeOH, 86%.

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°C followed by reaction with the aldehyde

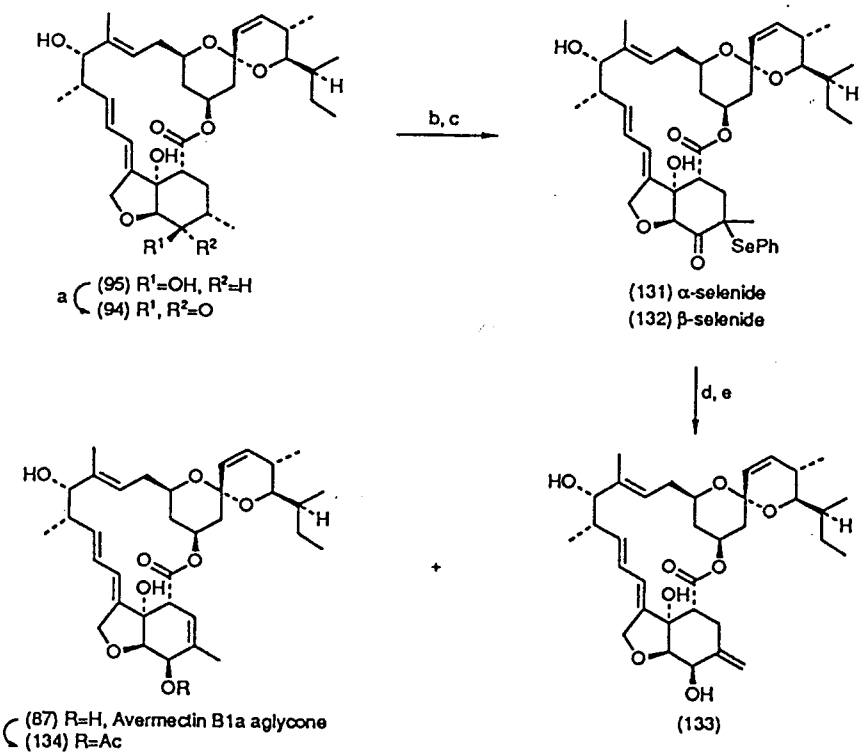
128 successfully effected the important coupling of the two major components, giving the hydroxysulfones **129**. Following reductive elimination, the *E*, *E*-diene **130** was obtained (Scheme 44). We then decided to take a very bold step and remove all the protecting groups by reacting **130** with 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[74] gave an intermediate aldehyde which was immediately oxidized further to the C_1-acid **96**. We believed that this would undergo intramolecular macrolactonization 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



SCHEME 44. (a) 2.2 equivalents *t*-BuLi, THF, −78°C, then add **128**, 74%. (b) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 34%. (c) TBAF, THF, Δ 94%. (d) $RuCl_2(PPh_3)_3$, benzene. (e) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH/H_2O, 29% from **97**. (f) 2-chloro-1-methyl-pyridinium iodide, Et_3N, CH_3CN, 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_5 and therefore thought that it was worth a try.[75] 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_5 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. *Syn*-elimination of the selenoxides from **131** using the Davis oxaziridine reagent gave the avermectin B1a aglycone (**87**)

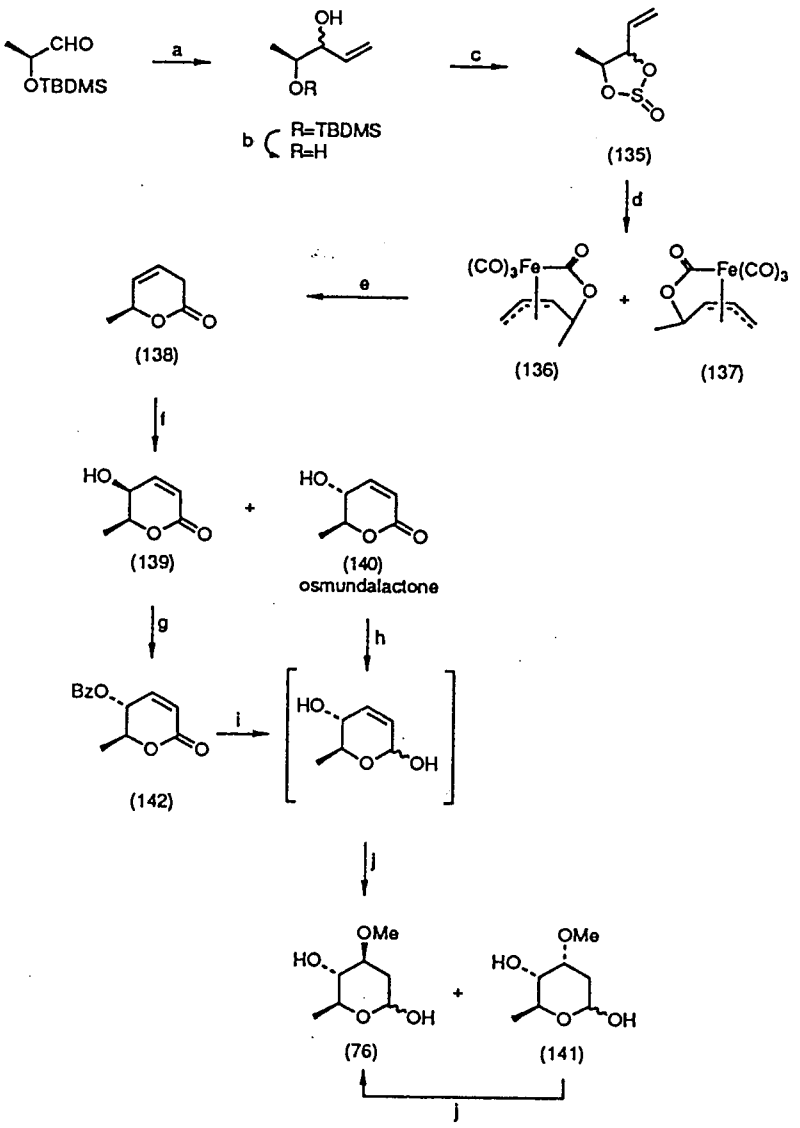


SCHEME 45. (a) TRAP, CH_2Cl_2, 60%. (b) TMSOTf, Et_3N, CH_2Cl_2, 0°C, 93%. (c) PhScCl, CH_2Cl_2, −78°C, 90%, then HF, CH_3CN, 88%, 1:1 131/132. (d) 2-phenylsulfonyl-3-(*p*-nitrophenyl)oxaziridine, $CHCl_3$, 25°C. (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH. 35% 87, 23% 11. (f) CH_3COCl, pyridine, 97%.

(35%) and the *exo*-methylene derivative **133** (23%) after reaction with cerium(III) chloride and sodium borohydride.[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 *exo*-methylene isomer **133** in these eliminations is annoying and we have not yet found a method either to produce the *endo*-isomer exclusively or to convert **133** to **87**. Similar elimination of the β-selenide **132** gives only the *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 *bis*-oleandrosyl disaccharide unit was known,[7,8,77,78] 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,[7,77,78,79] we chose to adopt a new approach, using π-allyltricarbonyliron lactone complexes. We had shown that alkenyl cyclic sulfites served as novel, non-volatile precursors for complex formation.[80] We therefore prepared the cyclic sulfite **135**, configurationally defined at the important C_4 center (Scheme 46). This was reacted with diiron nonacarbonyl in benzene under ultrasonic conditions to give the two diastereoisomeric complexes **136** and **137**. Carbonylation of these compounds in the presence of acrolein as an iron carbonyl scavenger to minimize double bond migration gave the β,γ-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 dimethyldioxirane 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.[81] In our original communication[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

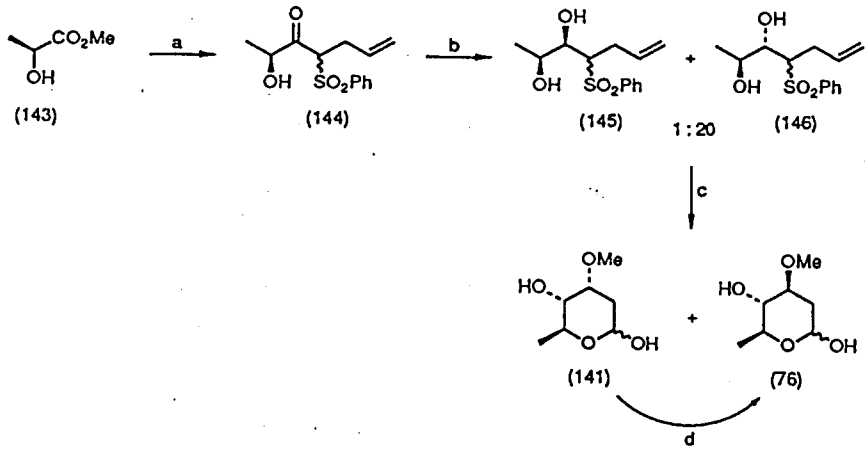


SCHEME 46. (a) Allylmagnesium bromide, THF, −60°C to 25°C, 74%. (b) Catalytic TsOH, MeOH, 92%. (c) $SOCl_2$, CCl_4, 100%. (d) $Fe_2(CO)_9$, benzene,))), 65%. (e) CO, Δ, acrolein, pressure, benzene, 51%. (f) Dimethyldioxirane, acetone, 0°, then 2% Et_3N/pyridine, 75%, 2:1 **139**:**140**. (g) Diethyl azodicarboxylate, PPh_3, Et_2O, $PhCO_2H$, 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, β-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.

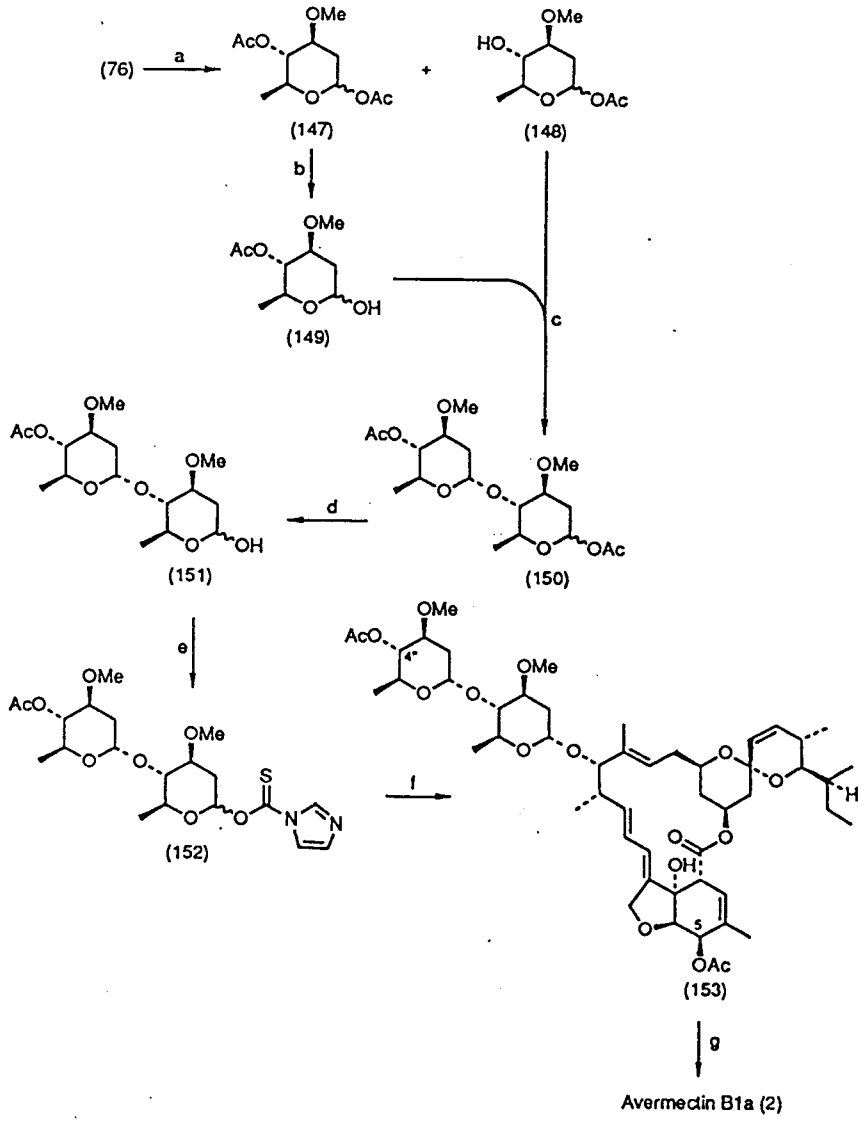
The other hydroxyl lactone isomer **139** required an inversion of configuration prior to its conversion to oleandrose. This was readily achieved by reaction under Mitsunobu conditions to give the benzoate **142**. Similar reduction of this compound with diisobutylaluminum hydride in toluene gave entry 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).[83] The process involves addition of an excess of (3-butenylsulfonyl) 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 α,β-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**.



SCHEME 47. (a) 2 equivalents of the anion derived from (3-butenylsulfonyl)benzene, THF, −78°C, 87%. (b) $NaBH_4$, $ZnBr_2$, 94%. (c) O_3, MeOH, then Me_2S, 32% **141**, 48% **76**. (d) DBU, MeOH, 60%.

We next studied dimerization reactions of oleandrose derivatives to provide the disaccharide, using a new glycosidation method which we had developed.[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 carbonyldiimidazole 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°C cleanly afforded the C_4 monoacetate **149** which is the second coupling unit. Conversion of **149** to its imidazoylylcarbonyl 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-β-anomer. Once again, selective deprotection of **150** worked extremely well at −78°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 imidazoylylthiocarbonyl glycoside **152** by treatment with thiocarbonyldiimida-



SCHEME 48. (a) Carbonyldiimidazole, AcOH, CH_2Cl_2, 93%, 1 : 1 mixture, (b) 2.5 equivalents $LiBHEt_3$, THF, −78°C, 95%. (c) Carbonyldiimidazole, THF, $AgClO_4$, 62%. (d) 2.5 equivalents $LiBHEt_3$, −78°C, 98%. (e) Thiocarbonyldiimidazole, THF, 57%. (f) **134**, $AgClO_4$, K_2CO_3, THF/toluene, 64%. (g) $LiBHEt_3$, THF, −78°C, 90%.

zole in THF since the corresponding imidazoylyl carbonyl derivative failed to undergo coupling with the very hindered C_{13} hydroxyl group of the avermectin aglycone. On the other hand, reaction of avermectin B1a aglycone C_5 monacetate **134** 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 C_5 and $C_{4''}$, was achieved by 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!

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