*Pure & Appl. Chem.*, Vol. 59, No. 3, pp. 299–316, 1987.
Printed in Great Britain.


# Progress in natural product chemistry by the chiron and related approaches—synthesis of avermectin $B_{1a}$

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Abstract - A strategy for the total synthesis of avermectin $B_{1a}$ is presented based on aspects of the utilization of chirons derived from naturally-occurring starting materials, asymmetric synthesis, and computer-assisted stereochemical analysis.

## INTRODUCTION

Over the years, Nature has been a generous and abundant supplier of products to the community of chemists and biologists. Through their separate and combined ingenuity, these groups of scientists have exploited Nature's gifts in many ways, the most dramatic of which has been in medicinal applications, hence directly related to our present-day quality of life. A number of life-saving drugs have their direct origins in Nature. Many others are the result of chemical modification of existing natural products, or synthetic endeavors. While the supply of new natural products and the emergence of novel structural types is ever so active, only a select few become serious candidates for in depth biological evaluation. Of these, perhaps a disappointingly small percentage are successful in more rigorous pharmacological and therapeutic scrutiny. Finally, after years of study on many fronts, there may emerge a product that combines the many features that constitute a novel drug, be it for human, animal or related use.

One such group of products is the avermectins consisting of isomeric macrocyclic lactones of unique structure (ref. 1) and exhibiting potent anthelmintic activity (ref. 1, 2). The most active component, avermectin $B_{1a}$ has been shown to have the structure shown in Figure 1, as a result of elegant structure elucidation studies involving degradative and X-ray crystallographic studies (ref. 3). The avermectins, consisting of several components which

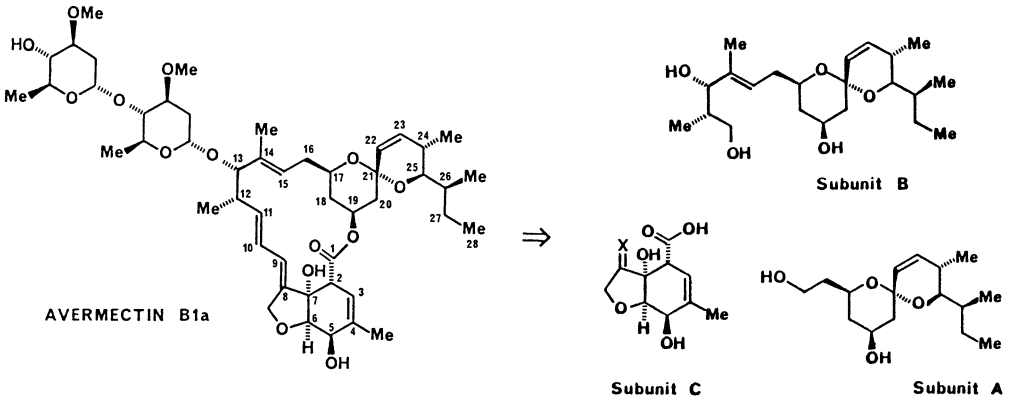


Fig. 1 The structure of avermectin $B_{1a}$ and retrosynthetically derived subunits

differ principally in the nature of the C-25 side-chain, the presence or absence of the $C_{21}$–$C_{22}$ double bond, and in the nature of the "southern" ester subunit, exert their unique activity by interfering with invertebrate neurotransmission (ref. 4). The milbemycins are another group of anthelmintic macrocyclic lactones that are related to the avermectins in overall structural features (ref. 5). However, they lack the disaccharide and oxygen functionality at $C_{13}$, they may contain a "southern" aromatic subunit in some members and also differ by the presence of a less-substituted spiroacetal subunit. Several papers have dealt with synthetic efforts focused on the milbemycins (ref. 6,7) and segments of the avermectins (ref. 8,9).

On the occasion of this 15th IUPAC conference on natural products, we present our results on the design and synthesis of avermectin $B_{1a}$ (ref. 10).

## ELABORATION OF SYNTHETIC BLUEPRINTS AND OVERALL STRATEGY

Considering the nature and degree of complexity of the structure of avermectin $B_{1a}$, it is evident that any aspirations toward a total synthesis must be based on sound planning, rational design and careful execution. Examination of the structure in question reveals the presence of unique geometric and topological features which are adorned with a delicate balance of strategically situated functionality. If in addition we attempt to decipher the stereochemical code of the plethora of asymmetric centers in the target, we come face to face with a herculean task of design, synthesis and assembly. While intuitive retrosynthetic analysis reveals several obvious strategic bond breaking and forming sites, one is still left with a number of subunits, (Fig. 1), each of which presents a challenge in its own right, and can be the subject of an independant synthetic study. The pursuit of such a goal was undertaken in our laboratory a few years ago (ref. 9). The synthesis of appropriate subunits and their component fragments culminating with the assembly of the "northern" subunit B in optically pure form was designated as an initial objective. Concurrent studies focused on approaches to the synthesis of the "southern" hexahydrobenzofuran subunit.

## DISCOVERY OF CHIRONS—VISUAL DIALOGUE VERSUS COMPUTER-ASSISTED PERCEPTION

The decoding of stereochemical and functional features in avermectin $B_{1a}$ aglycone by a visual process revealed that subunit A could be related to two other subunits, namely $A_1$ and $A_2$, each of which is derivable from D-glucose by appropriate chemical manipulation

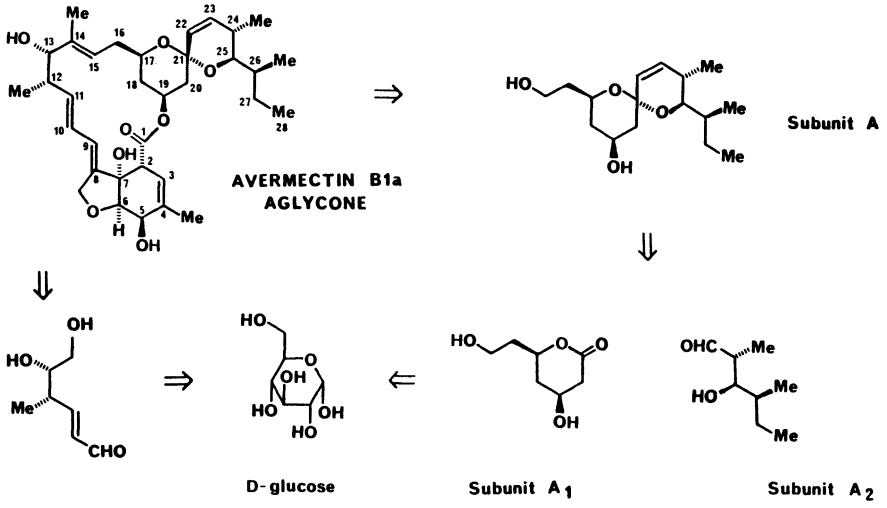


Fig. 2 Retrosynthetic Analysis - discovery of subunits related to D-glucose.

(Fig. 2). The total synthesis of subunit A based on such a strategy has already be reported from our laboratory (ref. 9). While this provided enantiomerically pure material and may have been acceptable as a first synthesis, we considered alternative, shorter approaches that utilized chirons (chiral synthons, see ref. 11) derived from (S)-malic acid. An integral feature of the carbohydrate "discovery" process in the framework of a target natural product takes advantage of the so-called "rule of five" (ref. 11). It is clear that another chiron, representing a six-carbon $C_9$-$C_{14}$ segment of avermectin $B_{1a}$ aglycone can also originate from a hexose (Fig. 2).

The process of visual dialogue with the target molecule revealed other possibilities with regard to potential chiral starting materials. Thus, Figure 3 shows the emergence of three molecules of (S)-malic acid from the left, middle and right-hand segments of avermectin $B_{1a}$ aglycone. Because of the hidden symmetry associated with the particular substitution pattern in the left and right hand segments, namely $C_{11}$-$C_{14}$ and $C_{23}$-$C_{26}$ respectively, we can see that a common chiron can nicely fulfill the functional and stereochemical requirements of these segments. In principle, three sets of (S)-malic acid molecules could provide twelve of the eighteen carbon atoms comprising the mainframe of the "northern" subunit B.

By viewing of the stereochemical code associated with the $C_{22}$-$C_{28}$ segment in a different perspective, the methyl group at $C_{26}$ can be related to that found in L-isoleucine (Fig. 3).

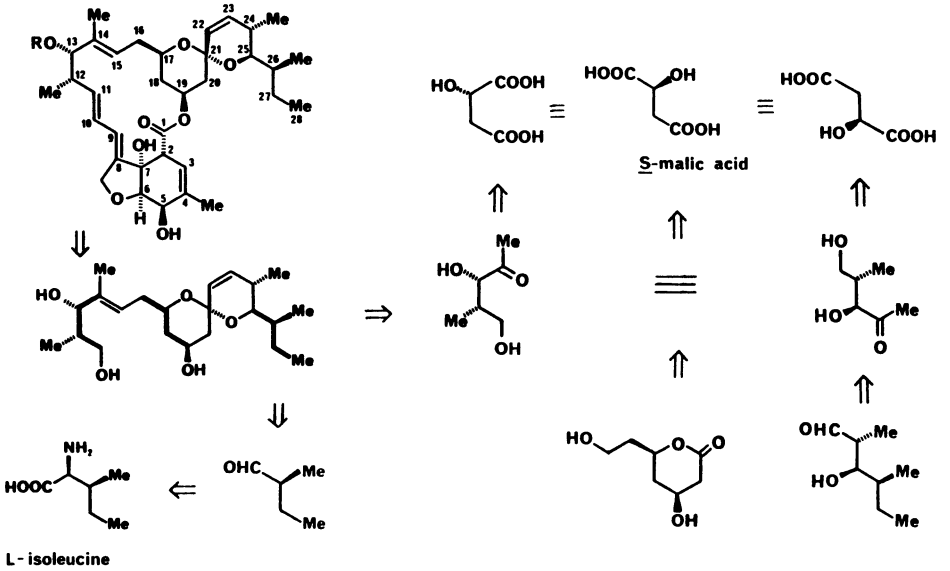


Fig. 3 Retrosynthetic analysis - discovery of chirons related to (S)-malic acid and L-isoleucine.

While the preceding exercise of discovering appropriate chirons for the assembly of subunits of avermectin $B_{1a}$ has practical significance, it should be remarked that it represents one perspective and a visual one at that. The question may therefore be asked if these visual deductions are valid, and perhaps more importantly, if there are other patterns that were missed. All of which brings us back to a fundamental issue in the daily practice of our profession, namely the manipulation of three-dimensional molecules. Yet,for the major part, we think, conceptualize and plan mostly in two dimensions such as on paper or the blackboard. Occasionally we may resort to the inspection of molecular models (if we can find them!). This is all the more important when we deal with the inevitable problem of deciphering stereochemistry, particularly in multifunctional molecules.

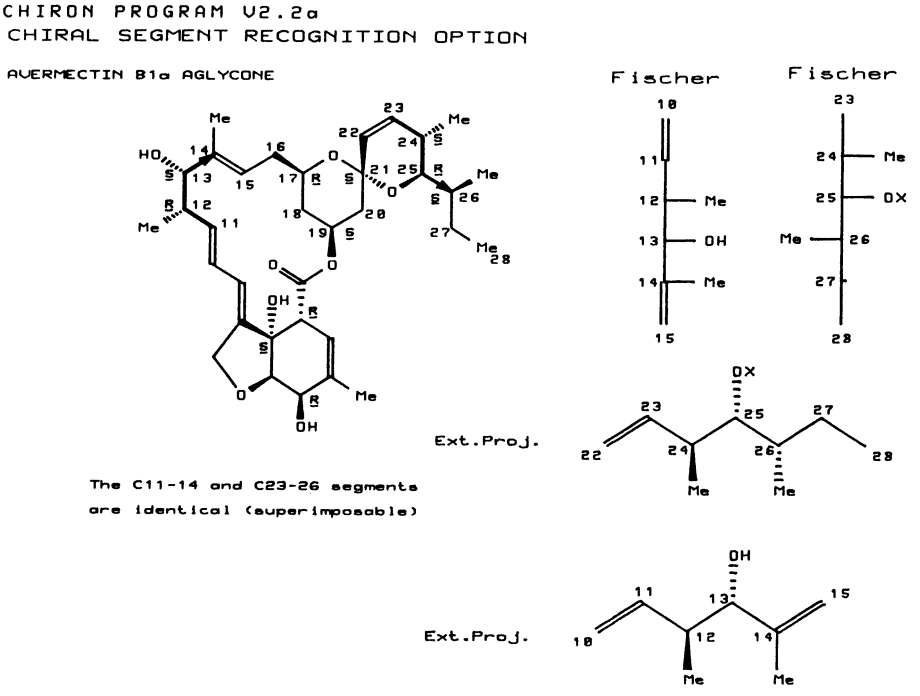


Fig. 4 Computer-generated stereochemical information by the CHIRON program. R/S notation, Fischer and extended projections, and the Chiral Segment Recognition Option (Substructure search)

We have developed a computer program called CHIRON which is aimed at the analysis and perception of functional and stereochemical features in molecules (ref. 13). Another important component of this program is assisting the chemist with the selection of appropriate starting materials for synthesis. Other options involve pharmacophore-type substructure search based on pattern recognition and 3-D perception. In addition to its utility to the practising chemist, CHIRON offers a much needed pedagogical tool for stereochemical perception of molecules. Thus, the task of decoding the stereochemical complexity of avermectin $B_{1a}$ aglycone seemed an appropriate one for CHIRON. Figure 4 illustrates three features present in CASA (Computer Assisted Stereochemical Analysis). Thus, R,S designations can be obtained virtually in a few seconds simply by touching a command in the menu. Fischer and extended projections can be obtained within a few seconds by designating the appropriate segment on the molecule. It can be seen that an identical set of contiguous asymmetric centers emerges from such an analysis. Thus the $C_{12}$-$C_{13}$ and $C_{24}$-$C_{25}$ subsegments are the same, a feature which may not be immediately apparent to the eye by viewing the molecule in two-dimensions. Another interesting feature in CASA is the Chiral Segment Recognition Option, in which the program probes for segments in a molecule that are identical and superimposable (D or L), enantiomeric (DL) or meso. Such an analysis is shown in Fig. 4, where it can be seen that the $C_{11}$-$C_{14}$ and $C_{23}$-$C_{26}$ segments are in fact identical. This type of stereochemical information can have important implications in the design and choice of starting materials for the synthesis of the "northern" subunit of avermectin $B_{1a}$ since it is clear that precursors common to two segments can be considered in the blueprint.

Armed with this information, one can now proceed with CAPS (Computer Assisted Precursor Selection) in the CHIRON program, and search for appropriate chiral starting materials from a bank of about 600 compounds stored in its memory. Figure 5 illustrates the graphical computer output from the Common Precursor Option, where (S)-malic acid was suggested in the first instance, and a readily available chiron which can be prepared from (S)-malic acid in the second (ref. 10). The percent priority score reflects the degree of convergence with the intended segment and the level of chemical feasibility. Thus, in this instance,visual

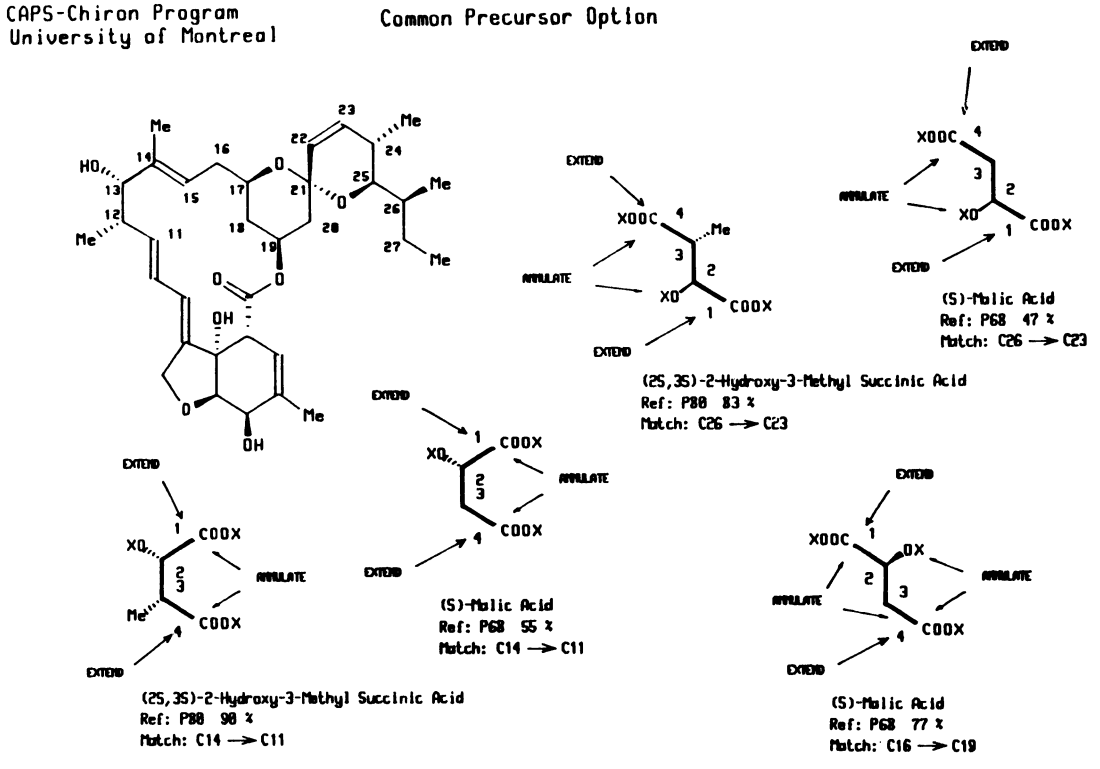


Fig. 5 A choice of chiral starting materials and transforms suggested by the CHIRON program. The common precursor option will generate precursors than can be used in more than one segment of the molecule. Note how the program reproduces the precursor in a perspective that matches the corresponding segment in the target.

dialogue and computer perception were united by an astute sense of observation on the one hand (human), and the unbiased but logically derived recognition process on the other (machine). Consider however the speed of perception and many other possibilities offered by the program, compared to visual dialogue.

## SYNTHESES OF $C_9$–$C_{14}$ and $C_{11}$–$C_{14}$ SEGMENTS VIA CYCLIC AND ACYCLIC TEMPLATES

### A. Carbohydrate route—cyclic templates

One of the basic tenets of the utilization of carbohydrates as starting materials in synthesis is the exploitation of the functional, stereochemical, topological and stereoelectronic features present in cyclic structures (ref. 11). The strategy has great predictive value because of the manner in which desired functionality can be systematically introduced in a cyclic carbohydrate structure. Provided that these manipulations are not extensive, and depending on the relative complexity of the intended target, the carbohydrate route can indeed be viable and practical. Figure 6 shows how D-glucose was manipulated to produce the six-carbon $C_{11}$–$C_{14}$ subunit 9. The desired syn-relationship of C-methyl and hydroxy groups was achieved by the judicious selection of protective groups and key reactions, and relying on principles of conformational bias. In spite of the extensive deoxygenation in D-glucose, one should note that the geometry of the double bond was correctly established and that the entire carbon framework of the sugar was utilized (ref. 12). The reader may therefore be interested in the key conversion of glucals to enals, which can be promoted by mercuric acetate (ref. 14).

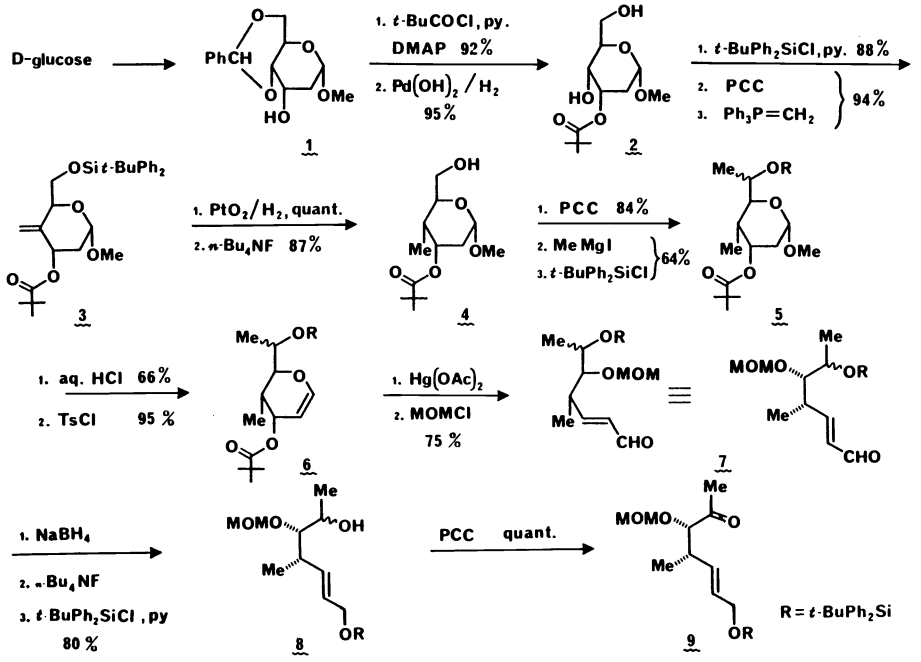


Fig. 6 Synthesis of the $C_9$–$C_{14}$ subunit from D-glucose.

### B. (S)-Malic acid route—acyclic templates

Recognizing the stereochemical congruence between (2S,3S)-2-hydroxy-3-methyl succinic acid 11 (ref. 15), hence (S)-malic acid 10, and the intended $C_{11}$–$C_{14}$ segment, we devised an efficient and practical route that takes advantage of asymmetric alkylation of an acyclic template (ref. 15) (Fig. 7). Thus the diester 11 was transformed into the lactone 13 in good overall yield by taking advantage of the presence of an α-hydroxy acid at one end of the molecule and subsequent selective functionalization. At this juncture, an important decision regarding O-protective groups had to be made. In a synthetic undertaking of such a magnitude, compatibility of protective groups and reactivity of advanced intermediates, particularly in organometallic type reactions, may become a crucial issue. Having selected a benzyl ether protective group, we proceeded to prepare the chiral ketone 15 in optically pure form and in excellent yield.

We now had clear access to chirons 9 and 15, representing the left-hand segment of our target. The plan was to react them with anionic partners via the ketone group, thus creating the $C_{14}$–$C_{15}$ trisubstituted double bond en route to subunit B.

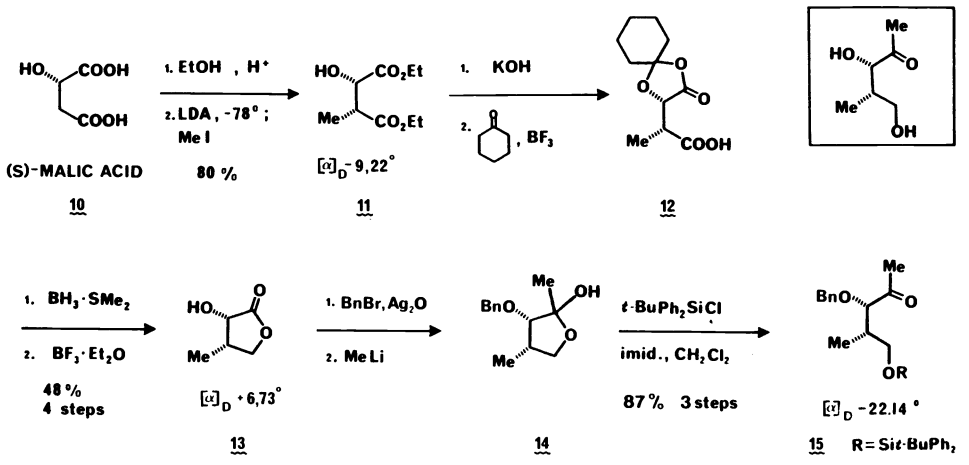


Fig. 7 Synthesis of the $C_{11}$–$C_{14}$ subunit from (S)-malic acid.

## SYNTHESIS OF $C_{23}$–$C_{28}$ SEGMENT (SUBUNIT $A_2$) VIA ACYCLIC TEMPLATES

### A. (S)-Malic acid route

As shown in Figures 3 and 5, a common precursor could be used to construct the left and right hand segments of avermectin $B_{1a}$. Thus, compound 11 was transformed to the α,β-unsaturated ester 17 in good overall yield. It was anticipated that a conjugate addition of lithium dimethylcuprate might proceed satisfactorily, and in the event provide us with the correct isomer by virtue of the existing chirality in the molecule. Several variations of such conjugate additions were tried without success. When the Yamamoto modification (ref. 16) involving the addition of a Lewis acid also failed, we decided to change our approach still capitalizing on the utilization of common precursors (Fig. 8).

Thus, lactone 13 was protected as the MOM ether 19, which was transformed into the open-chain ketone 20 and chain-extended to the mixture of ethylidene derivatives 21 in high overall yield. There remained to find a method for the stereoselective reduction of the double bond and to the desired isomer 22 in optically pure or enriched form. The most cooperative catalyst was found to be rhodium-on-alumina which at best rewarded us with a 1:1 mixture of 22 and its epimer 23.

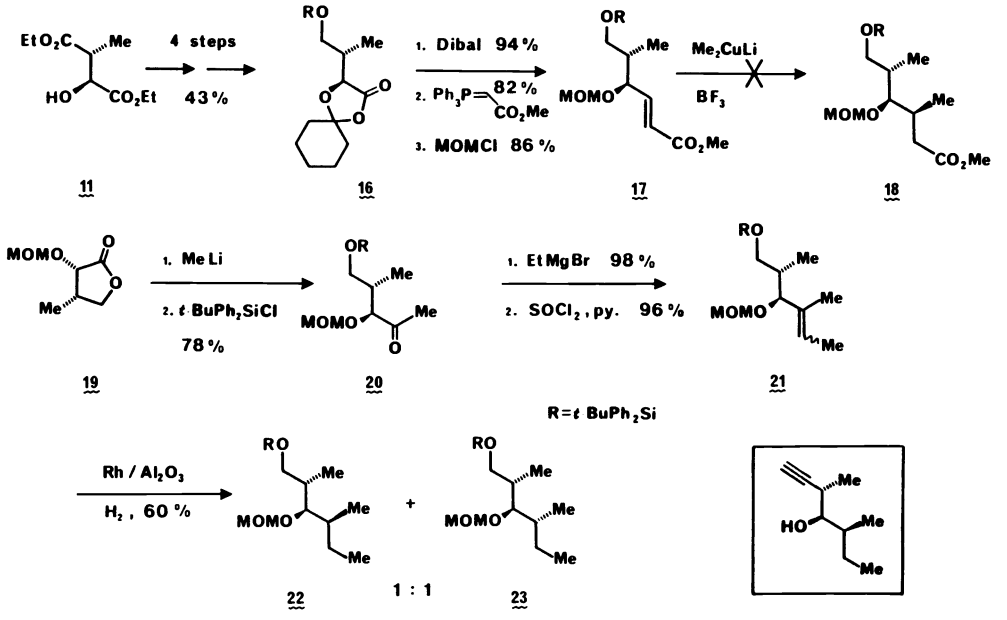


Fig. 8 Attempted syntheses of the $C_{23}$–$C_{28}$ subunit from (S)-malic acid.

### B. L-Isoleucine route

(S)-Isobutyraldehyde 24, readily available from L-isoleucine (ref. 17) appeared to be an ideal starting material (Fig. 9). What was needed was a two-carbon extension which would allow for the introduction of two new asymmetric centers with the correct regio and stereochemistry, and to provide a "handle" for further manipulation. A combination of Wittig, Sharpless (ref. 18) and organocuprate (ref. 19) methodologies proved highly efficient and successful in generating the virtually pure chiron 26. Subsequent manipulation of the hydroxy groups and chain-extension (ref. 20) led to the acetylenic chiron 29 in good overall yield.

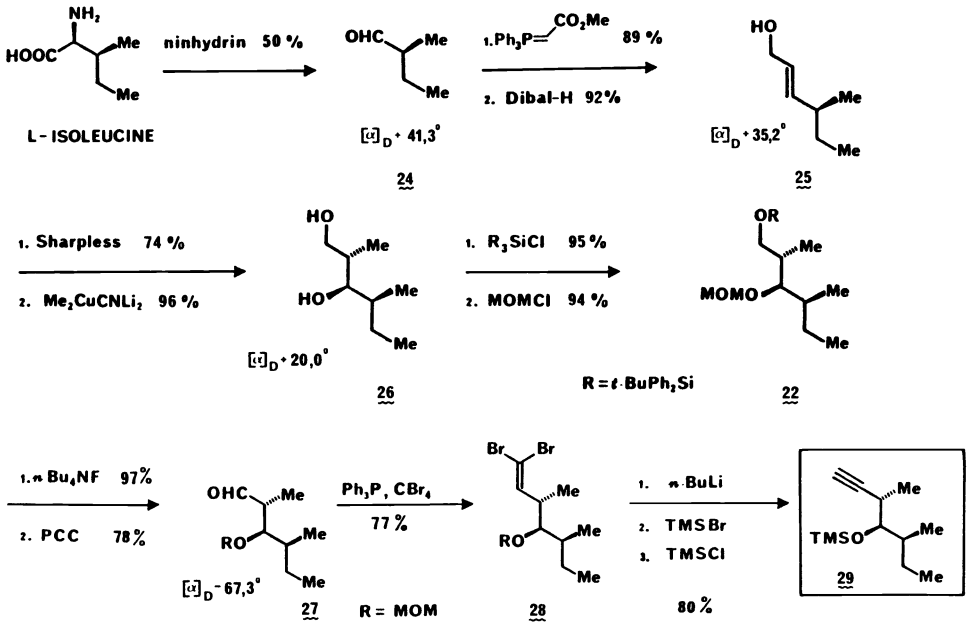


Fig. 9 Synthesis of the $C_{22}$–$C_{28}$ subunit from L-isoleucine

## SYNTHESIS OF $C_{15}$–$C_{21}$ SEGMENT (SUBUNIT $A_1$) VIA ACYCLIC TEMPLATES

### A. Carbohydrate route—cyclic templates

As is evident from its structure, a carbohydrate route to this segment can be envisaged from D-glucose, once again because of its ready availability and the stereochemical congruence of C-5 with $C_{17}$ of the intended subunit. Such a route has been described already by us (ref. 9), (Fig. 2).

### B. (S)-Malic acid route—acyclic templates

In keeping with the original plan in which common precursors could be efficiently utilized in the construction of various segments of avermectin $B_{1a}$, we had devised a route to the lactone subunit $A_1$ from (S)-malic acid (ref. 9). This is briefly discussed here for the sake of completion. Thus, the selectively protected (S)-butanetriol which is readily available from (S)-malic acid (ref. 21) was transformed into the aldehyde 31. (Fig. 10) It was hoped that a Grignard reaction with allylmagnesium bromide would not only provide the required carbon appendage, but also proceed with good stereoselectivity so as to produce the desired alcohol 32 in preponderance. Unfortunately, even after extensive experimentation (Lewis acids, etc.) this reaction gave a 1:1 mixture of diastereomers which could be separated after O-benzylation to give 33. It should be noted that the unwanted diastereomer would be an ideal precursor to the lactone portion of the compactins and mevinolins (ref. 22). Proceeding with known reactions, it was possible to transform 32 into the seven-carbon lactone 35, which represents one-half of the spiroacetal subunit A.

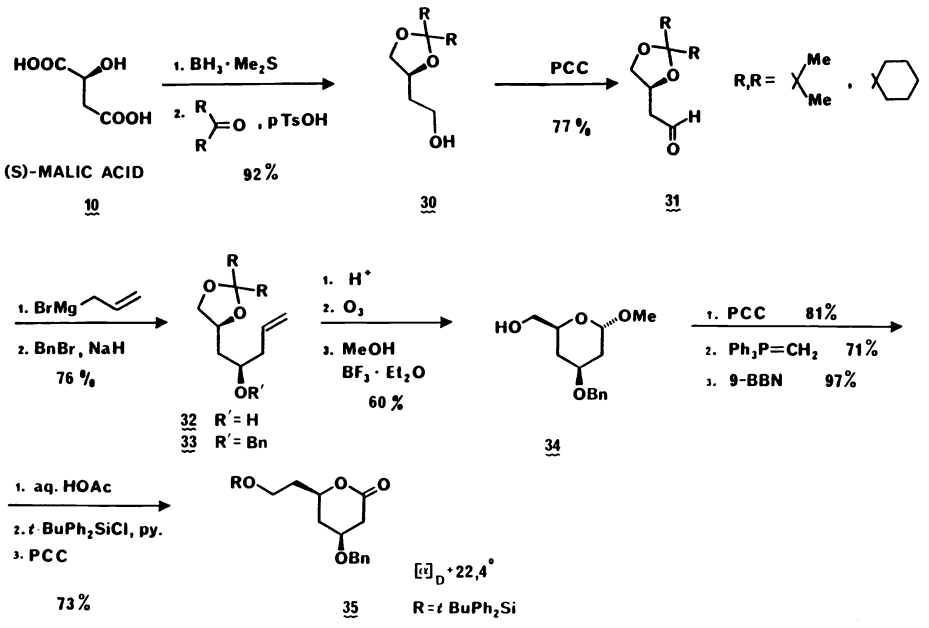


Fig. 10 Synthesis of the $C_{15}$–$C_{21}$ subunit from (S)-malic acid

At this juncture it would be of interest to group the various synthetic subunits and to trace their respective progenitors, (Fig. 11). With these chirons in hand, we proceeded to systematically assemble the more elaborate subunits en route to the intended target.

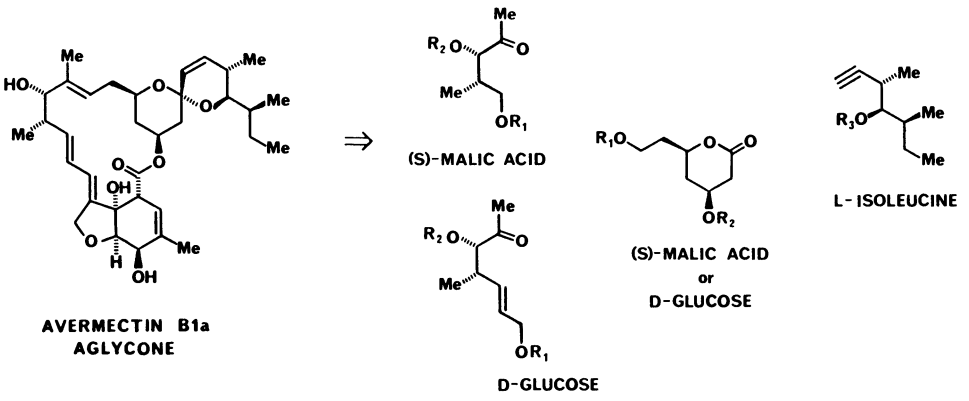


Fig. 11 Chirons derived from D-glucose, L-isoleucine and (S)-malic acid - Building blocks for the $C_9$–$C_{28}$ and $C_{11}$–$C_{28}$ "northern" subunits (Subunit B).

## ASSEMBLY OF $C_{15}$–$C_{28}$ SPIROACETAL (SUBUNIT A)

With the nucleophilic acetylene 29 and the electrophilic lactone 35 in hand, we succeeded in the coupling reaction for which there was ample precedent (ref. 23) (Fig. 12). Lindlar reduction of the resulting product 36, subsequent spiroacetalization (ref. 24), and deprotection led to 38 as a single anomer. Further elaboration of the primary hydroxy group gave the corresponding sulfone derivative 39.

## ASSEMBLY OF THE NORTHERN SUBUNIT OF AVERMECTIN $B_{1a}$

### A. $C_9$–$C_{28}$ segment

This segment was obtained by the condensation of the sulfone anion resulting from 39 and the ketone 9 to give the corresponding β-hydroxy sulfone coupling product 40 (ref. 25). Without separation of isomers, this was transformed into the desired trisubstituted olefin 41, albeit in modest overal yield (30–35%) (Fig. 13).

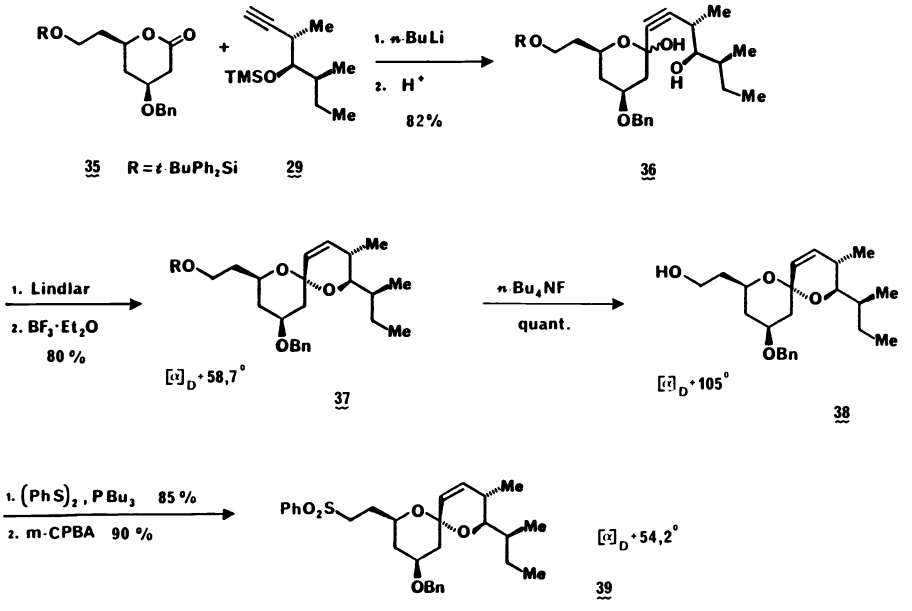


Fig. 12 Assembly of subunit A.

Although the necessary functionality was present and steric effects were not a factor as judged by examination of molecular models, a major difficulty in the condensation reaction was the unreactivity of the anion at low temperature. This can be attributed to the presence of several oxygen substituents which will undoubtedly coordinate with the lithium cation and lead to aggregated entities. Variations in the nature of the cation, the solvent (ether, HMPA, etc.), or the temperature, did not improve the situation or led to decomposition. It was found best to interrupt the reaction and recycle unreacted sulfone and ketone.

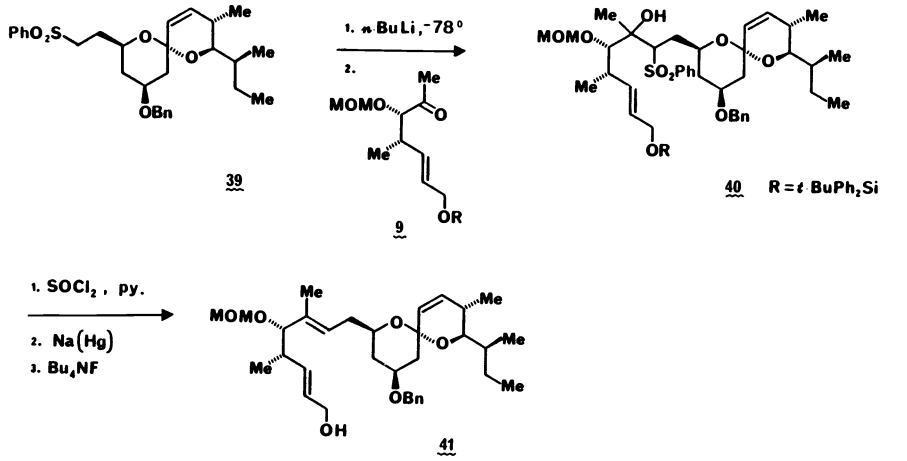


Fig. 13 Assembly of the $C_9$–$C_{28}$ segment of avermectin $B_{1a}$

### B. $C_{11}$–$C_{28}$ segment

The same condensation, when attempted with the ketone 15 also led to the expected condensation product 42. Optimum conditions required the recycling of unreacted sulfone and ketone, which led to a 40% isolated yield of 42 (95% based on recovered starting materials) (Fig. 14). The most favorable conditions did not necessitate the prior derivatization of the tertiary alcohol (ref. 25). Thus, treatment of 42 with sodium amalgam in phosphate buffer (ref. 26)

led to a 40% yield of the desired olefin with recovery of desulfonylated 42. Deprotection gave the $C_{11}$–$C_{28}$ segment 43 in optically pure form. At this juncture it should be mentioned that a sample obtained from degradation of the natural product (ref. 27) proved to be identical with 43 except for the presence of a corresponding segment from the $B_{1b}$ isomer (~15%) which is very difficult to separate. Subsequent chemical modification of 43 led to the sulfone 45 for an eventual coupling with an electrophilic "southern" segment.

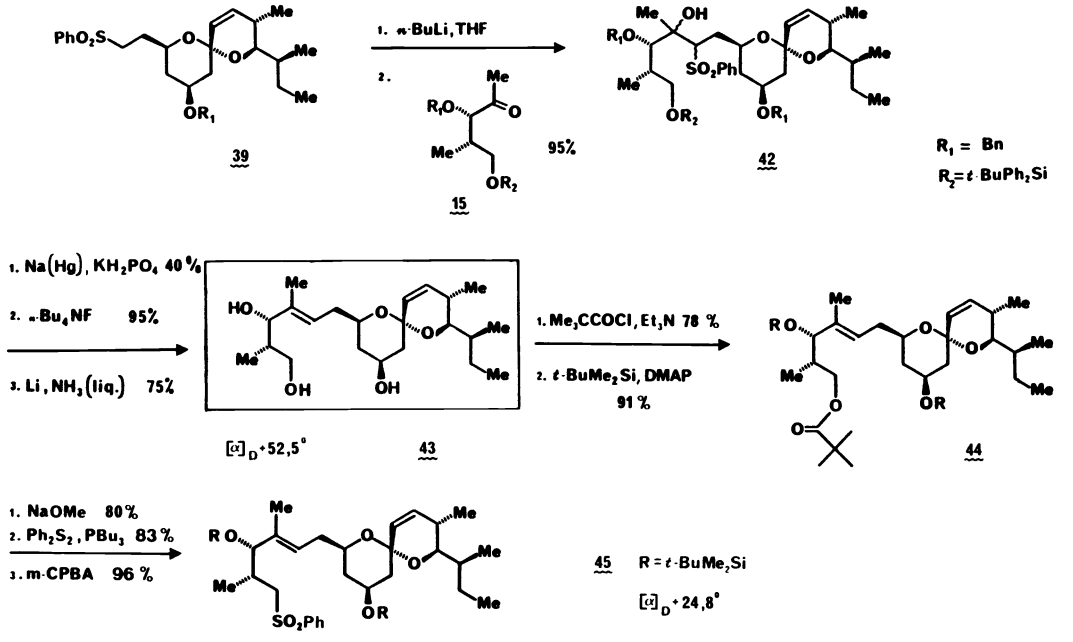


Fig. 14 Enantiospecific total synthesis of the optically pure $C_{11}$–$C_{28}$ "northern" subunit (subunit B).

## SYNTHESIS OF HEXAHYDROBENZOFURAN SUBUNIT (SUBUNIT C)

The "southern" hexahydrobenzofuran subunit of avermectin $B_{1a}$ presents a number of challenges in synthetic design. In addition to the unusual substitution pattern, notice should be taken for example of the tertiary hydroxy group which is prone to elimination (Fig. 1). Should this occur at any stage of the synthetic route, then the remaining steps might be in jeopardy because of the difficulty of reinstating it. The possibility of aromatization is another potential hazard. There are at present no less than four different approaches to this subunit, all of which lead up to the bicyclic system with a hydroxymethyl group in place of the carboxyl group (ref. 28).

Our approach was initially aimed at the synthesis of a racemic product, in order to test out the methodology (ref. 29) (Fig. 15). The synthesis starts with the known Diels-Alder product 48 (ref. 30) which undergoes hydroxylation and decarboxylation in a remarkable sequence involving initial acetyl migration to give 50 (ref. 31). When redrawn in the perspective of the intended target, the required regiochemistry of functionality for further transformations becomes apparent. Thus, selective protection, introduction of the tertiary methyl group and β-elimation produced 53. The plan was to introduce the required appendage at the allylic hydroxy group, to induce ring closure in a Michael fashion, and ultimately to address the delicate question of introducing an angular hydroxyl group. After considerable experimentation it was found that thallium ethoxide was the most reliable base, particularly in DMF as solvent. With the required appendage in place as in 54, we then proceeded with the first of several critical steps. Thus, radical-induced cyclization (ref. 32) led to the desired octahydrobenzofuran product 55 in good yield. The most critical reaction was now upon as, namely the introduction of the tertiary hydroxyl group. Ozonolysis of 55 gave the corresponding ketone 56 which when treated with lead tetraacetate in acetic acid gave the acetoxy ketone 57 in 75% yield! Interestingly, the olefin 55 also gave the same product under the same conditions, but the reaction time was longer. Presumably an oxidative cleavage is taking place to give the ketone 56 which undergoes the normal reaction. It is of interest that acetoxylation takes place at the tertiary position selectively since literature precedents involve mostly examples in the keto steroid area(ref. 33). The structures of the bicyclic products 55–57 where rigorously established by 400

MHz nmr studies (decoupling and NOE). From such studies it was also deduced that the carbomethoxy group in 56 had a β-orientation, which appears to be thermodynamically more stable than the corresponding α-isomer (energy mimimed β-isomer 57 corresponds to 9.869 Kcal/mol compared to 14.978 Kcal/mole for the α-isomer).

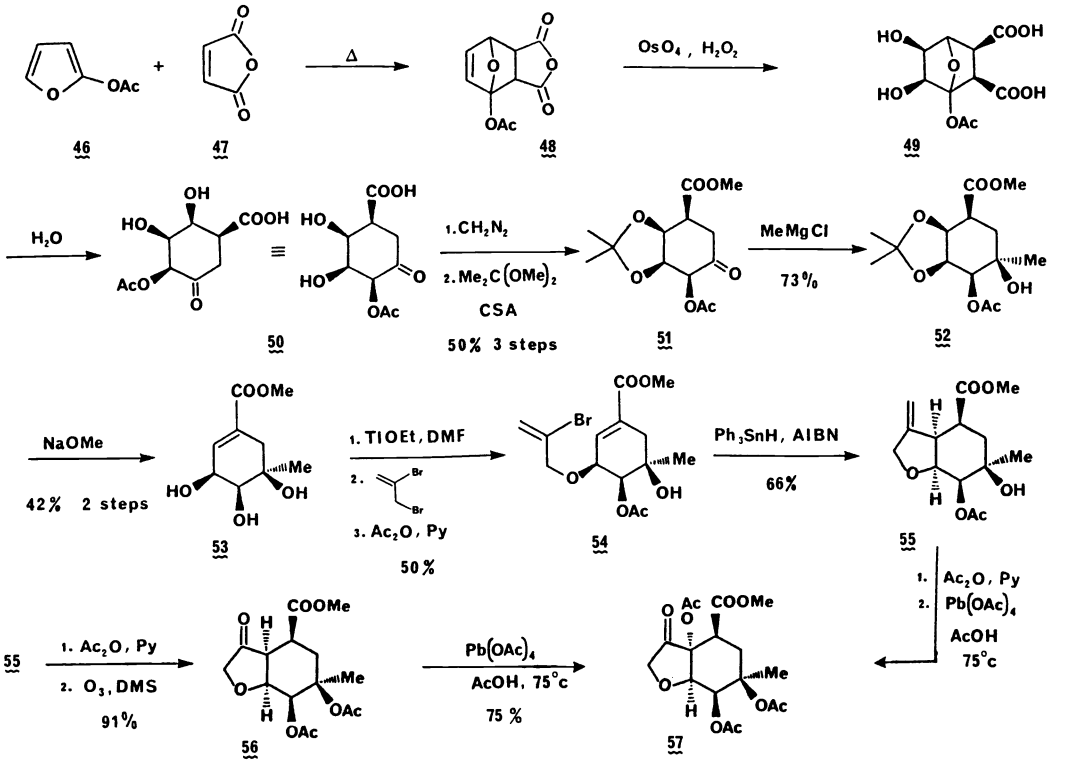


Fig. 15 Novel methodology for the total synthesis of octa- and hexahydrobenzofurans related to the "southern" subunit (C) of avermectin $B_{1a}$.

When the lead letraacetate oxidation was initially attempted on 55, the tricyclic product 58 was obtained by intramolecular attack of the tertiary hydroxyl group on the activated

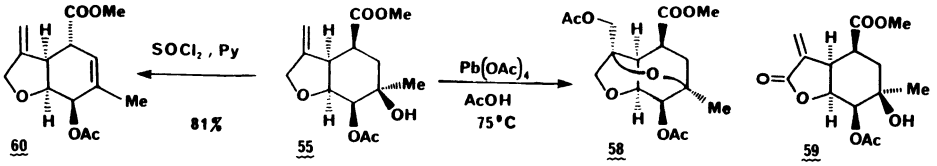


Fig. 16 Transformations leading to frustrating and surprising results.

olefinic intermediate (Fig. 16). Application of the Sharpless oxidation of allylic systems systems (ref. 34) gave the lactone 59 rather than hydroxylation at the tertiary carbon atom. The tertiary alcohol group in 55 was intended as a vehicle for elimination to furnish the β,γ-unsaturated system found in the subtarget. The feasibility of such a reaction was tested on 55, whereby treatment with thionyl chloride in pyridine furnished an excellent yield of the desired olefin 60. Interestingly the reaction was also accompanied by partial epimerization at the $C_2$-ester bearing carbon, thus bringing us closer to subunit C.

In pursuit of a synthesis of this subunit in optically pure form, we turned our attention to suitable optically active precursors. The readily available quinic acid 61 proved ideal, since it had already been transformed into intermediates that could be further manipulated for a convergent scheme (Fig. 27). Thus, adapting the methodology already developed (ref. 35) to our needs, we were able to convert quinic acid into the optically active derivative 65 which proved to be identical with a sample of racemic product prepared via the

Diels-Alder route (Fig. 15). Interestingly, when the CHIRON program was queried about chiral precursors, quinic acid was a promising candidate found among several others.

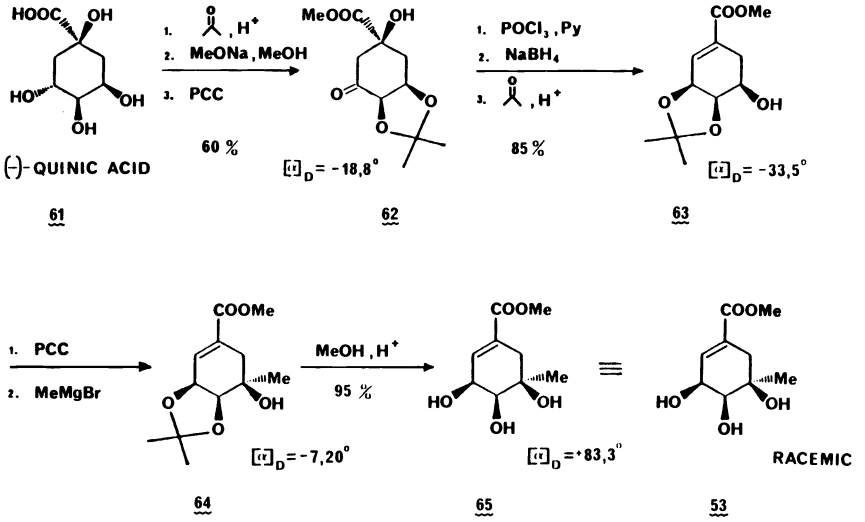


Fig. 17 Synthesis of an optically pure precursor to subunit C from (-)-quinic acid

## AN EFFICIENT DEGRADATION OF AVERMECTIN $B_{1a}$

At this juncture in our studies, it was deemed important to have authentic subunits from the natural product for purposes of structural correlation with synthetic samples and model studies. We developed an efficient degradation of avermectin $B_{1a}$ (which contains ~15% of the $B_{1b}$ component) based on a controlled ozonolysis in the presence of Sudan 7B (ref. 27, 36). Ozonolysis in the presence of dyes as indicators is a versatile process introduced by Mitscher and coworkers (ref. 37). Thus oxidation of the conjugated seco ester (prepared from avermectin $B_{1a}$ by treatment with base) led to the "northern" subunit 66 and the "southern" subunit 67 in excellent yield (Fig. 18). Although subunit 66 could not be used as a relay substance because of the presence of the $B_{1b}$ component (isopropyl side-chain), it could be used as a source for the intact disaccharide unit. The "southern" subunit 67 on the other hand, proved to be an ideal substrate for studies toward the completion of the synthesis. Moreover, as we had originally planned, the migration of the double bond into conjugation with the ester would minimize the chances for aromatization during subsequent transformations. Armed with the optically pure "northern" synthetic subunit 45 and the versatile "southern" subunit 67, we proceeded with our efforts towards the conquest of this prized target.

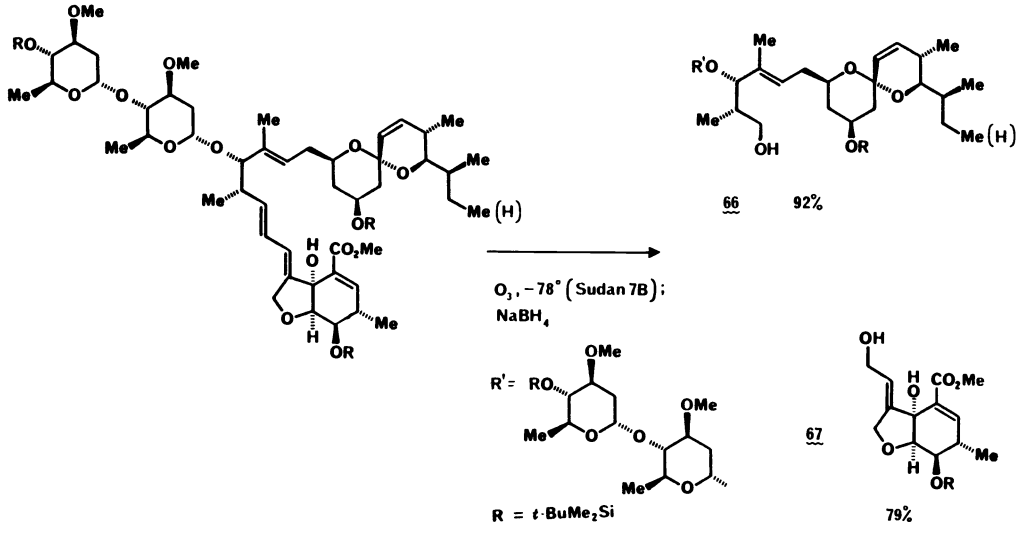


Fig. 18 Controlled ozonolysis of avermectin $B_{1a}$ conjugated seco-ester - (contains ~15% avermectin $B_{1b}$)

## ASSEMBLY OF AVERMECTIN $B_{1a}$ AGLYCONE FRAMEWORK

Condensation of the anion from sulfone 45 with the aldehyde 68 obtained by a PCC oxidation of 67 (ref. 10) gave a product, which when subjected to elimination and desilylation gave the conjugated seco-ester 69 in acceptable overall yield. Once again, it was best to interrupt the condensation and recover unreacted starting materials (47% yield; 77% based on recovery). Thus, the problem of substrates containing several ether-type functionalities in sulfone anion reactions emerged again, presenting us with a more difficult situation compared to its predecessor 39 (Fig. 14). The yield of the amalgam-induced elimination was modest (35%), no doubt because of the rather intricate structure, and the nature of the olefin itself. As a bonus however, the trans diene 69 was the only dienic product isolated. (Fig. 19).

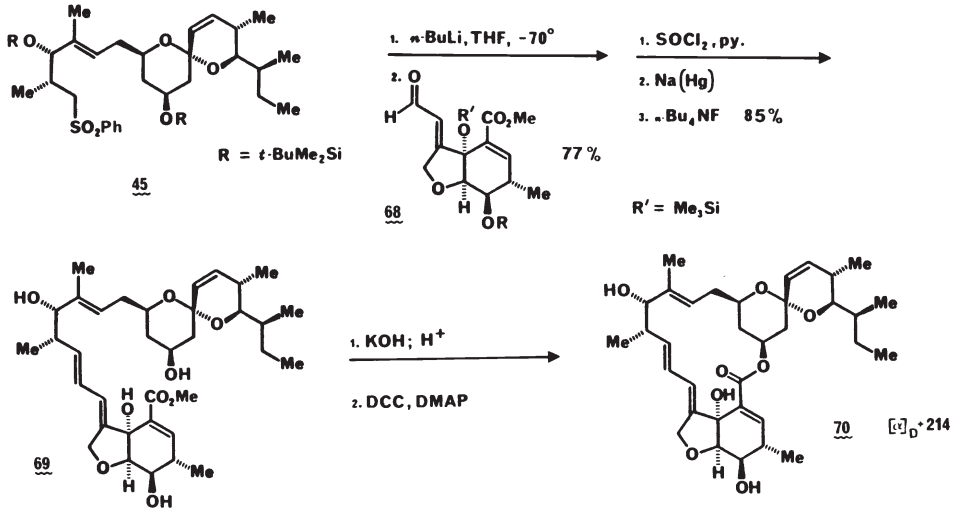


Fig. 19 Assembly of a "conjugated" avermectin $B_{1a}$ aglycone.

Hydrolysis of the ester and macrolactonization with DCC-DMAP (ref. 38) gave a 40% yield of the conjugated avermectin $B_{1a}$ aglycone 70. Efforts were made to improve the yield of the lactonization, but with little success. At this point, we were forcibly led to examine the nature of non-bonded interactions and possible steric effects in such a process, with the aid of CPK models. In fact the CPK model of avermectin $B_{1a}$ reveals the extremely compact nature of this structure (Fig. 20). Not only is there no "cavity" to speak of, but the orientation of the ester carbonyl group is clearly pointing "outward" and not "inward" as the drawn structures lead to believe. The difficulty in lactonization of the conjugated seco acid is therefore understandable.

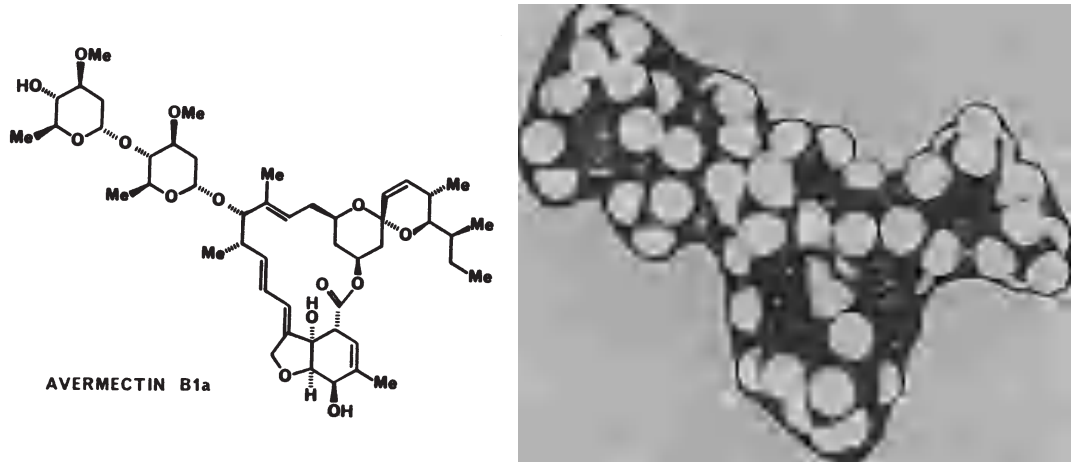


Fig. 20 CPK molecular model of avermectin $B_{1a}$ - wherein the macrolactone is the "cavity"?

## GLYCOSYLATION AND DECONJUGATION—THE CONQUEST OF AVERMECTIN $B_{1a}$

There now remained two crucial issues to address, namely the deconjugation of the double bond and the attachment of the disaccharide unit. Since the hydroxy groups in 70 would have to be preferentially protected, we elected to glycosylate the $C_{13}$ hydroxy group thereby "protecting" it with the disaccharide. For this we relied on a glycosylation method developed in our laboratory (ref. 39) which has proved useful in Woodward's total synthesis of erythromycin (ref. 40) (Fig. 21). Thus, treatment of the O-silylated derivative of 70 with the pyridylthioglycoside 71 in the presence of silver triflate gave a mixture of anomeric glycosides in which the desired α-anomer 72 was predominant (ref. 10, 41).

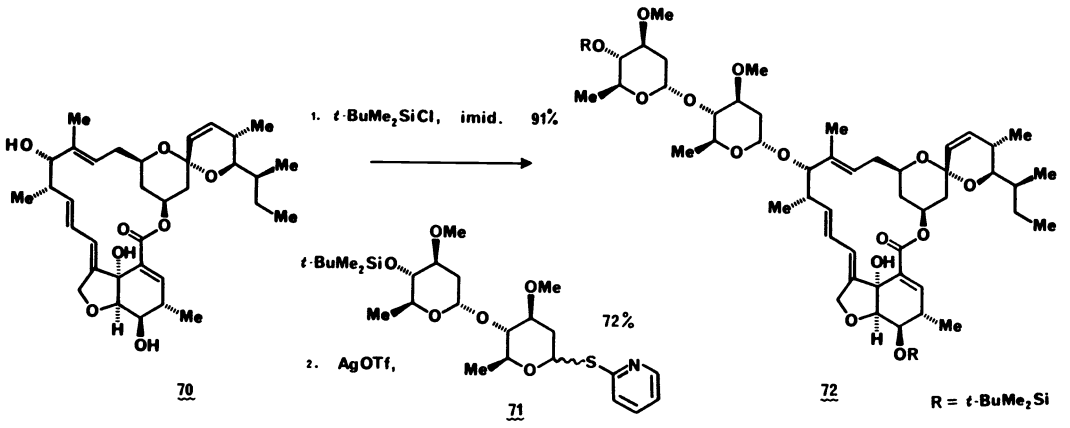


Fig. 21 Glycosylation via the pyridylthioglycoside method.

The last hurdle to overcome was the deconjugation of the α,β-unsaturated lactone 72. We reasoned that a ketene acetal derivative such as A would fragment under controlled acid hydrolysis conditions to give the expected α-orientated isomer C by virtue of a topside (β) proton delivery (Fig. 22). Whereas, in the case where $R^1$=H, internal quenching of the enolate might take place, thus leading to the undersired β-isomer D (ref. 42, 43).

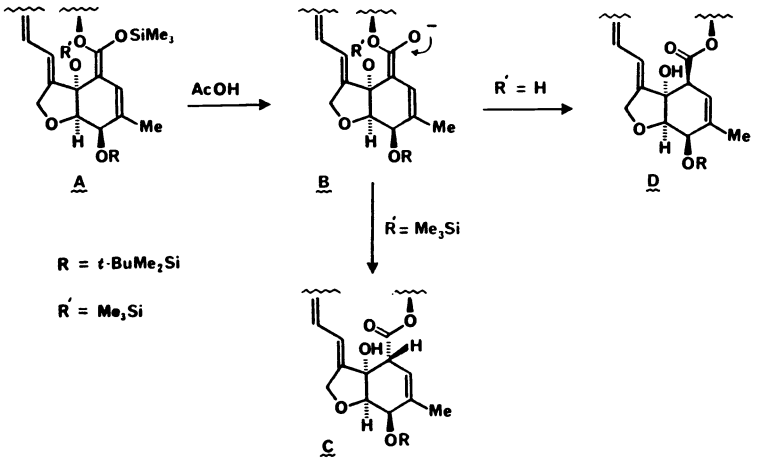


Fig. 22 Rationale for deconjugation of an alpha orientated α,β-unsaturated lactone.

Our reasoning was duly rewarded. Thus, silylation of the $C_7$ hydroxy group, followed by formation of the ketene acetal, subsequent careful acidification, and desilylation led to avermectin $B_{1a}$ $[\alpha]_D$ 55.1° ($CHCl_3$) identical to the natural product except for the absence of the $B_{1b}$ component (Fig. 23, 24).

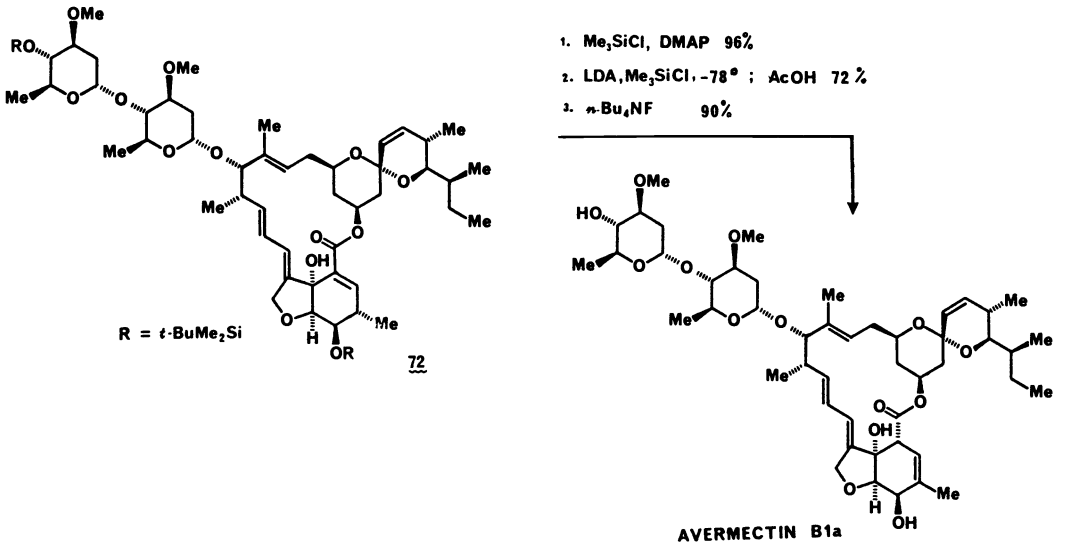


Fig. 23 Deconjugation of the α,β-unsaturated lactone - the last hurdle in the conquest of avermectin $B_{1a}$.

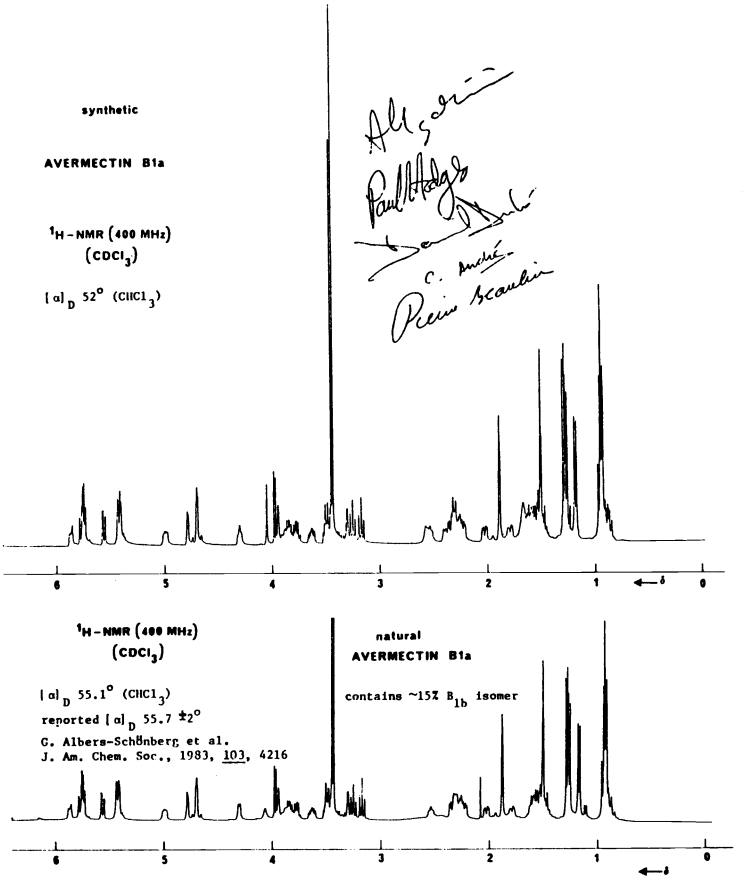


Fig. 24 Comparison of the $^1$H-NMR spectra of synthetic and natural avermectin $B_{1a}$ (contains ~ 15% $B_{1b}$ component)

## EPILOGUE

Our studies directed at the total synthesis of the avermectins have given us much insight into aspects of synthetic planning and execution. The successful completion of the synthesis of avermectin $B_{1a}$ was due in part to the decoding and simplification of the intricate array of stereochemical, functional and topological features present in this awesome megastructure. As is inevitable in such multistep syntheses, the question of protective groups, general functional group compatibility and reactivity were critical issues that had to be addressed and solved. It is hoped that the methodology developed in this work will be useful in the total and semi-synthesis of other members of the biologically important avermectin-milbemycin group of macrolides.

### Acknowledgement

We thank the National Scientific and Engineering Council of Canada, le Ministère de l'Education du Québec, Merck Frosst and Merck, Sharpe & Dohme for financial assistance. We also gratefully acknowledge receiving a sample of the avermectin complex for degradation studies, from the Merck Laboratories. We thank Dr. Phan Viet Tan for assisting in obtaining 2D H-n.m.r. spectra for several of the intermediates, and Michael Evans for mass spectra. We are grateful to Dr. B. Wilkes of IRCM (Montreal) for the energy minimization studies.

## REFERENCES

1. R.W. Burg, B.M. Miller, E.E. Baker, J. Birnbaum, S.A. Currie, R. Hartman, Y.L. Kong, R.L. Monaghan, G. Olson, I. Putter, J.B. Tunac, H. Wallick, E.O. Stapley, R. Oiwa, S. Omura, Antimicrob. Agents Chemother., 15, 361-367, (1979). T.W. Miller, L. Chaiet, D.J. Cole, J.E. Flor, R.T. Goegelman, V.P. Gullo, H. Joshua, A.J. Kempf, W.R. Krellwitz, R.L. Monaghan, R.E. Ormond, K.E. Wilson, G. Albers-Schönberg, I. Putter, Antimicrob. Agents Chemother., 15, 368-371 (1979).

2. H. Mrozik, P. Eskola, M.H. Fisher, Tetrahedron Lett., 23, 2377-2378, (1982) and references cited therein. J.C. Chabala, H. Mrozik, R.L. Tolman, P. Eskola, A. Lusi, L.H. Peterson, M.F. Woods, M.H. Fisher, W.C. Campbell, J.R. Egerton, D.A. Ostlind, J. Med. Chem., 23, 1134-1136, (1980). For a recent review, see W.F. Campbell, M.H. Fisher, E.O. Stapley, G. Albers-Schönberg, T.A. Jacob, Science., 221, 823-828, (1983).

3. G. Albers-Schönberg, B.H. Arison, J.C. Chabala, A.W. Douglas, P. Eskola, M.H. Fisher, A. Lusi, H. Mrozik, J.L. Smith, R.L. Tolman, J. Am. Chem. Soc., 103, 4216-4221, (1981). J.P. Springer, B.H. Arison, J.M. Hirshfield, K. Hoogsteen, J. Am. Chem. Soc., 103, 4221-4224, (1981). H. Mrozik, P. Eskola, B.H. Arison, G. Albers-Schöngerg, M.H. Fisher., J. Org. Chem., 47, 489-492, (1982).

4. S.S. Pong, C.C. Wang., J. Neurochem., 38, 375-379, (1982). J.C. Chabala, A. Rosegay, M.A.R. Walsh, J. Agric. Food Chem., 29, 881-884, (1981).

5. Y. Takiguchi, H. Mishima, M. Okuda, M. Terao, A. Aoki, R. Fukuda., J. Antibiot., 33, 1120-1127, (1980).

6. For total syntheses, see, A.B. Smith, III., S.R. Schow, J.D. Bloom, A.S. Thompson, K.N. Winzenburg, J. Am. Chem. Soc., 104, 4015-4018, (1982). D.R. Williams, B.A. Barner, K. Nishitani, J.G. Phillips, J. Am. Chem. Soc., 104, 4708-4710, (1982). R. Baker, M.J. O'Mahony, C.J. Swain, J. Chem. Soc., Chem. Commun., 1326-1328, (1985). D.A. Street, P. Kocienski, S.F. Campbell, J. Chem. Soc., Chem. Commun., 1386-1388, (1985). S.R. Schow, J.D. Bloom, A.S. Thompson, K.N. Winzenburg, A.B. Smith, III., J. Am. Chem. Soc., 108, 2662-2674, (1986). For a recent review, see, H.G. Davies, R.H. Green, Nat. Prod. Rep., 87-121, (1986).

7. For semi-syntheses, partial syntheses, etc. see ref. 2; see also, H. Mrozik, J.C. Chabala, P. Eskola, A. Matzuk, F. Waksmunski, M. Woods, M.H. Fisher, Tetrahedron Lett., 24, 5333-5336, (1983). R. Baker, M.J. O'Mahony, C.J. Swain, Tetrahedron Lett., 27, 3059-3062, (1986). A.B. Smith, III., A.S. Thompson, Tetrahedron Lett., 26, 4283-4286, (1985).

8. R. Baker, C.J. Swain, J.C. Head, J. Chem. Soc., Chem. Commun., 309-311, (1985). D. Culshaw, P. Grice, S.V. Ley, G.A. Strange, Tetrahedron Lett., 26, 5837-5840, (1985).

9. S. Hanessian, A. Ugolini, M. Therien, J. Org. Chem., 48, 4427-4429, (1983).

10. S. Hanessian, A. Ugolini, D. Dubé, P.J. Hodges, C. André, J. Am. Chem. Soc., 108, 2776-2778, (1986).

11. S. Hanessian in "Total Synthesis of Natural Products: The 'Chiron' Approach". J.E. Baldwin, ed., Pergamon Press, Oxford 1983. For other recent reviews, see, T.D. Inch, Advan. Carbohydr. Chem. Biochem., 27, 191-225, (1972). B. Fraser-Reid, Acc. Chem. Res., 8, 192-201, (1975). S. Hanessian, Acc. Chem. Res., 12, 159-165, (1979). A. Vasella in "Modern Synthetic Methods". R. Scheffold, ed.; Otto Salle Verlag, Frankfurt am Main, Germany, 1980, p. 173.

12. S. Hanessian, L. Forêt, L. Trépanier, S. Léger, F. Major, A. Glamyan; Computers and Organic Synthesis Symposium, ACS Meeting, New York, N.Y. April, 1985. Org. Abstract. Chem. Eng. News., June 24, 1985, p. 26.

13. S. Hanessian, A. Ugolini, unpublished results.

14. F. Gonzalez, S. Lesage, A.S. Perlin, Carbohydr. Res., 42, 267-274, (1975).

15. D.Seebach, D. Wasmuth, Helv. Chim. Acta., 63, 197-200, (1980).

16. Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, K. Maruyama, J. Org. Chem., 47, 119-126, (1982). Y. Yamamoto, K. Maruyama, J. Am. Chem. Soc., 100, 3240-3241, (1978).

17. W.S. Fores, J. Am. Chem. Soc., 76, 1377-1378, (1954).

18. T. Katsuki, K.B. Sharpless, J. Am. Chem. Soc., 102, 5974-5976, (1980).

19. B. Lipshutz, J. Kozlowski, R.S. Wilhelm, J. Am. Chem. Soc., 104, 2305-2307, (1982).

20. E.J. Corey, P.L. Fuchs, Tetrahedron Lett., 3769-3772, (1972).

21. S. Hanessian, A. Ugolini, D. Dubé, A. Glamyan, Can. J. Chem., 62, 2146-2147, (1984).

22. For a recent publication on the synthesis of the lactone portion of compactin from carbohydrates, see, J.D. Prugh, C.S. Rooney, A.A. Deana, H.G. Ramjit, J. Org. Chem., 51, 648-657, (1986), and references cited therein; for a recent review, see T. Rosen, C.H. Heathcock, Tetrahedron, in press.

23. H. Ogura, H. Takahashi, Synth. Commun., 3, 135-143, (1973). J.C. Chabala, J.E. Vincent, Tetrahedron Lett., 937-940, (1978). P. Deslongchamps, D.R. Rowan, N. Pothier, T. Sauvé, J.K. Saunders, Can. J. Chem., 59, 1105-1121, (1981). S. Hanessian, A. Ugolini, Carbohydr. Res., 130, 261-269, (1984).

24. P. Deslongchamps in "Stereoelectronic Effects in Organic Chemistry". J.E. Baldwin, ed., Pergamon Press, Oxford, 1983.

25. For pertinent examples of sulfone anion coupling with carbonyl derivatives, see, M.P. Edwards, S.V. Ley, S.G. Lister, B.D. Palmer, D.J. Williams, J. Org. Chem., 49, 3503-3516, (1984). P.J. Kocienski, B. Lythgoe, S. Ruston, J. Chem. Soc., Perkin Trans 1., 829-834, (1978). See also, P.D. Magnus, Tetrahedron., 33, 2019-2045, (1977). For a review, see, P. Kocienski, Phosphorus and Sulfur, 24, 97-127, (1985).

26. M. Julia, J.-M. Paris, Tetrahedron Lett., 4833-4836, (1973). J. Morzycki, H.K. Schnoes, H.F. Deluca, J. Org. Chem., 49, 2148-2151, (1984).

27. S. Hanessian, A. Ugolini, P.J. Hodges, D. Dubé, Tetrahedron Lett., 27, 2699-2702, (1986).

28. M.E. Jung, L.J. Street, J. Am. Chem. Soc., 106, 8327-8329, (1984). M. Prashad, B. Fraser-Reid, J. Org. Chem., 50, 1564-1566, (1985). A.P. Kozikowski, E. Maloney Huss, Tetrahedron Lett., 26, 5759-5762, (1985). M.T. Crimmins, J.G. Lever, Tetrahedron Lett., 27, 291, (1986).

29. S. Hanessian, P. Beaulieu, D. Dubé, Tetrahedron Lett., in press.

30. N. Clauson-Kaas, N. Elming, Acta. Chem. Scand., 6, 560-564, (1952). R. Daniels, J.L. Fischer, J. Org. Chem., 28, 320-322, (1963).

31. G.E. McCasland, S. Furuta, L.J. Durham, J. Org. Chem., 31, 1516-1521, (1966).

32. For some recent examples of radical-mediated carbocycle formation via vinyl halides, see N.N. Martinovic, H. Ramanathan, Tetrahedron Lett., 24, 1871-1874, (1983). G. Stork, N.H. Baine, J. Am. Chem. Soc., 104, 2321-2323, (1982). G. Stork, R. Mook, Jr., J. Am. Chem. Soc., 105, 3720-3722, (1983). See also, D.J. Hart., Science, 223, 883-887, (1984) for a recent review of the general subject.

33. See for example, T. Reichstein, C. Montigel, Helv. Chim. Acta., 22, 1212-1221, (1939). G.R. Chaudry, T.G. Halsall, E.R.H. Jones, J. Chem. Soc., 2725-2732. (1961) and references cited therein.

34. M.A. Warpehoski, B. Chabaud, K.B. Sharpless, J. Org. Chem., 47, 2897-2900, (1982).

35. G.A. Berchtold, D. Lesuisse, J. Org. Chem., 50, 888-890, (1985).

36. For an alternative method of degradation, see A.B. Smith, III., A.S. Thompson, Tetrahedron Lett., 26, 4279-4282, (1985). This method gives the 8-oxo derivative of the oxahydrindene subunit.

37. T. Veysoglu, L.S. Mitscher, J.K. Swayse, Synthesis, 807-810, (1980).

38. A. Hassner, V. Alexanian, Tetrahedron Lett., 4475, (1978).

39. S. Hanessian, C. Bacquet, N. LeHong, Carbohydr. Res., 80, C17-C22, (1980).

40. R.B. Woodward et al, J. Am. Chem. Soc., 103, 3215-3217, (1981). For a recent synthesis of glycosides of avermectin $B_{1a}$ aglycone, see K.C. Nicolaou, R.E. Dolle, D.P. Papahatjis, J.L. Randall, J. Am. Chem. Soc., 106, 4189-4192, (1984).

41. The disaccharide sub-unit was obtained from 66 (containing 15% of the $B_{1b}$ component) via the following sequence. i) PCC (90%). ii) $KN(SiMe_3)_2$, THF, -30°C (85%) and then isolation of the protected disaccharide, followed by treatment with dipyridyldisulfide and triphenylphosphine in dichloromethane.

42. For examples of deconjugation of α,β-unsaturated esters, see A.S. Kende, B.H. Toder, J. Org. Chem., 47, 163-167, (1982).

43. For examples of the formation of ketene acetals and subsequent transformations, see R.E. Ireland, D.W. Norbeck, J. Am. Chem. Soc., 107, 3729-3285, (1985).