RELAY STUDIES OF THE AVERMECTIN ANTIPARASITIC AGENTS

A Thesis Presented By

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Abstract

The thesis is divided into three sections. The first begins with an overview of the discovery and biological properties of the avermectins and milbemycins. This is followed by a review of degradative, modifying and semi-synthetic relay strategies to the avermectin / milbemycin natural products.

The third section describes relay studies of avermectin B_{1a}. Initial efforts to degrade avermectin B_{1a}, by ozonolysis, to suitable northern and southern fragments prior to C-10, C-11 Julia coupling are described. Subsequent model Julia and relay couplings are described. Finally, after gaining access to the synthetic intermediates via relay synthesis, introduction of the C-3, C-4 *endo* cyclic double bond in the southern hemisphere (employing selenoxide *syn* elimination) is investigated and successfully achieved.

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Finally, I would like to thank my parents, sister, brother and niece (Shaymoly) for understanding, patience and continual love and support.

Abbreviations

Ac	Acetyl
Aliquat®	Tricaprylylmethylammonium chloride
Bn	Benzyl
^{n}BuLi	^{n}Butyl lithium
^{t}BuLi	^{t}Butyl lithium
Bz	Benzoyl
CI	Chemical Ionisation
COSY	COrellated SpectroscopY
CSA	Camphorsulphonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPA	Diisopropyl amine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulphoxide
Ether	Diethyl ether
FAB	Fast Atom Bombardment
HCl	Hydrochloric acid
HF	Hydrofluoric acid
HMPA	Hexamethyl phosphoramide
Hplc	High performance liquid chromatography

Imid	Imidazole
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
L-Selectride	Lithium tri-sec-butyl -borohydride
KDA	Potassium diisopropylamide
K^{t}OBu	Potassium ^{t}-butyloxide
MEM	2-Methoxyethoxymethyl
Ms	Methanesulphonyl
NPSP	N-(Phenylseleno)phthalimide
Oxone®	Potassium peroxymonosulphate
PCC	Pyridinium chlorochromate
Petrol	40-60° Petroleum ether
Piv	Pivaloyl
Py	Pyridine
r.t.	Room temperature
s.m.	Starting material
TBAF	Tetra-n-butylammonium flouride
TBDMS	t-Butyldimetylsilyl
TBDPS	t-Butyldiphenylsilyl
Tf	Trifluoromethanesulphonyl
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetra-n-propylammonium perruthenate

Tr	Trityl
Ts	*p*-Toluenesulphonyl

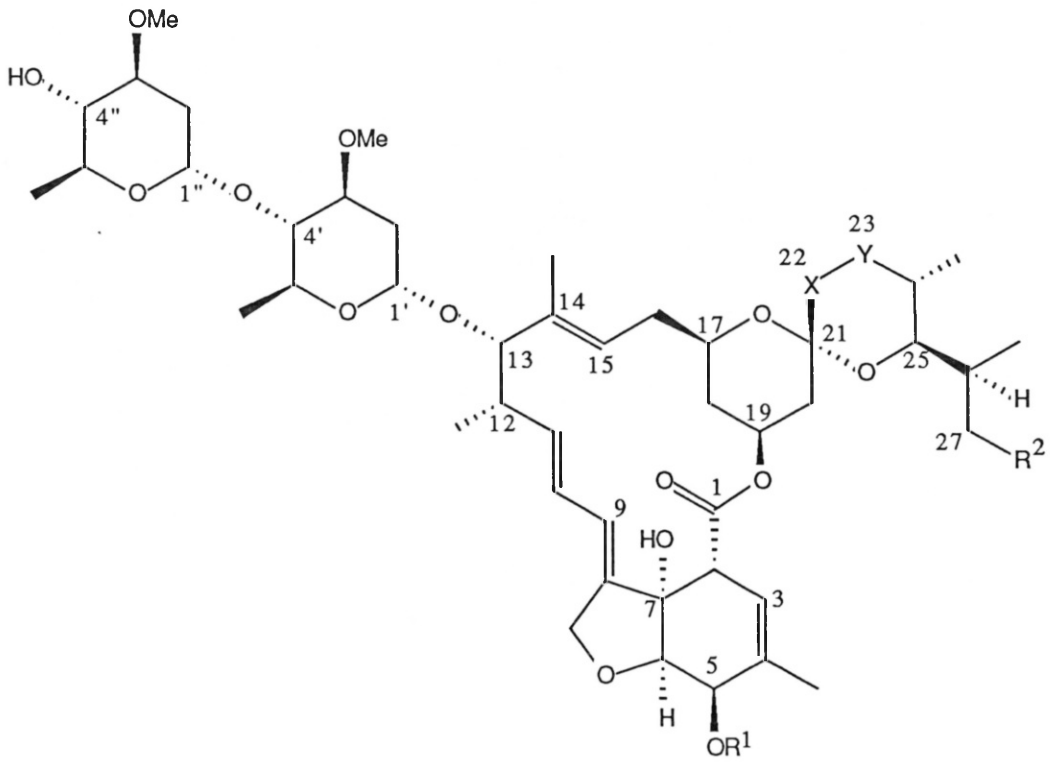
Introduction

The avermectins were discovered in 1976 by workers at Merck Sharp and Dohme through random screening for compounds with anthelmintic activity using an *in vivo* test on nematode-infected mice.[1] The species producing these compounds was found in a soil sample from Japan, and identified as a new actinomycete which was named *Streptomyces avermitilis*. This species was later modified by u.v. radiation to give a mutant capable of producing avermectins faster and for longer periods. Optimisation of the yield was achieved by careful selection of the fermentation medium.

Extraction of the fermentation broths, followed by extensive chromatography, provided eight active compounds,[2] which were found to be sixteen-membered macrocyclic lactones. Their precise structures, determined by the application of modern techniques,[3] are shown in fig.1 .

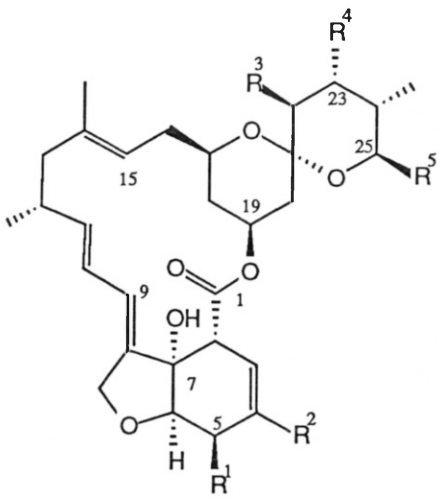
The close relationship with the milbemycins (fig. 2)[4] was noted early on and aided the interpretation of the spectroscopic data. (The nomenclature for the milbemycins used in fig. 2 is that originally proposed and generally accepted. It is used in preference to the alternative system proposed in 1980.[4a])

X-ray analysis of avermectins B_{1a} and B_{2a} aglycone[5] confirmed the spectroscopic assignments and allowed the absolute stereochemistry to be determined, since the sugar residues could be obtained by degradation of the natural products and characterised independently as α - L - oleandrose. The X-ray data agree closely with the n.m.r. data, suggesting that solid state and solution

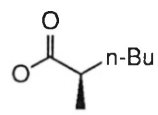


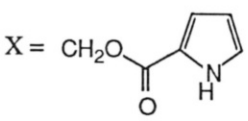
X - Y	R^1	R^2	Avermectin
CH=CH	Me	Me	A_{1a}
CH=CH	Me	H	A_{1b}
CH=CH	H	Me	B_{1a}
CH=CH	H	H	B_{1b}
CH_2—CH(OH)	Me	Me	A_{2a}
CH_2—CH(OH)	Me	H	A_{2b}
CH_2—CH(OH)	H	Me	B_{2a}
CH_2—CH(OH)	H	H	B_{2b}

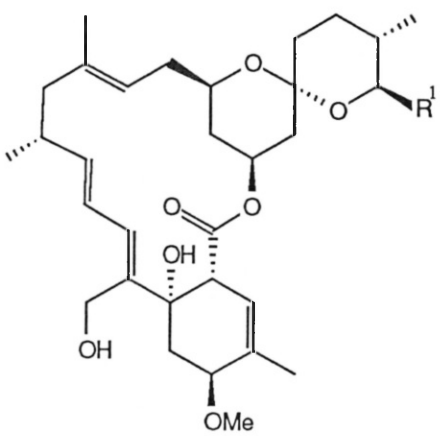
Figure 1. The Structures of the Principal Avermectins



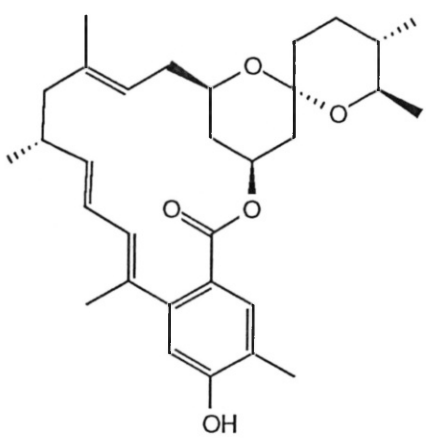
R^1	R^2	R^3	R^4	R^5	Milbemycin
OH	Me	H	H	Me	α_1
OMe	Me	H	H	Me	α_2
OH	Me	H	H	Et	α_3
OMe	Me	H	H	Et	α_4
OH	Me	OH	Y	Me	α_5
OMe	Me	OH	Y	Me	α_6
OH	Me	OH	Y	Et	α_7
OMe	Me	OH	Y	Et	α_8
OH	X	H	H	Me	α_9
OH	X	H	H	Et	α_{10}

Y = 

X = 



β_1 R^1 = Me
β_2 R^1 = Et



β_3

Figure 2. The Structures of the Principal Milbemycins

conformations are very similar. The absolute stereochemistry of the milbemycins was later confirmed by chemical conversion of 22,23- dihydroavermectin B_{1b} aglycone into milbemycin D by deoxygenation at C-13.[6]

Since the initial discovery of the two families of macrolide, further avermectins and milbemycins have been isolated showing a variety of functionality,[7] and the only consistent difference between the families is the presence of oxygenation at C-13 in the avermectins.

^{13}C-NMR analysis of the avermectin A_{1a}, A_{2a}, B_{1a} and B_{2a} produced by *Strepomyces avermitilis* culture 5192 after [1 - ^{13}C] - acetate and propionate feeding experiments showed that the carbon distribution of the macrolide was consistent with a biosynthetic model incorporating seven acetate and five propionate units.[8] The C-25 carbon atom and its sec-butyl substituent were however unlabelled and were shown to be derived from L - isoleucine.[8] Similarly the C-25 isopropyl substituent in the "b" series was shown to be derived from L - valine.

Further labelling studies[8] using sodium [1 - ^{13}C, $^{18}O_2$] propionate and sodium [1 - ^{13}C, $^{18}O_2$] acetate confirmed these findings and indicated that the spiroacetal was formed by ketalisation of a carbonyl group at C-21 by secondary hydroxyl groups at C-17 and C-25. Additionally the C-7 tertiary hydroxl group was shown to retain its propionate derived oxygen atom. This suggests that the C-2, C-7 bond is formed by simple aldol condensation either before or after macrolactonisation.

The C-13 oxygen atom of the avermectins is also derived from propionate. This may suggest the milbemycins are in fact derived from the avermectins by dehydration and reduction, as both families of natural products contain propionate

derived carbons at C-13 and C-14 and the C-14 methyl group.

The initial promising biological results [9] led to considerable testing, which showed that the avermectins (and the milbemycins) are highly potent against two major classes of parasite, nematodes (roundworms) and arthropods (insects, mites, ticks, lice).[10]

Studies on helminth-infected sheep by oral administration revealed differences in the activity of the individual avermectins. [11] The *B* series was found to be more active , in general, than the *A* series. The differences between the *1* and *2* series were dependent on the particular parasite and on the method of administration. There was effectively no difference in activity between the *a* and *b* series.

Chemical modification revealed the parts of the overall structure which were necessary for high activity. Hydrogenation of the C-22, C-23 double bond of avermectin B_1[12] does not reduce activity, but further reduction to the 3,4,22,23-tetrahydro derivative produced a significant loss of potency. Hydrolytic cleavage of one the sugars results in a four fold decrease in activity, while the corresponding aglycone retains only a thirtieth of the original potency. Interestingly, loss of the oxygenation at C-13 , giving milbemycin type compounds, restores activity to high levels.[7b, 10a] The importance of functionality at various remote sites of the avermectin structure for activity suggests a complicated mode of binding to the biological receptor. This may well preclude discovery of much simpler synthetic analogues with high activity, and indeed most active analogues to date have been derived by chemical modification of the natural products. The lack of observed activity of simple analogues containing spiroacetal[13] and macrolide moieties[14] substantiates this result.

The mode of action of the avermectins is novel and has been extensively researched. They appear to interfere with γ - aminobutyric acid (GABA) mediated neurotransmission.[10] They are not GABA antagonists, as they do not compete with GABA for its receptor site. Instead they seem to stimulate the release of GABA from pre-synaptic membrane and enhance the binding of GABA to its receptors.[15] These receptors are found on the post-synaptic membrane of an excitatory motor-neuron in nematodes and on the post-junction membrane of a muscle cell in arthropods. The enhanced binding is caused by increase in the number of GABA receptor sites, rather than an increase in the binding constant.[16] The enhanced GABA binding causes an irreversible opening of chloride ion channels in the post-synaptic membrane, which results in an increased flow of the chloride ions into the cell. Hyperpolarisation of the cell results and the terminal becomes unresponsive to further neurotransmission ; paralysis and often death follows.

This mode of action explains why the compounds are not active against cestodes (tapeworms) and trematodes (flukes), neither of which use GABA as a neurotransmitter.

The outstanding potency of the avermectins has stimulated research into their application both as antiparasitics for the treatment of livestock[10a,b] and as insecticides[18]. The variation in efficacy of the most potent B_1 and B_2, depending both on species tested and method of administration, led workers at Merck & Co. to synthesise the 22,23 - dihydro derivative of B_1, which has been named Ivermectin (a:b ~ 80:20).[10,11] It was found to be as active an antiparasitic agent as the natural product precursor, and proved to be efficacious both parenterally and orally in the treatment of livestock.[10a,b] It was introduced as an antiparasitic drug an 1981, marketed as 'Ivomec', and has been approved for use on many animal species.[10a] A

dosage of 0.2-0.3 mg/kg is recommended, although much lower doses are effective in many cases (e.g. a dosage of 0.05 mg/kg is effective for the elimination of hookworms from dogs[10a])[17], demonstrating the remarkable potency of the drug.

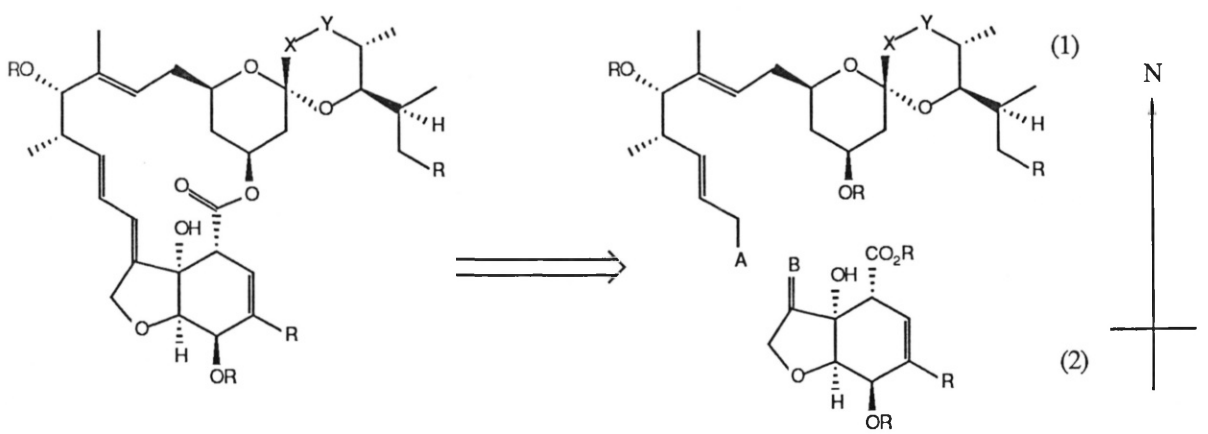
The safety margin associated with the use of ivermectin is large,[10b] and it has been shown that avermectin B_{2a} is not phytotoxic, even in excessive amounts (10 kg/hectare).[18] These properties considerably enhance the drug's potential. Furthermore, the application to the treatment of parasitic disorders in man has been successful, following trials showing high efficacy against filarial worm, *Onchocerca volvolus*, the agent responsible for the disease "River Blindness",[19] predominant in West Africa. Of particular importance here is the fact that the side-effects from ivermectin treatment of this disease are much milder than the severe side-effects encountered with the drugs in present usage. In addition, a dose of one of the present drugs would work for only a couple of weeks, necessitating treatment for as long as any breeding adult worms remained in the patient's body; this could be as long as a decade. There is always the risk of re-infection from a new blackfly bite, the carriers of the immature filarial worms. In contrast, one treatment of ivermectin will work for a year or so and in areas where people are treated with the drug, fewer blackfly are found to be infected with the worms. Thus flies are unlikely to become infected when they bite a human who is being administered ivermectin, so preventing the spread of the disease.[20]

Degradative and Relay Studies of Avermectins and Milbemycins

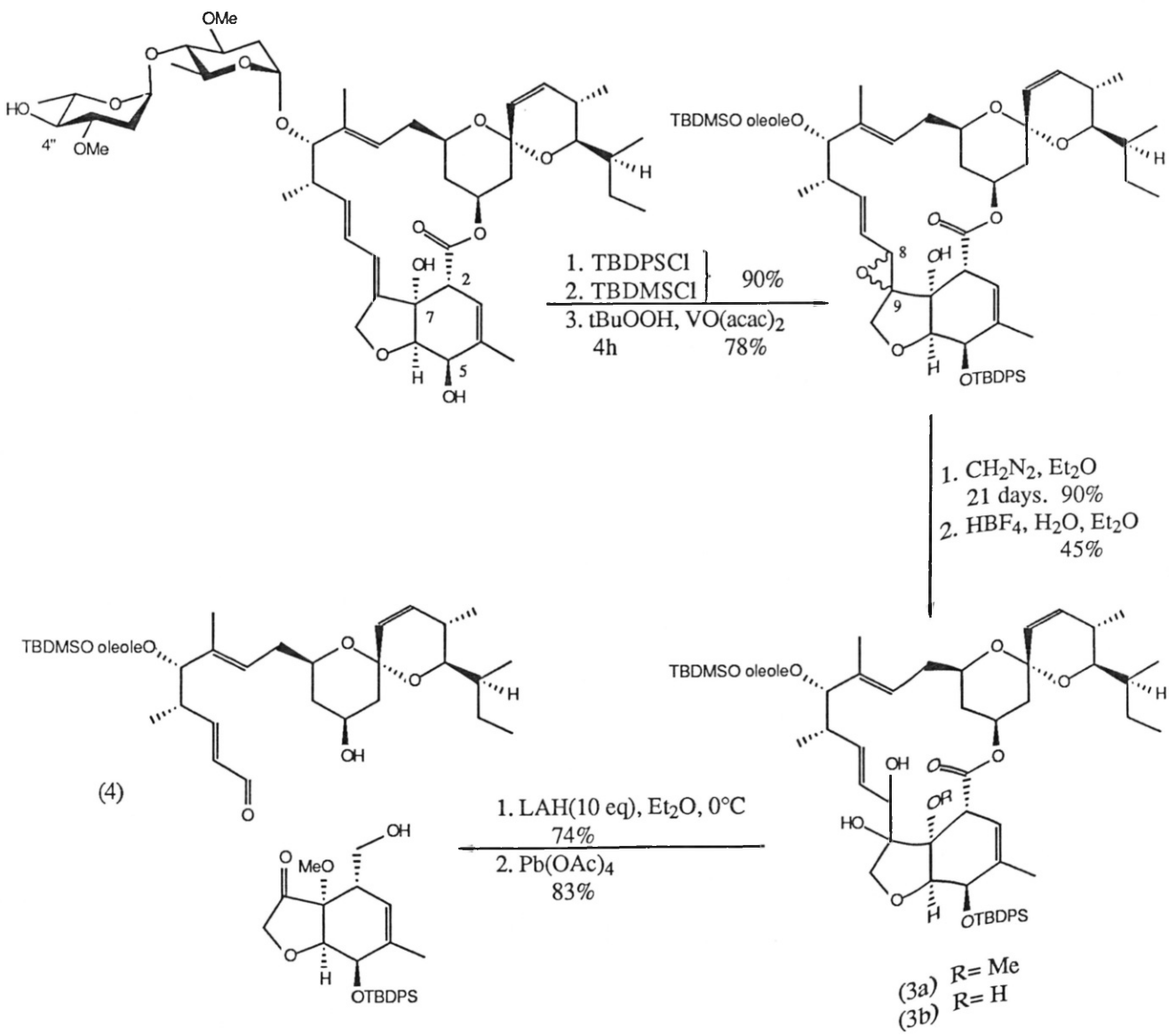
The avermectins and their structurally less complex relatives, the milbemycins, have stimulated a great deal of interest both industrially and in the organic synthesis community. They pose major challenges to the synthetic chemist because both of their highly functionalised nature and the complexity and plethora of stereochemistry.(Avermectin B_{1a} has 20 chiral centres).

In this section, a short overview of the recently developed controlled degradations, modifications and semi-syntheses of avermectin and related macrolactones is presented. Work prior to 1985 has been reviewed previously.[7c] Approaches to various subunits of avermectins and milbemycins, along with the eight syntheses to date of the aromatic milbemycin β_3, have also been reviewed.[21]

Convergent approaches to the synthesis of these classes of natural products have invariably envisaged disconnection of the target molecules into two major units - the northern (1) and southern hemispheres (2), with their union as a late step.



The goal of a total synthesis of a naturally occuring avermectin becomes more manageable if progress at crucial stages can be monitored by comparisons with degradation products.[7a,c] Moreover, systems derived in this way can be used to test the feasibility of planned key steps in the advanced stages of a synthesis. Furthermore, the sequence of degradation and synthesis can be used to construct hybrid or semi-synthetic analogues which are useful in probing the effects of structural variations on biological activity.

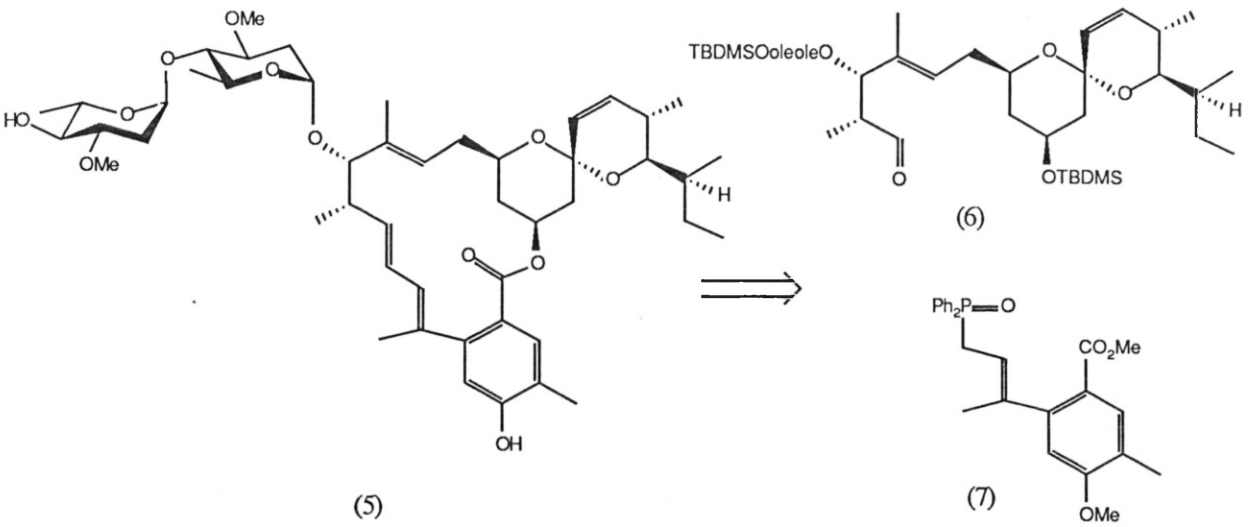


Scheme 1

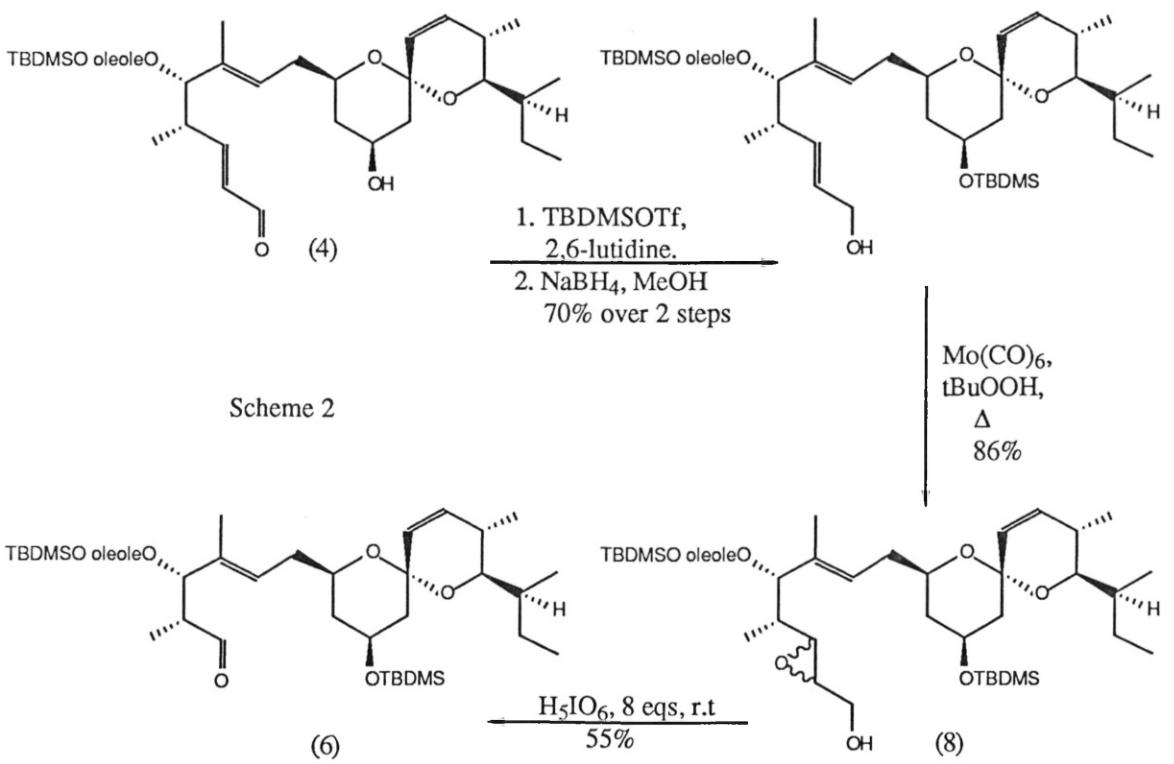
The latter sequence to obtain hybrids has been demonstrated by Smith.[22] The key step was the exploitation of a free hydroxyl group at C-7 to direct epoxidation (Sharpless ^{t}BuOOH, $VO(acac)_2$ protocol) to the C-8, C-9 double bond of avermectin B_{1a}, thereby achieving degradation of that linkage.(Scheme 1). The degradation is notable in that no stereochemistry is disrupted in the 7 step sequence. Conventional approaches (i.e. ozonolysis, macrolide hydrolysis) to this problem were not suitable. For example, saponification of the macrolide would be met with epimerisation at C-2 and eventually to aromatisation of the cyclohexene ring, while ozonolysis would result in oxidation of the C-3, C-4 olefin, thereby disrupting the hexahydrobenzofuran ring.

An interesting point in this degradation is the protection of the C-7 hydroxyl as a methyl ether, which was critical for successful isolation of the southern hemisphere. When the C-7 hydroxyl was not protected, he was unable to isolate any products from the southern hemisphere upon treatment with $Pb(OAc)_4$. It seems that the C-7, C-8 bond is first cleaved with $Pb(OAc)_4$, followed by cleavage of the C-8, C-9 bond to give the aldehyde (4). Support for this assumption derives from the observation that no aldehyde (i.e. (4)) is produced upon treatment of the C-7, -8, -9 -triol, derived from (3b), with 1.0 equivalent of $Pb(OAc)_4$; however, when a second equivalent is added aldehyde (4) is formed in 83% yield.

The sample of avermectin B_{1a} employed in Smith's degradation contained 10 -15% of avermectin B_{1b}, which incorporates an isopropyl group at C-25. The B_{1b} homologue is normally difficult to separate from the B_{1a}, and only after silylation of the secondary hydroxyl groups at C-4" and C-5 was this possible.



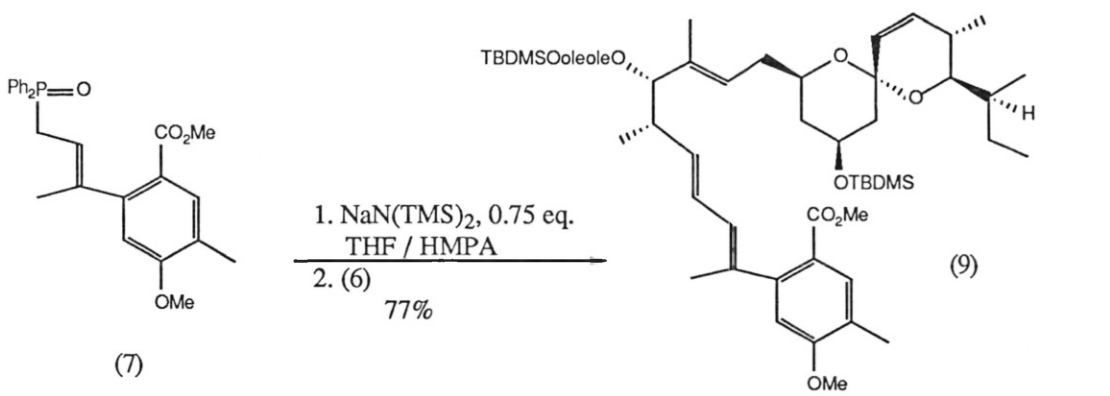
Smith[23] reports in the following letter the successful utilisation of his avermectin B_{1a} northern hemisphere (4). He constructs a milbemycin-avermectin hybrid (5), exploiting the chemistry developed during his synthesis of the structurally less complex milbemycin β_3.[24] Union of the aromatic phosphine oxide portion (7) with the northern portion (6) was planned using Horner-Wittig strategy.



Scheme 2

Aldehyde (6) was prepared in 4 steps (overall 33%) from the degraded northern hemisphere (4). (Scheme 2). Epoxidation employing the Sharpless molybdenum hexacarbonyl / tert-butylhydroperoxide protocol afforded a diastereomeric mixture of expoides (8), with final oxidative cleavage giving the desired aldehyde (6).

Initial attempts at coupling the northern and southern segments employing 2 eq. of $NaN(TMS)_2$ to generate the anion of phosphine oxide (7) [THF, HMPA (15 eqs), -78°C] led only to β-elimination of the sugar molecules.



1. TBAF, 93%.
2. KH (130 eq.), $KN(TMS)_2$ (1 eq.), 60%.
3. EtSNa, DMF, 75%.

Scheme 3

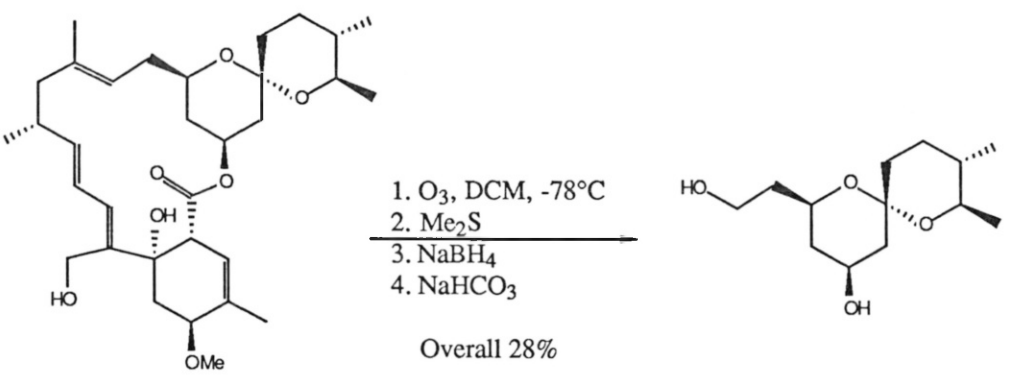
AVERMECTIN-MILBEMYCIN HYBRID (5).

The problem was circumvented by using an excess of the phosphine oxide (~ 4 eq) with only 3 eq of $NaN(TMS)_2$, giving the desired (E,E) - diene (9) in 77% yield (Scheme 3). No mention of (Z,E)-diene formation was made. In Smith's milbemycin β_3 synthesis[24] this Horner-Wittig coupling yielded the diene with a C-

(10, 11) E:Z ratio of 7:1 by n.m.r.

The hybrid synthesis was completed (2% overall for 14 steps from AvB_{1a}) as shown in Scheme 3, with macrolactonisation methodolgy developed earlier in the milbemycin field.[24]

Smith[24] has also employed an ozonoylitic degradative procedure, but applied to his milbemycin forays. (Scheme 4) He obtains the spiroacetal (10) in 28% yield (Scheme 4) for stereochemical and structural correlation, from milbemycin β_1(11) but does not mention isolation of the valuable southern moiety, suggesting a rather uncontrolled ozonolysis experiment, with cleavage of the C-3, C-4 double bond.

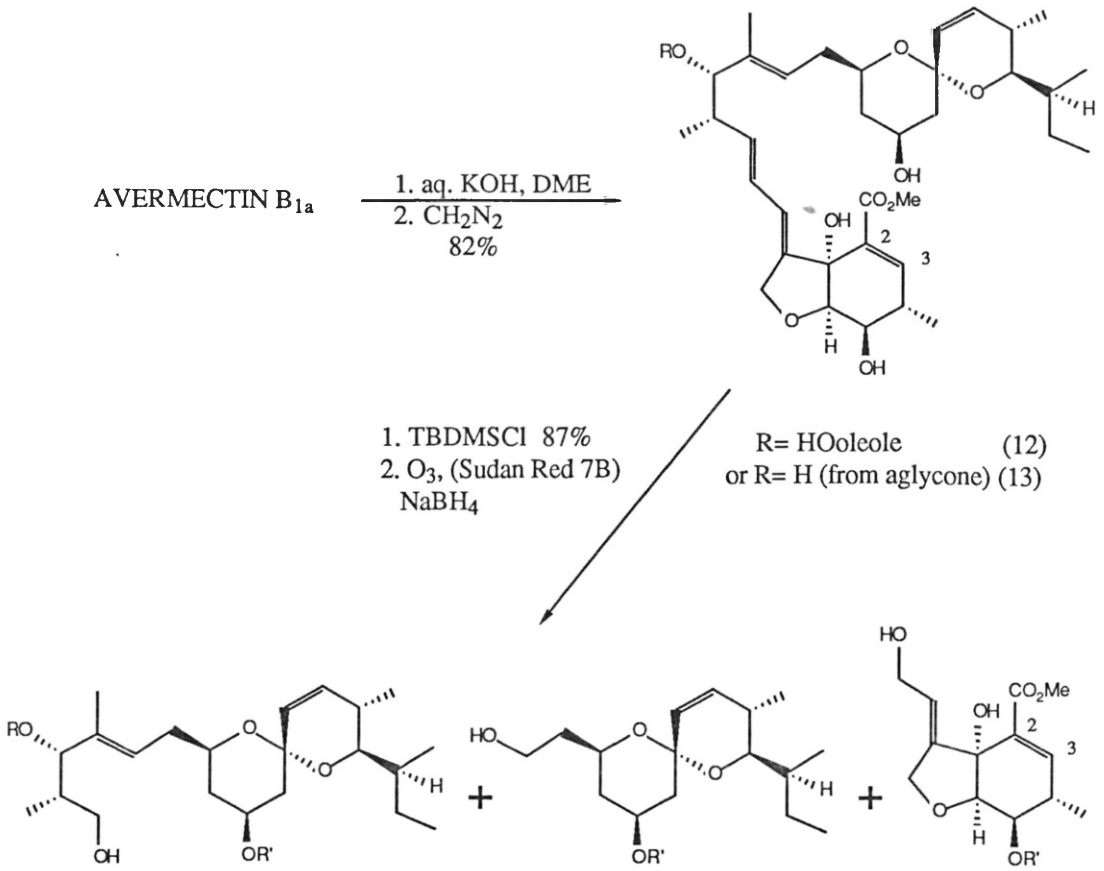


(11)
MILBEMYCIN β_1

(10)

Scheme 4

In the course of the studies which established the basis for a fully synthetic route to avermectin B_{1a}, Hanessian[25,26] demonstrated that the two seco acid derivatives, bearing conjugated (i.e. C-2, C-3) double bonds (12) and (13), underwent ozonolysis at C-10 to C-11 with good selectivity (Scheme 5).

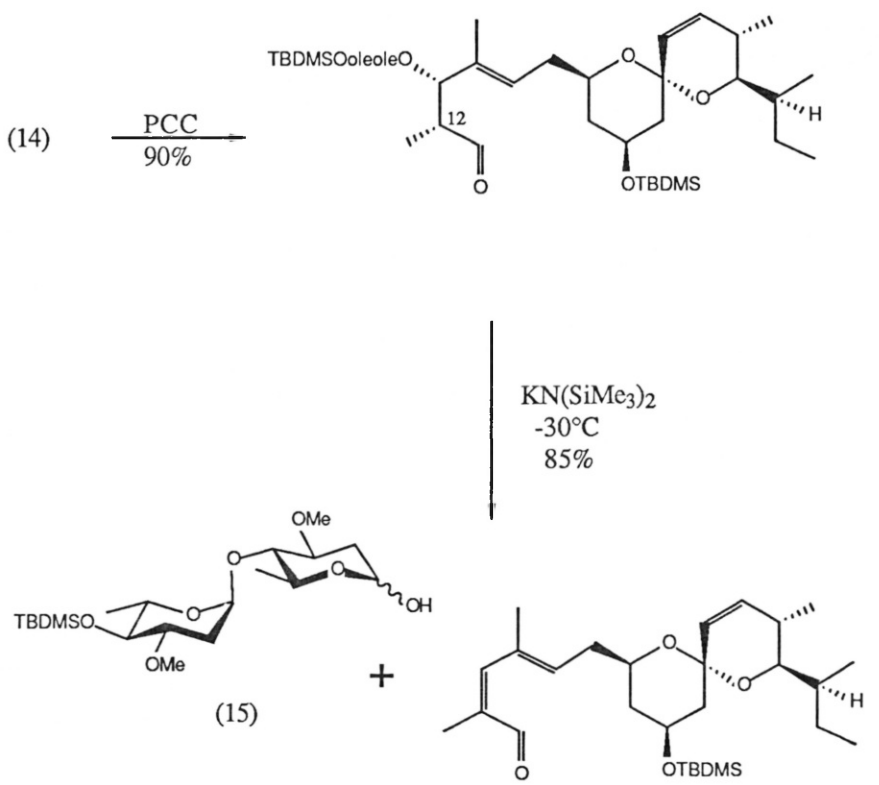


Scheme 5

The disaccharide sequence seems to be the most efficient at obtaining intact northern hemisphere.(14) (65% overall yield from avermectin B_{1a}, contaminated with 15% of B_{1b} component) The use of the TBDMS protecting group at the C-13 hydroxyl is of interest as this Si protecting group seems to minimise the extent of ozonolysis of the C-14, C-15 double bond, in contrast to the situation with a

benzoyloxy protecting group. (See Results and Discussion).

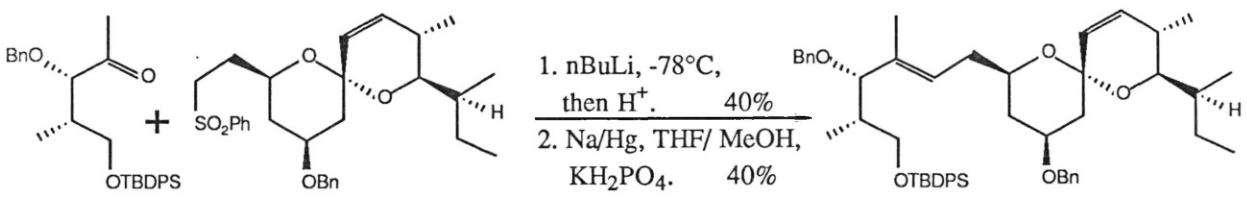
Hanessian also obtains intact 4"-O-t-butyldimethylsilyl disaccharide (15) (50% yield from avermectin), as an anomeric mixture, using a non-hydrolytic method, but sacrifices the stereochemistry as C-12 in the northern portion. Base induced elimination, as reported earlier by Smith[23] in his milbemycin-avermectin hybrid synthesis was the method of choice. (Scheme 6).



Scheme 6

In Hanessian's semi-synthesis of avermectin B_{1a} Julia olefination reactions played a central role in achieving geometric control of C-10, C-11 and C-14, C-15 double bonds.

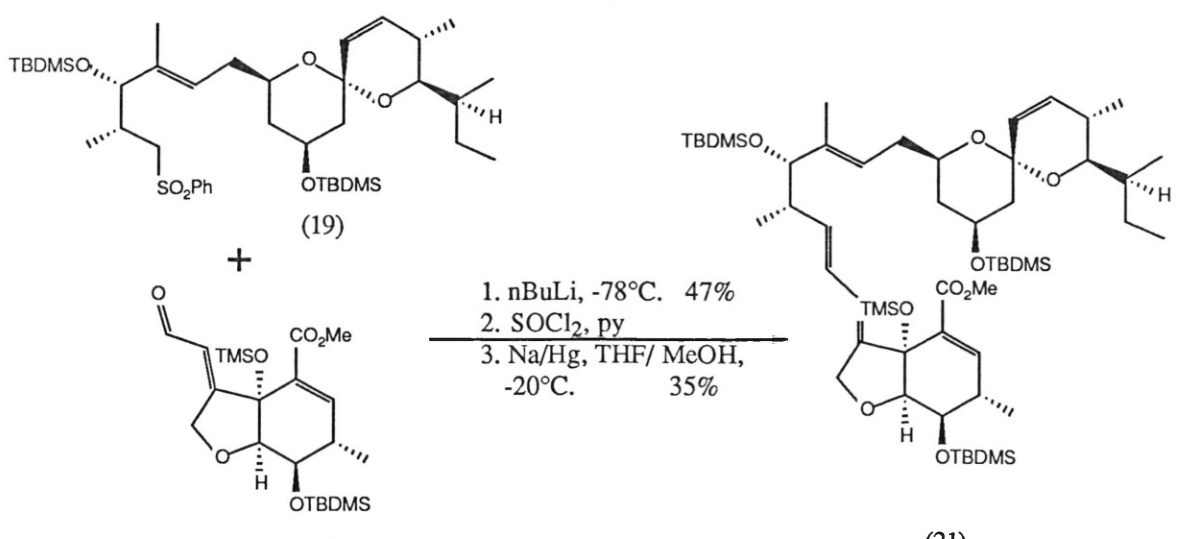
Coupling of the synthetic sulphone (17) and ketone (16) units was achieved in 16% overall yield, (38% on recovered sulphone). Reversibility of the initial anionic addition may explain the inefficiency of this process.[28]



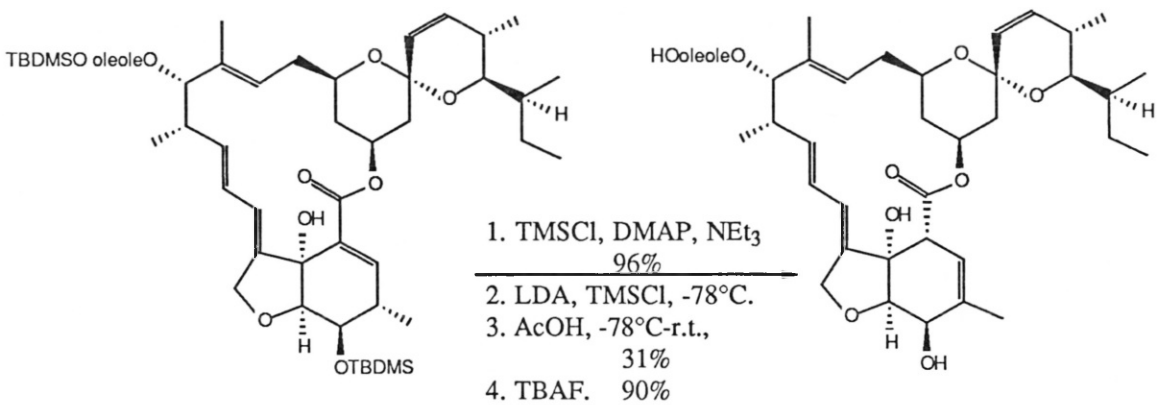
(16) (17) (18)

Two further chemical steps on (18) allowed physical correlation with a sample obtained from degradation.

In coupling synthetic northern hemisphere (19) with degradatively derived enal (20) only the trans alkene (21) was detected, in an overall yield of 16% (27% on recovered sulphone). This low yield may be attributable to competing reduction of the α,β unsaturated moiety during the sodium / amalgam reaction, which has been experienced in our hands.



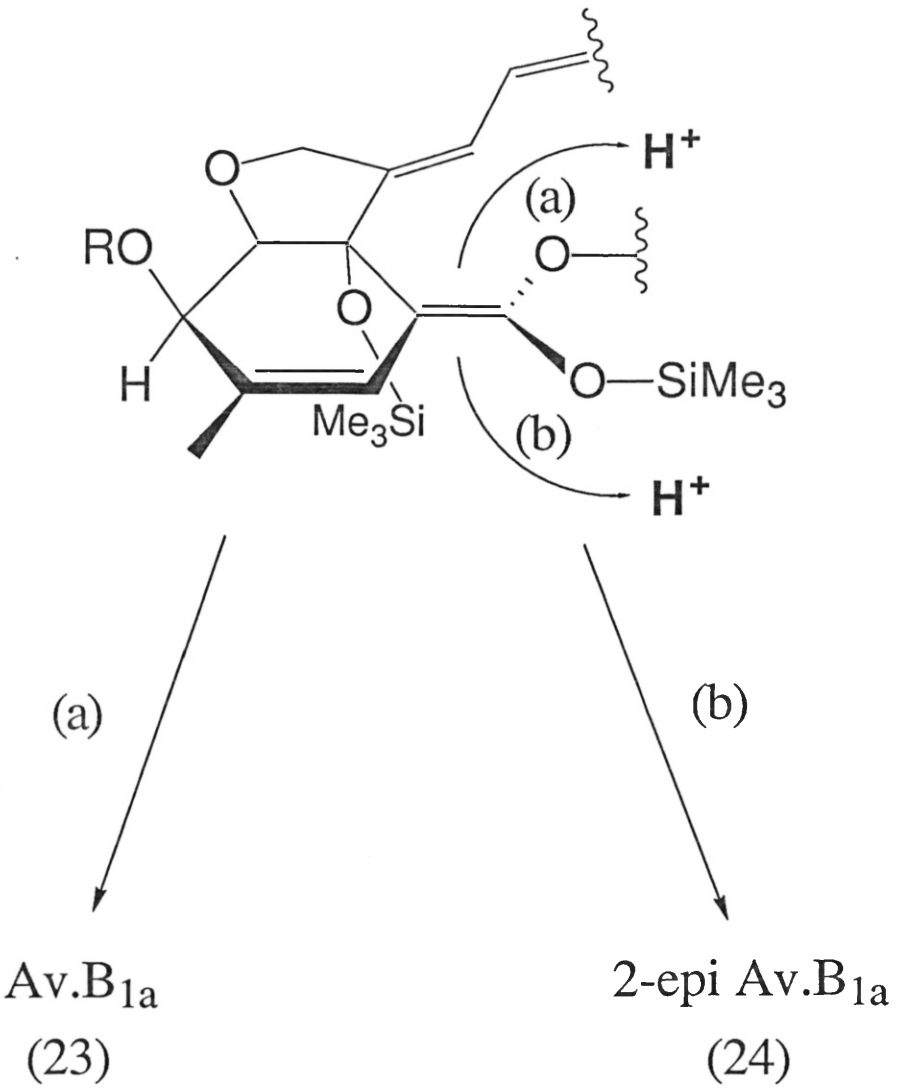
Further manipulation, DCC[29] mediated macrolactonisation, (30% for cyclisation) gave the conjugated avermectin B_{1a} aglycone. Attachment[30,31] of the L-oleandrose disaccharide residue, obtained from degradation, and protecting group adjustment afforded the α,β unsaturated avermectin B_{1a} (22).



(22) (23)

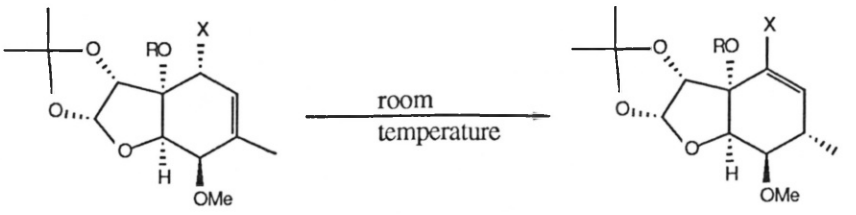
The critical deconjugation experiment was performed as follows. The C-7 hydroxl group was protected to block the α-face of the benzofuran moiety. *In seriatum*, ketene acetal formation, careful acidification and subsequent desilylation gave avermectin B_{1a} (23), identical in all respects to natural avermectin B_{1a}.

However, the stereochemical outcome of this deconjugation sequence has been fiercely contested by Fraser-Reid,[32] who under Hanessian's reported conditions obtained the C-2 epi-macrolide (24) (or the product from simple loss of the trimethylsilyl group), resulting from kinetic protonation of the α-face (convex side) of the benzofuran ring system. (Scheme 7)



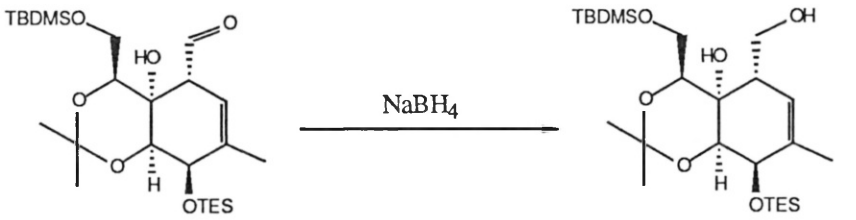
Scheme 7

Fraser-Reid has further evidence, with a very extensive range of deconjugation experiments, that deconjugation of Δ^2-isomers under kinetic control leads to the 2-epi isomer (24) and concludes that 3,4-alkanes, such as those in his synthesis (25) and (26), must be regarded as unreliable synthons for the "southern" oxahydrindene moiety of these molecules.



R= Bn X= CH_2OR' (25)
R= Tr or TBDMS X= CO_2Me (26)

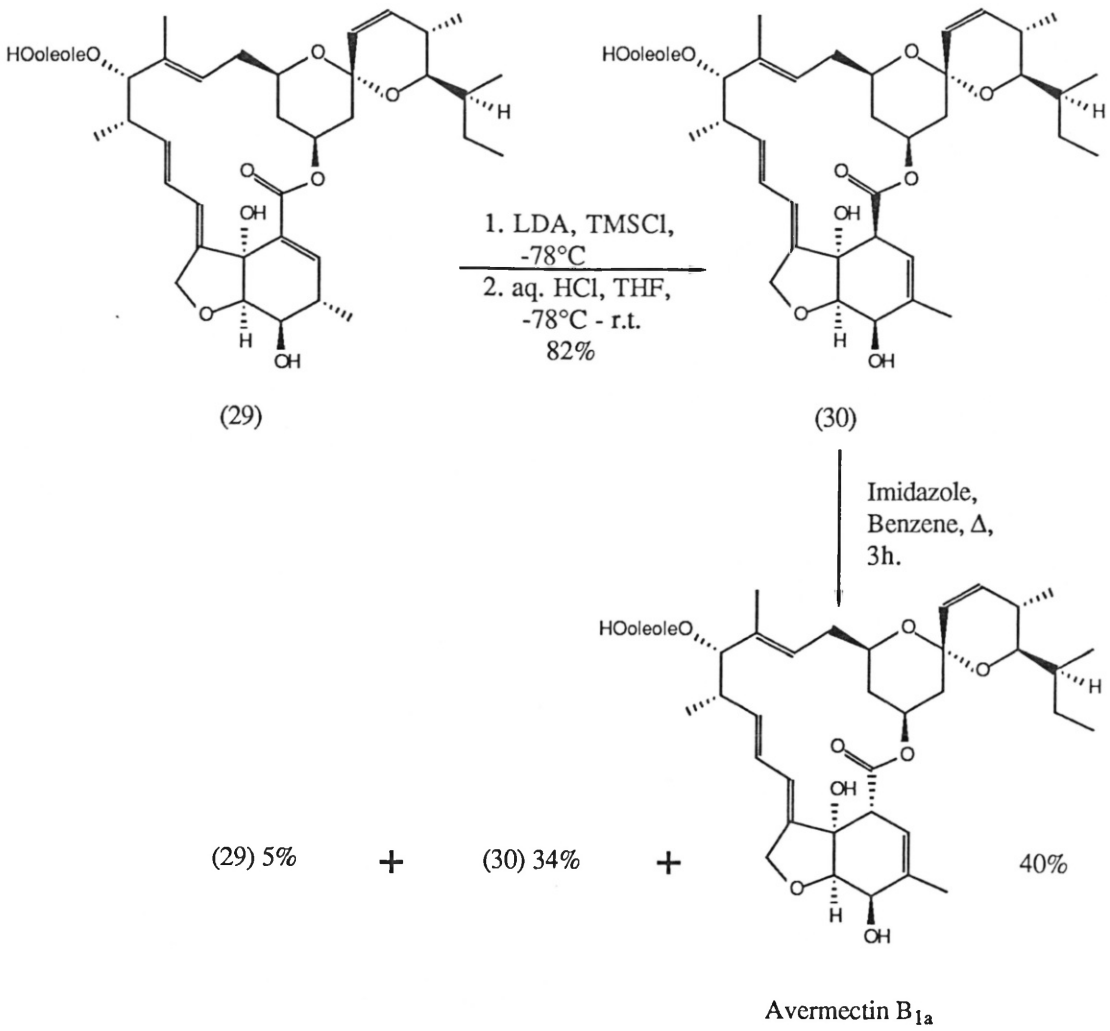
This tendency for the C-3,C-4 double bond to migrate to the stable C-2,C-3 position has also been observed by Hirama,[34] who circumvents this problem temporarily, by reducing the aldehyde (27) to the corresponding alcohol (28).



(27) (28)

Hanessian's response to Fraser-Reid's results is not one of retreat.[35] He admits that his protocol appeared to be successful initially, but the results using the original conditions were unrepeatable in his hands and extremely dependent on reaction conditions, scale of operation, or mode of work-up, as found by Fraser-Reid. In this paper he presents a more reproducible alternative, using a two step transformation of an O-protected Δ^2 avermectin into avermectin B_{1a} (*vide infra*).

The deconjugation of (29) through the action of LDA and trimethylsilylchloride in THF at -78°C followed by a rapid quenching with aq. HCl

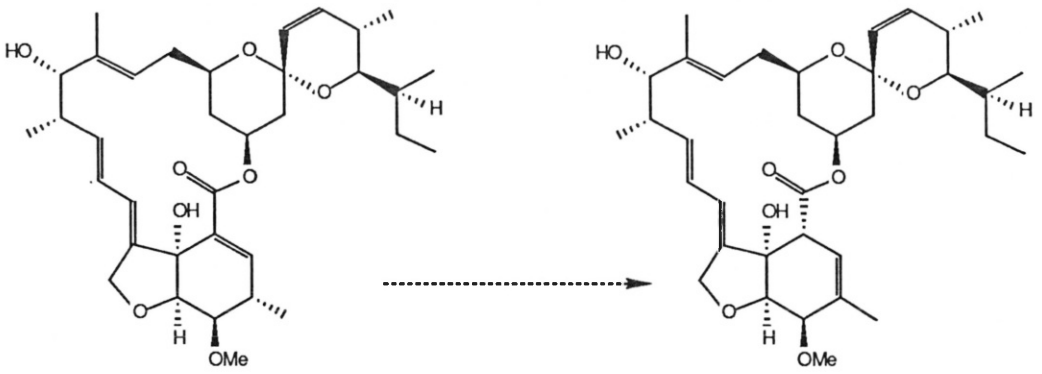


in THF consistently gave the 2-epi derivative (30) (82% yield). Reaction of (30) with a concentrated solution of imidazole in refluxing benzene afforded an equilibrium mixture of (29), (30) and avermectin B_{1a} in 5%, 34% and 40% isolated yield, respectively.

It seems likely that the material produced in Hanessian's original deconjugation[27] was not the primary product of deconjugation, but possibly the result of a subsequent epimerisation of an initially formed 2-epi isomer.

The efforts of Danishefsky[36] have culminated in the first total synthesis of a member of the avermectin family, the less potent A_{1a}, employing Hanessian's more

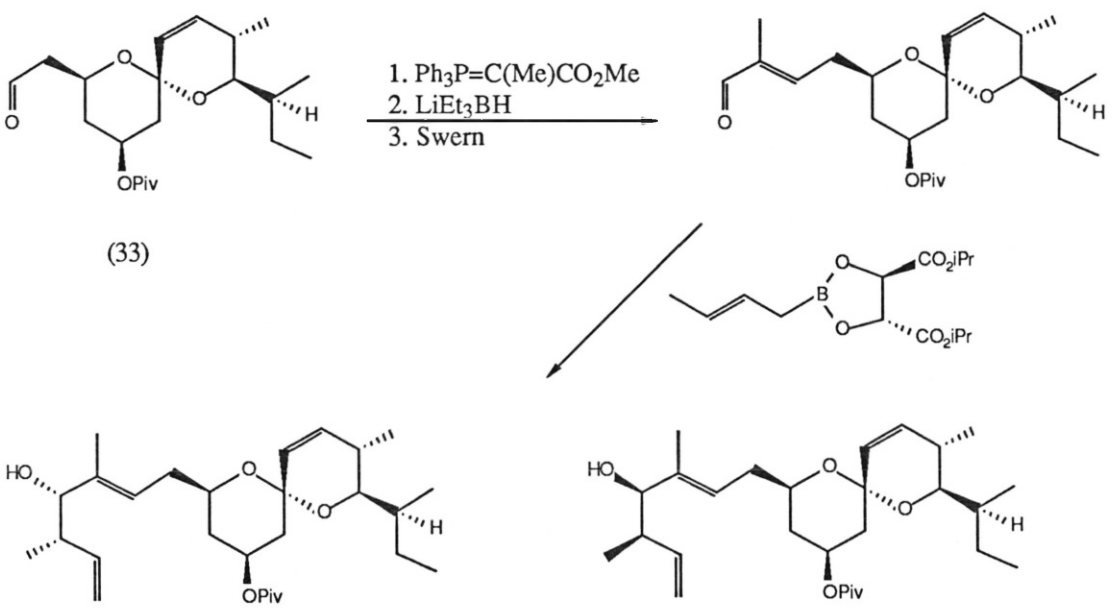
reproducible Δ^2-avermectin to avermectin conversion. (Scheme 8)



(31) (32)

Scheme 8

Stabilised Wittig methodology was used to control the C-14, C-15 double bond geometry. Subsequent introduction of C-12 and C-13 absolute stereochemistry was achieved by use of an asymmetric crotyl boronate reagent. (Scheme 9)

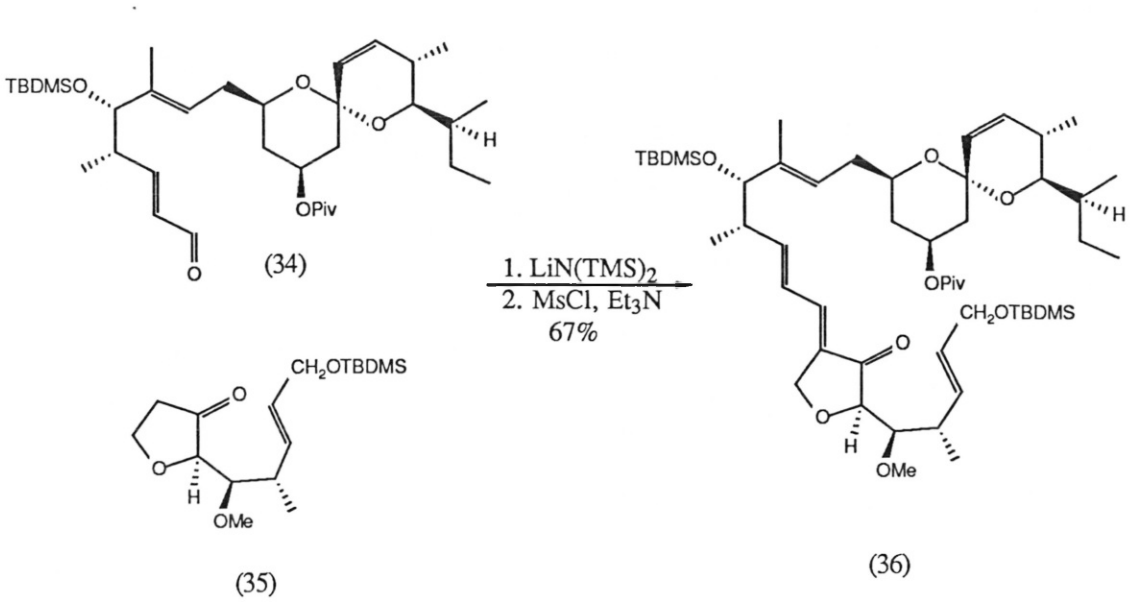


(33)

4 : 1

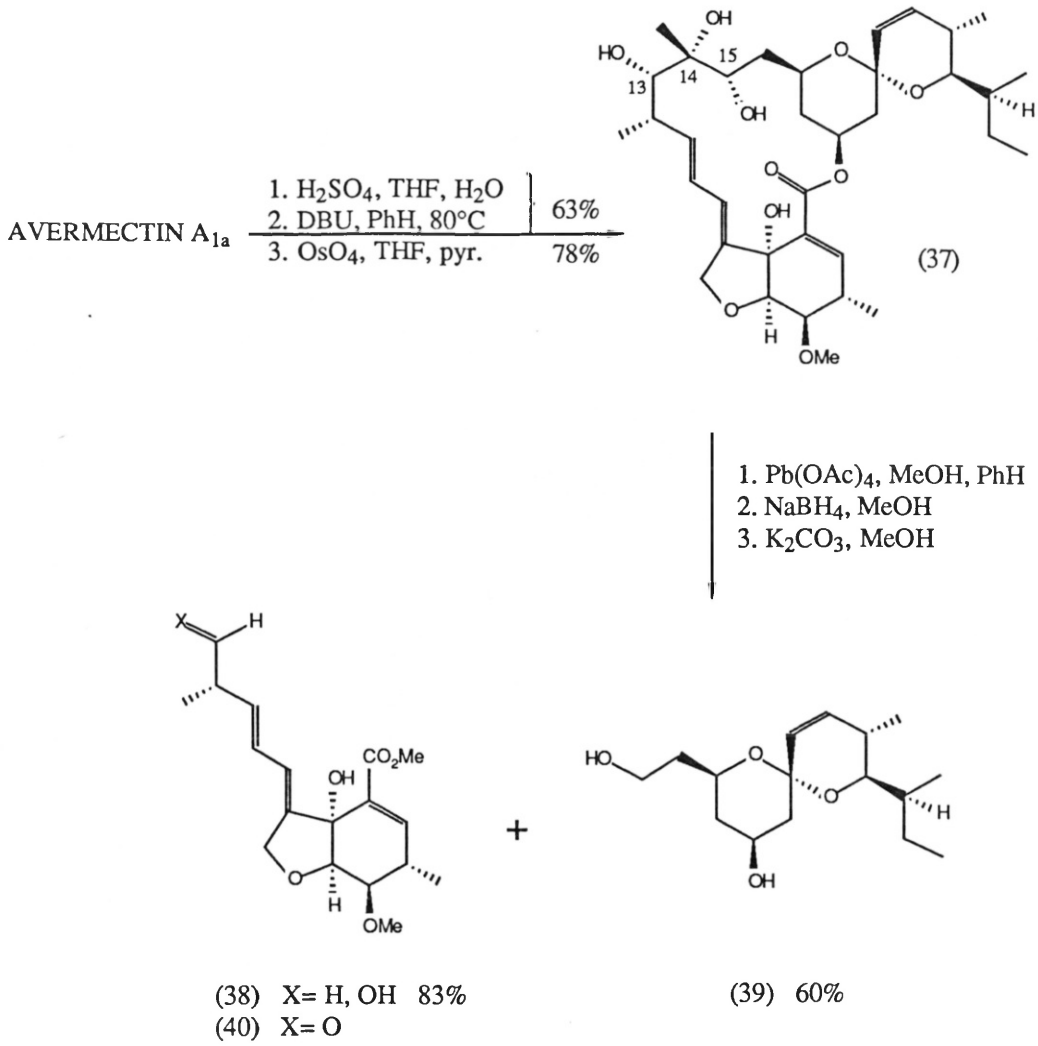
Scheme 9

Danishefsky chose to couple southern and northern units via C-8, C-9 connection. A classical crossed aldol condensation/dehydration sequence elegantly achieved this end. Thus the lithium enolate of ketone (35) reacted with enal (34), and sulphonylation of the intermediate afforded the enone (36) in good yield (67%).



Employment of an intramolecular Nozaki[37] reaction served to complete the benzofuran nucleus. Macrolactonisation using Mukaiyama's technology occured smoothly (67% yield) and liberation of the C-13 hydroxyl group afforded the conjugated Δ^2 tautomer (31) of avermectin A_{1a} aglycone. The conversion of lactone (31) to (32) (*vide supra*) gave an equilibrium mixture comprised of (31) 21%, (32) 32% and 2-epi avermectin A_{1a} aglycone 33%. The total synthesis was completed by the attachment of a synthetic L -oleandrose disaccharide residue.[31,36]

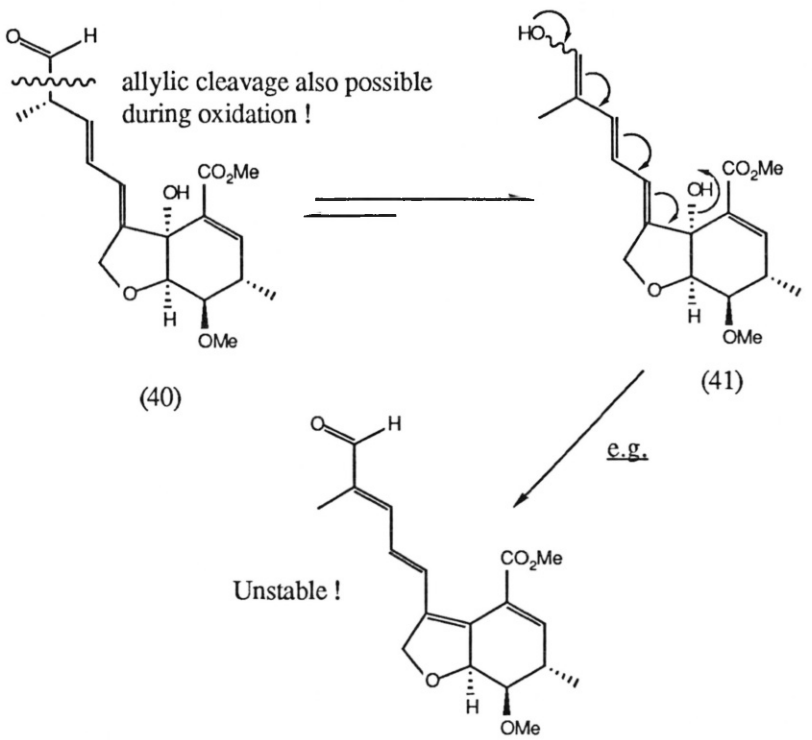
Danishefsky[39] has reported a novel degradation of avermectin A_{1a} in order to obtain fragments ameanable to his synthetic strategy. He effects cleavage at the C-14, C-15 double bond and the C-13,C-14 σ-bond. (Scheme 10)



Scheme 10

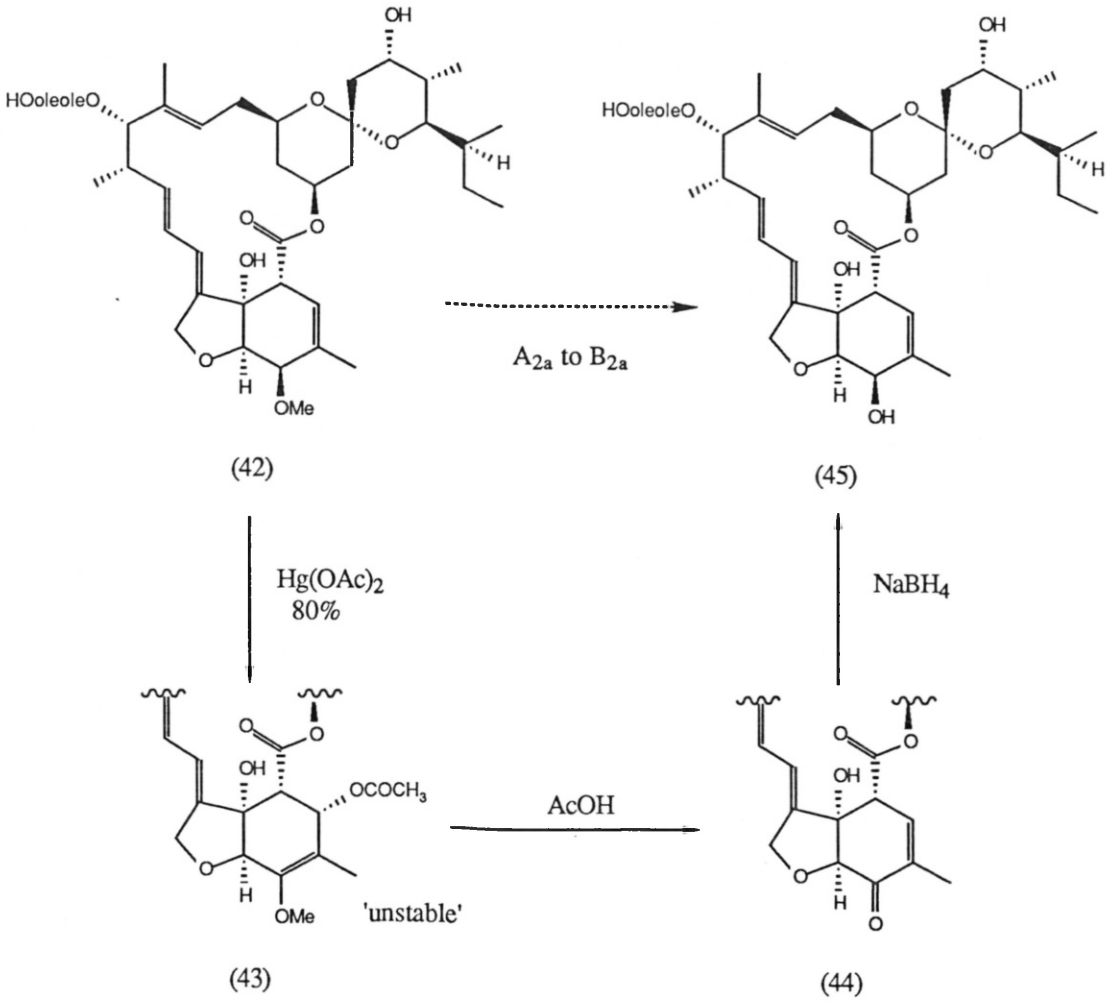
Detachment of the oleandrosyl groups by acidic treatment followed by intentional conjugation of the C-3, C-4 gave the Δ^2-aglycone in 63%. Stereospecific osmylation on the α-face of the macrocycle was effected with osmium tetroxide in 78%. Cleavage of the triol with excision of C-14 was accomplished through the action of lead tetracetate, with intermediate reduction of the secodialdehyde.Finally cleavage of the ester linkage afforded the diols (38) and(39) in overall yields of 67% and 29% respectively. The diol (39) was very useful for spectral and

chromatographic correlation with the diol derived from (33) by total synthesis,[37] and also for relay studies. Unfortunately diol (38) could not be utilised in a projected reconstruction, as the oxidation of the homoallyic alcohol to the β,γ-unsaturated aldehyde (40) afforded complex mixtures. This may not be so surprising as (40) could exist mainly in the tautomeric, highly conjugated, enol form (41) and be prone to decomposition. (Scheme 11)



Scheme 11

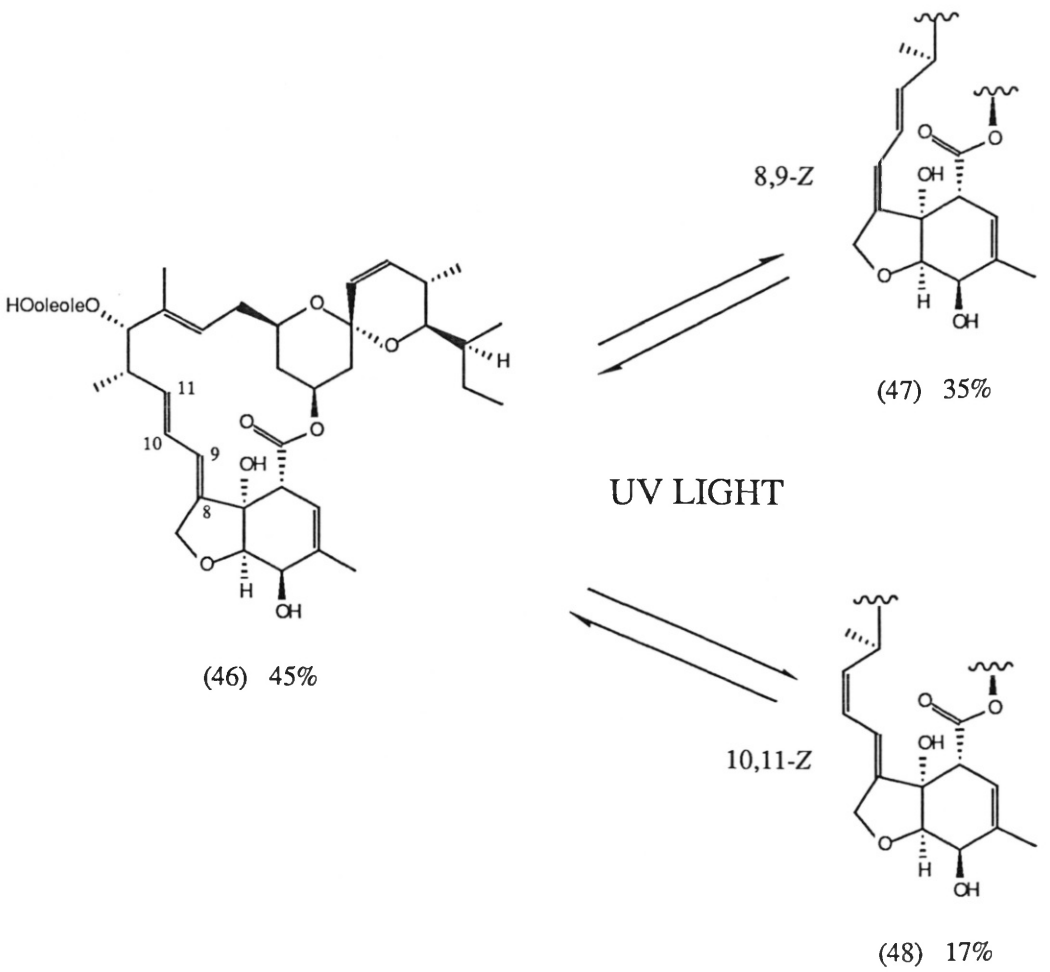
The monumental studies of Mrozik and Fisher[40] at Merck and Co. have resulted in a better understanding of the chemical stability of the avermectins. Mrozik and Fisher[41] report an interesting route to the selective cleavage of the allylic C-5-methoxy group of avermectin A_{2a} (42) and hence conversion to avermectin B_{2a} (45).



Mercuric acetate reacts selectively with the C-3, C-4 double bond to give the hydrolytically labile vinyl ether (43) as the initial major product in good yield. The acetoxy enol methyl ether (43) or its crude reaction mixture on treatment with glacial acetic acid and stereospecific reduction gave the naturally occuring avermectin B_{2a} (45).

More recently Mrozik and Fisher[42] have published on the reactivity of the avermectins towards irradiation with u.v. light. The results are pertinent since avermectins also show a great potential as insecticides for agricultural crops,[18] and in it is this application that the compounds are exposed to intense sunlight.

A careful study of the photoisomerisation of avermectin B_{1a}/B_{1b} (46) (94:6) revealed the attainment of an equilibrium mixture of the photoisomers 10,11-*Z* avermectin B_{1a} (48), 8,9-*Z* avermectin B_{1a} (47) and avermectin B_{1a} (46) in 17%, 35 % and 45% yield respectively. (Scheme 12)

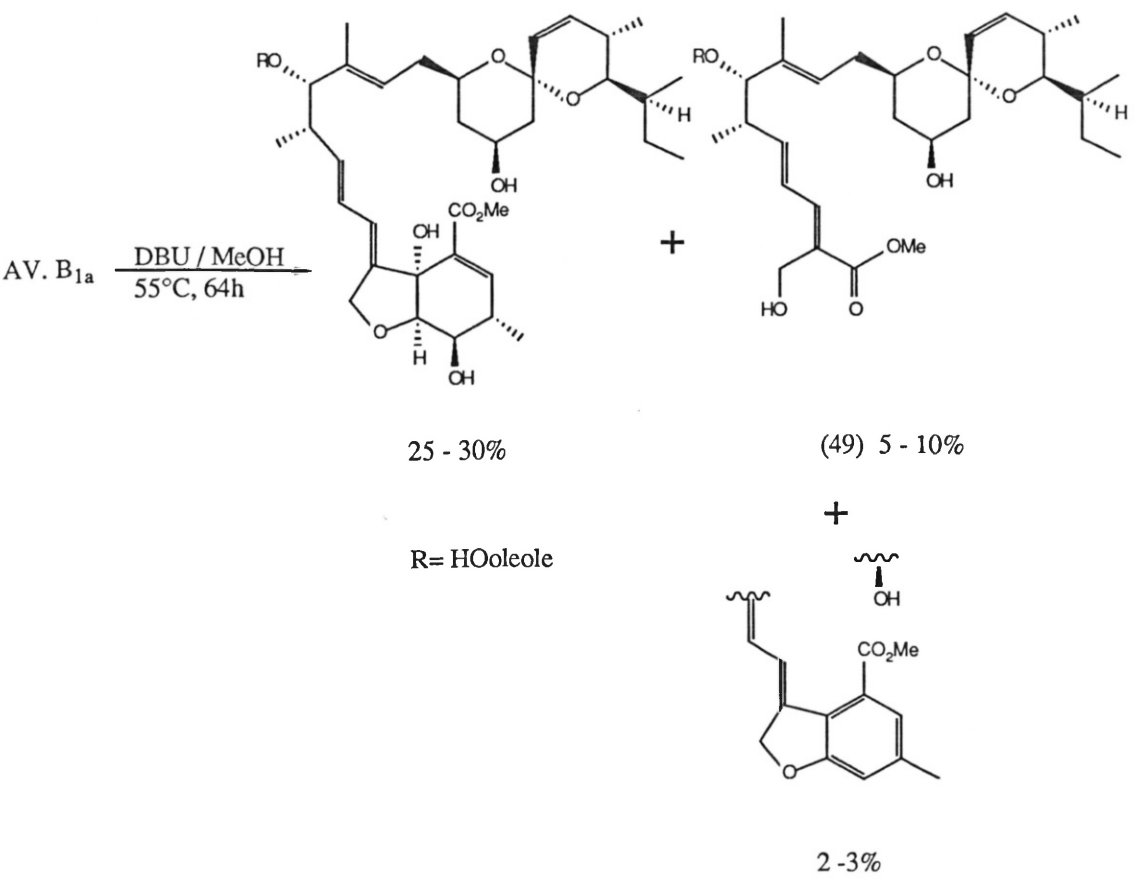


Scheme 12

When pure isomers (47) and (48) were separately irradiated, the identical three component equilibrium mixture as obtained from avermectin B_{1a}, was produced within 20 minutes. From empirical force field calculations they find that the strain energy of 10,11-*Z* (48) is greater than 8,9-*Z* (47) which at first sight,

from the flat two-dimensional structure projection, may seem surprising. From the 2-D representation, severe steric interactions in particular between carbons 1 and 10 could be expected for the 8,9-*Z* configuration (47), but on examination of 3-D models they find the lactone carbonyl oxygen in close contact with the carbon 10 in the 10, 11-*Z* (48) but not in the 8, 9-*Z* (47) model because of the nonplanar cis-fused oxahydrindene ring. This observation is reflected in the 'H NMR spectrum of (48) (deshielding of H-10 by the lactone carbonyl), and suggests steric restriction to free conformational changes at room temperature.

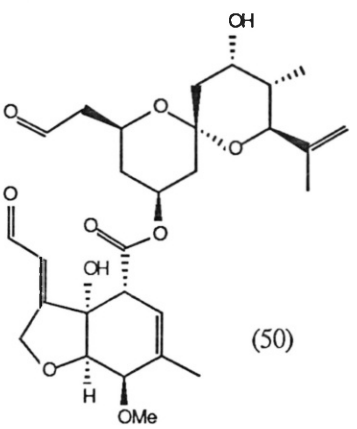
Mrozik and Fisher[43] have reported an interesting degradation reaction of avermectin B_{1a}. (Scheme 13)



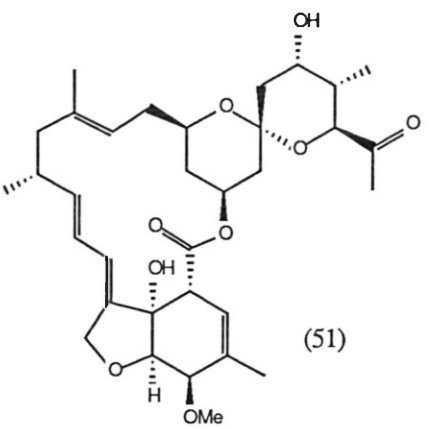
Scheme 13

The unexpected degradation product (49), which presumably arises from avermectin B_{1a} by a series of retro-aldol reactions, has potential as a starting material for avermectin analogues.

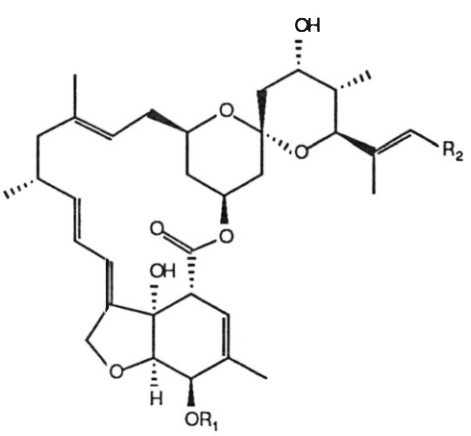
Roberts[44] has isolated large amounts of compounds of types (50) and (51) during his study on the ozonolysis of S541 factors (Scheme 14)[44,45], but has not reported on their use in a first synthesis of a Cyanamid/Glaxo surrogate, related to the avermectins and milbemycins.



(50)



(51)



S541 Factors

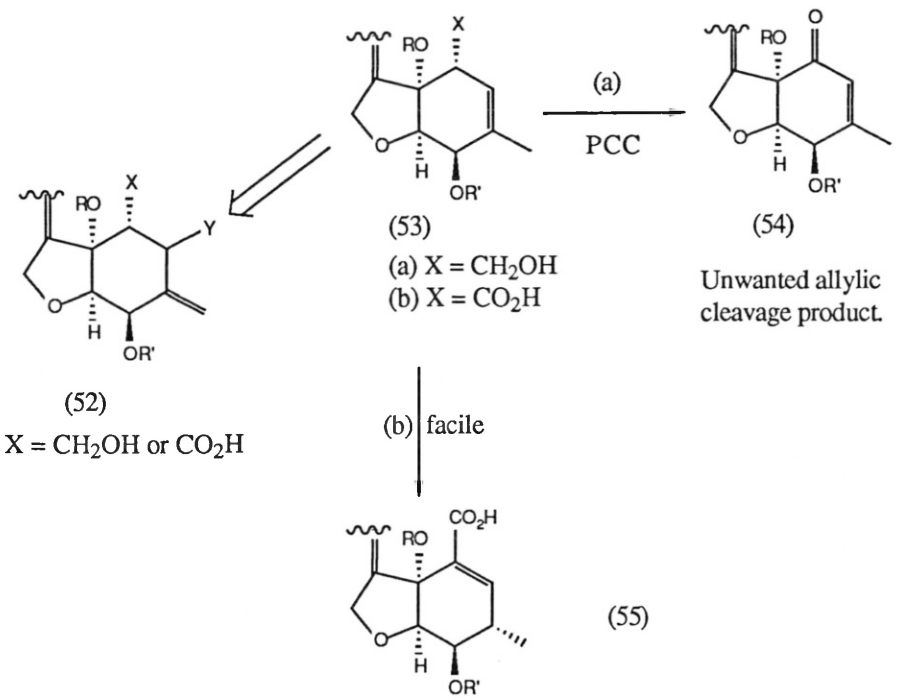
A : R_1 = H, R_2 = Me
B : R_1 = Me,R_2 = Me
C : R_1 = H, R_2 = Et
D : R_1 = H, R_2 = iPr

Scheme 14

Competitive ozonolysis of the C-3, C-4 double bond seems not to have been a

problem to Roberts with these 5-OMe lactones.

Lastly, Fraser-Reid[47] addresses the problem of the incorporation of the C-3, C-4 double bond at a late stage in synthesis, by "parking" this double bond as an *exo*cyclic methylene (52). (Scheme 15)

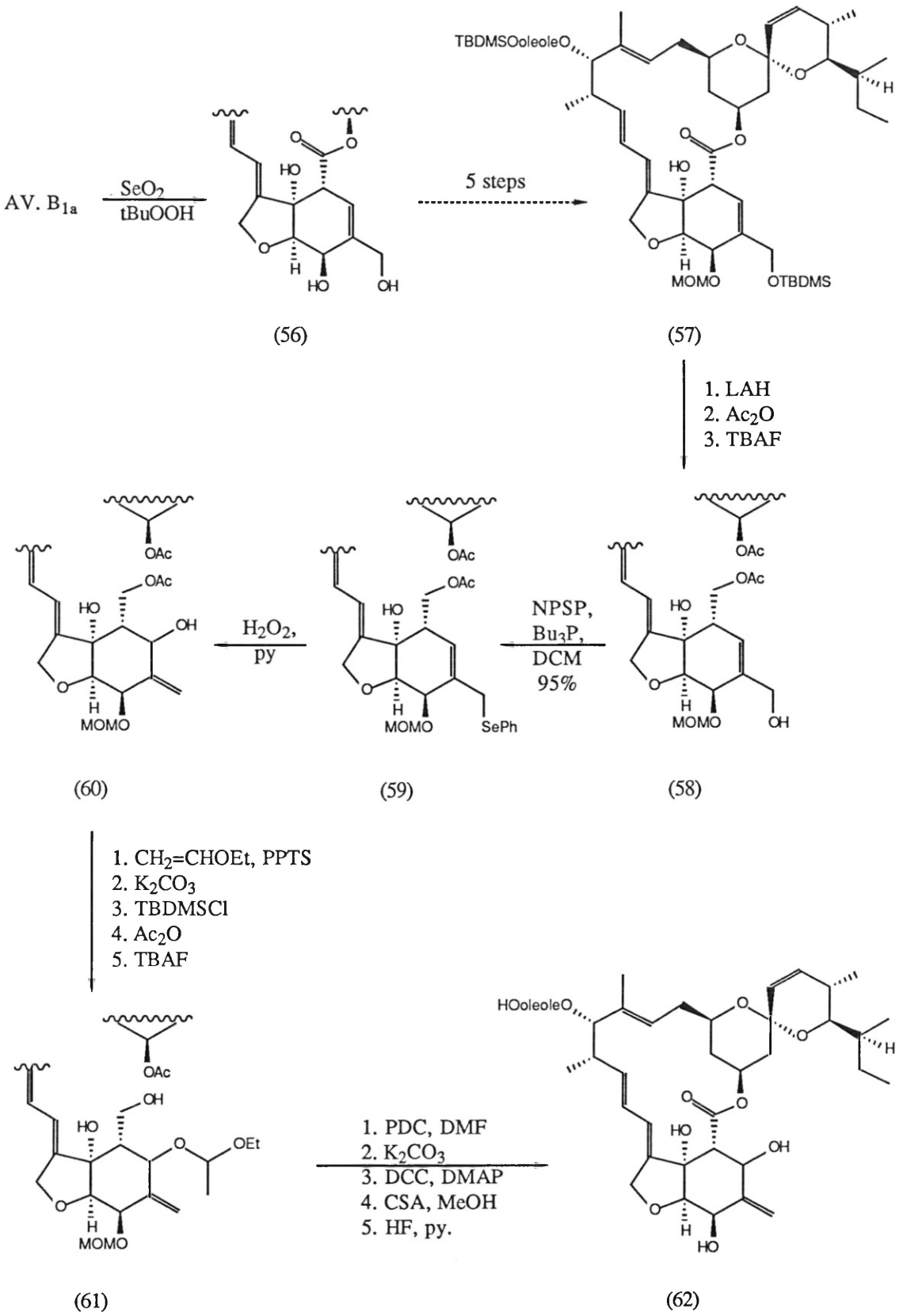


Scheme 15

He has previously observed that (53b) goes readily to (55), and problems of deconjugation of this sort of intermediate have already been highlighted.[27,32,35] Interestingly, he observed that oxidation of homoallylic alcohols, such as (53a), led to substantial amounts of allylic cleavage to give enones, such as (54). This homoallyic oxidation problem was also experienced by Danishefsky on his avermectin fragment.[39]

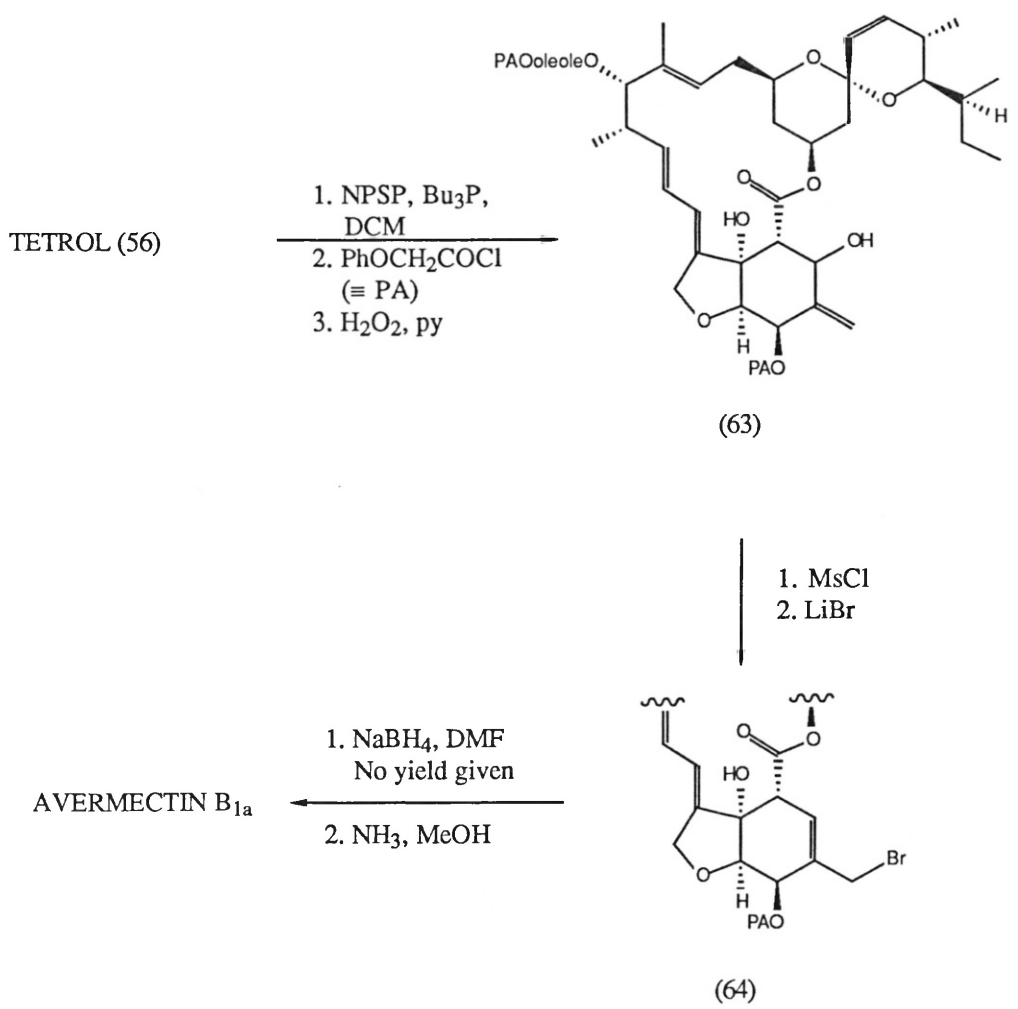
He demonstrates that macrolactonisation of an intermediate (61), with the

*exo*cyclic double bond in place is possible (Scheme16).



Scheme 16

Access to this *exo*cyclic intermediate (61) is gained from avermectin B_{1a}. Thus catalytic selenium dioxide/^{t}BuOOH allylic oxidation to give the 4-hydroxymethyl tetrol (56), followed by a 5 step protecting group manipulation sequence, lactone cleavage, further protecting group alterations and selenation using Nicolaou[48] methodology, generated the 4-phenylseleno methyl derivative (59). Double bond transposition was effected by Clive's [2,3]-sigmatropic selenoxide rearrangement,[49] to give the valuable *exo*cyclic system as a single isomer. After much laborious functional group manipulation, the macrolactonisation precursor (61) was obtained.



Scheme 17

Fraser-Reid then proceeds to establish a protocol for *exo*cyclic to *endo*cyclic rearrangement on the macrolactone intermediate (63), obtained from natural avermectin B_{1a} (scheme 17). Hence sulphonation followed by S_N2' brominolysis to give the allylbromide (64) and subsequent reductive debromination and also removal of the phenoxyacetate protecting groups furnished avermectin B_{1a}.

At first sight, and from the title, Fraser-Reid's paper appears to have solved the problems associated with incorporation of the $\Delta^{3,4}$ bond in a total synthesis, by appropriate relay studies. Upon closer examination he seems to cloud the issue, and proves nothing as far as a relay synthesis is concerned. The conversion of *exo*cyclic tetrol (62) to (63), containing the essential phenoxy acetate group, is not mentioned. This is invariably because selective C-4" and allylic C-5 hydroxyl protection, in the presence of the allylic C-2 hydroxyl has been problematic.

Conclusion

The employment of degradative and relay studies has figured prominently in much of the published work in the avermectin and milbemycin field. One of the most elegant and fecund uses has been very recently by Danishefsky, in his total synthesis of avermectin A_{1a}. This, to date, has been the only complete published total synthesis.

The paucity of reported total syntheses may be attributed to the difficulties

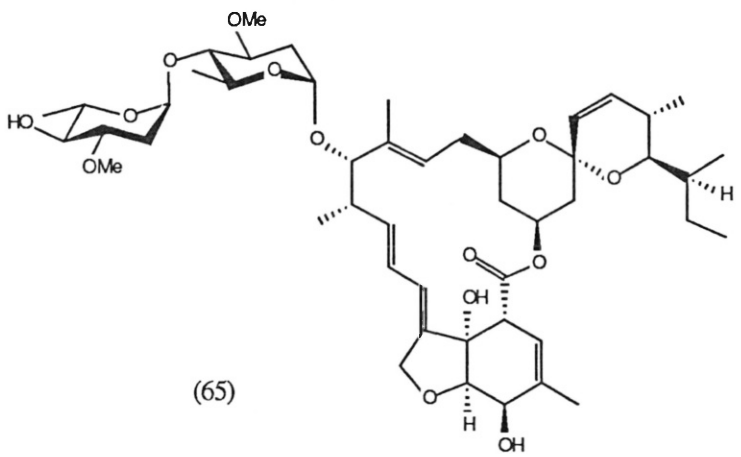
encountered during the synthesis of the southern hemisphere of these natural products[21b] and to the regioselective introduction of the C-3,C-4 double bond. The recent development of a deconjugation / equilibration protocol constitutes the first solution of this problem. The discovery of a exocyclic to endocyclic transposition on the macrocycle most recently, is an interesting alternative, but as yet has not been utilised in a total synthesis. However, efforts to discover more direct methods of introducing this functionality are still required and will surely ensue.

Another active area of research is in the construction of hybrids and modified avermectins which still retain much of the complex functionality, in the hope of improving biological activity.

One of the most fruitful outcomes of degradation and modification is the wealth of information one aquires about the chemical stability and reactivity of such complex natural products.[50]

Results and Discussion

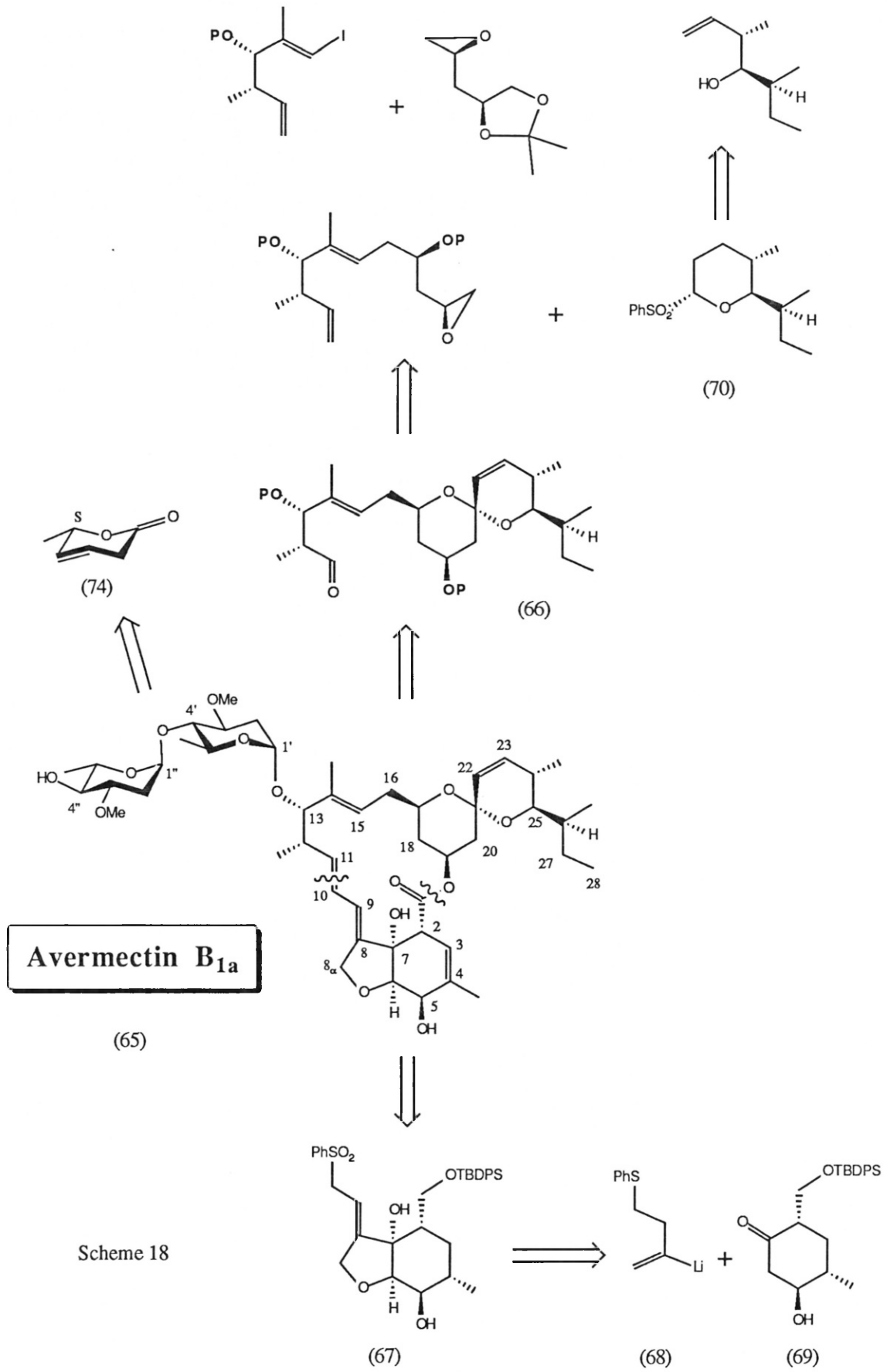
The results reported here form part of an ongoing programme directed towards the total synthesis of the avermectins, in particular the extremely potent avermectin B_{1a} (65).[3]



(65)

It was envisaged that the synthesis would employ much of the successful methodology that had recently been developed for our milbemycin β_1 synthesis.[51]

As in the milbemycin work, it was considered that a Julia[28] olefination reaction would be the most attractive method of effecting the union of northern (66) and southern (67) hemisphere fragments.[52] (Scheme 18). Application of this methodology to trisubstituted olefin synthesis was known to be poorly *trans* selective and often capricious. We were thus dissuaded from C-8, C-9 coupling strategy. In contrast, the control of C-10, C-11 double bond geometry was expected to be more amenable to the sulphone based coupling procedure. In particular, the


PO
I
O
O
O
HO
H
PO
OP
O
PhSO2
O
H
(70)
S
O
O
(74)
PO
O
H
O
OP
(66)
4'
OMe
1'
HO
1"
4"
OMe
O
13
15
16
18
22
23
25
H
20
27
28
11
10
9
OH
2
3
8
7
8α
4
O
H
5
OH
Avermectin B1a
(65)
PhSO2
OTBDPS
OH
O
H
OH
(67)
PhS
Li
(68)
+
OTBDPS
O
OH
(69)

Scheme 18

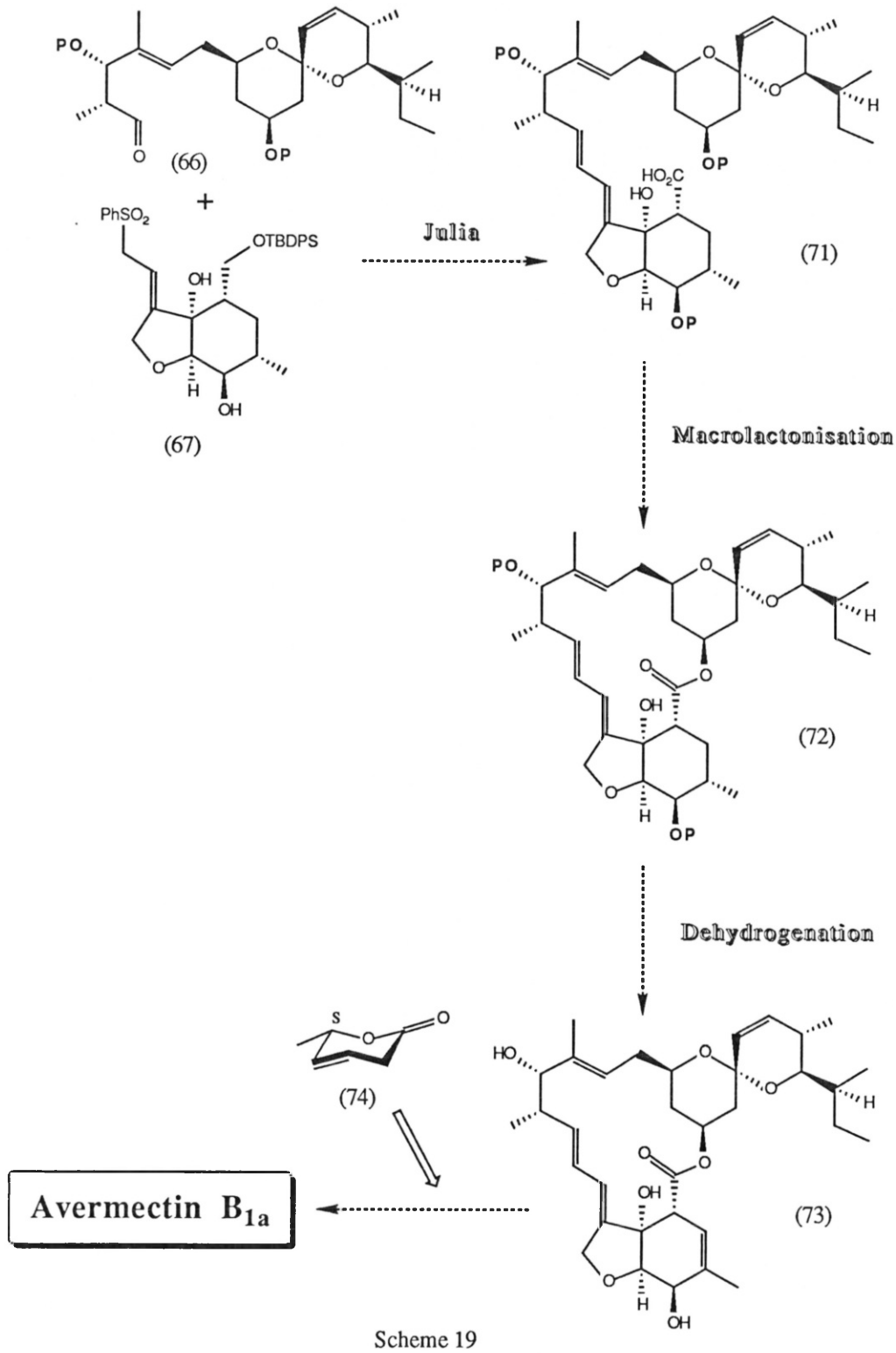
presence of α-branching[28] at C-12 was expected to enhance the intrinsic E-selectivity of the olefination process.

The introduction of the C-3, C-4 double bond at a late stage was, we believed, of crucial importance, since at the outset of our studies no reliable methods had been developed for its specific introduction. A southern region sulphone moiety (67) devoid of unsaturation at C-3, C-4, would circumvent all the possible problems of migration into conjugation or aromatisation..[21b,32,33,34,47] This sulphone fragment (67) could, in principle, be obtained in a stereocontrolled fashion from common intermediates (68) and (69) employed during our milbemycin studies.[51c]

Once again sulphone based methodology was used to construct the spiroacetal portion of the northern hemisphere (66).[53] Precedent for this approach was derived from the successful utilisation of a sulphone anion, similar to (70),in a coupling reaction with a bis-epoxide system used in the milbemycin northern segment work.[51d]

At the start of the synthetic programme no reports of the total synthesis of any of the avermectins or non-aromatic milbemycins existed. As we approached the conclusion of these studies only one total synthesis had appeared,[36] which heavily relied on the use of degradation of the natural product to provide appropriate coupling fragments.

Initially, the goal was to obtain both intact northern [C(11-28)] (66) and southern [C(1-10)] (67) units in order to confirm the structure of synthetic intermediates. Secondly, the availability of quantities of these advanced intermediates should assist in coupling studies to test key synthetic operations prior to their availability *via* total synthesis. In particular, the Julia couplings of (67) to

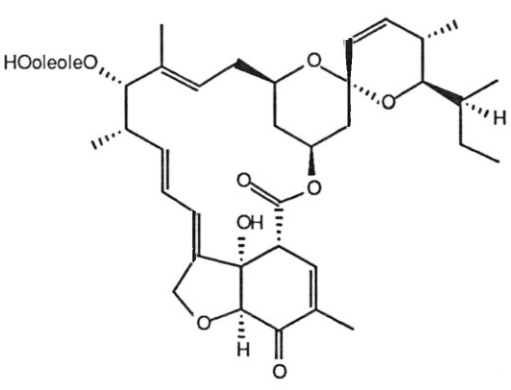

PO
O
H
OP
(66)
+
PhSO2
OTBDPS
OH
O
H
OH
(67)
Julia
HO2C
HO
(71)
Macrolactonisation
(72)
Dehydrogenation
S
O
(74)
HO
(73)
Avermectin B1a

Scheme 19

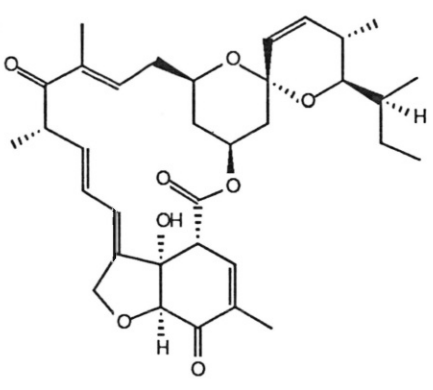
fragments such as (66), macrolactonisation protocol and incorporation of the *endo*cyclic C-3, C-4 double bond in (71) by selenium methodology to give the aglycone (73), were considered as potentially awkward operations.(Scheme 19). The attachment of the sugar residues by selective C-5 hydroxyl protection and coupling of a oleandrosyl moiety derived from lactone (74), should be relatively straightforward and would complete the synthesis.[31]

Ozonolytic Degradations.

At the start of this project only one degradation / relay report had been described by Smith,[22] although his fragments were not considered amenable to our synthetic approach. Initial efforts involved an ozonolysis of avermectin B_{1a} and intermediate structures such as (75) and (76) in order to selectively cleave the more reactive C-10, C11 double bond.



(75)



(76)

These attempts invariably led to complex mixtures of products, which were

unstable and difficult to purify. The presence of aldehydes and enones as ozonolysis products caused many isolation problems.

At this point, Hanessian reported a controlled ozonolysis of avermectin B_{1a}.[25] (See Scheme 5 in Review) This route seemed appealing as it allowed direct access to the required northern intermediate (66), by scission of the C-10, C-11 double bond, and also to a southern fragment with the correct carbon skeleton (67).

Hanessian had employed extensive silicon protection on the 4" or 13 and 15, 19 hydroxyl groups for his route. On the other hand, we required benzoxy group protection, since these occurred naturally through the use of Julia coupling.

The 4 step degradation sequence was first attempted on avermectin B1a. (Scheme 20), (See Appendix for n.m.r. of the natural product supplied by Merck & Co.).

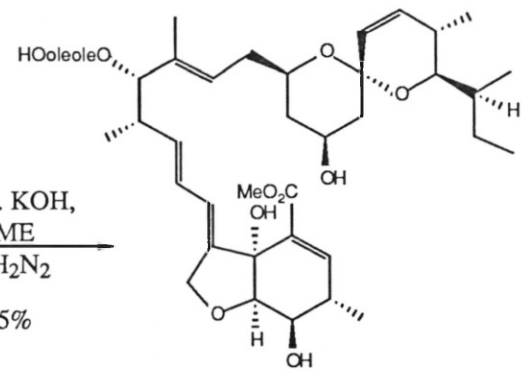
Thus, treatment of avermectin B_{1a}[54] with aqueous base followed by esterification gave the conjugated seco ester (77) in 75% yield. The planned migration of the double bond into conjugation with the ester served three salutary purposes. Firstly it would minimise the chances of aromatisation during subsequent transformations. Secondly, problems normally encountered with unwanted ozonolysis of the C-3, C-4 double bond were circumvented by making the double bond less reactive towards the dipolar electrophilic ozone reagent.[55] Lastly, it would furnish us with a southern benzofuran portion in which the α,β-unsaturated ester functionality could be readily elaborated to generate the required saturated bicyclic southern system (67) (i.e. 1,4-reduction and concomitant reintroduction of the C-2 stereochemistry). ^1H n.m.r analysis of the seco ester (77) (see Appendix) revealed interesting changes in chemical shift. Of particular note was the observation

Avermectin B_{1a}

(65)

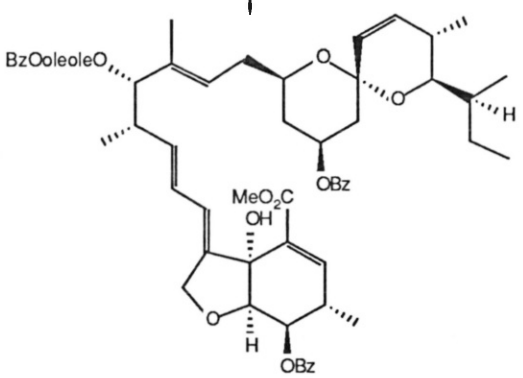
1. aq. KOH, DME
2. CH_2N_2

75%



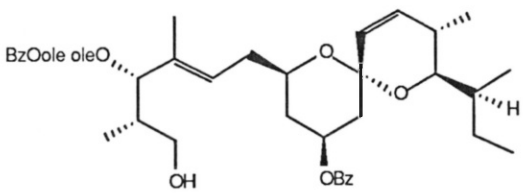
(77)

PhCOCl, py, DMAP
80%



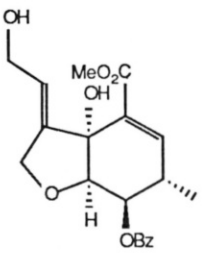
(78)

O_3, -78°C
DCM-EtOH
(Sudan 7B).
$NaBH_4$



(79) 92%

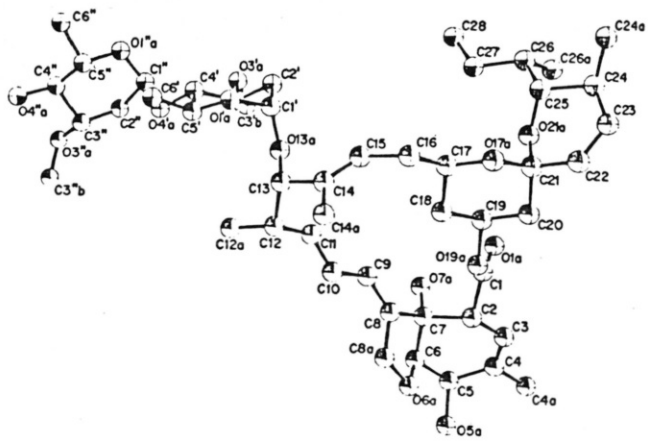
+



78% (80)

Scheme 20

that the high field resonance for 18-H_a, had moved appreciably downfield, indicative of a non-macrocyclic structure. The normal upfield resonance for 18-H_a in the natural product arises from shielding by the $\Delta^{14,15}$ unsaturation as a result of the macrocyclic conformation. (Fig. 3)



Computer generated drawing of avermectin B_{1a}, with hydrogens omitted for clarity.[5]

Figure 3

Also, the resonance corresponding to the C-19 methine hydrogen atom in (77) had undergone a significant upfield shift (ca. 1.4 ppm) relative to the corresponding resonance in avermectin B_{1a}, which was indicative that the C-19 was not now part of a lactone system.

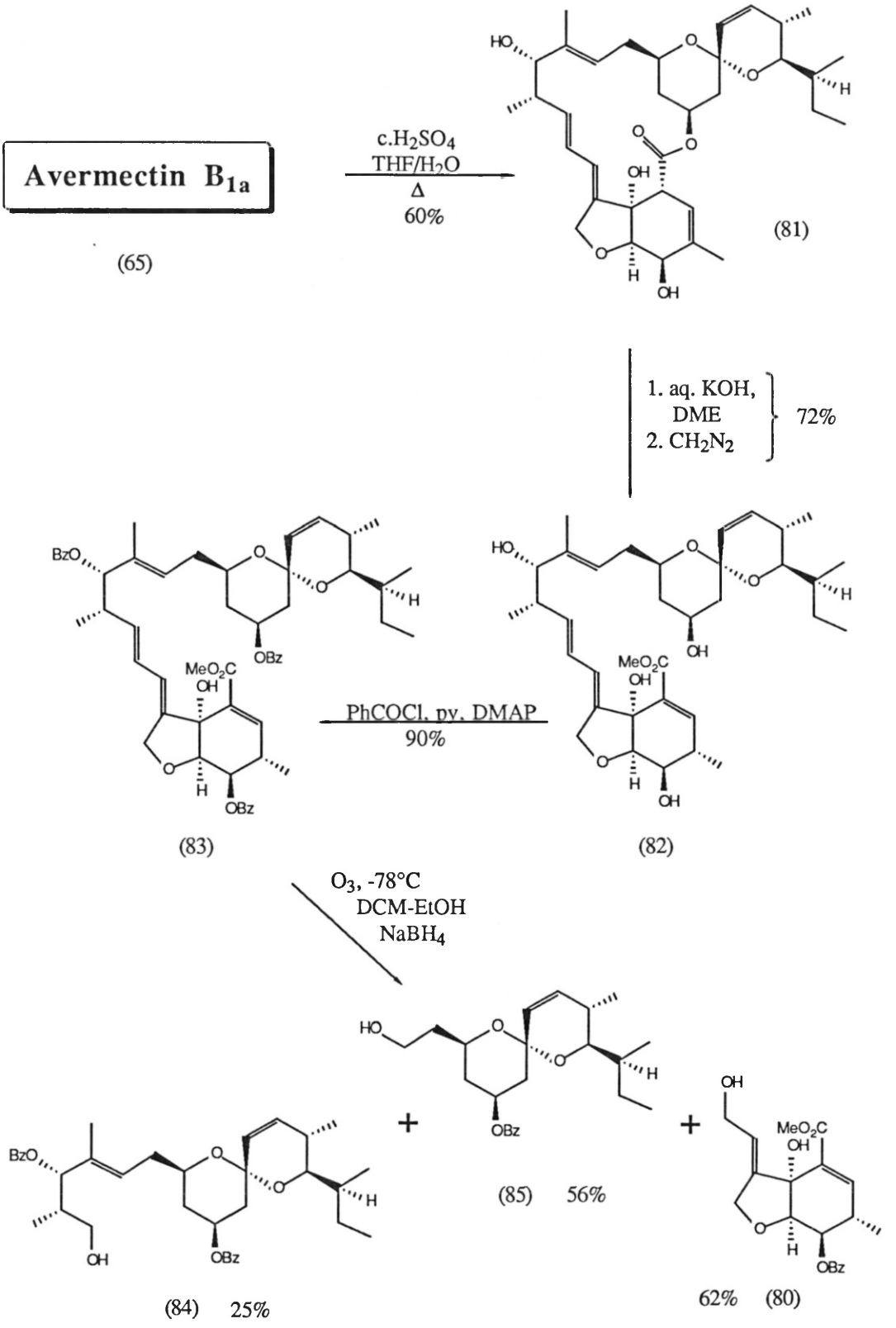
Benzoylation of (77), in the presence of presence of DMAP, afforded the tribenzoyloxy derivative (78) in 80% yield. Ozonolysis of natural products is a very

mild, well precedented degradative procedure, but in the literature there is a paucity of controlled degradations of systems containing multiple double bonds.[56,57] Ozonolysis in the presence of dyes as indicators is a versatile process first introduced by Mitscher and coworkers.[58] Controlled oxidation of the tribenzoyloxy seco ester (78) led to the intact tribenzoyloxy oleandrosyl northern hemisphere (79) and the monobenzoyloxy seco ester southern hemisphere as the only two products, in 92 and 78% yield respectively.

An analogous degradation sequence was attempted on the aglycone system. (Scheme 21) The aglycone (80) was obtained from avermectin B_{1a} by an improved modification of the procedure reported by Mrozik,[59] in 60% yield.

As before, treatment of (81) with base (KOH), followed by diazomethane generated the aglycone seco-ester (82) in 72% yield. Subsequent benzoylation gave the tribenzoyloxy seco ester (83) in 90% yield. A repeatable and interesting observation during this benzoylation experiment was that if aqueous copper sulphate was employed as the work-up to remove excess pyridine, yields ranged from 40-55%. In contrast, when 1M HCl was used in the same reaction the yield was an excellent 90%. Surprisingly, this result was not observed in the related sugar substituted series.

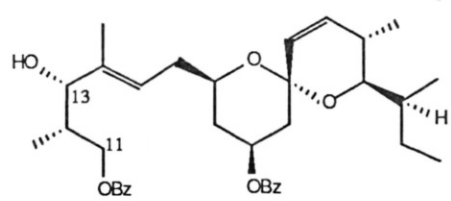
Controlled ozonolysis of (83) afforded, (after sodium borohydride work-up), intact northern aglycone (84), a spiroacetal fragment (85) as a result of cleavage of the 14,15 double bond, and the previously obtained southern fragment (80) in 25, 56 and 62% yield respectively. The low yield of intact northern aglycone (84) was rather disappointing, but nonetheless access to the unsaturated spiroacetal intermediate (85) was useful for structural correlation with the totally synthetic


Avermectin B1a
(65)
c.H2SO4
THF/H2O
Δ
60%
(81)
1. aq. KOH,
DME
2. CH2N2
72%
PhCOCl, py, DMAP
90%
(83)
(82)
O3, -78°C
DCM-EtOH
NaBH4
(85) 56%
(84) 25%
62% (80)

Scheme 21

compounds.[60] Ozonolysis at varying flow rates did not improve the yield of (84).

This particular ozonolysis was rather capricious, and it was found that the Sudan 7B dye did not act as a useful indicator for this substrate, despite earlier studies.[58] In fact, t.l.c. analysis proved to be more reliable. An important observation during the break-up of the ozonide intermediates, was that they should not be left in the presence of sodium borohydride at room temperature for prolonged periods, since this effected a benzoyl migration from the secondary C-13 hydroxyl to less sterically demanding C-11 primary hydroxyl to give (86). The 1,6 relationship between hydroxyl and acyl groups would also be expected to facilitate this process.



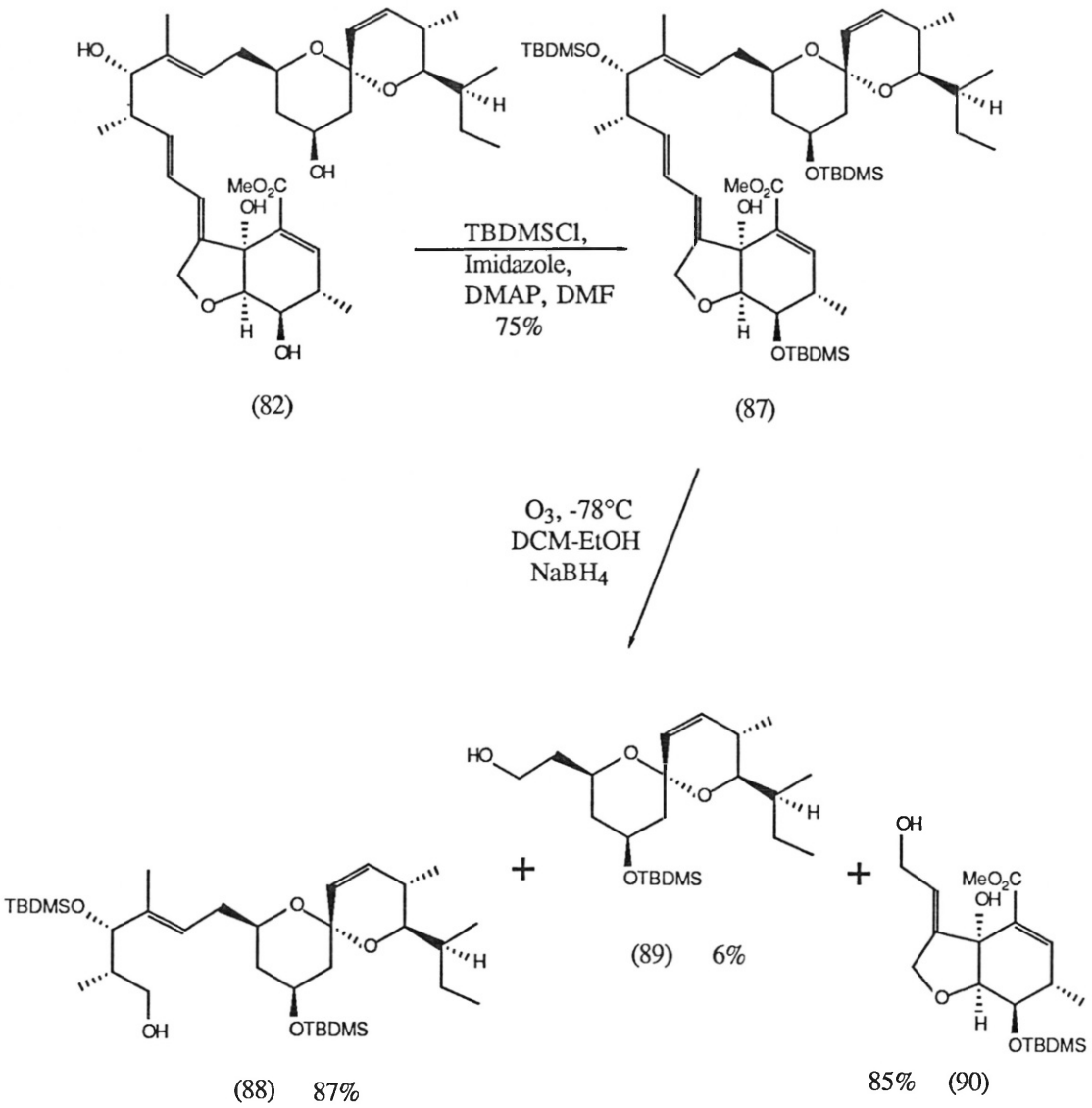
(86)

Access to large quantities of intact aglycone northern hemisphere was possible by using t butyldimethylsilylether protecting group instead of benzoyloxy.(Scheme 22).

Thus silylation of (82) in 75% yield, and subsequent ozonolysis of (87) afforded the intact aglycone northern hemisphere (88) and the southern hemisphere (90) together with only a trace of the over ozonolysed fragment (89) in 87, 85 and 6% yield respectively.

The origin of this difference in reactivity of the C-14, C-15 double bond

towards ozone, in (78), (83) and (87), could be stereoelectronic.[55,56]

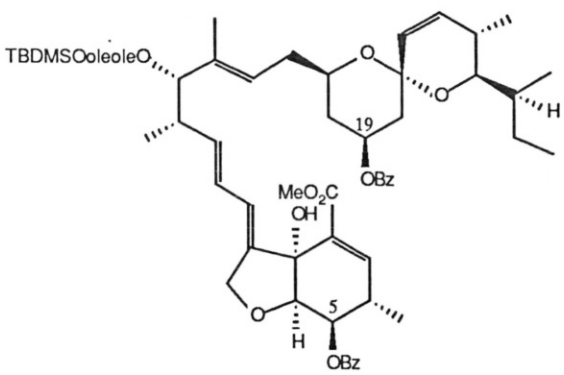


Scheme 22

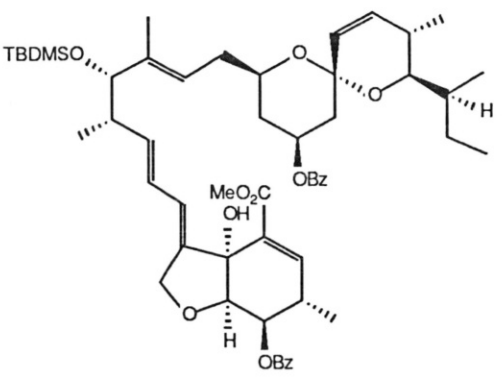
Ideally, a northern fragment with an acyl group on the C-19 hydroxyl and a silicon group on the C-13 hydroxyl or C-4" hydroxyl, was required. Protection on the C-5 was not so crucial, although we believed that an acyl group was preferable.

However, differential protection methods on the tetrol (82) and disaccharide

tetrol (77) in order to obtain selective intermediates (91) and (92) proved unsuccessful. The C-5 and C-19 hydroxyls in the sugar and aglycone series were found to be the most reactive towards silylation.



(91)

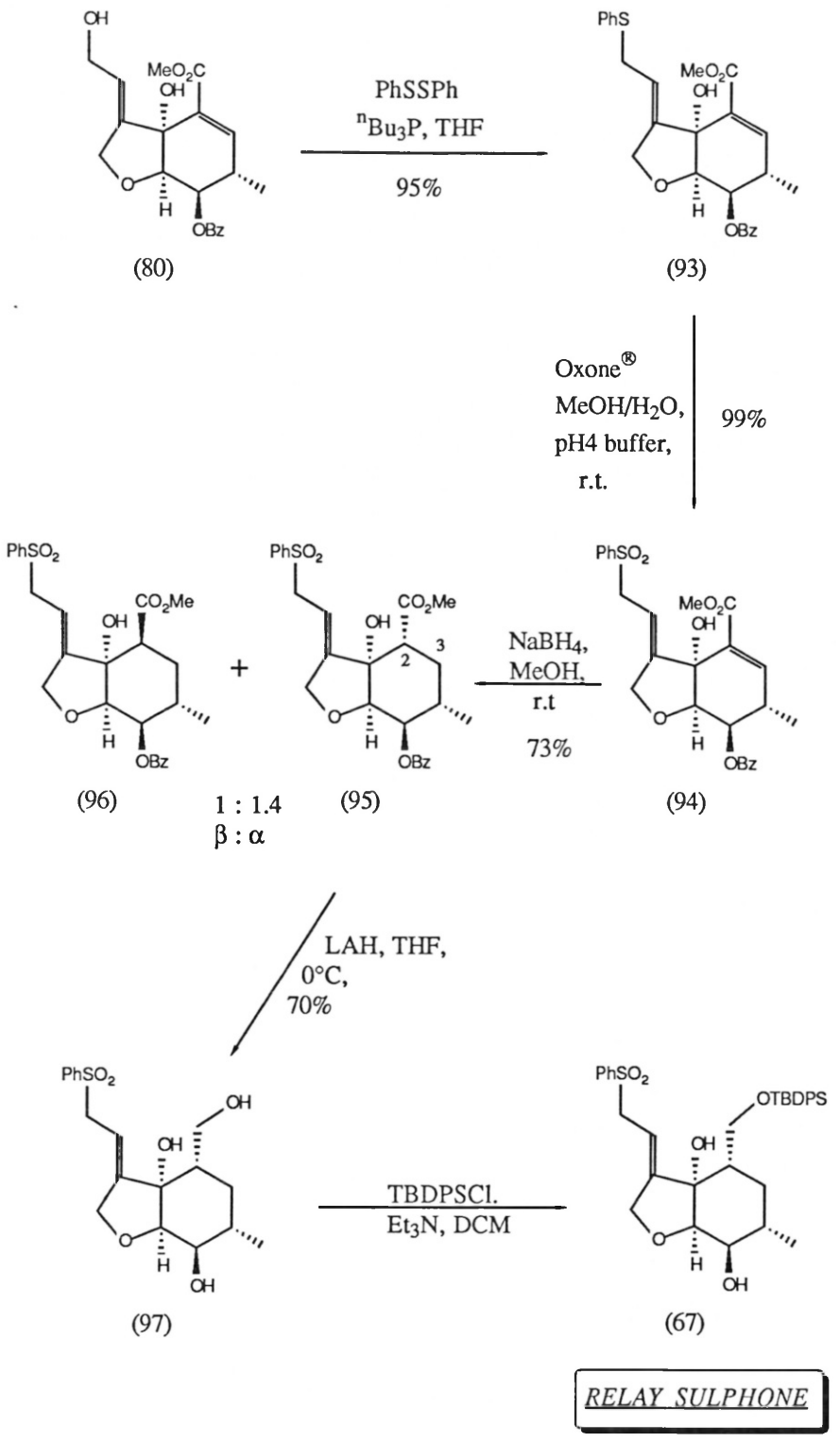


(92)

Elaboration of the southern ester fragment (80) to the sulphone (67) suitable for coupling was carried out in 5 steps.(Scheme 23).

Thus treatment of (80) with diphenylsulphide and tri-^{n}butyl phosphine[61] gave the allylic sulphide (93). Chemoselective oxidation of the sulphide to sulphone (94) , via the sulphoxide, was most conveniently achieved using Trost's buffered oxone reagent [62] in essentially quantitative yield.

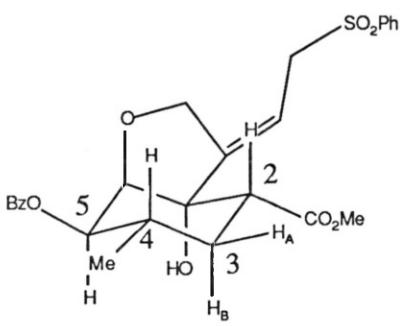
Selective conjugate reduction of the α,β-unsaturated ester (94) was achieved by the use of sodium borohydride in methanol at room temperature to give easily separable α–(95) and β–(96) esters in a ratio of 1.4:1. Initial attempts to conjugatively reduce the α,β unsaturated ester employing reagents more conventionally used in the literature,[63] such as Ganem's L-selectride,[64] Mg-methanol,[65] copper (I) hydride species[66] and dissolving metal reduction


OH
MeO2C
OH
O
H
OBz
PhSSPh
nBu3P, THF
95%
PhS
(80)
(93)
Oxone®
MeOH/H2O,
pH4 buffer,
r.t.
99%
PhSO2
CO2Me
(96)
1 : 1.4
β : α
(95)
NaBH4,
MeOH,
r.t
73%
(94)
LAH, THF,
0°C,
70%
TBDPSCl.
Et3N, DCM
OTBDPS
(97)
(67)
RELAY SULPHONE

Scheme 23

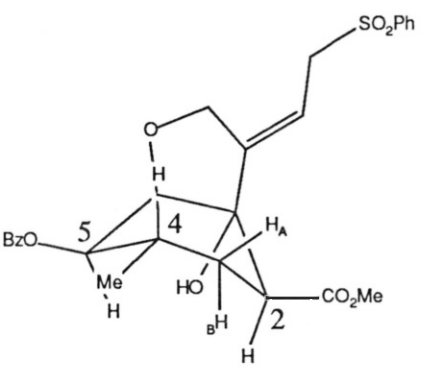
($Li/NH_3(l)$), led to no reaction, over reduction of the ester functions or desulphonylated products.

The stereochemistry at C-2 of the two esters was implied by coupling constant analysis (fig 4) and confirmed by a single crystal X-ray analysis of (95) (See Appendix). The only conformation fully consistent with the ^1H nmr for the β-ester is a boat-like conformer (96).



(95)

H-2 , dd, $J_{2,3B}$ 13 Hz, $J_{2,3A}$ 3.5 Hz
H-3_A , dt, $J_{3A,3B}$ 13 Hz, $J_{3A,2+4}$ 3.5 Hz
H-3_B, q, $J_{3B,3A+2+4}$ 13 Hz
H-5, dd, $J_{5,4}$ 11.5 Hz, $J_{5,6}$ 3.5 Hz



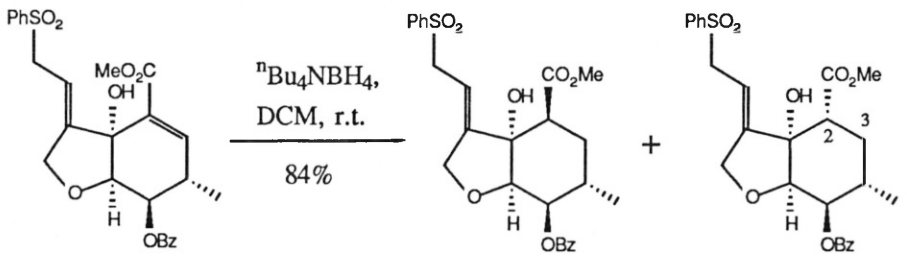
(96)

H-2 , dd, $J_{2,3B}$ 3.5 Hz, $J_{2,3A}$ 12 Hz
H-3_A , ddd, $J_{3A,3B}$ 14.5 Hz, $J_{3A,2}$ 12 Hz, $J_{3A,4}$ 6 Hz
H-3_B, dt, $J_{3B,3A}$ 14.5 Hz, $J_{3B,2+4}$ 3.5 Hz
H-5, dd, $J_{5,4}$ 8 Hz, $J_{5,6}$ 3.5 Hz

Figure 4.

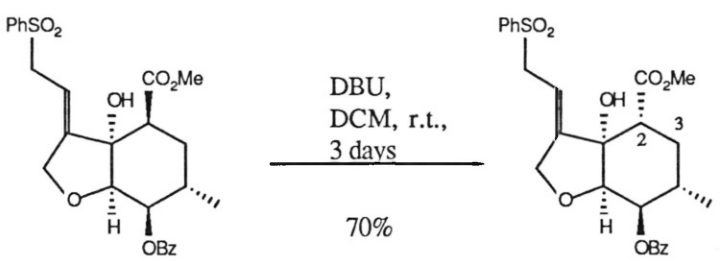
Attempts to improve the borohydride 1,4-reduction ratio by altering the solvent were unsuccessful. In fact, by using tetra-^{n}butyl ammonium borohydride in dichloromethane the proportion of the unwanted β-isomer increased (α:β = 1:2). The ratio is as one would expect for predominant approach of a proton, during work

up, from the more exposed concave side, of this 6,5-ring system. With sodium borohydride/methanol, one would expect a similar ratio, but under these basic conditions, partial epimerisation to the thermodynamically more stable α-ester occurs to give the observed 1.4:1 ratio. Also possible complexation of a $(MeO)_xBH_y$ species to the angular 7-OH would cause steric hindrance to an incoming proton from the α-face.



(94) (96) 2 : 1 β : α (95)

However, we found that the β-ester was easily recycled to the required α-ester by epimerisation with DBU.

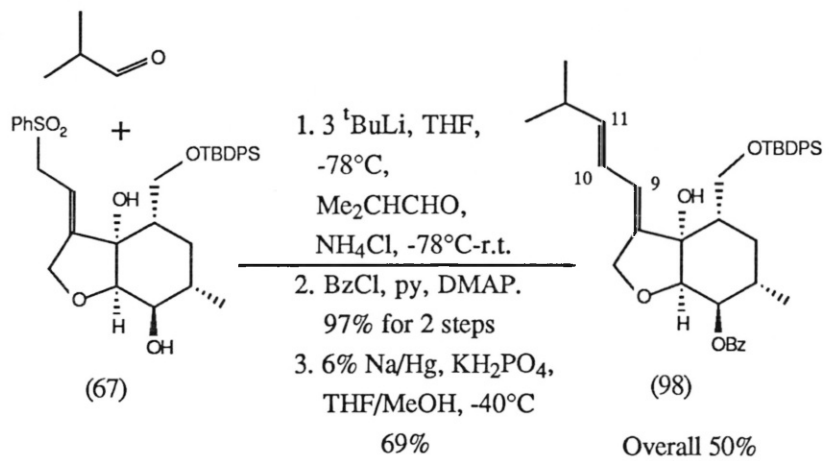


(96) (95)

Reduction of the two ester functions of (95) followed by selective mono silylation with ^{t}butyldiphenylsilyl chloride furnished the requisite 3,4-dihydro allyl sulphone (67). (Scheme 23.)

Julia Couplings.

The reactivity of this relay sulphone (67) towards Julia[28] reactions was then tested using isobutyraldehyde as a model.



(67) (98)

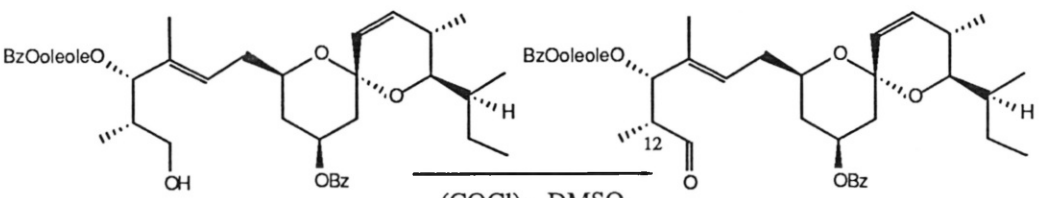
Overall 50%

Addition of isobutyraldehyde to the deep red trianion, and subsequent benzoylation gave a diastereomeric mixture of benzoyloxysulphones in excellent yield for this types of coupling reaction, in comparison to literature examples.

After optimisation of the reductive elimination conditions, the desired *E,E*-diene (98) was obtained in 50% overall yield. The *E,E*-diene geometry was evident from the large coupling constant J_{trans} 15Hz, clearly indicative of a *trans* double bond geometry

At this juncture, large quantities of intact northern hemisphere (79) were

available and it would be necessary to test the reactivity of such an avermectin northern portion towards Julia olefination. The aldehyde precursor (99) was easily obtained from the alcohol (79) by use of a 2-fold excess of Swern[67] reagent in very good yield. No epimerisation at C-12 was detected under these conditions (^{13}C, also $[\alpha]_D$ constant for subsequent experiments), and the aldehyde was stable for several months in the freezer.

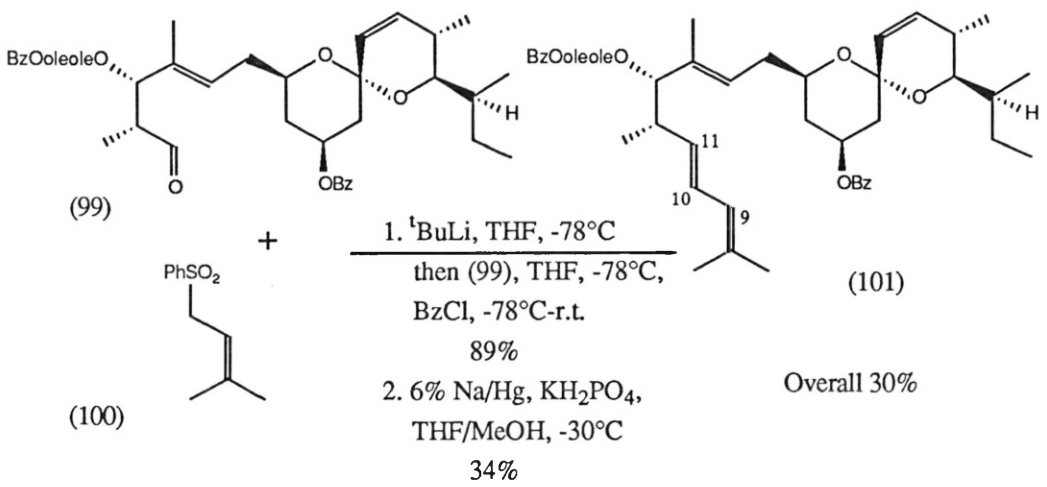


(79) (99)

The aldehyde (99) was also obtained in 75% yield by employment of TPAP (tetra-^{n}propylammonium perruthenate, ($^{n}Pr_4N$)[RuO_4]) with N-methylmorpholine-N-oxide as co-oxidant, a system recently developed in our laboratories.[68] The optical rotation and ^{1}H nmr were identical to the aldehyde obtained by the Swern method.

Julia olefination was carried out using a model allyl sulphone (100) prepared easily from the corresponding isoprenyl alcohol. Thus generation of the yellow anion at -78°C followed by slow addition of avermectin B_{1a} northern hemisphere aldehyde (99) and in situ benzoylation afforded what appeared by t.l.c to be a diastereomeric mixture of closely running benzoyloxysulphone adducts, in very good yield.

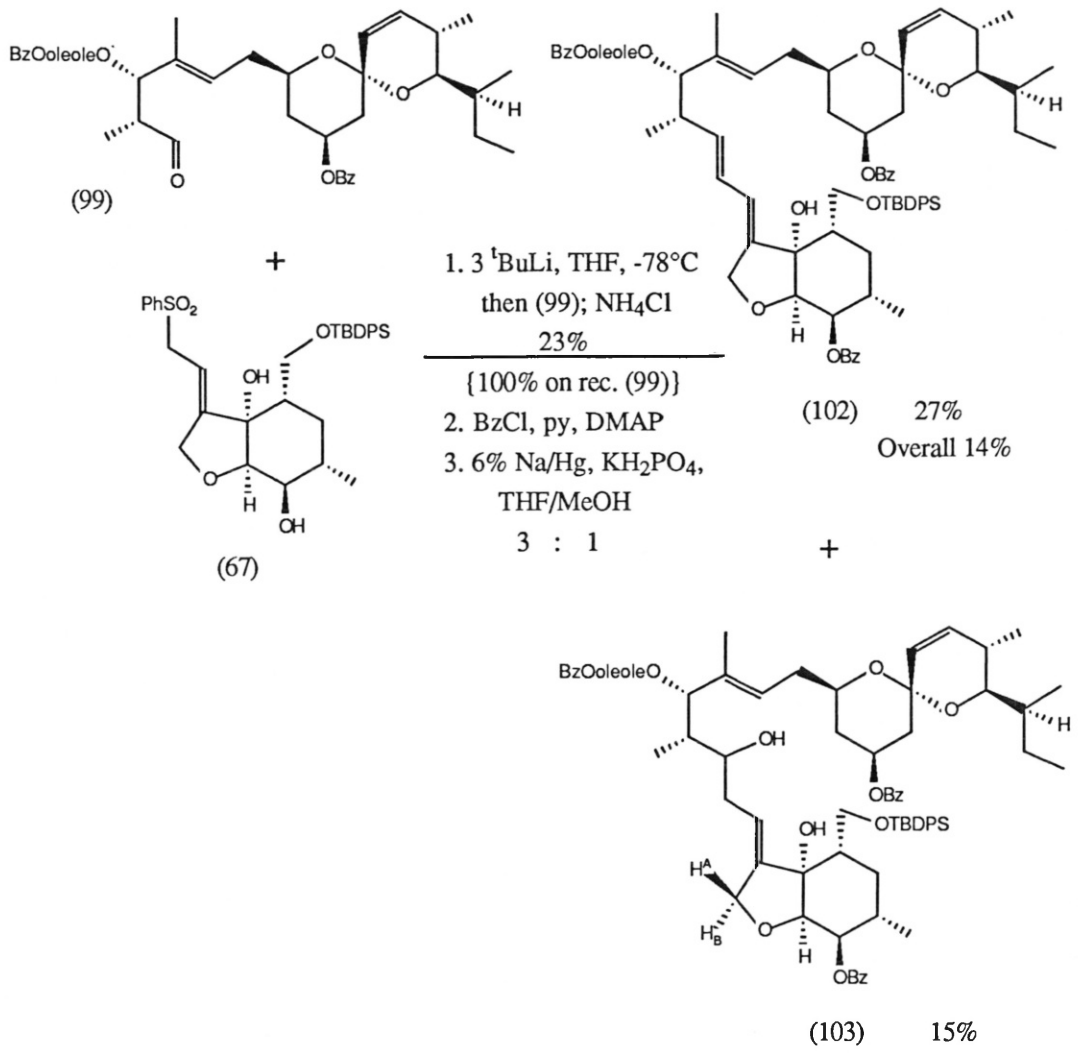
Reductive elimination of this mixture gave the model *E,E*-diene in 30% overall yield. No *cis* isomer was detected, suggesting that the α-branching at C-12 had indeed influenced the transition state during the elimination process to give good *E*-selectivity. The *trans* geometry was clearly evident from the large coupling constant, J_{trans} 15Hz, between H-10 and H-11.



Following from these encouraging results, Julia reaction between aldehyde (99) and sulphone (67) was next attempted.

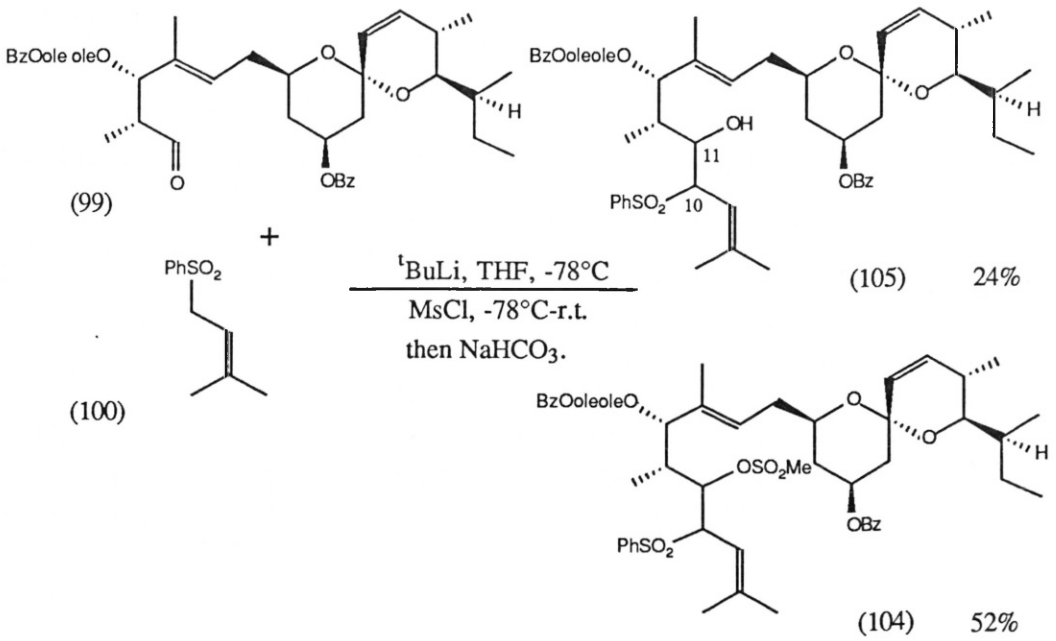
In order to recover any unreacted sulphone, *in situ* benzoylation of the reaction was not carried out. The hydroxy sulphones were isolated in 23% (100% based on recovered aldehyde). Benzoylation, followed by reductive elimination, afforded the required *E,E*-diene (102) in 27% yield (14% overall) and the desulphonylated 11-hydroxy compound (103) as a single diastereomer (17%). The presence of the 5,9 and 4" benzoyloxy in (103) and also its diastereomeric purity

suggested that it may have arisen from unsuccessful 11-hydroxyl benzoylation of one of the hydroxy sulphone diastereomers.



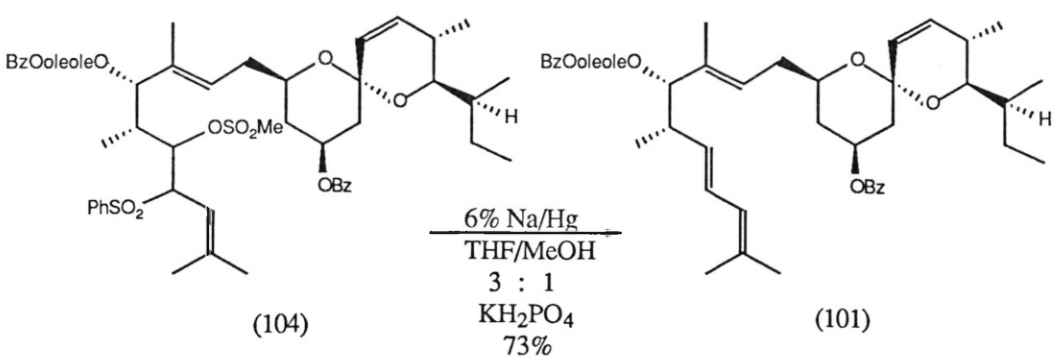
This was later confirmed during a Julia reaction between the northern hemisphere aldehyde (99) and model allyl sulphone (100), where the intermediate alkoxy adduct was treated with mesyl chloride.[69]

In this case, as opposed to the example where *in situ* benzoylation was



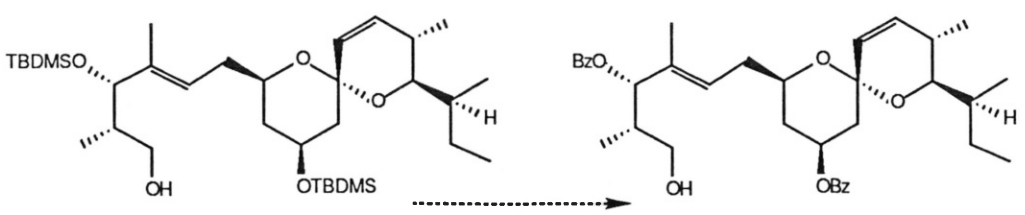
employed, a distinct change in the R_f of the product during t.l.c. analysis of the reaction mixture was observed. In 70% ether-petrol a product of R_f 0.35 and one of R_f 0.30 were observed. The more polar product was indeed the expected 11-mesyl-sulphone (104) (24%) but the less polar product was a pure diastereomer of 11-hydroxy sulphone (105) (52%) (^{1}H nmr assignments were confirmed by COSY).

Reductive elimination of the mesylsulphone proceeded very well to give the previously obtained *E,E*-diene (101) in 73%. (Overall yield of Julia based on aldehyde is 23%)



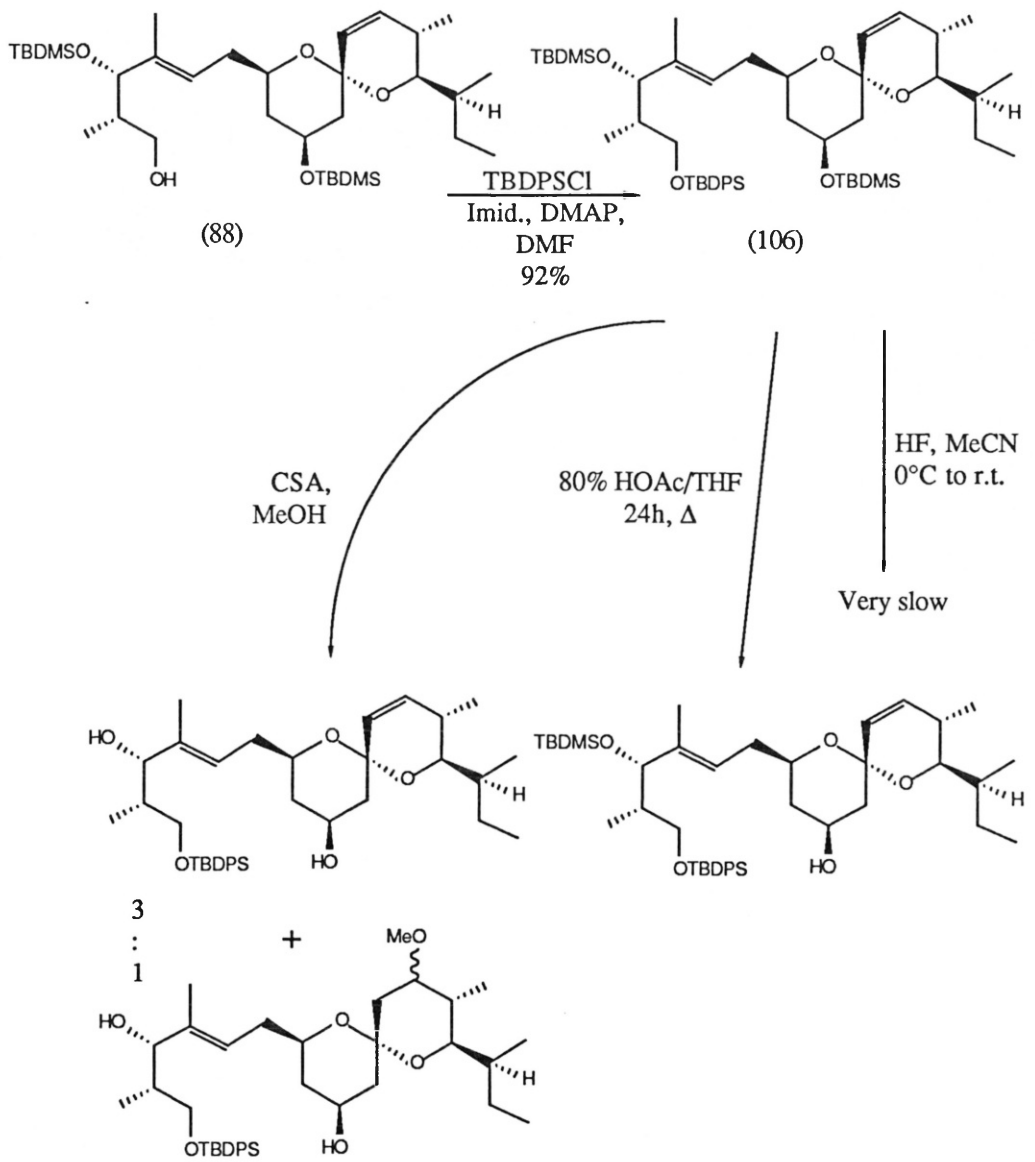
All attempts to acylate the 11-hydroxy in (105) prior to amalgam elimination failed. It seems that this hydroxy diastereomer is sterically encumbered, and may be involved in a hydrogen bond to the C-13 oxygen. Examination of Dreiding models of (105) shows this to be very plausible. Furthermore, the problem of unsuccessful acylation of a Julia adduct was not encountered in our milbemycin β_1 studies,[21b,51a,b] which leads one to believe that 13-oxygenation is indeed the source of the problem.

In order to ascertain whether this would also be a problem in the critical Julia between the relay sulphone (67) and a northern aglycone portion (84), access to the suitably functionalised fragment (84) was required from the degraded aglycone fragment (88).



(88) (84)

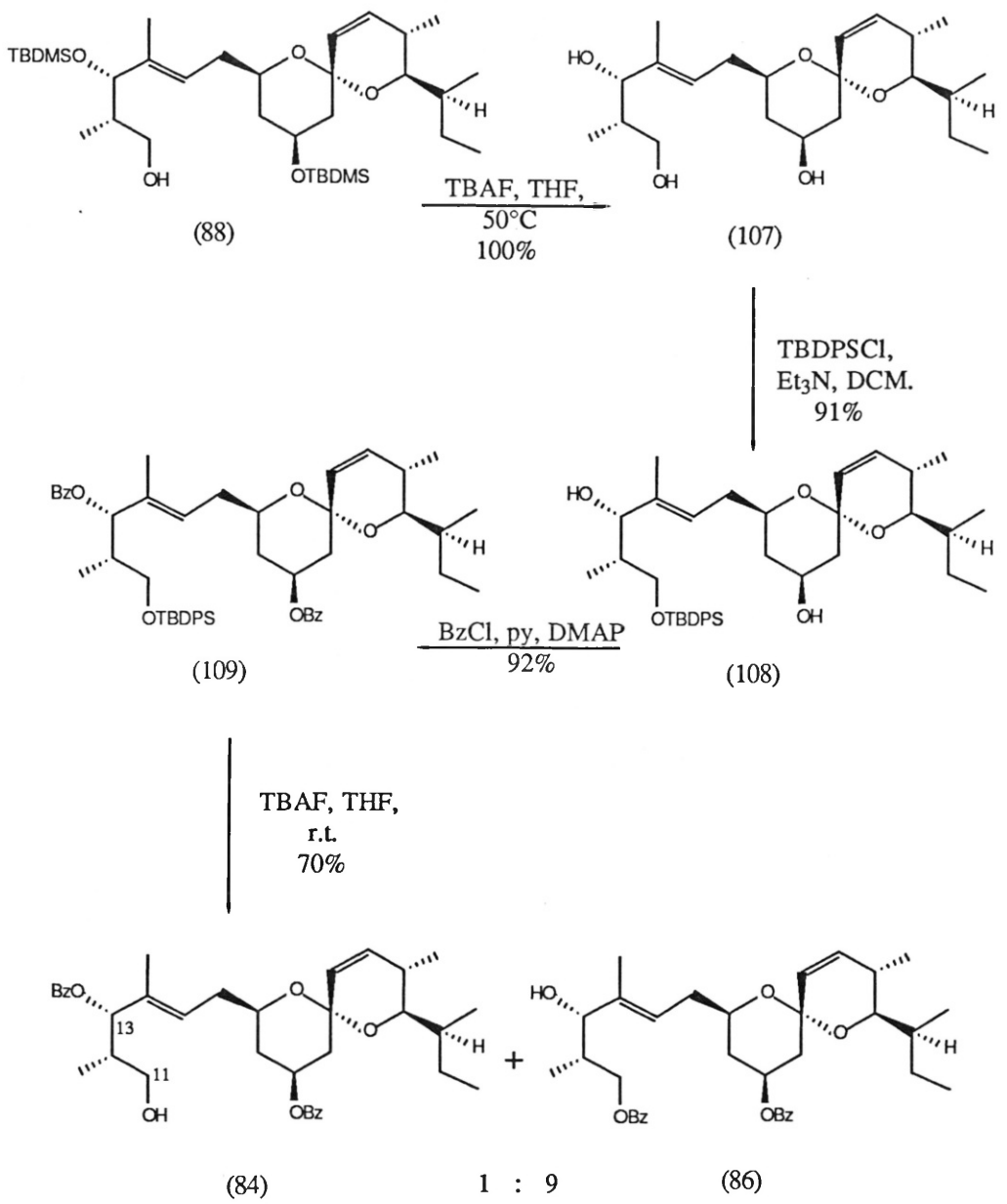
Primary hydroxyl protection as the t-butyldiphenylsilylether was carried out, but endeavours to efficiently remove the less stable t-butyldimethylsilyether groups on (106) failed.[70] (Scheme 24).



Scheme 24.

An alternative approach was attempted. (Scheme 25). Thus removal of the silicon groups of (88) was quantitatively achieved with tetra-n-butylammonium fluoride,[71] to give (107). Selective mono protection of the least hindered primary hydroxyl as the ^{t}butyldiphenylsilylether to give (108), followed by dibenzoylation, afforded the spiroacetal (109) in very good overall yield. The last hurdle to

overcome was the liberation of the C-11 hydroxyl functionality.



Scheme 25.

Treatment of (109) with TBAF[72] proceeded to give a disappointing mixture of the required northern aglycone fragment (84) and the rearranged C-13 alcohol (86) in a 1:9 ratio respectively. This 11-13 acyl migration was unexpected, but had

been observed in an earlier ozonolytic degradation of the tribenzoyloxy derivative (78).[73]

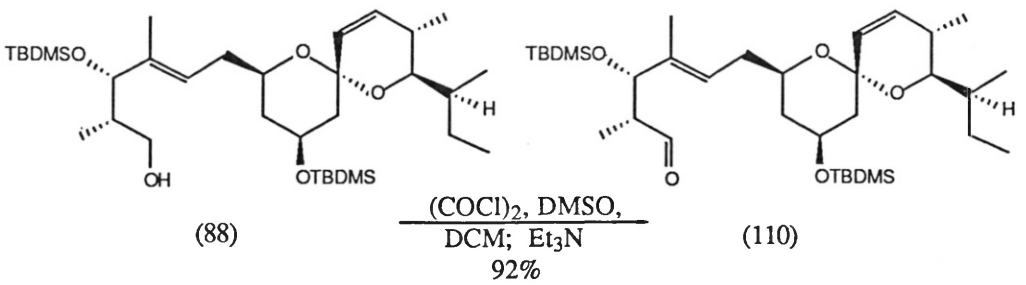
To circumvent this problem of acyl migration an acidic method of silyl cleavage was sought. Aqueous hydrofluoric acid, aqueous acetic acid in THF at reflux, aqueous trifluoroacetic acid in THF, Amberlyst IR120 at reflux, 3% hydrogen chloride in methanol and p-toluene sulphonic acid in acetone/water all failed to give the required alcohol efficiently. The latter method was most successful, but only 60% conversion and a ratio of 3:1 of (84) to (86) was achieved.

Lithium fluoride in acetonitrile had been used to remove silicon protecting groups in the literature,[70] and in this case looked extremely promising. It was thought that fluoride attack on the silicon would occur with the incipient C-11 alkoxide being tightly coordinated to the lithium counter ion hence preventing acyl migration. Unfortunately substrate (109) failed to react after several days with the lithium fluoride.

The choice of the TBDPS protecting group as C-11 had not been successful so a very acid labile, sterically demanding group was therefore investigated. Triphenyl methyl (Trityl) ether seemed ideal, as it could be put on selectively at the C-11 hydroxy of the triol (107), using trityl chloride, DMAP in triethylamine, and easily cleaved under a variety of mildly acidic conditions.[74]. Unfortunately the reaction of the triol (107) with trityl chloride unexpectedly gave a multitude of products.

Access to large quantities of the dibenzoyloxy fragment (84) seemed difficult so Julia coupling between the readily available disilyl fragment (110) and the relay sulphone (67) was undertaken.

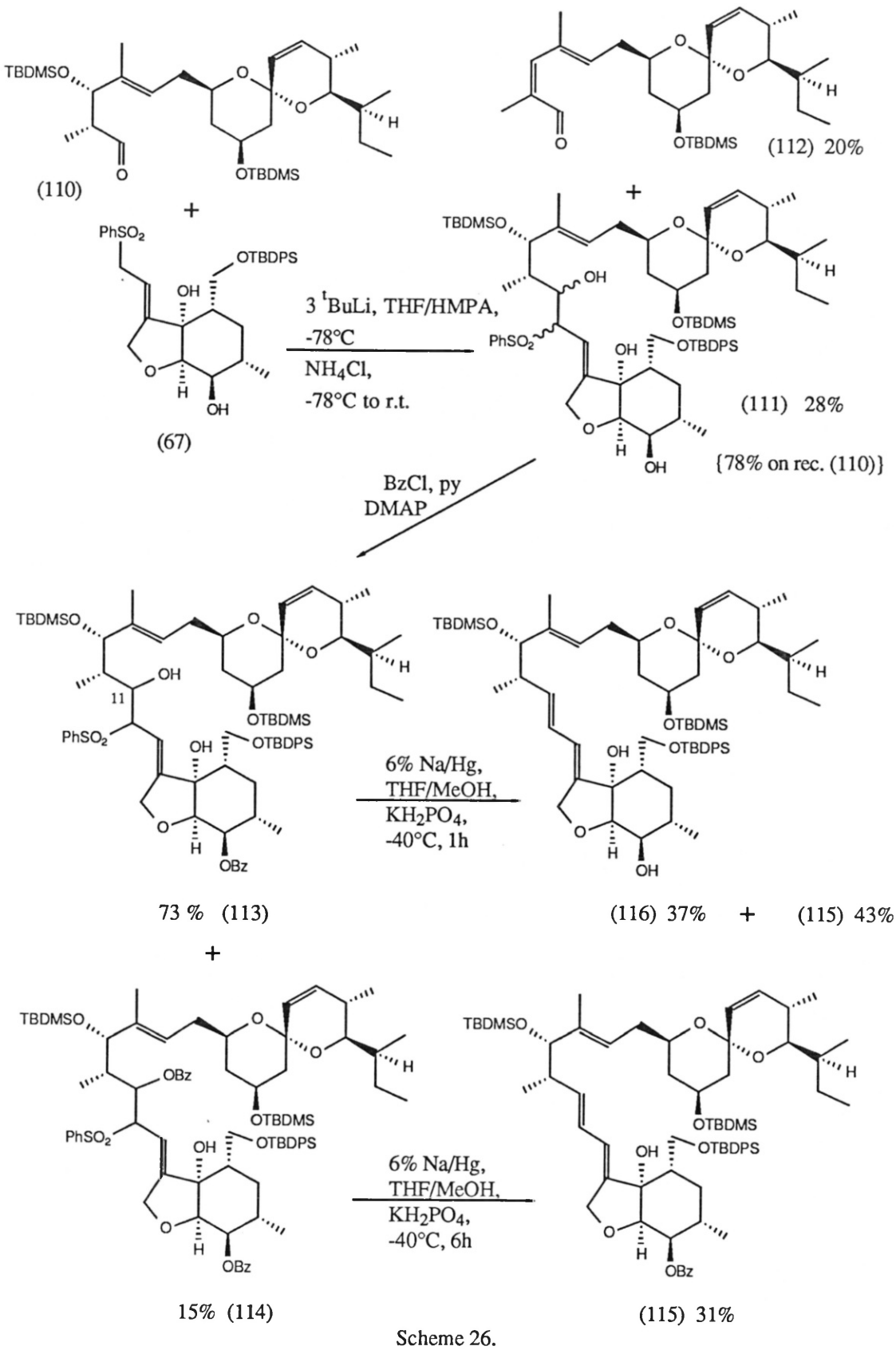
Conversion of the alcohol (88) to the aldehyde using Swern conditions was straightforward, with no detectable epimerisation at the C-12 centre.



Generation of the tri-lithio anion of (67), in the presence of HMPA, in order to solubilise and dissociate the anion, gave a clear deep red solution. The aldehyde (110) was added slowly and after work-up the mixture of hydroxy sulphones (111) was isolated in moderate yield.[75] (Scheme 26). Unreacted sulphone (67), unepimerised aldehyde (110) and enone (112) were also recovered, making up the mass balance. The formation of the enone (112) from β-elimination of the C-13 OTBDMS group was unwanted. This implied that the use of a dibenzoyloxy aldehyde, as originally envisaged, would have to be avoided, the benzoate group being a better leaving group than the silyoxly group.

Attempted dibenzoylation of the hydroxy sulphone diastereomers (111) gave the expected 5,11-benzoyloxy sulphone (114) in 15% and 5-benzoyloxy, 11-hydroxy sulphone (113) in 73%. (Confirmed by COSY experiments). The previously observed acylation problem at C-11 had once again occured.

The 11-benzoyloxy derivative (114) was reductively cleaved with amalgam to give the required *E,E*-diene (115) in 31% (unoptimised yield) with no detectable *cis* product.


TBDMSO
OTBDMS
(110)
(112) 20%
PhSO2
OTBDPS
OH
(67)
3 tBuLi, THF/HMPA,
-78°C
NH4Cl,
-78°C to r.t.
(111) 28%
{78% on rec. (110)}
BzCl, py
DMAP
11
OBz
6% Na/Hg,
THF/MeOH,
KH2PO4,
-40°C, 1h
73 % (113)
(116) 37%
+
(115) 43%
15% (114)
(115) 31%

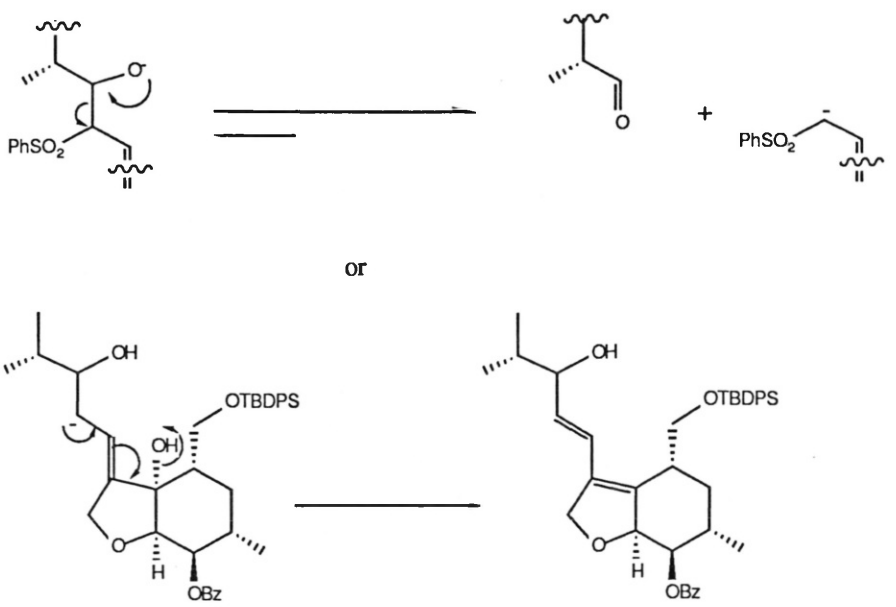
Scheme 26.

Attempts to acylate the other diastereomerically pure hydroxy sulphone (113), by regenerating the dialkoxy anion with ^{t}BuLi and rebenzoylation or acetylation failed, affording only unchanged hydroxysulphone (113)

(113) $\xrightarrow[\text{1,10-phenanthroline}\\ \text{BzCl, -78°C to 40°C}]{^{t}\text{BuLi, THF, -78°C}}$ No Reaction.

$\xrightarrow[\text{DMAP}]{\text{AcCl, py}}$ No Reaction.

These results were initially disappointing until it occurred to us that direct reductive elimination of the hydroxy sulphone (113) in THF:methanol (3:1) may succeed.[75]



Scheme 27.

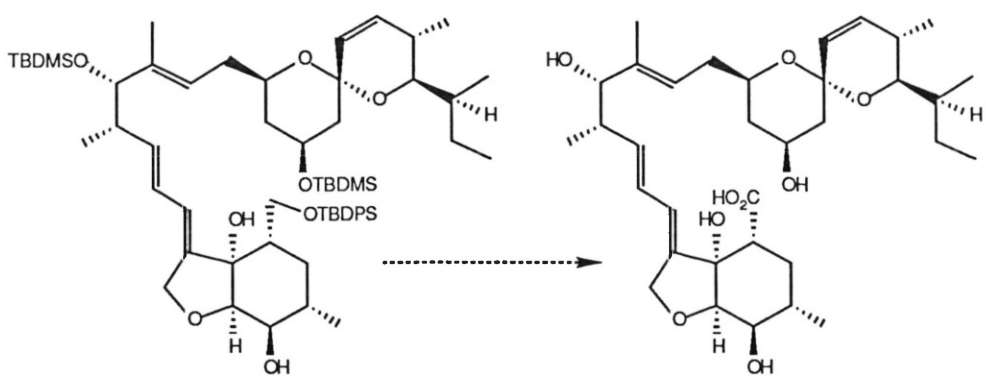
This step was not attempted earlier as there were fears that retro-Julia reaction, which had occurred on other systems in the literature, or elimination of the 7-hydroxy would preferentially occur. (Scheme 27).

Gratifyingly, when (113) was treated with amalgam two *E,E*-diene products were isolated, (Scheme 26). The less polar one was the 5-benzoyloxy-*E,E*-diene (115) in 34% yield, obtained previously from (114), and the more polar product was the 5-hydroxy-*E,E*-diene (116) in 34%, from methoxide hydrolysis of the diene (115). The rate of diene formation from the hydroxysulphone (113) was appreciably faster than from the benzoyloxy sulphone (114).

From these results it was evident that the Julia olefination could be carried out without acylation of the intermediate sulphone adduct, to give the diene product (116).

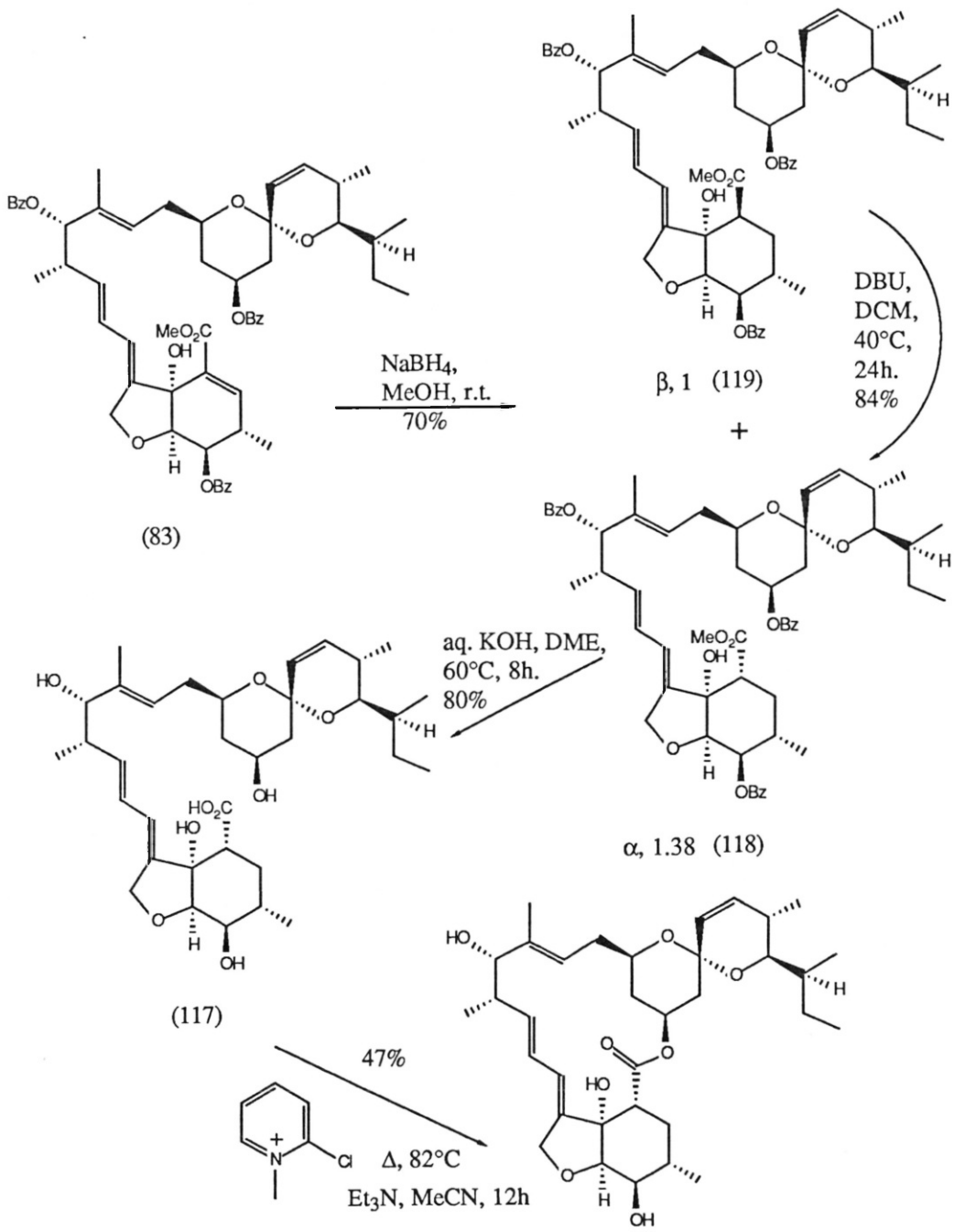
Macrolactonisation.

The next few stages of the synthesis, to the macrolactone precursor (117) mimicked our milbemycin work.[21b,51a]



(116) (117)

It had already been shown that the tribenzoyloxy seco ester (83) was not useful for ozonoytic degradation and, as quantities of this material were available, its use in a relay to the triol seco acid (117) was examined. (Scheme 28).

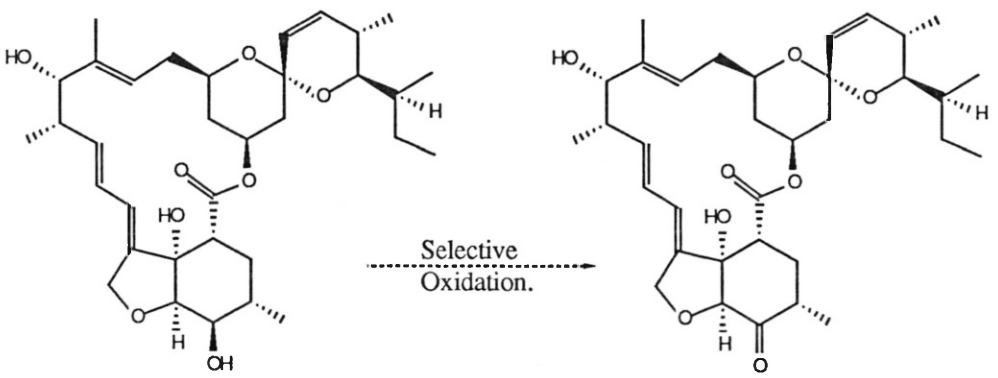


Scheme 28.

Sodium borohydride conjugate reduction of (83), as before, gave a separable mixture of α (118) and β (119) esters in a ratio of 1.38:1. The unwanted β ester could be efficiently epimerised to the α-ester with DBU in warm DCM. Hydrolysis of the α-ester (118) with base gave the very polar trihydroxy acid (117), and subsequent macrolactonisation with the Mukaiyama reagent,[76] afforded the 3,4-dihydro aglycone lactone in very good yield. Fortunately no diolides or dimers were detected. Demonstration that the trihydroxy seco acid intermediate underwent efficient macrolaconisation means that it could fall on a relay pathway to B_{1a}.

Selenoxide Eliminations.

All that remained in the relay approach were the last few steps of the synthesis involving incorporation of the 3,4-double bond and hence generation of avermectin B_{1a} (81). This, we believed, would involve selenium based methodology as outlined in Scheme 29.



(120) (121)

Selenation,
syn elimination,
then stereospecific
reduction.

Scheme 29.

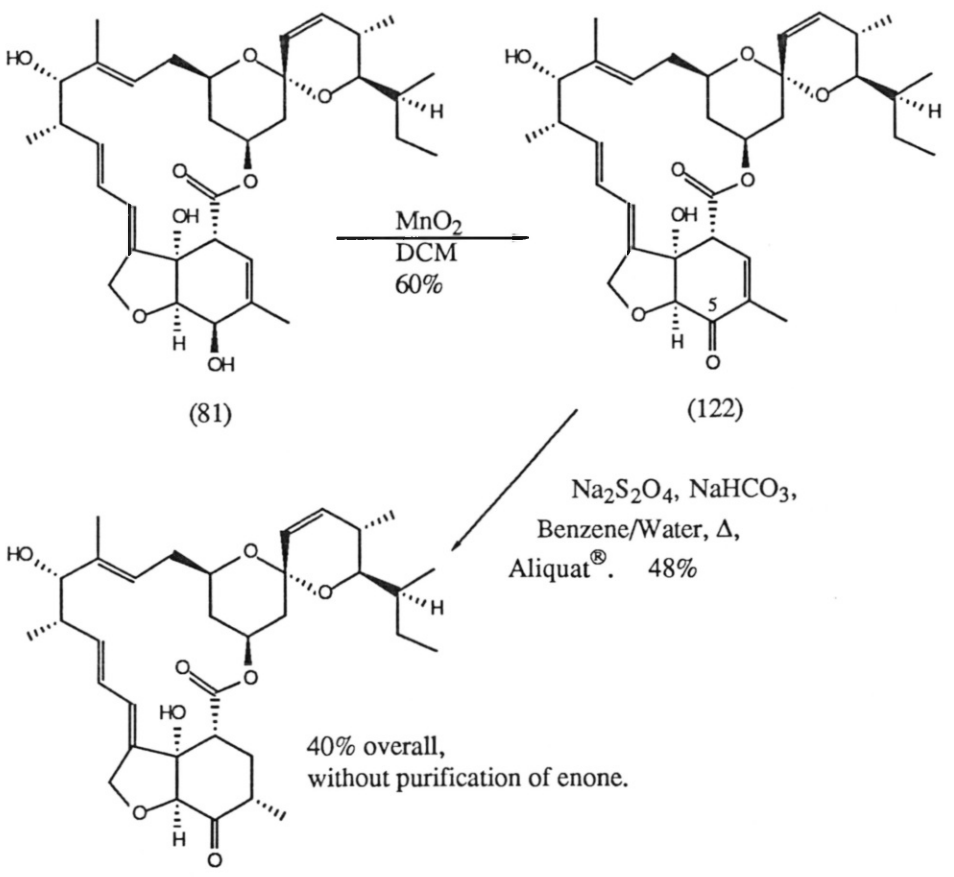
avermectin B1a aglycone

(81)

It was found, from earlier selective protection experiments, that the most reactive hydroxyl in the triol (120) was the C-5-hydroxyl group. Thus, a selective oxidant or 5-protection, 13-protection, 5-deprotection and oxidation sequence should afford the required C-5 carbonyl group . What was more critical was the

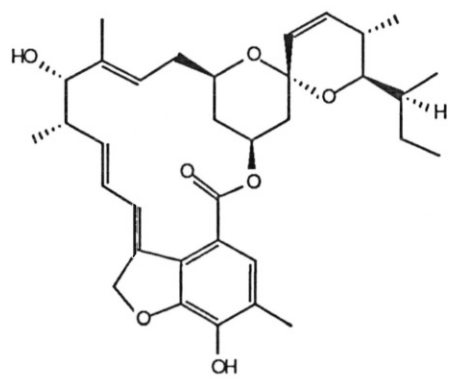
selenoxide elimination to generate the required *endo* cyclic 3,4 double bond. At this time a partial solution to the 3,4 double bond problem was reported by Hanessian.[35] (See Review)

The 5-ketone (121) was obtained from the aglycone (81) in two steps. (Scheme 30). Hence, selective manganese dioxide oxidation gave the enone (122). Several methods for the conjugate reduction of this enone such as transition metal catalysed hydrosilation (Et_3SiH, $(Ph_3P)_3RhCl$[77a] ; Ph_2SiH_2 / $Pd(PPh_3)_4$ / $ZnCl_2.H_20$[77b]), and sodium hydrogen telluride[78], were tried, giving varying amounts of the required 5-ketone in low yield. In all cases purification of the product was difficult as a consequence of the many side products.



Scheme 30.

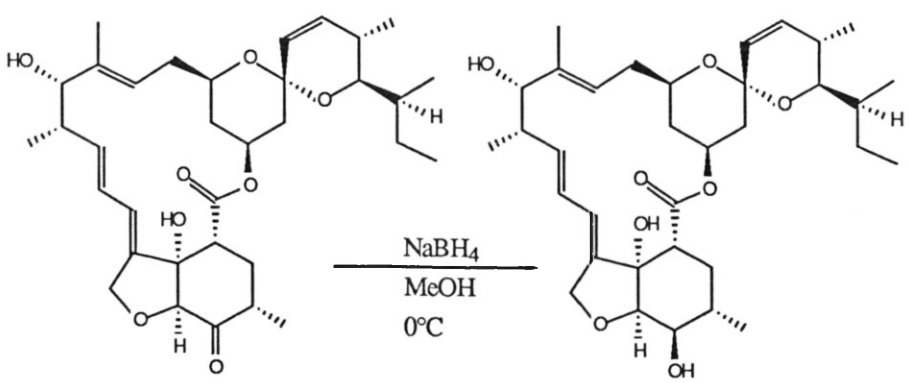
Reduction of the enone was finally effected using the inexpensive sodium dithionite reducing agent, with a phase transfer catalyst, in a two-phase benzene/water mixture, in 48% yield. The reaction was complete in 15 mins. and the only other product was 8% of the aromatic aglycone (124).



(124)

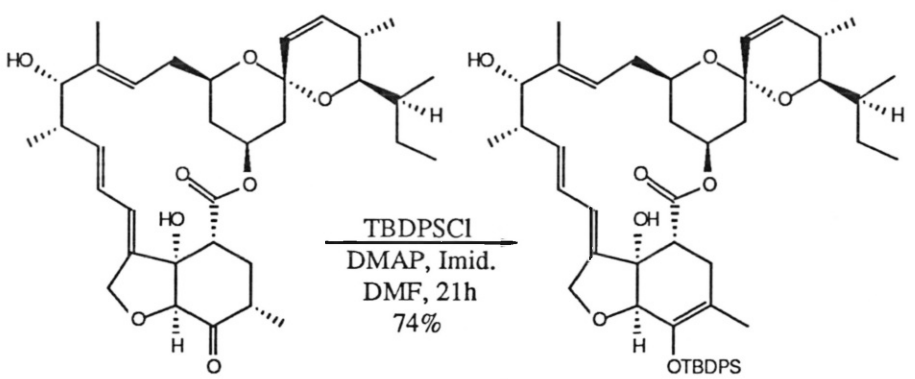
The yield for the aglycone (81) to 5-ketone (121) transformation was increased if dithionite reduction was carried out on the crude enone (122).

Stereoselective sodium borohydride reduction of the 5-keto derivative (121) gave only the 3,4 dihydro triol (120) previously obtained, confirming that indeed the 4-Me was in the most stable equatorial position in (121).



(121) (120)

During reactivity studies of the 5-ketone (121), it was found, as in the case of avermectin B_{1a} aglycone, that the 13-OH was not as reactive as one would expect for an allylic alcohol. It is sterically constrained and the π-orbital of the 14,15 double bond cannot interact easily with the orbitals of the C13-oxygen bond to give this hydroxyl increased allylic activity. In fact, on reaction with TBDPSCl, DMAP, imidazole in DMF, reaction at the C-13 position did not occur, but TBDPS enol ether formation at C-5 was observed to give (123) in good yield.

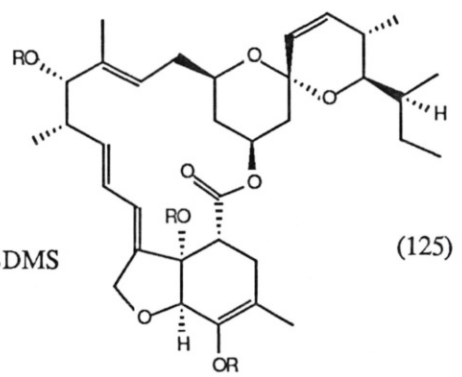


(121) (123)

In our milbemycin β_1 synthesis α-selenylation of a similar macrocyclic 5-ketone derivative, under Sharpless[79] conditions (EtOAc/PhSeCl) failed due to competitive addition of electrophilic selenium to the diene. Also conversion of the milbemycin ketone to the trimethylsilyl enol ether with TMS triflate[80] was complicated by side reactions, perhaps a consequence of the Lewis acidity of this reagent. However, *in situ* selenylation at 0°C of the crude TBDMS enol ether,

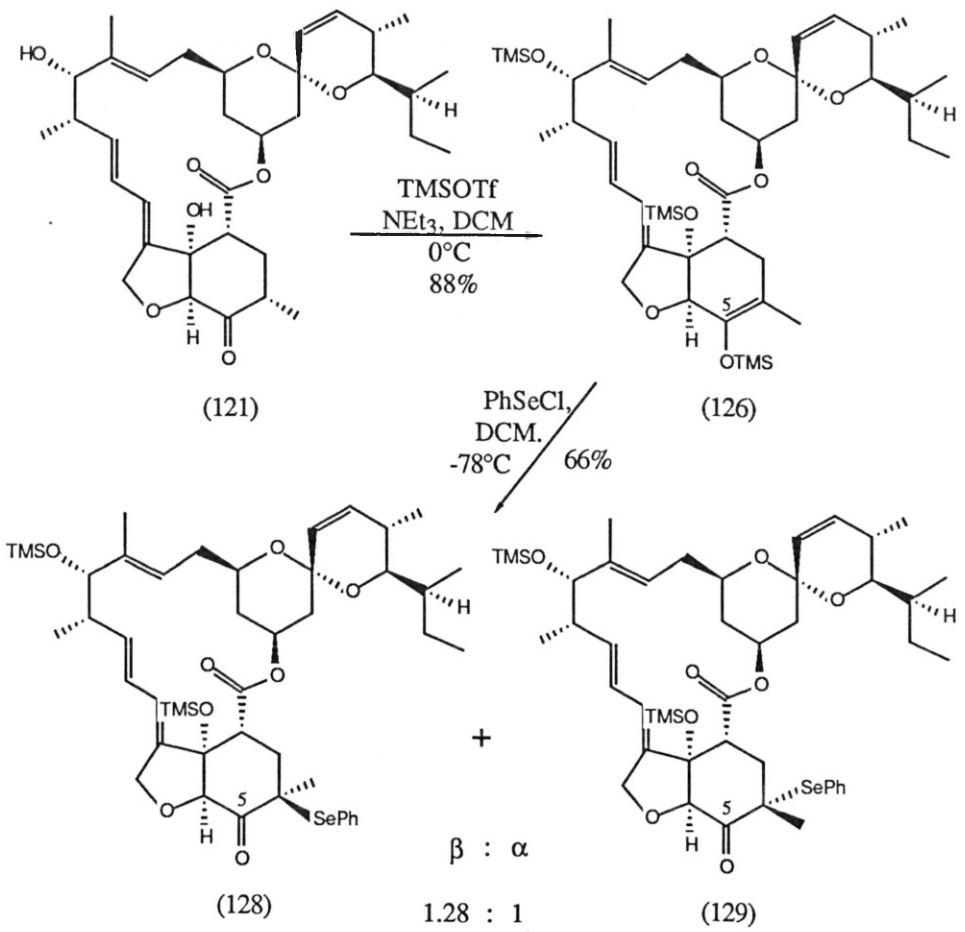
effected the required α-selenylation.[21b,51a]

In the avermectin studies it was found that the TBDMS enol ether (125) was unreactive towards phenylselenyl chloride at temperatures (< -50°C) low enough to prevent the unwanted addition of phenylselenyl chloride across the 22,23 spiroacetal double bond, which was observed on earlier higher temperature experiments.



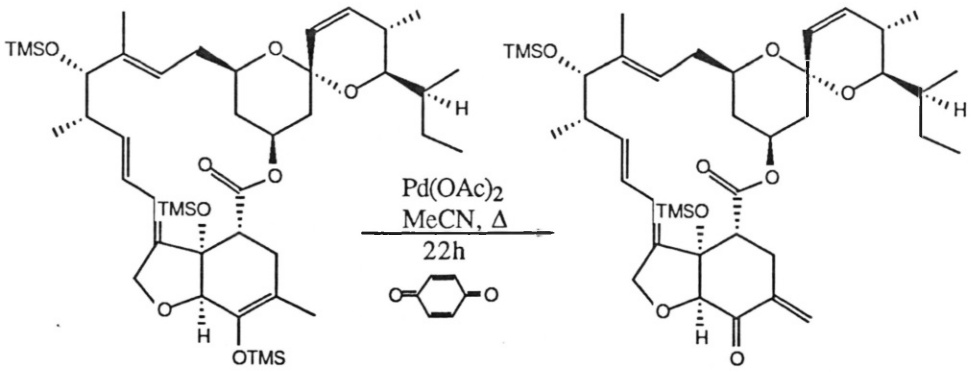
R = TBDMS (125)

In contrast to the milbemycin β1 precedent, the TMS enol ether (126) was easily obtained, by treatment of the 5-ketone diol (121) with excess TMS triflate at 0°C, in very good yield as a stable white foam. (Scheme 31)



Scheme 31.

Palladium (II) catalysed dehydrogenation[81] of this silyl enol ether (126) was attempted in the hope of direct access to the *endo* cyclic enone, however, only the *exo* cyclic enone (127) was obtained, in low yield. (^{1}H n.m.r. resonances for the 4-methylene protons at δ 6.18 and δ 5.42, characteristic for the *exo* enone).



(126) (127) 20%

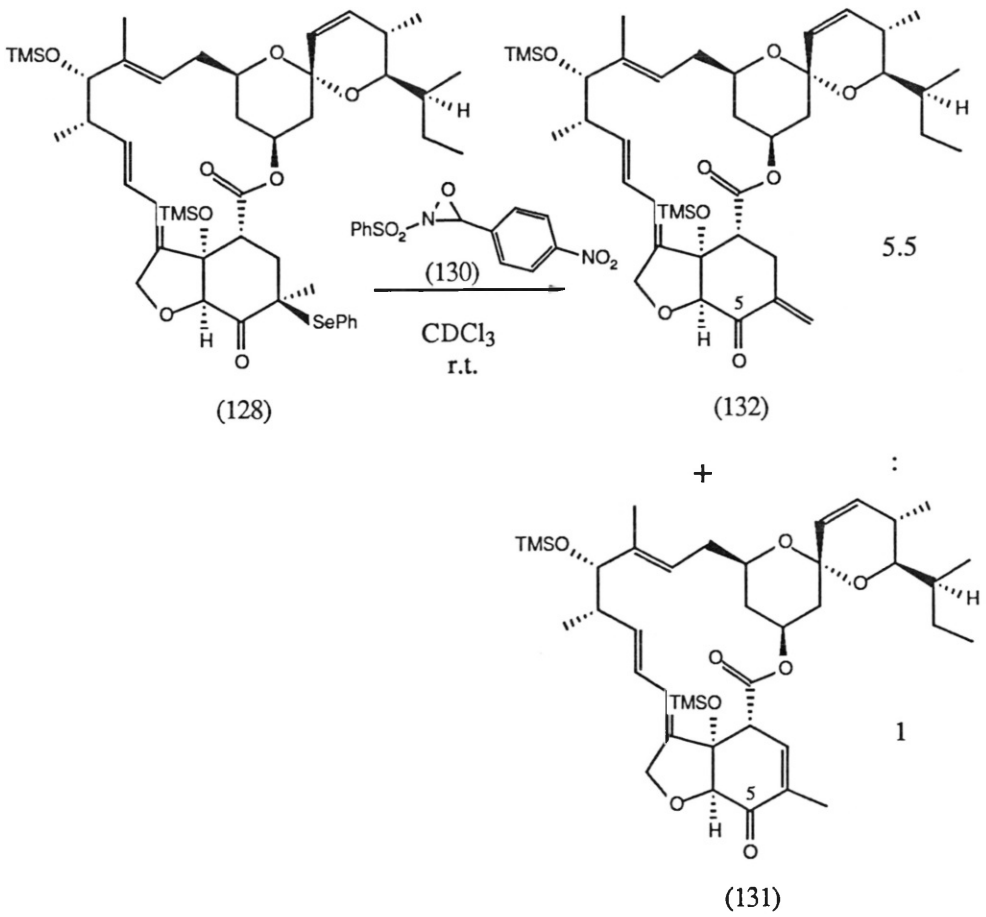
With this result the α-selenylation method seemed the best route to pursue. Reaction of the TMS enol ether (126) with phenylselenyl chloride gave an easily separable mixture of α-seleno ketone (129) and β-seleno ketone (128) in 29 and 37% respectively. (Scheme 31) The diastereomers were assigned as shown from nOe experiments. (See Appendix). For the α-selenide irradiation of firstly the 4-Me caused a clear enhancement of the 2-H and 3-H_A protons and then irradiation of the 6-H showed only an enhancement of a 7-OTMS Me group.

The extremely low-field shift of the 6-H proton (δ5.03) is consistent with the phenylselenyl group being on the α-face in (129).

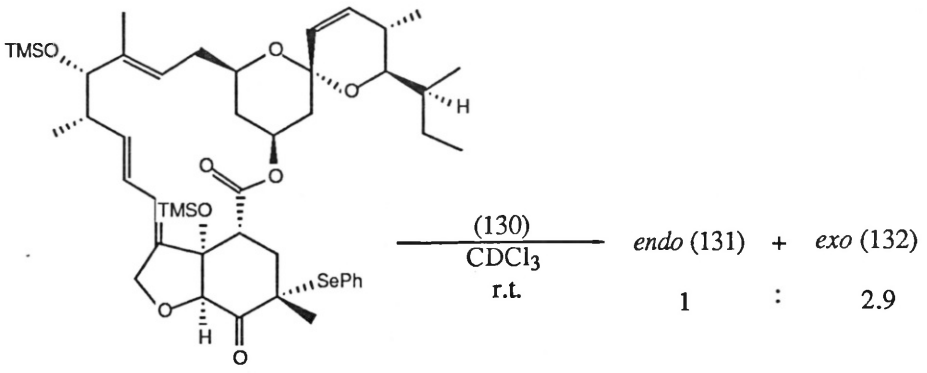
For the β-selenide, irradiation of the 4-Me caused a clear enhancement of the 3-H_A and 3-H_B protons. The chemical shift of the H-2 proton in this case was also indicative of the β-selenide diastereomer as (128).

The stage was now set to investigate the crucial selenoxide elimination reaction. The regio selectivity of the process is controlled by a transition state conformation in which the dipole-moments of the carbonyl and selenoxide groups are opposed. This alignment minimises the overall dipole moment of the molecule and hopefully will favour *endo* cyclic proton abstraction.[82,83]

Oxidation of the β-selenide (128) with the oxaziridine (130) resulted in a mixture of *exo* cyclic (132) and *endo* cyclic (131) enones in a ratio, by n.m.r., of 5.5:1 respectively.



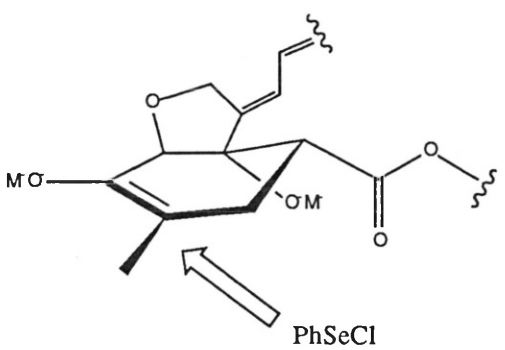
Oxidation of the α-selenide (129) with the oxaziridine and concomitant elimination gave a mixture of *exo* cyclic (132) and *endo* cyclic (131) enones in a slightly better ratio of 2.9:1 respectively by n.m.r.



(129)

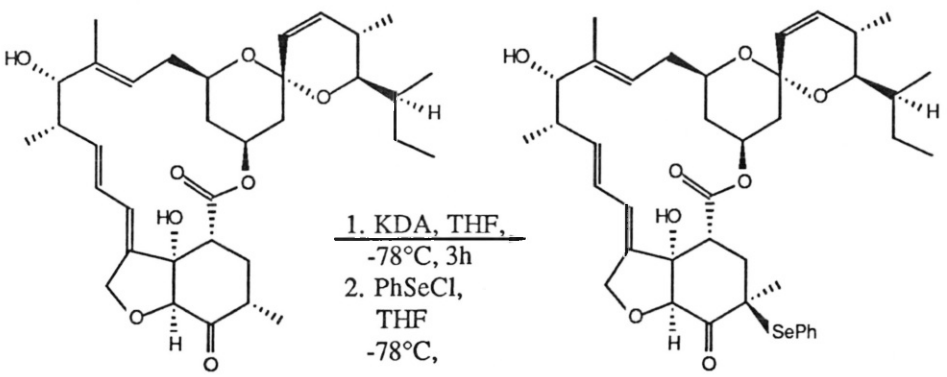
These results were rather disappointing, as *exo* cyclic elimination seemed to be the major process. Nonetheless, it appeared that with the selenoxide group on the α-face a statistical ratio (1:3, endo:exo) of enones was produced.

Eliminations using the free 7-hydroxyl derivatives were investigated next. Direct access to these selenides would hopefully be obtained by the treatment of the dihydroxy-5-ketone (121) with a strong base and in situ selenation. The expected major product would be from attack of the selenium reagent from the most exposed convex α-face of the benzofuran moiety. (Scheme 32).



Scheme 32.

To our surprise, treatment of the ketone (121) with KDA at -78°C and *in situ* selenation afforded the β-selenide (133) as the only diastereomer, (for confirmation of β-selenide see later), corunning, by t.l.c., with 10% starting ketone (121) (separable by reversed phase HPLC. See Appendix). The low yield of product and loss of starting material may be attributable to the instability of the intermediate trialkoxy enolate species, which would be prone to, for example, C-6, C-7 cleavage.

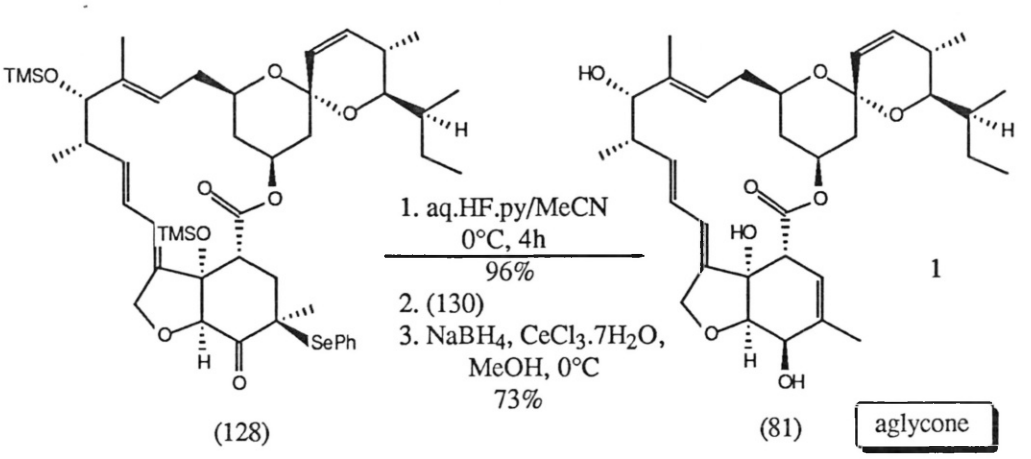


(121) (133) 20%

Easy access to the unprotected keto selenides was finally achieved from the di TMS keto selenides (128) and (129), by simply removal of the TMS groups. Of the several mild methods tried for this conversion, TFA/DCM (-10°C), $AcOH/H_2O/THF$ (r.t.), 1M HCl/THF (r.t.), $MeOH/K_2CO_3$ (0°C) and aq. HF, py/MeCN (0°C), only the latter was efficient and allowed easy separation of the products.

Removal of the silicon groups from the β-selenide (128), (this product was identical to the one obtained previously by the KDA/PhSeCl β-selenation), elimination and stereoselective 1,2 reduction of the mixture of enone with sodium

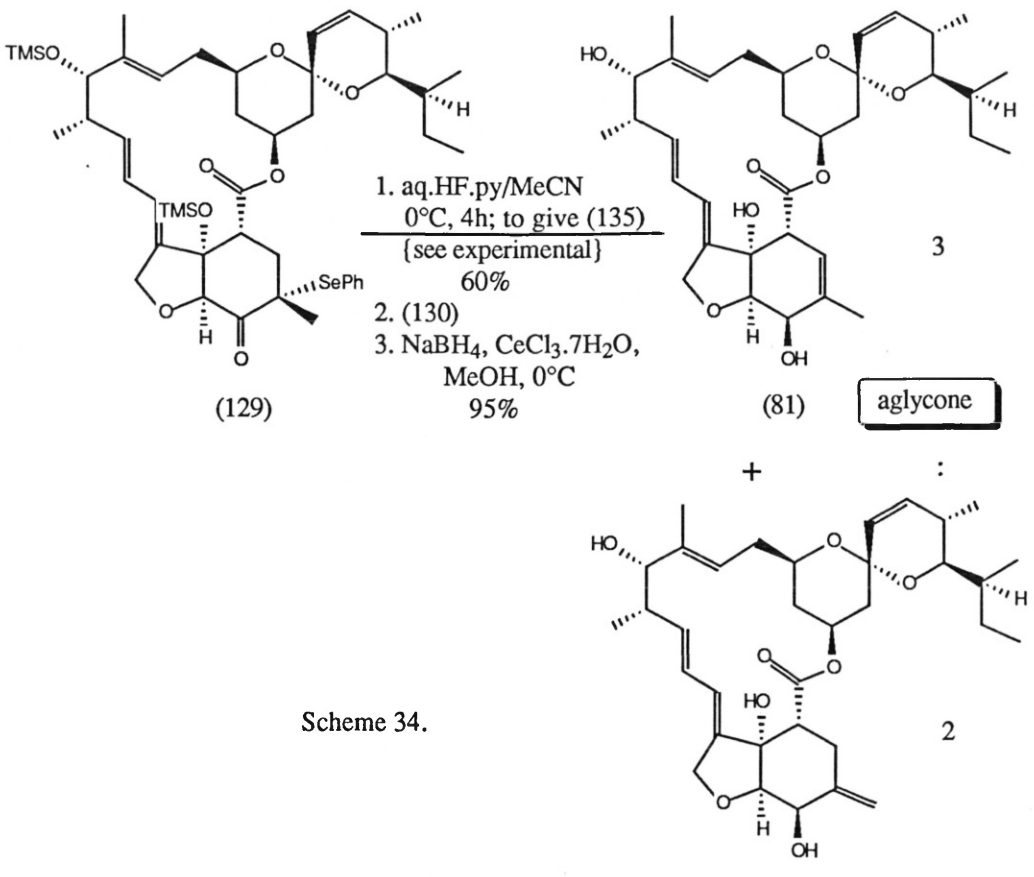
borohydride/cerium (III) chloride.heptahydrate in methanol afforded again a disappointing 1:5 ratio of *endo* cyclic avermectin aglycone (81) and *exo* cyclic aglycone (134) in 73% yield. (Separable by HPLC. See Appendix)



Scheme 33.

The above sequence was repeated using the di TMS α-selenide (129) to give the required avermectin B_{1a} aglycone (81) as the major product. (*endo:exo* ratio 3:2). (Scheme 34). The mixture was easily separable by reversed phase HPLC (See Appendix) to give the *exo* aglycone (134) as before and the pure aglycone (81),

which was identical in all respects to the natural aglycone of avermectin B_{1a}.



Scheme 34.

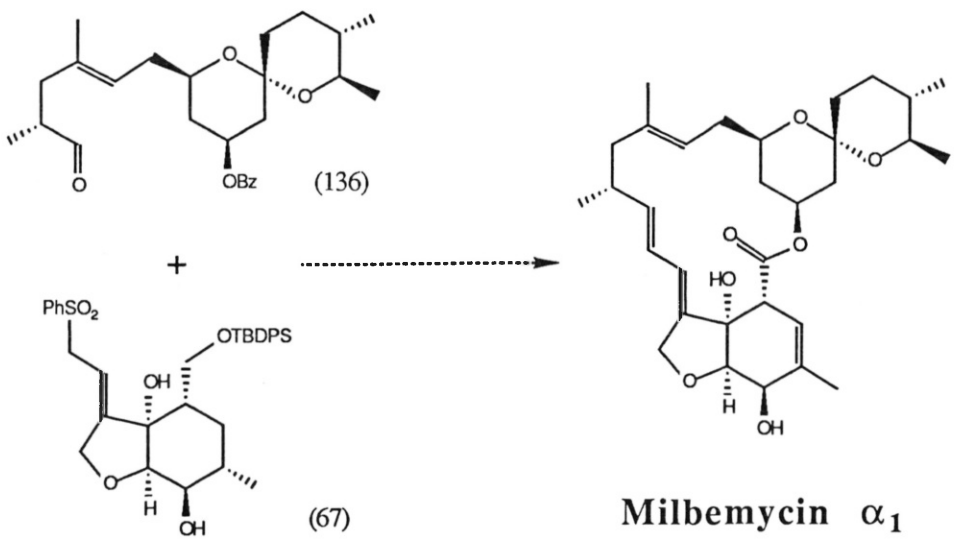
The presence of so many oxygen atoms close to the reaction centre implies that the idea of carbonyl dipole-selenoxide replusion[82] was a rather simplified theory for determining the direction of this *syn*-elimination. The matter is further complicated by the fact that selenoxides are known to be configurationally unstable in the presence of aqueous acid or base.[85] These diastereomeric selenoxides are likely to eliminate at different rates and with different regioselectivities; the rates of epimerisation at selenium will be comparable to those of selenoxide elimination.[85a]

Epilogue

Our studies into the chemistry of avermectin B_{1a} have demonstrated the feasibility of nearly all the late stages of the proposed synthesis. Julia coupling has been successfully accomplished and introduction of the C-3, C-4 unsaturation in the macrolide has been achieved. (This overall process could be improved by reductive deselenation[86] of the β-selenide and recycling the ketone product or by developing a method for *exo* to *endo* cyclic transposition.[87])

The culmination of syntheses of avermectin B_{1a} and milbemycin β_1 from our group will be unique in that a common sulphone southern intermediate has been employed, other sulphone couplings and much of the later stages also utilising common methodology.

This opens up the possibility of hybrid synthesis and synthesis of other recently discovered congeners in this vast family of natural products. Presently the sulphone fragment (67) is being used in a synthesis of milbemycin α_1, the northern fragment (136) having been already employed in the synthesis of milbemycin β_1.



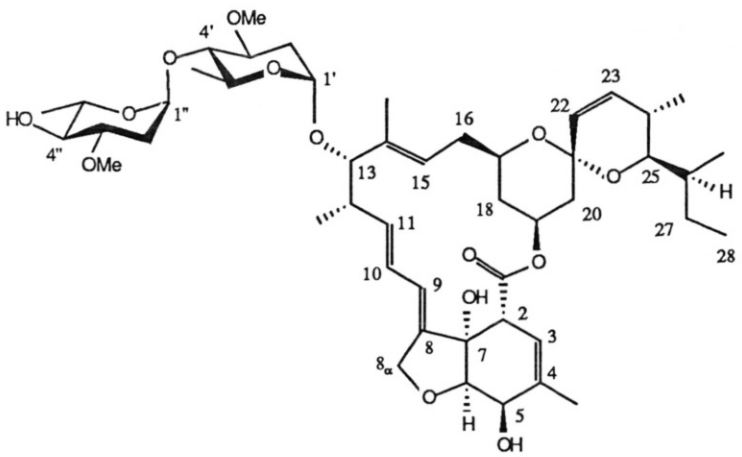
Scheme 35.

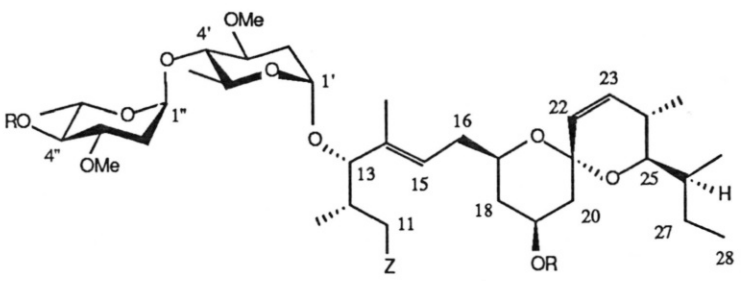
Experimental

Infra red spectra were recorded on a Perkin Elmer 983G Infrared Spectrophotometer. ^1H n.m.r were recorded in $CDCl_3$ unless otherwise stated at 90, 250, 400 or 500 MHz on Jeol FX 90Q, Bruker WM 250, Bruker WH 400 or Bruker AM 500 spectrometers respectively. Mass spectra were recorded on a VG micromass 7070 B spectrometer at 25°C. Optical rotations were measured on an Optical Activity AA-1000 polarimeter. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. Elemental miocroanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Diethyl ether and THF were distilled from sodium-benzophenone ketyl; dichloromethane from phosphorus pentoxide; toluene from sodium and acetonitrile from calcium hydride. Other solvents and reagents were purified by standard procedures as necessary. Petrol refers to light petroleum ether, b.p. 40-60°C, and was distilled prior to use. Ether refers to diethyl ether. Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualisation utilised U.V., acidic ammonium molybdate (IV), acidic palladium (II) chloride or iodine. Preparative chromatography was performed under pressure on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated. Florisil refers to the BDH Ltd. 200-300 U.S. mesh Florisil.

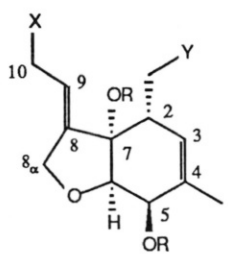
Hplc was performed using the Waters Delta Prep. 3000 system, on reverse phase Dynamax C18 analytical or preparative columns (U.V. Diode array detection)

The compounds throughout the previous sections have used the avermectin numbering system. This experimental will not deviate from this numbering system. The naming of various modified fragments will be based on the major degraded northern hemisphere and southern benzofuran skeletons, as these fragments were derived from the natural product (*vide infra*):



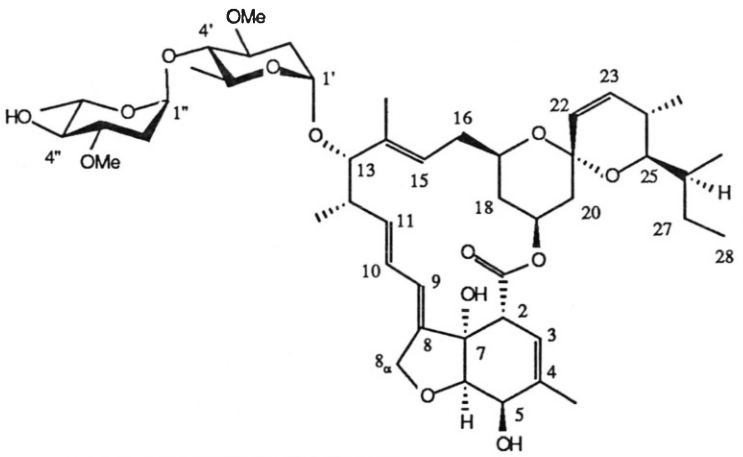


Northern Hemisphere.



Benzofuran.

AVERMECTIN B1a.

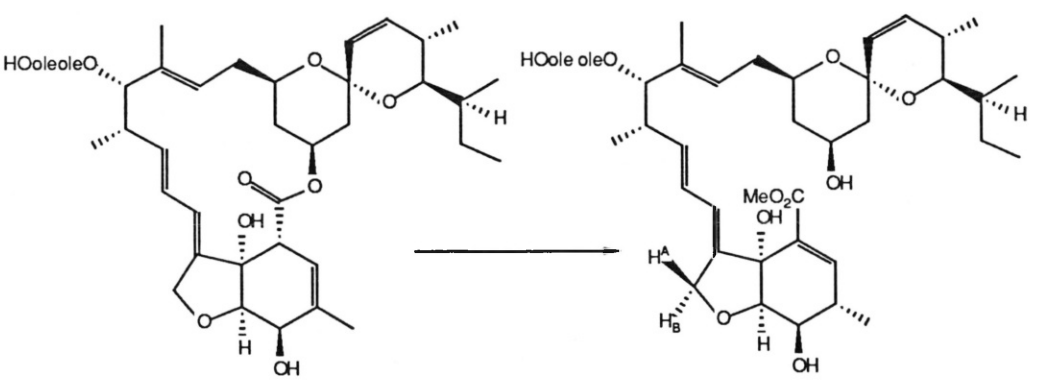


Avermectin B_{1a} (65)

(65) White powder, $[\alpha]_D^{20}$ +65.1° (c=1.35, $CHCl_3$); ν_{max}(film) 3449, 2966, 1713, 1450, 1379, 1160, 1118, 1052, 986, 869 and 735 cm^{-1}; δ (400 MHz) 5.86 (1H, m, 9-H), 5.77 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.74 (1H, dd, J 15.0 and 10.0 Hz, 11-H), 5.74 (1H, obs.dd, 10-H), 5.555 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.43 (1H, m, 3-H), 5,41 (1H, d, J 3.0 Hz, 1"-H), 5.40 (1H, obs.m, 19-H), 4.99 (1H, br.d, J 10 Hz, 15-H), 4.77 (1H, d, J 3.0 Hz, 1'-H), 4.69 (2H, 2xdd, J 12.0 and 2.5 Hz, 8_α-H_2), 4.30 (1H, d, J 6.0 Hz,5-H), 4.05 (1H, br.s, 7-OH), 3.97 (1H, d, J 6.0 Hz 6-H), 3.94 (1H, m, 13-H), 3.87 (1H, m, 17-H), 3.84 (1H, dq, J 9.5 and 6.0 Hz, 5'-H), 3.77 (1H, dq, J 9.5 and 6.0 Hz, 5"-H), 3.63 (1H, ddd, J 11.0, 8.5 and 5.0 Hz, 3'-H), 3.485 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.45 (1H, obs.m, 3"-H), 3.44 (3H, s, 3"-OMe), 3.42 (3H, s, 3'-OMe), 3.30

(1H, m, J 2.0 Hz, 2-H), 3.25 (1H, t, J, 9.0 Hz, 4"-H), 3.17 (1H, t, J 9.0 Hz, 4'-H), 2.60 (1H, br.s, 5-OH), 2.53 (1H, m, 12-H), 2.41 1H, br.s, 4"-OH), 2.34 (1H, dd, J 12.5 and 5.5 Hz, 2"-H), 2.31-2.29 (3H, obs.m, 16-H_2, 24-H), 2.23 (1H, dd, J 12.5 and 5.5 Hz, 2'-H), 2.02 (1H, ddd, J 12.0, 5.0 and 2.0 Hz, 20-He), 1.88 (3H, s, 4-Me), 1.78 (1H, br.d, J 12.0 Hz, 18-H_e), 1.65- 1.45 (2'-H, 2"-H, 20-H_a, 26-H, 27-H_2), 1.50 (3H, s, 14-Me), 1.28 (3H, d, J 6.5 Hz, 5"-Me), 1.26 (3H, d, J 6.5 Hz, 5'-H), 1.17 (3H, d, J 7.0 Hz, 12-Me), 0.94 (3H, t, J 8.0 Hz, 28-H_3), 0.92 (3H, d, J 7.0 Hz, 24-Me), 0.92 (3H, d, J 7.0 Hz, 26-Me),0.88 (1H, q, J 12.0 Hz, 18-H_a); m/z 872 (M, $C_{48}H_{72}O_{14}^+$), 728 (M^+-$C_7H_{12}O_3$[ole]), 584 ($C_{34}H_{48}O_8^+$ = M^+-HOoleOole), 566 ($C_{34}H_{48}O_8^+$-H_2O), 456 ($C_{29}H_{42}O_5^+$), 305 ($C_{20}H_{31}O_3^+$), 289 ($C_{14}H_{25}O_6^+$ = HOoleOole$^+$), 261 ($C_{15}H_{17}O_4^+$), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$), 169 ($C_{10}H_{17}O_2^+$), 111 ($C_6H_6O_2^+$).

1. Preparation of 19-hydroxy-1-methoxycarbonyl-Δ^2-avermectin B_{1a} (77).

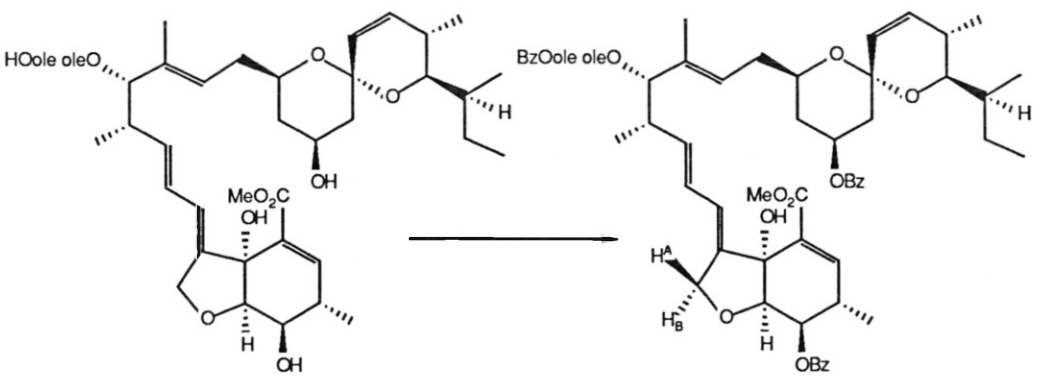


(65) (77)

A solution of avermectin B_{1a} (65) (10.0 g, 11.45 mmol) in DME (100 ml) was treated dropwise with aqueous potassium hydroxide (1.0 M, 34.4 ml, 34.36 mmol). After stirring for 60 h at r.t. the mixture was cooled to 0°C and diluted with THF (600 ml). 6 M HCl was added dropwise until the solution was at pH 2. Solid sodium chloride was added and the organic layer was decanted, dried ($MgSO_4$) and concentrated *in vacuo* (to~200 ml). Diazomethane was bubbled through this solution until the carboxylic acid present had reacted (t.l.c). The solvent was evaporated *in vacuo*. Flash chromatography (40% ethyl acetate-dichloromethane afforded the seco ester (77) (7.77 g, 75%) as a white foam. $[\alpha]_D^{20}$+73.8° (c = 0.24, $CHCl_3$); ν_{max}(film) 3431, 2928, 1697, 1450,1380, 1273, 1198, 1121, 1052, 984, 935, 864, 836 and 769 cm^{-1}; δ (400 MHz) + COSY, 6.67 (1H, d, J 2.0 Hz, 3-H), 6.34 (1H, m, J 9.5 Hz, 9-H), 5.96-5.89 (2H, obs.m, 11-H, 10-H), 5.78 (1H, dd, J 10.0 and 2.0 Hz, 22-H), 5.56 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.39 (1H, t, J 7.0 Hz, 15-H), 5.30 (1H, d, J 3.5 Hz, 1"-H), 4.84 (1H, br.s, 7-OH), 4.73 (1H, d, J 3.5 Hz, 1'-H), 4.68 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B), 4.55 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_A), 4.12 (1H, tt, J 11.0 and 4.5 Hz, 19-H), 4.04 (1H, d, J 2.5 Hz, 6-H), 3.77 (1H, s, 1-OMe), 3.79-3.65 (5H, m, 5-OH, 5-H, 17-H, 5'-H, 5"-H), 3.65 (1H, d, J 7 Hz, 13-H), 3.56 (1H, dd, J 10.0 and 2.5 Hz, 25-H), 3.55-3.45 (2H, m, 3'-H, 3"-H), 3.43 (3H, s, 3"-OMe), 3.38 (3H, s, 3'-OMe), 3.15 (2H, t, J 9 Hz, 4'-H, 4"-H), 2.63 (1H, m, 4-H), 2.59 (1H, br.s, 4"-OH), 2.45 (1H, q, J 7.0 Hz, 12-H), 2.38-2.20 (5H, m, 19-OH, 16-H_2, 24-H, 2"-H), 2.11 (1H, dd, J 12.5 and 5.0 Hz, 2'-H), 2.01 (1H,, dd, J 12.0 and 4.0 Hz, 20-H_e), 1.95 (1H, br.d, J 12.0 Hz, 18-H_e), 1,54 (3H, s, 14-Me), 1.55-1.35 (6H, m, 20-H_a, 26-H, 27-CH_2, 2'-H, 2"-H), 1.28 (3H, d, J 6.5 Hz, 5"-Me), 1.26 (3H,

d, J 6.5 Hz, 5'-Me), 1.135 (3H, d, J 6.5 Hz, 4-Me), 0.95-0.86 (12H, m, 12-Me, 24-Me, 26-Me, 28-H_3); m/z FAB, 927 ($M+Na^+$), 453, 433, 411, 391, 369, 327, 275, 217, 205, 183, 173, 145, 113 and 95; (Found: $M+Na^+$, 927.5082 $C_{49}H_{26}O_{15}Na$ requires M+Na, 927.5073).

2. Preparation of 5.19.4"-tribenzoyloxy-1-methoxycarbonyl-Δ^2-avermectin B_{1a} (78).

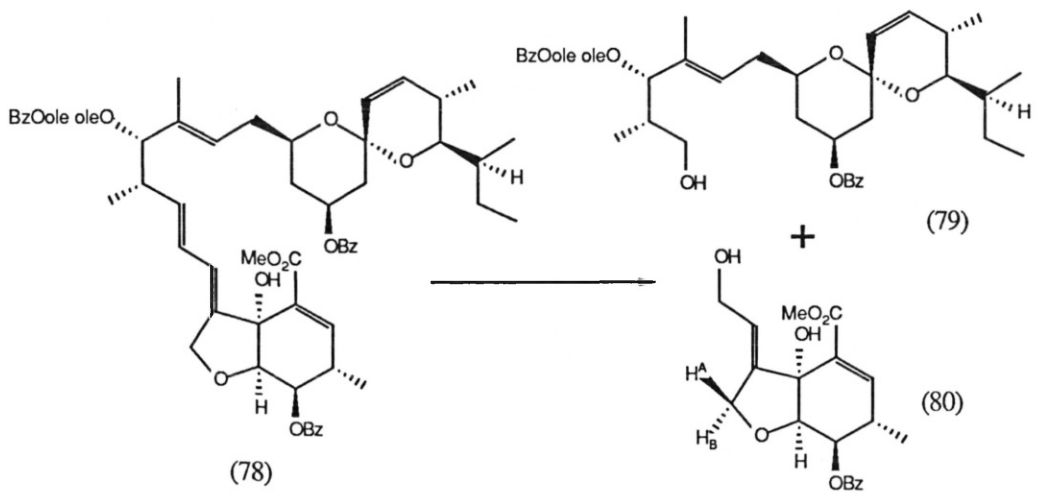


(77) (78)

To a solution of the seco ester (77) (7.57 g, 8.36 mmol) and DMAP (0.051 g, 0.42 mmol) in dry pyridine (290 ml) at 0°C under argon was added benzoyl chloride (3.5 ml, 30.10 mmol). The mixture was left stirring at r.t. for 24 h., after which time it was cooled to 0°C, 3-dimethylaminopropylamine (3.37 ml, 30 mmol) was added and the mixture stirred at r.t. for 30 min. The mixture was poured into 1M HCl and extracted with ether. The combined organic extracts were washed with saturated sodium hydrogencarbonate, brine, dried ($MgSO_4$) and evaporated *in*

vacuo. Flash chromatography (50% ether-petrol) afforded the tribenzoyloxy seco ester (78) (8.14 g, 80%) as a white foam. $[\alpha]_D^{20}$+51.3° (c= 1.05, $CHCl_3$); ν_{max}(film) 3600, 2960, 1718, 1604, 1416 and 1115 cm^{-1}; δ (400 MHz) + COSY, 8.12-8.01 (6H, m, Ph(o)), 7.61-7.41 (9H, m, Ph(m),(p)), 6.73 (1H, d, J 2.5 Hz, 3-H), 6.38 (1H, m, J 10.0 Hz, 9-H), 6.985 (1H, dd, J 15.0 and 6.5 Hz, 11-H), 5.91 (1H, dd, J 15.0 and 10.0 Hz, 10-H), 5.75 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.59 (1H, dd, J 10.0 and 3.0 Hz, 23-H), 5.49-5.39 (3H, obs.m, 15-H, 19-H, 1"-H), 5.21 (1H, dd, J 10.0 and 2.0 Hz, 5-H), 4.96 (1H, t, J 9.5 Hz, 4'-H), 4.705 (1H, dd, J 13.5 and 3.0 Hz, 8_α-H_B), 4.59 (1H, dd, J 13.5 and 2.5 Hz, 8_α-H_A), 4.64 (1H, s, 7-OH), 4.21 (1H,d, J 2.0 Hz, 6-H), 4.02 (1H, m, 5"-H), 3.95 (1H, m, 17-H), 3.81 (3H, s, 1-OMe), 3.79-3.70 (2H, m, 5'-H, 3"-H), 3.66 (1H, d, J 8.0 Hz, 13-H), 3.60 (1H, m, 3'-H), 3.44 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.37 (3H, s, 3"-OMe), 3.36 (3H, s, 3'-OMe), 3.23 (2H, t, J 9.0 Hz, 4'-H, 4"-H), 3.04 (1H, m, 4-H), 2.50 -2.11 (8H, m, 12-H, 16-H_2, 18-H_e, 20-H_e, 24-H, 2'-H, 2"-H), 1.78 (1H, m, 2"-H), 1.70-1.40 (6H, m, 18-H_a, 20-H_a, 26-H, 27-CH_2, 2'-H), 1.62 (3H, s, 14-Me), 1.22 (3H, d, J 6.5 Hz, 5"-Me), 1.21 (3H, d, J 6.5 Hz, 5'-Me), 1.11 (3H, d, J 7.5 Hz, 4-Me), 0.97-0.86 (12H, m, 12-Me, 26-Me, 28-H_3); m/z FAB 1239 ($M+Na^+$), 925, 911, 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$), 177, 105 ($PhCO^+$); (Found C, 69.20 ; H, 7.29 . $C_{70}H_{88}O_{18}$ requires C, 69.1 ; H, 7.3%).

3. Preparation of 19,4"-bezoyloxy-11-hydroxy-avermectin B_{1a} northern hemisphere (79) and 5-benzoyloxy-10-hydroxy-1-methoxycarbonyl-Δ^2-avermectin B_{1a} benzofuran (80).

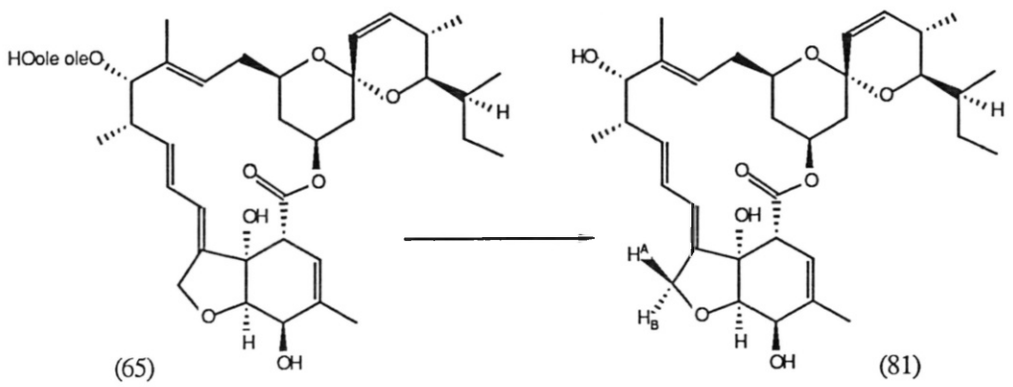


To a magnetically stirred solution of diene (78) (6.79 g, 5.58 mmol) in DCM (272 ml) and ethanol (102 ml) was added a pinch of Sudan Red 7B dye so as to give a pale pink solution. The solution was cooled to -78°C and ozone (50 $lmin^{-1}$, 80 V; Wallace and Tiernan Ozonator) was bubbled through. The reaction was monitored by colour change of the indicator dye. As the solution decolourised (ca. 16h) t.l.c.'s were taken every 5 min until complete consumption of starting material (17h). The solution was purged with argon for 30 min, and solid sodium borohydride (2.11g, 55.8 mmol) was added in one portion at -78°C. The stirred solution was allowed to warm to 0°C over 1.5h, and then stirred at r.t. until no more ozonides were seen by t.l.c. The solution was cooled to 0°C, and ice-cold 1M HCl was added dropwise until it was at pH 6. The mixture was buffered with aq. KH_2PO_4 and extracted with

saturated sodium hydrogencarbonate, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (65% ether-petrol to give (79) and 45% ethyl acetate-petrol to give (80)) afforded the northern alcohol (79) (4.51 g, 92%) and the southern alcohol (80) (1.63 g, 78%) as white foams. Less polar: (79), $[\alpha]_D^{20}$ -40.1° (c= 0.1, $CHCl_3$); ν_{max}(film) 3682, 1720, 1604 and 1115 cm^{-1}; δ (500 MHz) +COSY, 8.09-7.99 (4H, d, Ph(o)), 7.58-7.40 (6H, m, Ph(m), (p)), 5.73 (1H, dd.J 10.0 and 1.7 Hz, 22-H), 5.57 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.49 (1H, br.t, J 7.0 Hz, 15H), 5.42 (1H, tt, J 11.0 and 4.5 Hz, 19-H), 5.36 (1H, d, J 3.0 Hz, 1"-H), 4.92 (1H, t, J 9.0 Hz, 4"-H), 4.80 (1H, d, J 3.0 Hz, 1'-H), 3.98 (1H, m, 5"-H), 3.94 (1H, m, 17-H), 3.80 (1H, d, J 10.0 Hz, 13-H), 3.76-3.62 (4H, m, 11-CH_2, 5'-H, 3"-H), 3.49 (1H, m, 3'-H), 3.41 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.35 (6H, s, 3'-OMe, 3"-OMe), 3.21 (1H, t, J 9.0 Hz, 4'-H), 2.62 (1H, br.d, 11-OH), 2.41- 2.11 (7H, m, 16-H_2, 18-H_e, 20-H_e, 24-H, 2'-H, 2"-H), 1.96 (1H, m, 12-H), 1.75-1.51 (7H, s+m, 14-Me, 20-H_a, 26-H, 2'-H, 2"-H), 1.45 (2H, m, 27-H_2), 1.37 (1H, q, J 12 Hz, 18-H_a), 1.21 (3H, d, J 6.0Hz, 5"-Me), 1.18 (3H, d, J 6.0 Hz, 5'-Me), 0.95-0.86 (9H, m, 24-Me, 26-Me, 28-H_3), 0.79 (3H, d, J 7.0 Hz, 12-Me); m/z 878 (M^+), 221($C_{14}H_{20}O_2^+$), 207, 193($C_{13}H_{19}O^+$), 173, 151; (Found C, 68.16; H, 8.00. $C_{50}H_{70}O_{13}$ requires C, 68.3; H, 8.0%). More polar: (80), $[\alpha]_D^{20}$ +105.5° (c= 0.15, $CHCl_3$); ν_{max}(film) 3500, 1718, 1603 and 1116 cm^{-1}, δ (400 MHz) +COSY 8.10 (2H, d, Ph(o)), 7.58 (1H, tt, Ph(p)), 7.46 (2H, m, Ph(m)), 6.74 (1H, d, J 2 Hz, 3-H), 5.96 (1H, m, 9-H), 5.24 (1H, dd, J 9.5 and 2.0 Hz, 5-H), 4.70 (1H, s, 7-OH), 4,61 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B), 4.49 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_A), 4.19 (1H, d, J 2.0 Hz, 6-H), 4.13 (2H, m, 10-H2), 3.81 (3H, s, 1-OMe), 3.05 (1H, m, 4-H), 1.60 (1H, s, 10-OH), 1.22

(3H, d, J 7.0 Hz, 4-Me); m/z 356 (M^+-H_2O), 279 (M^+-H_2O-Ph), 105 ($PhCO^+$), 77 (Ph^+); (Found: C, 64.05; H, 5.97, $C_{20}H_{22}O_7$ requires C, 64.2; H 5.9%).

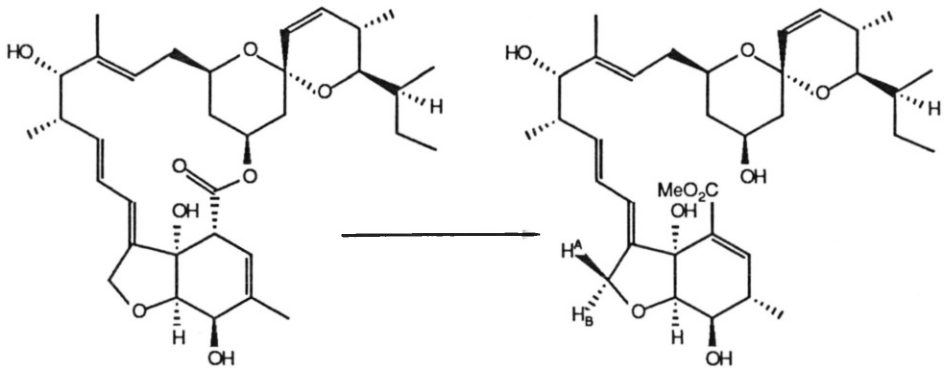
4. Preparation of Avermectin B_{1a} aglycone (81)



Avermectin B_{1a} (65) (2.0 g, 2.29 mmol) in THF (100 ml) at 0°C was treated with a mixture of conc. H_2SO_4 (29 g), water (20 ml), THF (130 ml) and then brought to reflux. T.l.c after 40 min. showed complete consumption of starting material and monosaccharide. The mixture was cooled to 0°C, solid sodium hydrogencarbonate was added carefully until neutral pH and the mixture was filtered through celite, eluting with ethyl acetate. The filtrate was evaporated *in vacuo*. Flash chromatography (40% ethyl acetate-petrol) afforded the aglycone (81) (0.804 g, 60%), as a yellow foam. $[\alpha]_D^{25}$+88.7° (c= 3.8, $CHCl_3$); ν_{max}(film) 3454, 2962, 2926, 2874, 1710,1182, 1160,995 and 733 cm^{-1}; δ (500 MHz) 5.83 (1H, d, J 10 Hz, 9-H), 5.76 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.70-5.77 (2H, m, 10-H, 11-H), 5.54 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.41 (1H, m, 3-H), 5.35 (1H, m,

15-H), 4.68 (2H, 2xdd, J 14.0 and 2.0 Hz, 8_{α}-H_2), 4.29 (1H, d, J 6 Hz, 5-H), 4.00 (1H, m, 13-H), 3.96 (1H, d, J 6.0 Hz, 6-H), 3.87 (1H, m, 17-H), 3.46 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.27 (1H, q, J 2.0 Hz, 2-H), 2.53 (1H, m, 12-H), 2.35-2.20 (5H, obs m, 16-H_2, 24-H, 5-OH, 13-OH), 2.20 (1H, ddd, J 12.0, 5.0 and 1.5 Hz, 20-H_e), 1.86 (3H, m, 4-Me), 1.77 (1H, ddd, J 12.5 Hz, 18H_e), 1.59 (1H, m, J 7 Hz, 26-H), 1.70 (3H, m, 14-Me), 1.49 (2H, m, J 7.0 Hz, 27-H_2), 1.46 (1H, m, J 12.0 Hz, 20-H_a), 1.16 (3H, d, J 7.0, 12-Me), 0.96 (3H, t, J 7.0 Hz, 28-H_3), 0.915 (3H, d, J 7.0 Hz, 24-Me), 0.915 (3H, d, J 7Hz, 26-Me), 0.85 (1H, q, J 12.0 Hz, 18-H_a); m/z 584 (M^+), 566 (M^+-H_2O), 305 ($C_{20}H_{31}O_3^+$), 291, 261, 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$), 169 ($C_{10}H_{17}O_2^+$).

5. Preparation of 19-hydroxy-1-methoxycarbonyl-Δ^2-avermectin B_{1a} aglycone (82).

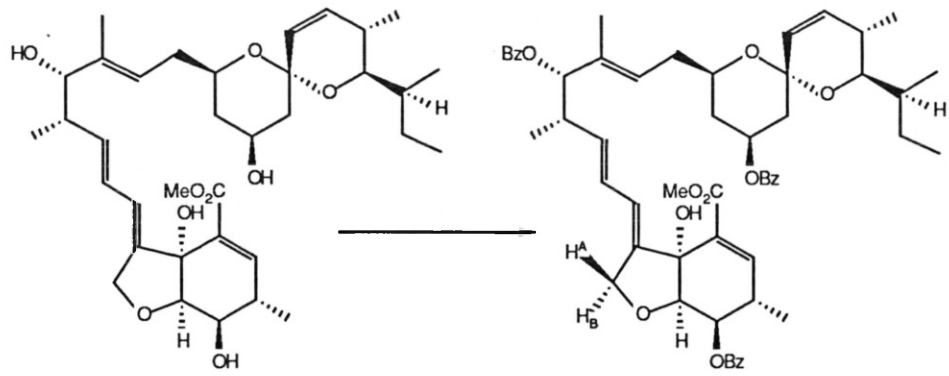


(81) (82)

A solution of aglycone (81) (3.88g, 6.64 mmol) in DME (50 ml) was treated

dropwise with aqueous potassium hydroxide (1.0 M, 23 ml, 23 mmol). After stirring for 69h at r.t., the mixture was cooled to 0°C and diluted with THF (250 ml). 6M HCl was added until the solution was at pH 2. Solid sodium chloride was added and the organic layer decanted, dried ($MgSO_4$) and concentrated *in vacuo* (ca. 100 ml). Diazomethane was bubbled through this solution until the carboxylic acid present had reacted (t.l.c.). The solvent was evaporated *in vacuo*. Flash chromatography (60% ethyl acetate-petrol) afforded the aglycone seco ester (82) (2.95g, 72%) as a yellow foam. $[\alpha]_D^{20}$ +96.2° (c=0.47,$CHCl_3$); ν_{max}(film) 3430, 3034, 2961, 2929, 2876, 1700, 1630, 1452, 1378, 1272, 1148, 1120, 1096, 1070, 1033, 985 and 861 cm^{-1}; δ (400 MHz) + COSY, 6.65 (1H, d, J 2.0 Hz, 3-H), 6.33 (1H, dt, J 11.0 and 2.0 Hz, 9-H), 5.97 (1H, dd, J15.0 and 11.0 Hz, 10-H), 5.75-5.67 (2H, m, 11-H, 22-H), 5.56 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.42 (1H, t, J 7.0 Hz, 15-H), 4.81 (1H, br.s, 7-OH), 4.66 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B), 4.51 (1H,dd, J 14.0 and 2.0 Hz, 8_α-H_A), 4.13 (1H, tt, J 11.0 and 4.5 Hz, 19-H), 4.05 (1H, d, J 2.5 Hz, 6-H), 3.80 (1H, m, 17-H), 3.79 (3H, s, 1-OMe), 3.71 (1H, m, J 8.5 Hz, 13-H), 3.56 (1H, dd, J 9.5 and 2.5 Hz, 5-H), 3.41 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.60 (1H, m, 4-H), 2.44-2.31 (2H, m, 12-H, 16-H), 2.27-2.18 (2H, m, 16-H, 24-H), 2.07-1.67 (5H, m, 18-H_e,20-H_e, 5-OH, 13-OH, 19-OH), 1.62 (3H, s, 14-Me), 1.57 (1H, m, 26-H), 1.47-1.34 (3H, m, 20-H_a, 27-CH_2), 1.26 (3H, d, J 7.0 Hz, 4-Me), 1.19-1.10 (1H, q, J 12.0 Hz, 18-H_a), 0.95-0.86 (12H, m, 12-Me, 24-Me, 26-Me, 28-H_3); m/z 616 (M^+), 457, 129; (Found: M+Na^+, 639.3532. $C_{35}H_{52}O_9Na$ requires M, 639.3509).

6. Preparation of 5,13,19-tribenzoyloxy-1-methoxycarbonyl-Δ^2-avermectinB$_{1a}$ aglycone (83).

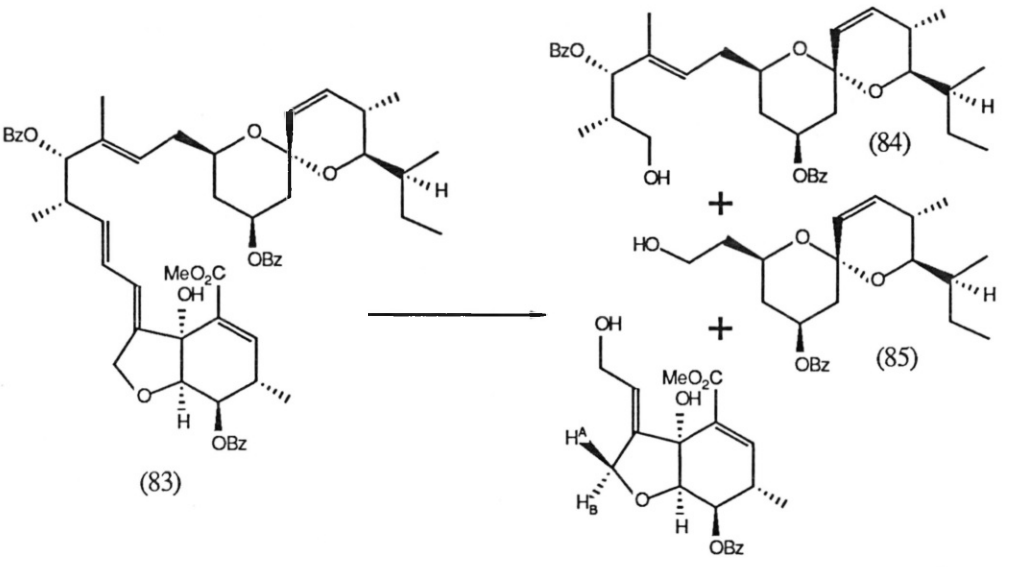


(82) (83)

To a solution of the aglycone seco ester (82) (73 mg, 0.188 mmol) and DMAP (5 mg, 0.041 mmol) in dry pyridine (2.5 ml) at 0°C under argon was added dropwise benzoyl chloride (0.05 ml, 0.426 mmol). The mixture was left stirring at r.t. for 8h, after which time it was cooled to 0°C; 3-dimethylaminopropyl (0.053 ml, 0.425 mmol) was added and the mixture stirred at r.t. for 30 min. The mixture was poured into 1 M HCl and extracted with ether. The combined organic extracts were washed with saturated sodium hydrogencarbonate, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (25% ether-petrol) afforded the tribenzoyloxy aglycone seco ester (83) (99 mg, 90%) as a white foam. $[\alpha]_D^{20}$ +158.6° (c= 0.86, $CHCl_3$); ν_{max}(film) 3510, 2959, 1715, 1602, 1450 and 1115 cm^{-1}; δ (500 MHz) + COSY, 6.61 (1H, d, J 2.0 Hz, 3-H), 6.20 (1H, m, 9-H), 5.85 (1H, dd, J 15.0 and 11.0 Hz, 10-H), 5.73-5.63 (3H, m, 11-H, 15-H, 22-H), 5.54 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.42 (1H, tt, J 11.0 and 4.5 Hz, 19-H),

5.21 (1H, d, J 8.25 Hz, 13-H), 5.19 (1H, dd, J 9.75 and 2.25 Hz, 5-H), 4.55 (1H, s, 7-OH), 4.54 (1H, dd, J 14.0 and 2.0 Hz, 8_{α}-H_B), 4.24 (1H, dd, J 14.0 and 2.0 Hz, 8_{α}-H_A), 4.13 (1H, d, J 2.25 Hz, 6-H), 3.94 (1H, m, 17-H), 3.67(3-H, s, 1-OMe), 3.39 (1H, dd, J 10.0 and1.5 Hz, 25-H), 2.99 (1H, m, 4-H), 2.67 (1H, m, 12-H), 2.34-2.21 (3H, m, 16-H_2, 24-H), 2.18-2.11 (2H, m, 18-H_e, 20-H_e), 1.68 (3H, s, 14-Me), 1.66-1.50 (3H, m, 18-H_a, 20-H_a, 26-H), 1.41 (2H, m, 27-CH_2), 1.19 (3H, d, J 7.5 Hz, 4-Me), 1.10 (3H, d, J 7.5 Hz, 12-Me), 0.91-0.83 (9H, m, 24-Me, 26-Me, 28-H_3); m/z 928 (M^+), 912, 808, 686; (Found: M+Na^+, 951.4333. $C_{56}H_{64}O_{12}Na$ requires 951.4295).

7. Preparation of 13,19-benzoyloxy-11-hydroxy-avermectin B_{1a} aglycone northern hemisphere (84), 19-benzoyloxy-15-hydroxy-avermectin B_{1a}-dioxaspiroundecene (85) and 1-methoxycarbonyl-5-benzoyloxy-10-hydroxy-Δ^2-avermectin B_{1a} benzofuran (80).

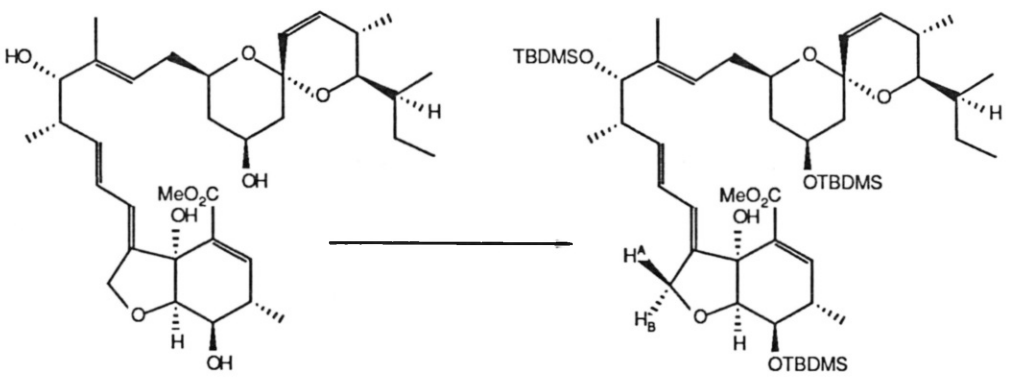


To a magnetically stirred solution of diene (83) (50 mg, 0.0538 mmol) in DCM (1.8 ml) and ethanol (1.0 ml) was added a pinch of Sudan Red 7B dye so as to give a pale pink solution. The solution was cooled to -78°C and ozone (50 $lmin^{-1}$, 80 V, Wallace and Tierman Ozonator) was bubbled through. The reaction was monitored by t.l.c., as the indicator decolourised well before the starting material had disappeared. Upon complete consumption of starting material (1 h.) the solution was purged with argon for 10 min. and solid sodium borohydride (20 mg, 0.538 mmol) was added in one portion at -78°C. The solution was stirred at -78°C for 25 min., -30°C for 15 min. and at r.t. (ca. 15 min.) until no ozonides were seen by

t.l.c. The solution was cooled to 0°C, and ice-cold 1M HCl was added dropwise until it was at pH 6. The mixture was buffered with aq. KH_2PO_4 and extracted with DCM. The combined organics were washed with saturated sodium hydrogencarbonate, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (20% ether-petrol gradient to 40% ethyl acetate-petrol to give (84) and (85) and 50% ethyl acetate-petrol to give (80)) afforded the northern aglycone alcohol (84) (7.82 mg, 25%) as a white foam, the over ozonised spiroacetal portion (85) (10.94 mg,56%) as a clear oil and the southern alcohol (80) (12.35 mg, 62%) as a wite foam. Less polar: (85), $[\alpha]_D^{20}$ +54.9 (c= 0.45, $CHCl_3$); ν_{max}(film) 3510, 2922, 2852, 1716, 1602, 1450, 1378, 1273, 1217, 1162, 1112, 1070, 1026, 993 and 737 cm^{-1}; δ (400 MHz) 8.02 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.65 (1H, br.t, J 7.5 Hz, 15-H), 5.57 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.44 (1H, tt, J 11.0 and 5 Hz, 19-H), 5.34 (1H, d, J 9.5 Hz, 13-H), 3.96 (1H, m, 17-H), 3.61 (2H, m, 11-H_2), 3.41 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.40-2.05 (6H, m, 12-H, 16-H_2, 18-H_e, 20-H_e, 24-H), 1.76 (3H, s, 14-Me), 1.64 (1H, s, 11-OH), 1.54 (1H, m, 26-H), 1.45- 1.35 (3H, obs.m, 18-H_a, 27-H_2), 0.90 (3H, d, J 7 Hz, 12-Me) 0.91-0.85 (9H, m, 24-Me, 26-Me, 28-H_3); m/z 608 ($M+NH_4^+$), 591 ($M+H^+$), 573 ($M+H^+-H_2O$), 486 ($M+NH_4^+-PhCO_2H$) 383, 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$); (Found: C, 73.04; H, 7.82. $C_{36}H_{46}O_7$ requires C, 73.2; H, 7.8%). More polar: (84) ν_{max}(film) 3460, 2960, 1716, 1602, 1450, 1380 and 1273 cm^{-1}; δ (400 Mz) 8.02 (2H, d Ph(o)), 7.56 (1H, t, Ph(p)), 7.44 (2H, t, Ph(m)), 5.76 (1H,dd, J 10.0 and 2.0 Hz, 22-H), 5.59 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.46 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 4.19 (1H, m, 17-H), 3.81 (2H, m, 15-H_2), 3.40 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.28 (1H, m, 24-H), 2.18 (1H,

dd, J 12.0 and 4.5 Hz, 20-H_e), 2.00-1.70 (5H, m, 15-OH, 16-H_2, 18-H_e, 20-H_a), 1.62 (1H, m, 26-H), 1.50 (3H, m, 18-H_a, 27-H_2), 0.99 (3H, t, J 7.0 Hz, 28-H_3), 0.94 (3H, d, J 7.2 Hz, 24-Me), 0.93 (3H, d, J 6.9 Hz, 26-Me). Most polar: (80) Identical in all respects to previously obtained sample.

8. Preparation of 5,13,19-tri-t-butyldimethylsilyloxy-1-methoxycarbonyl-Δ^2-avermectin B1a aglycone (87).[35]

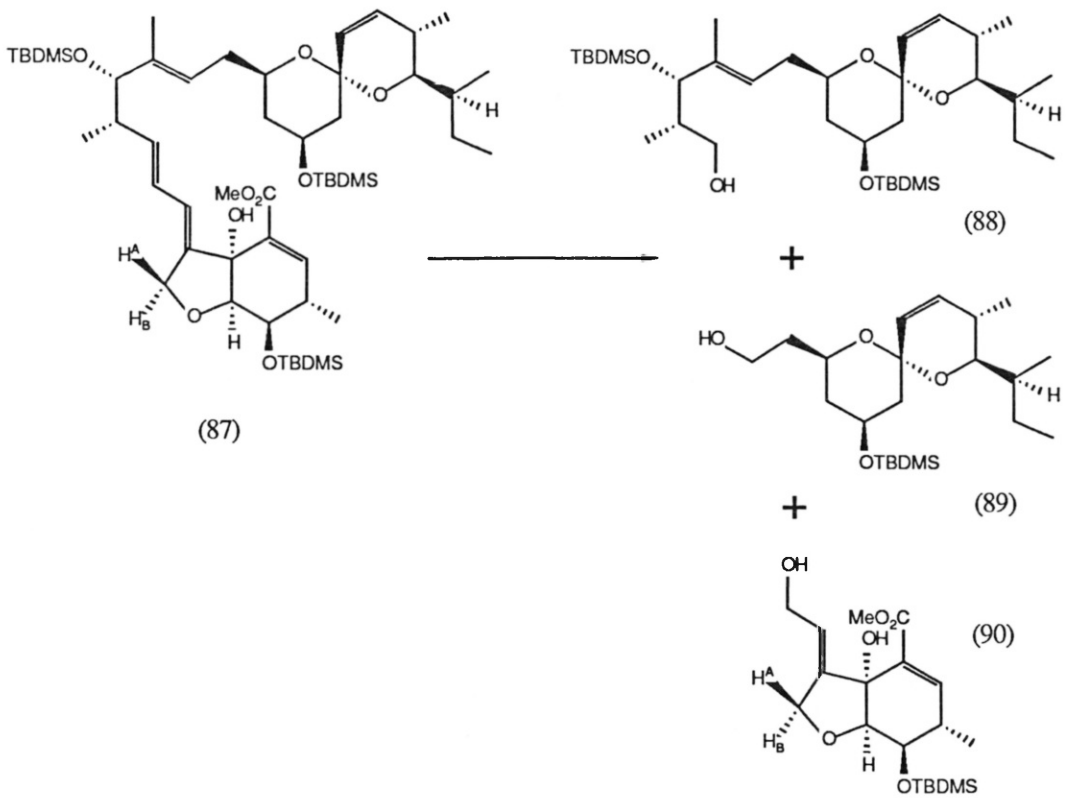


(82) (87)

The aglycone seco ester (82) (1.67 g, 2.71 mmol) in dry DMF (15 ml) under argon was treated with imidazole (1.75 g, 25.7 mmol), TBDMS-Cl (1.63 g, 10.8 mmol) and DMAP (0.132 g, 1.08 mmol) at room temperature. The solution was stirred at r.t. over night and then cooled to 0°C prior to the addition of water (100 ml) and ether (6x30 ml). The organic layer was separated and the aqueous layer extracted with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (5% ether-petrol gradient to 10% ether-petrol) affordeed the tri

TBDMS ester (87) (75%, 1.94 g) as a white foam. ν_{max}(film) 3520, 2960, 2860, 1705, 1465, 1385, 1255 and 1080 cm^{-1}; δ (500 MHz) 6.60 (1H, d, J 1.7 Hz, 3-H), 6.23 (1H, dt, J 11.0 and 1.7 Hz, 9-H), 5.82 (1H, dd, J 15.0 and 10.0 Hz, 10-H), 5.68 (1H, dd, J 10.0 and 1.7 Hz, 22-H), 5.61 (1H, dd, J 15.0 and 8.7 Hz, 11-H). 5.55 (1H, dd, J 10.0 and 2.5, 23-H), 5.25 (1H, br.t, J 6.7 Hz, 15-H), 4.65 (1H, s, 7-OH), 4.64 (1H, dd, J 13.5 and 1.7 Hz, 8_{α}-H_B), 4.46 (1H, dd, J 13.5 and 1.7 Hz, 8_{α}-H_A), 4.10 (1H, m, 17-H), 3.74 (3H, s, 1-OMe), 3.66 (1H, dd, J 9.5 and 2.0 Hz, 5-H), 3.59 (1H, d, J 9.0 Hz, 13-H), 3.40 (1H, dd, J 9.5 and 1.8 Hz, 25-H), 2.72 (1H, m, 4-H), 2.38-2.09 (4H, m, 12-H, 18-H_e, 20-H_e, 24-H), 1.91-1.80 (2H, m, 16-H), 1.60-1.54 (1H, m, 26-H), 1.54 (3H, br.s, 14-Me), 1.48-1.33 (4H, 18-H_a, 20-H_a, 27-H_2), 1,18 (3H, d, J 7.2 Hz, 4-Me), 0.98-0.75 (12H, obs.m, 12-Me, 24-Me, 26-Me, 28-H_3), 0.94, 0.87 and 0.80 (9H each, 3s, -Si^{t}Bu), 0.13, 0.12, 0.06, 0.05, -0.07 and -0.08 (3H each, 6s, -SiMe); m/z 941 (M^+-H_2O), 902 (M^+-^{t}Bu), 884 (M^+-H_2O-^{t}Bu), 751, 551, 353, 187.

9. Preparation of 13,19-di^{t}Butyldimethylsilyloxy-11-hydroxy-avermectin B_{1a}-aglycone northern hemisphere (88), 19-^{t}butyldimethylsilyloxy-15-hydroxy-avermectin B_{1a} dioxaspiroundecene portion (89) and 5-^{t}butyldimethylsilyloxy-10-hydroxy-1-methoxycarbonyl-Δ^{2}-avermectin B_{1a}-benzofuran (90).

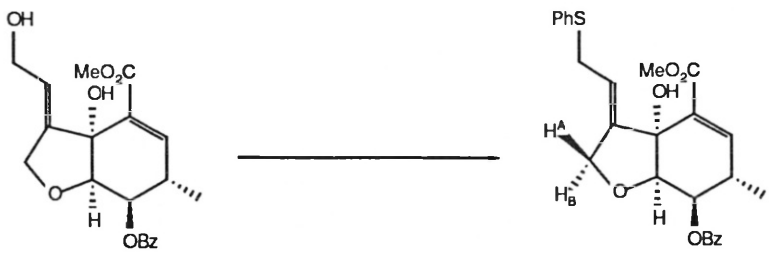


To a magnetically stirred solution of diene (87) (1.942 g, 2 mmol) in DCM (68 ml) and ethanol (37 ml) was added a pinch of Sudan Red 7B dye so as to give a pale pink solution. The solution was cooled to -78°°C and ozone (50 lmin-1, 80 V, Wallace and Tierman Ozonator) was bubbled through. The reaction was monitored by colour change of the indicator dye. As the solution decolourised (ca. 4.25h).

t.l.c's were taken every 5 min until complete consumption (4.5h) of starting material. The solution was purged with argon for 10 mins and solid sodium borohydride (0.77g, 20.2mmol) was added in one portion at -78°C. The stirrerd solution was allowed to warm to 0°C over 1h, and then stirred at r.t. for 40 min. The solution was cooled to 0°C, and ice cold 1M HCl was added dropwise until it was at pH6. The mixture was buffered with aq. KH_2PO_4 and extracted with DCM. The combined organics were washed with saturated sodium hydrogencarbonate, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (8% ethyl acetate-petrol to give (88), 20% ethyl acetate-petrol to give (89) and 50% ethyl acetate - petrol to give (90)) afforded DiTBDMS northern hemisphere (88) (87%, 1.072 g), over-ozonised monoTBDMS spiroacetal (88) (6%, 0.0509g) and the monoTBDMS southern hemisphere (90) (85%, 0.662 g) as viscous clear oils. Less polar: (88) $[\alpha]_D^{25}$ +38.1 (c= 1.0, $CHCl_3$); ν_{max}(film) 3471, 2930, 2830, 2857, 1461, 1381, 1254, 1155, 1117, 1076, 999 and 874 cm-1, δ (500 MHz) 5.69 (1H, dd, J 10.0 and 1,8 Hz, 22-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.34 (1H, br.t, J 6.5 Hz, 15-H), 4.11 (1H, tt, J 11.5 and 4.5 Hz, 19-H), 3.85 (1H, d, J 8.0 Hz, 13-H), 3.76 (1H, m, 17-H), 3.61 (2H, m, 11-H_2), 3.39 (1H, dd, J 10.0 and 2.0 Hz, 25-H), 2.90 (1H, br.s, 11-OH), 2.38-2.12 (3H, m, 16-H_2, 24-H), 1.90-1.80 (3H, m, 12-H, 18-H_e, 20-H_e), 1.58 (3H, s, 14-Me), 1.60-1.50 (1H, m, 26-H), 1.48-1.30 (3H, m, 20-H_a, 27-H_2), 1.20 (1H, q, J 11.0 Hz, 18-H_a), 0.93 (3H, t, J 7.0 Hz, 28-H_3), 0.90 (3H, d, J 7.0 Hz, 24-Me), 0.90 and 0.88 (9H each, 2s, Si^{t}Bu), 0.86 (3H, d, J 6.5 Hz, 26-Me), 0.77 (3H, d, J 7 Hz, 12-Me), 0.09, 0.06, 0.05 and 0.00 (3H each, 4s, $SiMe_3$). More polar: (89) ν_{max}(film) 3409, 2930, 1461, 1383, 1255, 1157, 1117, 1076, 997, 872, 836, 775 and 663 cm^{-1}; δ (500 MHz) 5.69 (1H, dd,

J 10.0 and 1.8 Hz, 22-H), 5.52 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 4.12 (1H, tt, J 11.0 and 4.5 Hz, 19-H), 3.89 (1H, m ,17-H), 3,75 (2H, m, 15-H_2), 3.32 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.89 (1H, br.s, 15-OH), 2.24 (1H, m, 24-H) , 1.88 (1H, ddd, J 11.0, 4.5 and 2.0 Hz), 1.84-1.66 (3H, m, 16-H2, 20-He), 1.58 (1H, m, 26-H), 1.50-1.40 (2H, m, 27-H_2), 1.24 (1H, q, J 11.0 Hz, 18-H_a), 0.96 (3H, t, J 7.5 Hz, 28-H_3), 0.91 (3H, d, J 7.0 Hz, 24-Me), 0.89 (9H, s, Si^{t}Bu), 0.88 (3H, d, J 7.0 Hz, 26-Me), 0.07 and 0.07 (3H each, 2s, SiMe). Most polar: (90) ν_{max}(film) 3492, 2954, 2930, 2857, 1700, 1249, 1129 and 1074 cm^{-1}; δ (500 MHz) 6.65 (1H, d, J 2.0 Hz, 3-H), 5.90 (1H, tt, J 7.0 and 2.5 Hz, (-H), 4.70 (1H, s, 7-OH), 4.58 (1H, dd, J 14.0 and 2.5 Hz, 8α-H_B), 4.42 (1H, dd, J 14.0 and 2.5 Hz, 8α-H_A), 4.14-4.07 (2H, 2xdd, J 13.5 and 7.0 Hz, 10-H_2), 3.92 (1H, d, J 2.0 Hz, 6-H), 3.77 (3H, s, 1-OMe), 3.65 (1H, dd, J 9.0 and 2.0 Hz, 5-H), 2.71 (1H, m, 4-H), 1.17 (3H, d, J 7.0 Hz, 4-Me), 0.92 (9H, s, Si^{t}Bu), 0.12 and 0.11 (6H, 2s, SiMe).

10. Preparation of 5-benzoyloxy-1-methoxycarbonyl-10-phenylthio-Δ^2-avermectin B_{1a} benzofuran (93).

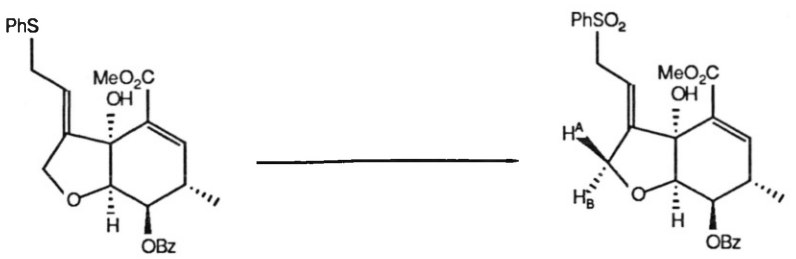


(80) (93)

Tri ^{n}butylphosphine (1.2 g, 3.21 mmol) followed by the alcohol (80) (1.6 ml, 6.42 mmol) in dry THF (14.5 ml) was added dropwise to diphenylsulphide (1.4 g, 6.42 mmol) in dry THF (14.5 ml) under argon at 0°C. After stirring at r.t. for 4h. it was poured into water overlayed with ether. The aqueous phase was extracted with ether. The aqueous phase was extracted with ether, the combined organics were washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (45% ether-petrol) afforded the sulphide (93) (1.42 g, 95%) as a white solid. M.p. 113-114 °C; $[\alpha]_D^{20}$ +173.1° (c= 0.87, $CHCl_3$); ν_{max}(film) 3497, 1718, 1635, 1601, 1583, 1116, 1070, 1027, 874, 711, 690 and 662 cm^{-1}; δ (400 MHz) 8.09 (2H, dd, J 8.0 Hz, PhCO(o)), 7.60-7.20 (8H, m, PhCO(m),(p), PhS), 6.68 (1H, d, J 2.0 Hz, 3-H), 5.90 (1H, tt, J 8.0 and 2.5 Hz, 9-H), 5.19 (1H, dd, J 10.0 and 2.0 Hz, 5-H), 4.65 (1H, s, 7-OH), 4.30 (1H, dd, J 13.5 and 2,0 Hz, 8_α-H_B), 4.10 (1H, dd, J 13.5 and 2.0 Hz, 8_α-H_A), 4.11 (1H, d, J 2.0 Hz, 6-H), 3.79 (3H, s, 1-OMe), 3.42, 3.34 (2H, 2xdd, J 13.0 and 8.0 Hz, 10-H2), 2.99 (1H, m, 4-H), 1.19 (3H, d, J 7.0Hz, 4-Me); m/z 356 (M^+-PhSH), 110

(PhSH), 105 $PhCO^+$), 77 (Ph^+); (Found: M^+, 356.1260. $C_{20}H_{20}O_6$ requires M, 356.1272).

11. Preparation of 5-benzoyloxy-1-methoxycarbonyl-10-phenylsulphonyl-Δ^2-avermectin B_{1a} benzofuran (94).

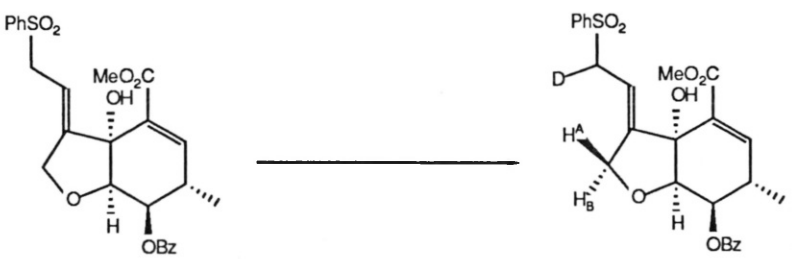


(93) (94)

pH4 buffer (0.2 ml) was added to the sulphide (93) (1.4 g, 3.0 mmol) in methanol (12 ml) and THF (12 ml). The solution was cooled to 0°C and a solution of oxone ®(2.77 g, 9 mmol) in water (12 ml) was added dropwise over 30 min. The resulting cloudy slurry was stirred at r.t. for 3h. (By t.l.c. conversion to sulphoxide was rapid, but to sulphone was slower). The solution was diluted with water, extracted with DCM and the combined organics washed with water, brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (90% ether-petrol) afforded the sulphone (94) (1.473 g, 99%) as a white solid. M.p. 137 °C; $[\alpha]_D^{20}$ +132.9° (c= 0.87, $CHCl_3$); ν_{max}(film) 3506, 3049, 2960, 1718, 1605, 1153, 1115, 1071, 1027, 901 and 767 cm^{-1}; The stereochemistry at C-4 of this compound was proved by an X-RAY (see Appendix + results and discussion) δ (500 MHz)

8.05-7.40 (10H, m, Ph), 6.66 (1H, d, J 1.8 Hz, 3-H), 5.81 (1H, tt, J 9.0 and 2.5 Hz, 9-H), 5.15 (1H, dd, J 10.0 and 2.0 Hz, 5-H), 4.68 (1H, s, 7-OH), 4.10 (1H,dd, J 14.0 and 2.0 Hz, 8α-H_B), 4.03 (1H, d, J 2.0 Hz, 6-H), 3.88 (1H,dd, J 14.0 and 2.0 Hz, 8α-H_A), 3.90 (3H, s, 1-OMe), 3.75 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 3.61 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 2.96 (1H, m, 4-H), 1.19 (3H, d, J 7.4 Hz, 4-Me); m/z 376 (M^+-$PhCO_2H$), 356 (M-$PhSO_2H$), 105 ($PhCO^+$), 77 (Ph^+); (Found; C, 62.68; H, 5.13. $C_{26}H_{26}O_8S$ requires C, 62.6; H,5.3%.).

12. Preparation of 5-benzoyloxy-10-deutero-1-methoxycarbonyl-10-phenylsulphonyl-Δ^2-avermectin B_{1a} benzofuran (94b).



(94) (94b)

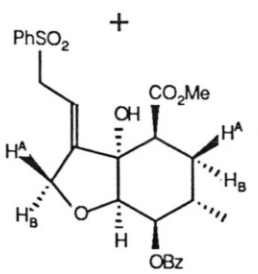
^{n}BuLi (0.090 ml, 0.221 mmol) was added dropwise at -78°C to the sulphone (94) (50 mg, 0.1003 mmol) in dry THF (1 ml). The deep orange solution was stirred for 20 min at -78°C before being quenched with D_2O (0.004 ml) and then warmed to r.t. As the solution warmed up the deep orange colour faded to give a yellow solution. Ether and saturated ammonium chloride solution were added and then aqueous phase extracted with ether. The combined organics were dried

($MgSO_4$) and evaporated *in vacuo* to a white foam (94b) (40 mg, 90%). δ (500 MHz) 8.10-7.40 (10H, m, Ph), 6.69 (!h, d, J 2.2 Hz, 3-H), 5.80 (1H, dt, J 8.0 and 2.0 Hz, 9-H), 5.14 (1H, dd, J 10.0 and 2.0 Hz, 5-H), 4.62 (1H, s, 7-OH), 4.08 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B), 4.02 (1H, br.s, 6-H), 3.88 (1H, m, 8_α-H_A), 3.85 (3H, s, 1-OMe), 3.72 (1H, d, J 8.0 Hz, 10-H), 2.82 (1H, m, 4-H), 1.14 (3H, d, J 7.5 Hz, 4-Me); m/z 357 (M^+-$PhSO_2H$), 340, 105 ($PhCO^+$), 77 (Ph^+).

13. Preparation of 5-benzoyloxy-1-methoxycarbonyl-10-phenylsulphonyl-2α-3,4-dihydro avermectin B_{1a} benzofuran (95) and 5-benzoyloxy-1-methoxycarbonyl-10-phenylsulphonyl-2β-3,4-dihydro avermectin B_{1a}-benzofuran (96)



(94) (95)

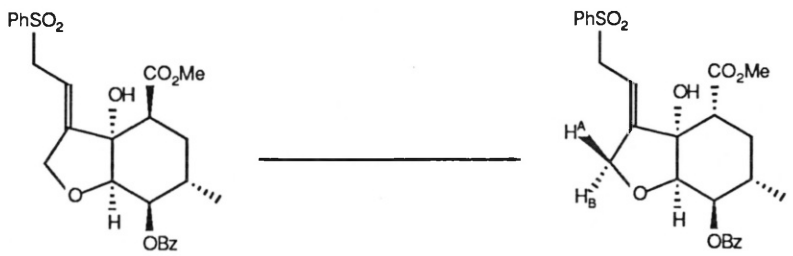


(96)

The α,β-unsaturated ester (94) (1.345 g, 2.70 mmol) was dissolved in dry methanol (80 ml) under argon and solid sodium borohydride (2.654 g, 70.1 mmol) was added in two portions (t= 0 ~ 1.0 g, t= 1h ~ 1.654 g) at 0°C and once effervesence had ceased the mixture was brought to r.t. and stirred for a total of 1h 30min, at which time t.l.c. analysis showed complete consumption of starting material. The mixture was cooled to 0°C and 1M MCl was added dropwise until the mixture was pH3-4. The mixture was buffered with aq. KH_2PO_4 and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated *in*

vacuo. Flash chromatography (70% ether-petrol) afforded the α-ester (95) (0.509 g) and the β-ester (96) (0.471 g) (Total yield 73%: n.m.r ratio α:β, 1.38:1) as white foams. Less polar: (95) $[\alpha]_D^{20}$ +46.1° (c= 0.21, $CHCl_3$); ν_{max}(film) 3478, 2961, 1714, 1583 and 1150 cm^{-1}; δ (500 MHz) 8.08-7.45 (10H, m, Ph), 5.44 (1H, tt, J 8.0 and 2.5 Hz, (-H), 5.10 (1H, dd, J 11.5 and 3.5 Hz, 5-H), 5.08 (1H, s, 7-OH), 4.07 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B), 4.00 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_A), 3.83 (3H, s, 1-Me), 3.81 (1H, d, 6-H), 3.73 (1H, dd, J 14.0 and 7.5 Hz, 10-H), 3.56 (1H, dd, J 14.0 and 7.5 Hz, 10-H), 2.62 (1H, dd, J 13.0 and 3.5 Hz, 2-H). 2.23 (1H, m, 4-H), 1.92 (1H, dt, J 13.0 and 3.5 Hz, 3-H_A), 1,79 (1H, q, J 13.0 Hz, 3-H_B), 1.01 (3H, d, J 7 Hz, 4-Me); m/z 469 (M^+-OMe), 378 (M^+-$PhCO_2H$), 105 ($PhCO^+$), 77 (Ph^+); (Found: C, 62.52; H, 5.62, $C_{26}H_{28}O_8S$ requires C, 62.4; H,5.6%). The stereochemistry at C-1 was proved by X-RAY (see Appendix + results and discussion). More polar; (96) $[\alpha]_D^{20}$ +4.6° (c= 0.43, $CHCl_3$); ν_{max}(film) 3462, 2962, 1716, 1585 and 1150 cm^{-1}; δ (500 MHz) 7.98-7.40 (10H, m, Ph), 5.81 (1H, tt, J 8.0 and 2.5 Hz, 9-H), 5.16 (1H, dd, J 8.0 and 3.5 Hz, 5-H), 4.05 (1H, dd J 14.0 and 2.0 Hz, 8_α-H_B), 4.03 (1H, s, 7-OH), 3.93 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_A), 3.83 (3H, s, 1-OMe), 3.83 (1H, d, 6-H), 3.72 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 3.60 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 3.01 (1H, dd, J 12.0 and 3.5 Hz, 2-H), 2.34 (1H, m, 4-H), 1.95 (1H, ddd, 14.5, 12.0 and 6 Hz, 3-H_A), 1.73 (1H, dt, J 14.5 and 3.5 Hz, 3-H_B), 1.08 (3H, d, J 7.5 Hz, 4-Me); m/z 500 (M^+), 482 (M^+H_2O), 378 (M^+-$PhCO_2H$), 359, 341; (Found;M^+, 482.1408. $C_{26}H_{26}O_7S$ requires M, 482.1399).

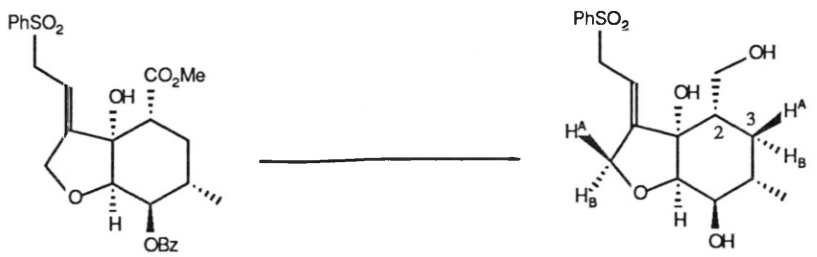
14. Preparation of 5-benzoyloxy-1-methoxycarbonyl-10-phenylsulphonyl-2α-,4-dihydro avermectin B_{1a} benzofuran (95)



(96) (95)

The β-methyl ester (96) (0.471 g, 0.94 mmol) was azeotropically dried with toluene and then dissolved in dry DCM (5 ml) under argon. DBU (2.2 ml, excess) was added at r.t. and the mixture left stirring until t.l.c. showed complete conversion to a-ester (~4 days). The mixture was cooled to 0°C and 1M HCl added. The aqueous solution was extrcted with DCM and the combined organics dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (70% ether-petrol) afforded the α-ester (95) (0.282 g, 60%) as a white foam. Identical in all respects to previously obtained sample.

15. Preparation of 1-hydroxy-2α–3,4-dihydro-5-hydroxy-10-phenylsulphonyl-avermectin B_{1a} benzofuran (97)



(95) (97)

To LAH (0.183 g, 4.22 mmol) in dry THF (4 ml) under argon at 0°C was added a solution of diester (95) (0.125 g, 0.250 mmol) in dry THF (6 ml). The mixture was left stirring at 0°C for 1h 30min., after which time a further 5 eqs. of LAH was added. After a further 30 min. it was cooled to 0°C and ethyl acetate was added followed by saturated sodium sulphate solution and the mixture stirred at r.t. until a cloudy precipitate formed. (Further ethyl acetate and some solid sodium sulphate was added to help the formation of the alums). The mixture was filtered and evaporated *in vacuo*. Flash chromatography (90% ethyl acetate-petrol) afforded the triol (97) (0.675 g, 73%) as a white foam. $[\alpha]_D^{20}$ +34.5° (c= 0.4, $CHCl_3$); ν_{max}(film) 3394, 2925, 2854, 1587 and 1151 cm^{-1}; δ (500 MHz) 7.89-7.55 (5H, m, Ph), 5.52 (1H, tt, J 7.8 and 2 Hz, 9-H), 4.63 (1H, s, 7-OH), 4.20-4.05 (2H, obs.m, 8_α-H_A, 8_α-H_B 1-H), 3.80 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 3.67 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 3.64 (1H, dd, J 11.0 and 2.0 Hz, 1-H), 3.57 (1H, d, J 3.5 Hz, 6-H), 3.42 (1H, br.m, 5-H), 2.88 (1H, br.s, 5-OH), 2.07 (1H, br.s, 1-OH), 1.78 (1H, br,m, 4-H), 1.67 (1H, q, J 13 Hz, 3-H_B), 1.53 (1H, dt, J 13.0

and 3.0 Hz, 3-H_A), 1.39 (1H, br.d, J 13 Hz, 2-H), 1.05 (3H, d, J 6.5 Hz, 4-Me); m/z 368 (M^+), 350 (M^+-H_2O), 208 (M^+-H_2O-$PhSO_2H$); (Found M^+, 350.1188. $C_{18}H_{22}O_5S$ requires M, 350.1188).

16. Preparation of 1-^{t}Butyldiphenylsilyloxy-2α–3,4-dihydro-5-hydroxy-10-phenylsulphonyl-avermectin B_{1a} benzofuran (67)

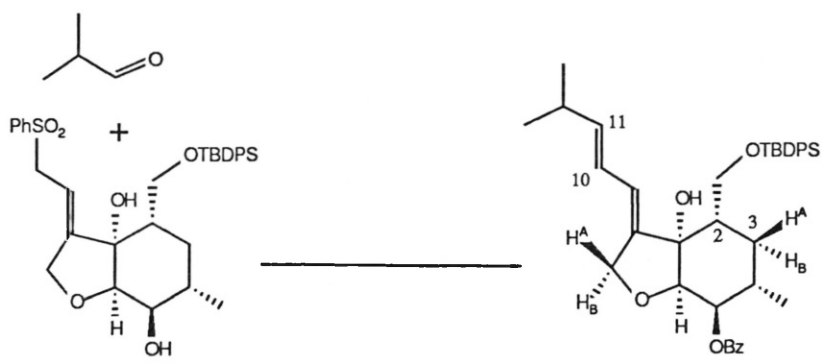


(97) (67)

Triethylamine (0.122 g, 0.873 mmol) followed by TBDPSCl (0.113 mmol, 0.436 mmol) was added to the (97) (0.134 g, 0.364 mmol) in dry DCM (1ml) under argon at 0°C. After stirring at r.t. for 24h ether was added and the mixture poured into water. The aqueous phase was extracted with ether. Salt was added to the aqueous phase to saturate it and it was reextracted with ethyl acetate. The combined organics were washed once with brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (50% ethyl acetate-petrol) afforded the diol sulphone (67) (0.163 g, 74%); $[\alpha]_D^{20}$ +6.9° (c= 0.52, $CHCl_3$); ν_{max}(film) 3436, 2926, 2857, 1587 and 1150 cm^{-1}; δ (500 MHz) 7.80-7.35 (15H, m, Ph), 5.46 (1H, tt, J 8.0 and 2.5 Hz, 9-H), 5.19 (1H, s, 7-OH), 4.08 (1H, dd, J 11.0 and 2.0 Hz, 1-H),

4.04 (1H, dd, J 14.0 and 2.0 Hz, 8_{α}-H_B), 3.95 (1H, dd, J 14.0 and 2.5 Hz, 8_{α}-H_A), 3.75 (1H, dd, J 14.o and 7.5 Hz, 10-H), 3.60-3.55 (3H, m, 10-H, 6-H, 1-H), 3.45 (1H, dt, 5-H), 1.78 (1H, q, J 13.0 Hz, 3-H_B), 1.72 (1H, m, 4-H), 1.66 (1H, d, 5-OH), 1.35 (1H, br.d, J 13.0 Hz, 2-H), 1.27 (1H, dt, J 13.0 and 3.0 Hz, 3-H_A), 1.10 (9H, s, ^{t}BuSi), 1.07 (3H, d, J 6.0 Hz, 4-Me); m/z 549 (M^+-^{t}Bu), 407 (M^+-^{t}Bu-$PhSO_2H$), 389 (M^+-^{t}Bu-$PhSO_2H$-H_2O), 142 ($PhSO_2H^+$); (Found; C, 67.31; H, 6.99. $C_{34}H_{42}O_6SSi$ requires C, 67.3; H, 6.98%).

17. Preparation of (*E*,*E*)-5-benzoyloxy-10-(2-methylpropylidene)-1-^{t}butyldiphenylsilyloxy-2α–3,4-dihydro-avermectin B_{1a} benzofuran (98)



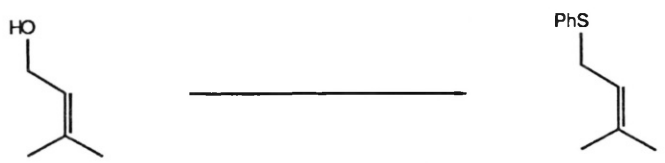
(67) (98)

The diol sulphone (67) (40 mg, 0.0659 mmol) was dissolved in dry THF (0.5 ml) under argon and cooled to -78°C. ^{t}Buli (0.122 ml of a 1.7M pentane solution, 0.208 mmol) was added dropwise over 2 min. After complete addition of base a deep orange viscous liquid formed with traces of insoluble material. Addition

of more dry THF (0.2 ml) did not solubilise this material. T.l.c. of the trianion showed undecomposed starting material. The solution was stirred for a total of 10 min. with the base. Dry and distilled isobutyraldehyde (0.030 ml, 0.330 mmol) in dry THF (0.5 ml) was added mdropwise at -78°C to the trianion. The mixture discoloured slowly to pale yellow after 5 min., and stirring was continued for a further 25 min., followed by quenching with saturated ammonium chloride at -78°C. The pale yellow colour disappeared and the mixture was allowed to come to r.t. Water was added, extracted with ethyl acetate, dried (Na_2SO_4) and evaporated *in vacuo*.Flash chromatography (50% gradient to 70% ethyl acetate-petrol) afforded the diastereomeric hydroxy sulphones (33 mg, 74%). Benzoyl chloride (0.113 ml, 0.972 mmol) was added to the hydroxy sulphones (33 mg, 0.0486 mmol) and DMAP (3 mg, 0.0243 mmol) in dry pyridine (2 ml) under argon at 0°C. After stirring the solution the pink solution at 0°C for 12 h, 3-dimethylaminopropylamine (0.11 ml, 0.874 mmol) was added and the mixture stirred at r.t. for 30 min. It was poured into 1M HCl / DCM and the acid layer extracted *in vacuo*. Flash chromatography (20% ether-petrol) afforded the *E,E*-diene (98) (6.8 mg, 48%) as a foam and the more polar debenzoylated diene (2.5 mg) which on rebenzoylation afforded the *E,E*-diene (98) (2.9mg): Total yield of *E,E*-diene is 69%, 9.7 mg. Overall yield for Julia is 50%. ν_{max}(film) 3451, 3069, 2958, 2930, 2857, 1716, 1602, 1458, 1427, 1270, 1112, 1068, 997 and 872 cm^{-1}; δ (500 MHz) 8.10-7.35 (15-H, m, Ph), 5.92 (1H, dt, J 11.0 and 2.5 Hz, 9-H), 5.76 (1H, dd, J 15.0 and 11.0 Hz, 10-H), 5.60 (1H, dd, J 15.0 and 7.0 Hz), 5.22 (1H, dd, J 11.5 and 3.5 Hz, 5-H), 4.75 (1H, s, 7-OH), 4.58 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B), 4.48 (1H, dd, J 14.0 and 2 Hz, 8_α-H_A), 4.12 (1H, dd, J 11.0 and 2.5 Hz, 1-H), 3.89 (1H, d, J 3.5, 6-H),3.67 (1H, dd, J 11.0 and 2.5 Hz, 1-H), 2.34 (1H, m, 12-H),

2.28 (1H, m, 4-H), 1.99 (1H, q, J 12.5 Hz, 3-H_B), 1.65-1.59 (2H, m, 2-H, 3-H_A), 1.13 (3H, d, J 6.0 Hz, 4-Me), 1.123 (9H, s, ^{t}BuSi), 1.05 (3H, d, J 7 Hz, 12-Me), 1.02 (3H, d, J 7.0 Hz, 12-Me); m/z 609 (M^+-Me), 567 (M^+-^{t}Bu), 445 (M^+-^{t}Bu-$PhCO_2H$); (Found: M, 567.2578; M^+-^{t}Bu requires M^+, 567.2567).

18. Preparation of 3-methyl-2-butenyl-1-phenylsulphide.



Tri-n-butylphosphine (23.5 ml, 0.116 mmol) folowed by 3-methyl-2-buten-1-ol (5g, 0.058 mmol) in dry THF (15 ml) was added to diphenyldisulphide (23.35g, 0.116 mmol) in dry THF (40 ml) at 0°C, under argon. The reaction was stirred at r.t. for 1h and then poured into ether/water (500/200ml). The aqueous phase was extracted with ether and the combined organics washed with 1M NaOH, water, dried ($MgSO_4$) and evaporated *in vacuo*. Distillation of the crude oil afforded the sulphide as a oil (9.57 g, 93%). B.p. 69-70 °C / 0.5 mmHg (lit.[88], 69-70 °C / 0.5 mmHg); ν_{max}(film) 2927, 1665, 1583, 1478 and 1385 cm^{-1}; δ (90 MHz) 7.38-7.12 (5H, m, Ph), 5.30 (1H, app.t, J 7.5 Hz, 2-H), 3.53 (2H, d, J 7.5 Hz, 1H), 1.70, 1.58 (6H. 2s, Me); m/z 178 (M^+), 69 (M^+-PhS).

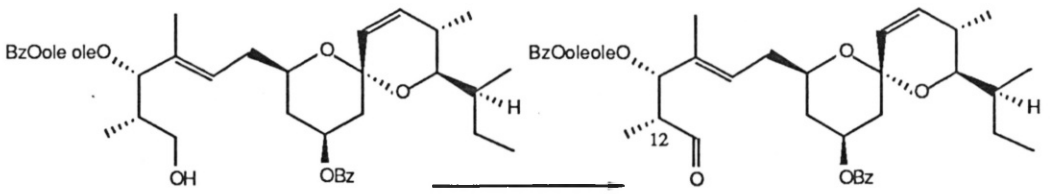
19. Preparation of 3-methyl-2-butenyl-1-phenylsulphone (100).



(100)

pH 4 buffer (5 ml) was added to the sulphide (1.37g, 7.68 mmol) in methanol (30 ml). The solution was cooled to 0°C and a solution of oxone® (7.08 g, 23.04 mmol) in water (30 ml) was added dropwise over 30 min. The resulting slurry was stirred at r.t. for 18 h.,and then extracted with DCM, The combined organics were washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (40% ether-petrol) afforded the sulphone (100) (1.00 g, 63%) as a white solid. ν_{max}(film) 2974, 2916, 1666, 1585, 1447, 1306, 1150, 1132, 1086, 774 and 740 cm^{-1}; δ (90 MHz) 7.90-7.45 (5H, m, Ph), 5.19 (1H, tt, J 7.5 and 2.5 Hz, 2-H), 3.79 (2H, d, J 7.5 Hz, 1-H), 1.75, 1.32 (6H, 2s, Me); m/z 210 (M^+), 77, 69 (M-$PhSO_2^+$); (Found: C, 62.77; H, 6.61. $C_{11}H_{14}SO_2$ requires C, 62.8; H, 6.7%).

20. 4",19-dibenzoyloxy-11-formyl-avermectin B_{1a} northern hemisphere (99).

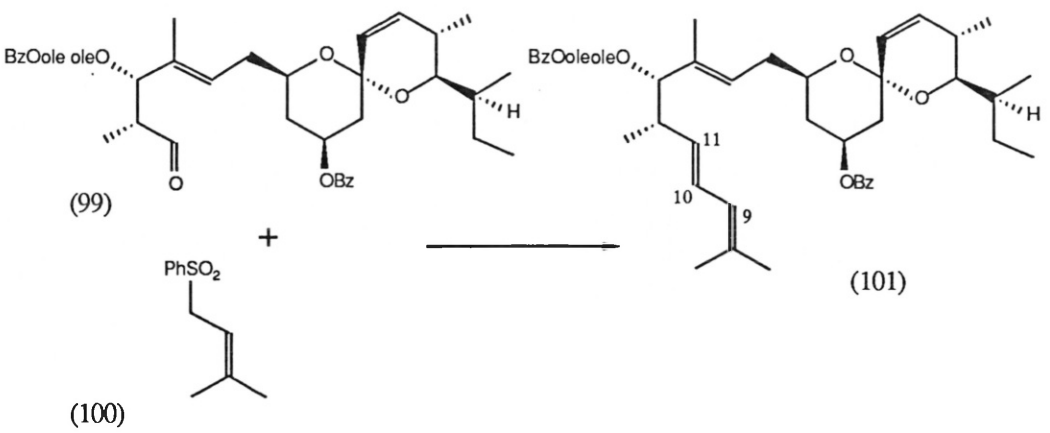


(79) (99)

DMSO (0.170 mmol, 2.39 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.104 ml, 1.19 mmol) in dry DCM (6 ml) under argon, at -60°C. After 10 min, the alcohol (79) (0.50g, 0.569 mmol) in dry DCM (9ml) was added dropwise. (After one half of the alcohol had been added a white precipitate was seen.) After a further 30 min. at -60°C, triethylamine (0.396 ml, 2.84 mmol) was added. The mixture was allowed to warm to r.t., poured into water and extracted with DCM. The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (50% ether-petrol) afforded the aldehyde (99) (90%, 0.449 g) as a foam. $[\alpha]_D^{20}$ = -30.5° (c= 0.95, $CHCl_3$); ν_{max}(film) 2965, 2933, 1724, 1720, 1602 and 1114 cm^{-1}; δ (500 MHz) 9.579 (1H, d, J 3.5 Hz, 11-H), 8.12-7.40 (10H, m, Ph), 5.74 (1H. dd. J 10.0 and 1.8 Hz, 22-H), 5.59 (1H, br.t, J 7.0 Hz, 15 H), 5.58 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.44 (1H, tt, J 11.5 and 4.5 Hz, 19-H), 5.36 (1H, d, J 3Hz, 1"-H), 4.92 (1H, t, 9 Hz, 4"-H), 4.79 (1H, d, J 3.0 Hz, 1'-H), 4.11(1H, d, J 10.0 Hz, 13-H), 3.95 (2H, obs.m, 5"-H, 17-H), 3.76 (1H, m, 3"-H), 3.56 (1H, m, 5'-H), 3.49 (1H, m, 3'-H), 3.40 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.35 (3H, s, 3"-OMe), 3.34 (3H,

s, 3'-OMe), 3.18 (1H, t, J 9.0 Hz, 4'-H), 2.65 (1H, m, 12-H), 2.42-2.10 (7H, m, 16-H_2, 18-H_e, 20-H_e, 24-H, 2'-H, 2"-H), 1.79-1.40 (6H, m, 20-H_a, 26-H, 27-H_2, 2'-H, 2"-H), 1.36 (1H, q, J 12 Hz, 18-H_a), 1.25 (3H, d, J 6Hz, 5"-Me), 1.16 (3H, d, J 6 Hz, 5'-Me), 0.94-0.80 (12H, m, 12-Me, 24-Me, 26-Me, 28-H_3); 13C ppm (500 MHz) 204.39 (C-11), 165.87 (COPh), 135.79 (C-22), 133.00 (C-Ph), 132.89 (C-Ph), 131.96 (C-Ph), 130,96 (C-Ph), 130.53 (C-Ph), 130.20 (C-Ph), 129.80 (C-Ph), 129.50 (C-Ph), 128.93 (C-Ph), 128.37 (C-Ph), 128.32 (2xC-Ph), 127.94 (C-23), 98.77 (C-1"), 95.61 (C-21), 92.99 (C-1'), 82.16 (C-13), 81.43 (C-15),77.26-76.75 (C-3', C-3", C-4', C-4"), 75.87 (C-25), 68.63 (C-17), 68.06(C-19), 67.18 (C-5"), 66.65 (C-5'), 57.37 (C-3'OMe), 56.48 (C-3"OMe), 48.05 (C-12), 40.54 (C-20), 36.75 (C-18), 35.39 (C-26), 35.33 (C-2"), 34.58 (C-2'), 34.23 (C-16), 30.52(C-24), 27.86 (C-27), 18.53 (C-12Me), 17.46 (C-5"Me), 16.47 (C-5'Me), 12.41 (C-24Me), 11.21 (C-26Me), 10.66 (C-28); m/z (FAB) 899 ($M+Na^+$), 323, 295, 265, 237, 207, 173, 115, 81; (Found: M^+, 899 4558. $C_{50}H_{68}O_{13}Na$ requires M, 899.4558).

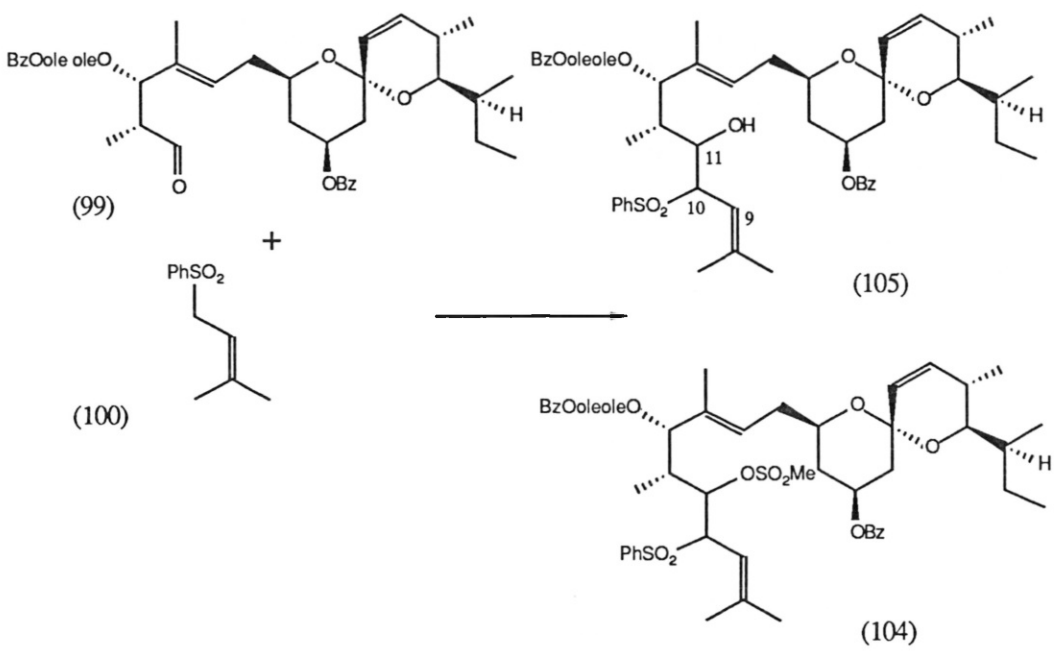
21. Preparation of (*E,E*)-4",19-dibenzoyloxy-11-(3-methyl-2-butenylidene) avermectin B_{1a} northern hemisphere (101).



The sulphone (100) (14.4 mg, 0.0684 mmol) was dissolved in dry THF:Toluene,1:1 (0.5 ml) under argon and cooled to -78°C. ^{n}Buli (0.031 ml of a 2.46M pentane solution, 0.752 mmol) was added dropwise and the deep yellow solution was stirred at -78°C for 20 min. The aldehyde (99) (50 mg, 0.057 mmol) in dry THF:Toluene,1:1 (0.6 ml) was added dropwise at -78°C and stirring continued for 30 min. to give a very pale yellow solution. Benzoyl chloride (0.026 ml, 0.228 mmol) was added dropwise at -78°C, the solution allowed to come to r.t and stirring continued for 1h. to give a clear solution. (Only slight change in R_f. of adduct after benzoylation). 3-Dimethylaminopropylamine (0.05 ml) was added at 0°C and the mixture stirred at r.t. for 15 min., before pouring into ether/1M HCl. The aqueous phase was extrcted with ether and the combined organics washed with saturated sodium bicarbonate, brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (58% ether-petrol) afforded the benzyloxy sulphones (89%, 60.5 mg) as a foam. Powdered 6% sodium amalgam (97%, 0.254 mmol) was added to a

vigorously stirred slurry of potassium dihydrogen orthophosphate (276 mg, 2.03 mmol) and benzyloxy sulphones (60.5 mg, 0.0508 mmol) in THF:methanol, 3:1, (3 ml) under argon at -30°C. After 3h t.l.c showed unreacted benzoxy sulphones so a further portion of powdered 6% sodium amalgam (58 mg, 0.152 mmol) and buffer (138 mg, 1.02 mmol) was added. Stirring was continued for 30 min. at -30°C before cooling to -60°C. Ethyl acetate (10 ml) and powdered ammonium chloride were then added and the cold mixture filtered rapidly through a pad of ammonium chloride and silica gel. The filtrate was evaporated *in vacuo*. Flash chromatography (30% ether-petrol) afforded the *E,E*-diene (101) (34%, 16 mg) as a foam. Overall yield for Julia 30%. $[\alpha]_D^{20}$ -29.2° (c= 1.0, $CHCl_3$); ν_{max}(film) 3046, 2969, 1717, 1603, 1116 and 986 cm^{-1}; δ (500 MHz) 8.12-8.00 (4H, 2xd, Ph(o)), 7.60-7.40 (6H, Ph(m),(p)), 6.31 (1H,dd, J 15.0 and 11.0 Hz, 10-H), 5.86 (1-H, br.d, J 11.0 Hz, 9-H), 5.75 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.59 (1H, j 10.0 and 2.5 Hz, 23-H), 5.54 (1H, dd, J 15.0 and 2.5 Hz, 11-H), 5.46-5.40 (2H, m, 15-H, 19-H), 5.35 (1H, d, J 3.0 Hz, 1"-H), 4.95 (1H, t, J 9.0 Hz, 4"-H), 4.74 (1H, d, J 3.0 Hz, 1'-H), 4.05-3.91 (2H, m, 5"-H, 17-H), 3.80-3.70 (2H, m, 5'-H, 3"-H), 3.60 (1H, d, J 9.0 Hz, 13-H), 3.59-3.54 (1H, m, 3'-H), 3.44 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.35 (3H, s, 3"-OMe), 3.34 (3H, s, 3'-OMe), 3.171H, t, J 9.0 Hz, 4'-H), 2.46-2.09 (8H, m, 12-H, 16-H_2, 18-H_e, 20-H_e, 24-H, 2'-H, 2"-H), 1.83 (3H, s, 8-Me), 1.81 (3H, s, 8-Me), 1.92-1.26 (7H, m, 18-H_a, 20-H_a, 26-H, 27-H_2, 2'-H2), 1.22 (3H, d, J 6.0 Hz, 5"-H), 1.120 (3H, d, J 6.0 Hz, 5'-Me), 0.97-0.89 (12H, m, 12-Me, 24-Me, 26-Me, 28-H_3) ; m/z (See Appendix); (Found: C, 70.93; H, 8.42. $C_{55}H_{76}O_{12}$ requires C, 71.1; H, 8.2%).

22. Preparation of 4",19-dibenzoyloxy-11-hydroxy-11-[1-(phenylsulphonyl)-3-methyl-2-butenyll-avermectin B_{1a} northern hemisphere (105) and 4",19-dibenzoyloxy-11-methanesulphonate-11-[1-(phenylsulphonyl)-3-methyl-2-butenyll-avermectin B_{1a} northern hemisphere (104).



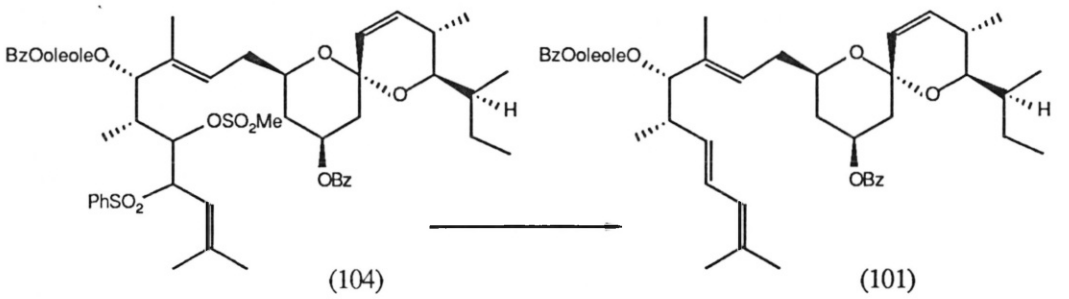
The sulphone (100) (28.8 mg, 0.137 mmol) was dissolved in dry THF (1 ml) under argon and cooled to -78°C,. ^{t}BuLi (0.0885 ml of a 1.7 M pentane solution, 0.150 mmol) was added dropwise and the deep yellow solution stirred for 5 min at -78°C. The aldehyde (99) (100 mg, 0.114 mmol) in dry THF (1 ml) was added dropwise at -78°C and the now pale yellow solution stirred for 25 min (no sulphone by t.l.c.). Methanesulphonyl chloride (0.342 mmol, 26.5 ml) was added at -78°C, the solution immediately discoloured and stirring continued for 30 min. T.l.c. analysis suggested incomplete mesylation of the adduct, so triethylamine (0.080 ml,

0.114 mmol), and methanesulphonyl chloride (0.013 ml, 0.171 mmol) were added at 0°C and the mixture stirred at r.t. for 20 min. No change was observed by t.l.c., so saturated sodium bicarbonate was added and the mixture extracted with DCM. The combined organics wrwe dried (MgSO4), passed through a pad of florisil and evaporated *in vacuo*. Flash chromatography (50% ether-petrol) afforded the hydroxy sulphone (105) (52%, 64 mg) and the mesyl sulphone (104) (24%, 32 mg) as foams. Less polar: (105), ν_{max}(film) 3511, 2968, 2933, 1719, 1601, 1584, 1449, 1300, 1271, 1162, 1142, 1116, 10689, 1051, 1027 and 988 cm^{-1}; δ (500 MHz) and COSY, 8.10-8.00 (4H, 2xdd, J 7.0 and 1.5 Hz, PhCO(o)), 7.88 (2H, dd, J 9.0 and 2.0 Hz, $PhSO_2$(o)), 7.68-7.42 (9H, m, Ph(m), (p)), 5.75 (1H, dd, J 10.0 and 1.8 H, 22-H), 5.58 (1H, dd, J 10.0 and 3.0 Hz, 23-H), 5.54 (1H, br.t, J 7.0 Hz, 15-H), 5.48 (1H, d, J 3.5 Hz, 1"-H), 5.44(1H, m, 9-H), 5.42 (1H, m, 19-H), 4.96(1H, t, J 01.0 Hz, 4"-H), 4.77 (1H, d, J 3.5 Hz, 1'-H), 4.59 (1H, d, J 11.0 Hz, 11-OH), 4.52 (1H, d, J 10.0 Hz, 11-H), 4.08 (1H, obs.m, 5"-H), 4.08 (1H, d, J 10.0 Hz, 13-H), 3.97 (1H, t, J 10.0 Hz, 10-H), 3.93 (2H, obs.m, 17-H, 5'-H), 3.82 (1H, m, 3"-H), 3.60 (1H, m, 3'-H), 3.41 (1H, dd, J 11.0 and 2.5 Hz, 25-H), 3.35(3H., s, 3"-OMe), 3.29 (1H, t, J 9.5 Hz, 4'-H), 3.24 (3H, s, 3'-OMe), 2.48-2.08 (8H, m, 12-H, 16-H_2, 18-H_e, 20-H_e, 24-H, 2"-H, 2'-H), 1.84-1.30 (7H, m, 18-H_a, 20-H_a, 26-H, 27-H_2, 2"-H, 2'-H), 1.73 (3H, s, 14-Me), 1.51 (3H, s, 9-Me), 1.41 (3H, s, 9-Me), 1.35 (3H, d, J 6.0 Hz, 5"-Me), 1.21 (3H, d, J 6.0 Hz, 5'-Me), 0.93-0.89 (9H, m, 24-Me, 26-Me, 28-H_3), 0.61 (3H, d, J 7.0 Hz, 12-Me); m/z FAB 1093 (M+ Li^+), 951, 935, 883, 698, 630, 554, 536, 428, 298, 249, 221, 203, 192, 178, 142, 122; (Found: M, see Appendix).

More polar: (104), ν_{max}(film) 3061, 2963, 2932, 2856, 1723, 1603, 1585, 1509,

1450, 1355, 1270, 1150, 1071, 1027 and 936 cm^{-1}; δ (500 MHz) and COSY, 8.07-7.97 (6H, 3d, J 7.5 Hz, Ph(o)), 7.67-7.46 (9H, m, Ph(m), (p)), 5.76 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.58 (2H, dd+obs.t, J 10.0 and 2.5 Hz, 23-H, 15-H), 5.50 (2H, d, J 2.5 Hz, 9-H, 1"-H), 5.43 (1H, m, 19-H), 4.96 (1H, t, J 9.5 Hz, 4"-H), 4.84 (1H, d, J 2.5 Hz, 1'-H), 4.15-4.03 (6H, m, 10-H, 11-H, 11-OH, 13-H, 5"-H, 5'-H), 3.97 (1H, m, 17-H), 3.82 (1H, m, 3"-H),3.66 (1H, m, 3'-H), 3.42 (1H, dd, J 11.0 and 1.5 Hz, 25-H), 3.34 (3H, s, 3"-OMe), 3.27 (3H, s, 3'-OMe), 3.15 (3H, s, SO_2Me), 2.48-2.04 (8H, m, 12-H, 16-H_2, 18-H_e,20-H_e, 24-H, 2"-H, 2'-H), 1.85-1.40 (7H, obs.m, 18-H_a, 20-H_a, 26-H, 27-H_2, 2"-H, 2'-H), 1.78 (3-H, s, 14-Me), 1.60 (3H, s, 9-Me), 1.44 (3H, d, J 6.0 Hz, 5"-Me), 1.39 (3H, s, 9-Me), 1.22 (3H, d, J 6.0 Hz, 5'-Me), 0.97-0.90 (12H, m, 12-Me, 24-Me, 26-Me, 28-H_3); m/z FAB 1172 ($M+Li^+$), 1075 (M^+-$MeSO_3$-Li), 933, 399, 312, 301, 249, 233, 221, 203 ($C_{14}H_{20}O_2^+$); (Found: see Appendix).

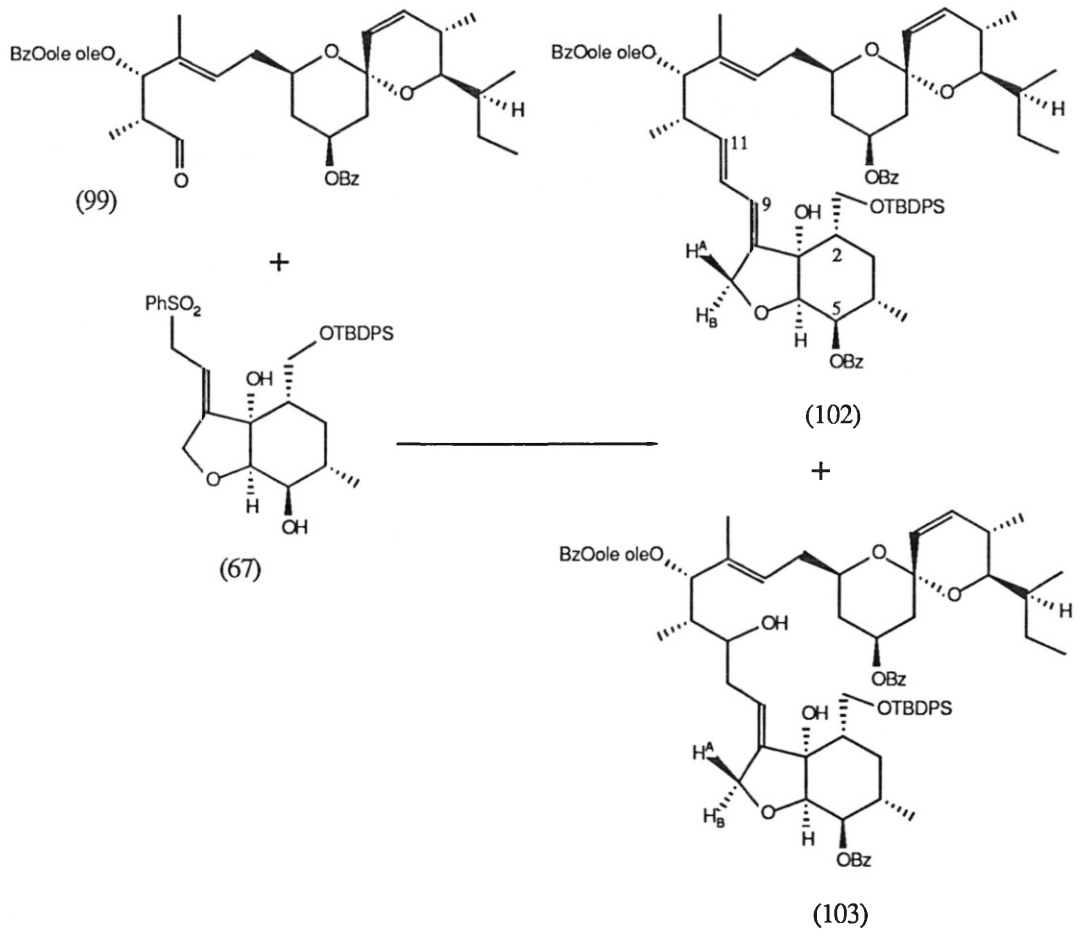
23. Preparation of (*E,E*)-4",19-dibenzoyloxy-11-(3-methyl-2-butenylidene) avermectin B_{1a} northern hemisphere (101).



(104) (101)

Powdered 6% sodium amalgam (0.099 g, 0.257 mmol), was added to a vigorously stirred slurry of potassium dihydrogen orthophosphate (0.140 g,1.03 mmol), and mesyl sulphone (0.030 g, 0.0257 mmol) in THF:methanol, 3:1, (1 ml) under argon at -30°C. After 30 min t.l.c. showed complete consumption of starting material. The mixture was cooled to -60°C, ethyl acetate (5 ml) and powdered ammonium chloride were added, and the cold mixture filtered through a pad of ammonium chloride and silica gel. The filtrate was evaporated *in vacuo*. Flash chromatography (30% ether-petrol) afforded the *E,E*-diene (101) (11.2 mg, 47%) as a white foam and more polar material (13.7 mg) which on rebenzoylation afforded more *E,E*-diene (101) (6.2 mg, 26%): Total yield of *E,E*-diene (17.5 mg, 73%). Overall Julia is 17%. Identcal in all respects to previous model diene .

24. Preparation of 1-^{t}butyldiphenylsilyloxy-2α–3,4-dihydro-5,19,4"-tribenzoyloxy-avermectin B_{1a} (102) and 1-^{t}butyldiphenylsilyloxy-2α–3,4-dihydro-5,19,4"-tribenzoyloxy-10-hydro-11-hydroxy-avermectin B_{1a} (103)



The diol sulphone (67) (18 mg, 0.0297 mmol) was dissolved in dry THF (0.5 ml) under argon and cooled to -78°C. ^{t}BuLi (0.058 ml of a 1.7M pentane solution, 0.0979 mmol) was added dropwise over 2 min and the deep orange viscous solution was stirred for 5 min. at -78°C. The aldehyde (99) (25 mg, 0.0282 mmol) in dry THF (0.3 ml) was added dropwise at -78°C to the trianion. The mixture was stirred for 1h 15 min (pale yellow solution) after which time saturated

ammonium chloride was added dropwise at -78°C. On warming to r.t. the solution became colourless and water was added. The mixture was extracted with ether, the combined organics dried (Na_2SO_4), evaporated in vacuo. Flash chromatography (50% ethyl acetate-petrol) afforded least polar unreacted aldehyde (99) (18 mg), the more polar hydroxy sulphones (23%, 14 mg) and the most polar unreacted sulphone (67) (12 mg). Yield of hydroxy sulphones based on recovered aldehyde is 100%.

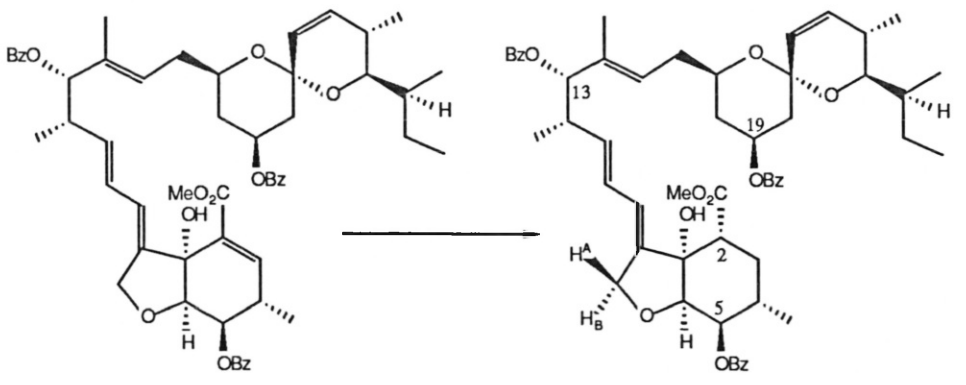
Benzoyl chloride (0.011 ml, 0.188 mmol) was added to the hydroxy sulphones (14 mg, 0.0094 mmol) and DMAP (0.5 mg, 0.0047 mmol) in dry pyridine (1 ml) under argon at 0°C. After stirring at room temperature for 12h at r.t. , 3-dimethylaminopropylamine (0.015 ml, 0.119 mmol) was added at 0°C and the mixture stirred at r.t. for 15 min. It was poured into 1M HCl/DCM and the acid layer extracted with DCM, dried (MgSO4) and evaporated *in vacuo*. Flash chromatography (35% ethyl acetate-petrol) afforded the diastereomeric benzoyloxy sulphones (16 mg, 0.00946 mmol) as a foam (R_f in 40% ethyl acetate-petrol 0.5-0.6).

Powdered 6% sodium amalgam (36 mg, 0.0946 mmol) was added to a vigorously stirred slurry of potassium dihydrogen orthophosphate (54 mg, 0.378 mmol) and benzoyloxy sulphones (16 mg, 0.00946 mmol) in THF:methanol, 3:1, (1 ml) under argon at -40°C. After 2h, the reaction was cooled to -60°C, ethyl acetate (5 ml) and powdered ammonium chloride were added and the cold mixture filtered rapidly through a pad of ammonium chloride and silica gel. The filtrate was evaporated *in vacuo*. Flash chromatography (40% ether-petrol) afforded the less polar *E,E*-diene (102) (27 mg, 3.7 mg) and the more polar diastereomerically pure 11-hydroxy-10-hydro adduct (103) (17%, 1.8 mg) as clear glasses. Less polar:

(102) ν_{max}(film) 3400, 2926, 1717, 1450, 1270, 1112, 1068, 985, 711 and 663 cm^{-1}; δ (500 MHz) 8.10-8.00 (6H, m, PhCO(o)), 7.75-7.64 (4H, m, PhSi(o)), 7.58-7.30 (15H, m, Ph(m), (p)), 6.02 (1H, m, 10-H), 5.87 (1H, m, 9-H) 5.75 (1H, dd< j 10.0 and 1.5 Hz), 5.59 (1H, dd, J 10.0 and 2.5 Hz), 5.47 (1H, t, J 7.5 Hz, 15-H), 5.55-5.40 (3H, m, 1-H, 19-H, 1"-H), 5.20 (1H, dd, J 11.5 and 3.5 Hz, 5-H), 4.90 (1H, t, J 9.5 Hz, 4"-H), 4.83 (1H, s, 7-OH), 4.77 (1H, d, J 3.5 Hz, 1'-H), 4.61 (1H, dd, J 14,5 and 2.0 Hz, 8_{α}-H_B), 4.52 (1H, dd,J 11.0 and 2.0 Hz, 8_{α}-H_A). 4.15 ((1H, dd, J 10.5 and 2.5 Hz, 1-H). 3.98-3.90 (3H, m, 6-H, 17-H,5"-H), 3.74-3.50 (5H, m, 1-H, 13-H, 25-H, 3"-H, 3'-H, 5'-H), 3.42 (1H, dd, J 11.0 and 2.5 Hz, 25-H), 3.34 (3H, s, 3"-OMe), 3.24 (1H, t, J 9.5 Hz, 4'-H), 2.45-2.14 (8H, m, 12-H, 16-H_2, 18-H_e, 20-H_e, 24-H, 2"-H, 2'-H), 2.03-1.95 (2H, m+obs.q, J 13.0, 4-H, 3-H_B), 1.75-1.40 (8H, m, 2-H, 3-H_A, 20-H_a, 26-H, 27-H_2, 2"-H, 2'-H), 1.35 (1H, q, J 12.0 Hz, 18-H_a), 1.18-1.12 (6H, 2xd, J 6.5 Hz, 5"-H. 5-H'), 1.10 (9H, s, ^{t}BuSi), 0.95-0.82 (15H, m, 4-Me, 12-Me, 24-Me, 26-Me, 28-H_3); m/z FAB Lithium doped: 1436 ($M+Li^+$); Sodium doped: 1435 ($M+Na^+$), 1309, 897. More polar: (103) ν_{max}(film) 3400, 2927, 1717, 1450, 1270, 1069, 987, 709 and 663 cm^{-1}; δ (500 MHz) 8.10-7.35 (25H, m, Ph), 5.73 (1H, dd, J 10.0 and 1.8 Hz, 22-H), 5.57 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.51 (1H, t, J 7.0 Hz, 15-H), 5.45-5.40 (2H, m+obs.d, J 3.5 Hz, 19-H, 1"-H), 5.18 (1H, dd, J 11.5 and 3.5 Hz, 5-H), 4.92 (1H, t, J 9.5 Hz, 4"-H), 4.82 (2H, s+obs.d, J 3.5 Hz, 7-OH, 1'-H), 4.55 and 4.39 (2H, 2xd, J 14 Hz, 8a-H_2), 4.14 (1H, dd, J 10.5 and 2.5 Hz, 1-H), 4.04-3.95 (3H, m, 11-H, 13-H, 5"-H), 3.94 (1H, d, J 3.5 Hz, 6-H), 3.80 (1H, m, 5'-H), 3.72 (1H, m, 3"-H), 3.67 (1H, dd, J 10.5 and 2.2 Hz, 1-H), 3.57 (1H, m, 3'-H), 3.43 (1H, dd, J 11.0 and 2.5 Hz, 25-H), 3.34 (3H, s, 3"-OMe), 3.28 (3H, s, 3'-OMe), 2.55 (1H, br.d, 11-OH), 2.40-

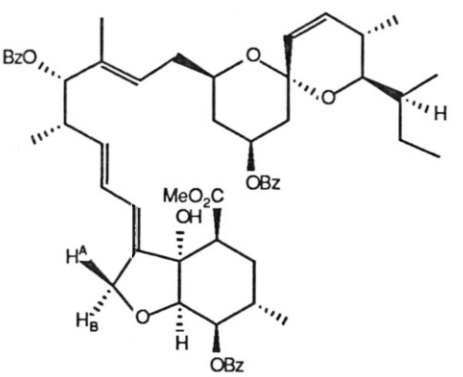
2.14 (10-H, m, 10-H_2, 12-H, 16-H_2, 18-H_e, 20-H_e, 24-H, 2"-H, 2'-H), 1.99-1.90 (2H, m, 3-HB, 4-H), 1.82-1.40 (8H, m, 2H, 3-H_A, 20-H_A, 26-H, 27-H_2, 2"-H, 2'-H),1.48 (3H, s, 14-Me), 1.35 (1H, m, 18-H_a), 1.30 (1H, d, J 6.5 Hz, 5"-H), 1.18 (3H, d, J 6.5 Hz, 5'-H), 1.08 (9H, s, ^{t}BuSi), 1.05 (3H, d, J 6.0 Hz, 4-Me), 0.95-0.85 (9H, m, 24-Me, 26-Me, 28-H_3), 0.78 (3H, d, J 7.0 Hz, 12-Me); ; m/z FAB, Lithium doped: 1454 ($M+Li^+$); Sodium doped: 1470 ($M+Na^+$).

25. Preparation of 5,13,19-tribenzoyloxy-1-methoxycarbonyl-2α-3,4-dihydro-avermectin B_{1a} aglycone (118) and 5,13,19-tribenzoyloxy-1-methoxycarbonyl-2β-3,4-dihydro-avermectin B_{1a} aglycone (119).



(83) (118)

+



(119)

The α,β-unsaturated ester (83) (0.234 g, 0.252 mmol), was dissolved in dry methanol (15 ml) under argon and solid sodium borohydride (0.248 g, 0.655 mmol) was added in two portions (t=0 min.~ 0.120 g, t=30 min. ~ 0.128 g) at 0°C. Once effervesence had ceased the mixture was brought to room temperature and stirred for a total of 1h 15 min. at which time t.l.c. analysis showed complete consumption of

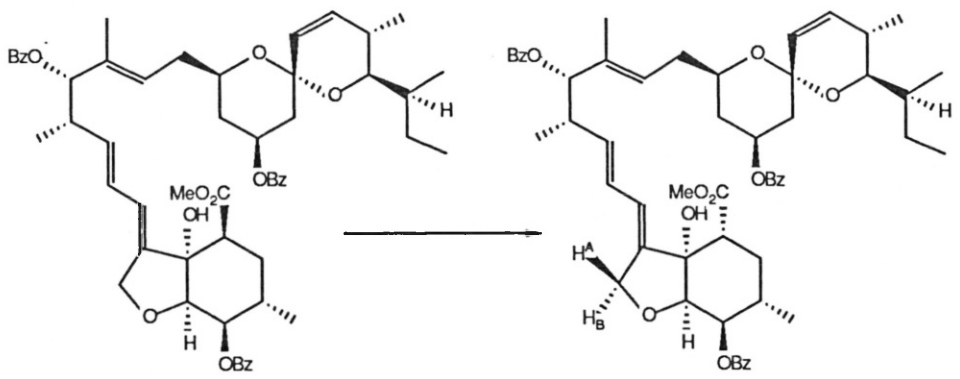
starting material. The mixture was cooled to 0°C and 1M HCl added dropwise until the mixture was pH3-4. The mixture was buffered with aq. KH_2PO_4 and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography afforded the α-ester (118) (0.094 g) and the β-ester (119) (0.068 g) (Total yield 70%: α:β, 1.38:1) as white foams.

Less polar: (118) $[\alpha]_D^{20}$ +56.5° (c= 0.49, $CHCl_3$); ν_{max}(film) 3464, 3062, 2962, 1716, 1601, 1584, 1450, 1314, 1111, 1069, 1026 and 966 cm^{-1}; δ (500 MHz) + COSY, 8.10-7.40 (15H, m, Ph), 5.85-5.76 (2H, m, 9-H, 10-H), 5.73 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.66 (1H, t, J 7.0 Hz, 15-H), 5.59 (1H, dd, J 15.0 and 7.0 Hz, 11-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.43 (1H, m, 19-H), 5.20 (1H, d, J 9.5 Hz, 13-H), 5.14 (1H, dd, J 11.5 and 3.5 Hz, 5-H), 4.80 (1H, s, 7-Oh), 4.50 (1H, dd, J 14.5 and 1.5 Hz, 8_{α}-H_B), 4.31 (1H, dd, J 14.5 and 1.5 Hz, 8-$_{\alpha}H_A$), 3.95 (1H, m, 17-H), 3.92 (1H, d, J 3.5 Hz, 6-H), 3.53 (3H, s, 1-OMe), 3.40 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.64 (1H, m, 12-H), 2.55 (1H, dd, J 13.0 and 3.5 Hz, 2-H), 2.35 (1H, m, 16-H), 2.28-2.20 (4H, m, 4-H, 16-H_2, 24-H), 2.20-2.12 (2H, m, 18-H_e, 20-H_e), 1.84 (1H, dt, J 13.0 and 3.5 Hz, 3-H_A, 1.77 (1H, q, J 13.0 Hz, 3-HB), 1.70 (3H, s, 14-Me), 1.64 (1H, m, 20-H_a), 1.54 (1H, m, 26-H), 1.42 (2H, m, 27-H_2), 1.38 (1H, q, J 12.0 Hz, 18-H_a), 1.05 (3H, d, J 6.5 Hz, 4-Me), 0.98 (3H, d, J 7.0 Hz, 12-Me), 0.91-0.84 (9H, obs.d, 24-Me, 26-Me, 28-H_3); m/z 790 (M^+-$PhCO_2H$-H_2O), 688 (M^+-2$PhCO_2H$-H_2O), 546 (M^+-3$PhCO_2H$-H_2O), 221 ($C_{14}H_{20}O_2^{+)}$, 122; (Found: C, 71.96; H, 7.23. $C_{56}H_{66}O_{12}$ requires C, 72.2; H, 7.1%).

More polar: (119) $[\alpha]_D^{20}$ +71.0° (c=0.46, $CHCl_3$); ν_{max}(film) 3442, 2961, 2926, 1716, 1601, 1584, 1491, 1377, 1271, 1199, 1162, 1069 and 994 cm^{-1}; δ

(500 MHz) + COSY, 8.05-7.38 (15H, m, Ph), 5.89 (1H, m, 10-H), 5.86 (1H, m, 9-H), 5.74 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.70-5.65 (2H, m, 11-H, 15-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.43 (1H, m, 19-H), 5.23 (1H, d J 9.5 Hz, 13-H), 5.16 (1H, dd, J 8.0 and 3.0 Hz, 5-H), 4.53 (1H, d, J 14.0 Hz, 8_{α}-H_B), 4.41 (1H, d, J 14.0 Hz, 8_{α}-H_A) 4.08 (1H, d, J 3 Hz, 6-H), 3.94 (1H, m, 17-H), 3.43 (3H, s, 1-OMe), 3.40 (1H, dd, J 10.0 and 1,5 Hz, 25-H), 3.22 (1H, br.s, 7-OH), 2.92 (1H, dd J 11.0 and 4.0 Hz, 2-H), 2.72 (1H, m, 12-H), 2.43 (1H, m, 4-H), 2.35 (1H, m, 16-H), 2.29-2.21 (2H, m, 16-H, 24-H), 2.19 (1H, m, 18-H_e), 2.15 (1H, m, 20-H_e), 1.91 (1H, ddd, J 14.0, 11.0 and 6.5 Hz, 3-H_A), 1.71 (3H, s, 14-Me), 1.65 (1H, obs.m, 3-H_B), 1.60 (1H, m, 20-H_a), 1.52 (1H, m, 26-H), 1.41 (2H, m, 27-H_2), 1.36 (1H, q, J 12.0 Hz, 18-H_e), 1.06 (3H, d, J 7.0 Hz, 4-Me), 1.00 (3H, d, J 7.0 Hz, 12-Me), 0.92-0.84 (9H, obs. 3xd, 24-Me, 26-Me, 28-H_3); m/z 790 (M^+-$PhCO_2H$-H_2O), 668 (M^+-2$PhCO_2H$-H_2O), 546 (M^+-3$PhCO_2H$-H_2O), 548 (M^+-3$PhCO_2H$-2H_2O), 221 ($C_{14}H_{20}O_2^+$), 122; (Found: C, 72.01; H, 7.37. $C_{56}H_{66}O_{12}$ requires C, 72.2; H, 7.1%).

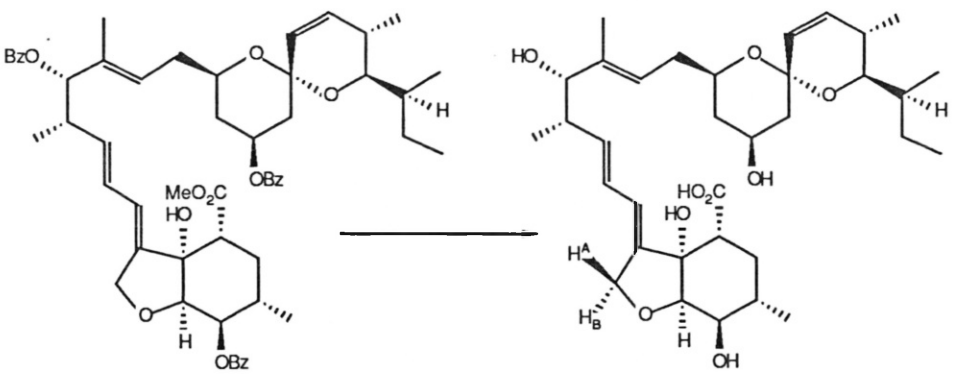
26. Preparation of 5,13,19-tribenzoyloxy-1-methoxycarbonyl-2α-3,4-dihydro-avermectin B_{1a} aglycone (118).



(119) (118)

The β-methyl ester (119) (0.056 g, 0.0601 mmol) was azeotropically dried with toluene and dissolved in dry DCM (1 ml) under argon. DBU (0.14 ml, excess) was added at r.t. and the mixture heated to 40°C and left stirring until t.l.c.showed complete conversion to the α-ester (~24 h.). The mixture was cooled to 0°C and 1M HCl added. The aqueous solution was extracted with DCM the combined organics dried (MgSO4) and evaporated *in vacuo*. Flash chromatography (15% ethyl acetate-petrol) afforded the α-ester (118) (84%, 0.047 g) as a foam Identical in all respects to previously obtained sample.

27. Preparation of 5,13,19-tribenzoyloxy-1-carboxy-2α-3,4-dihydro-avermectin B_{1a} aglycone (117).

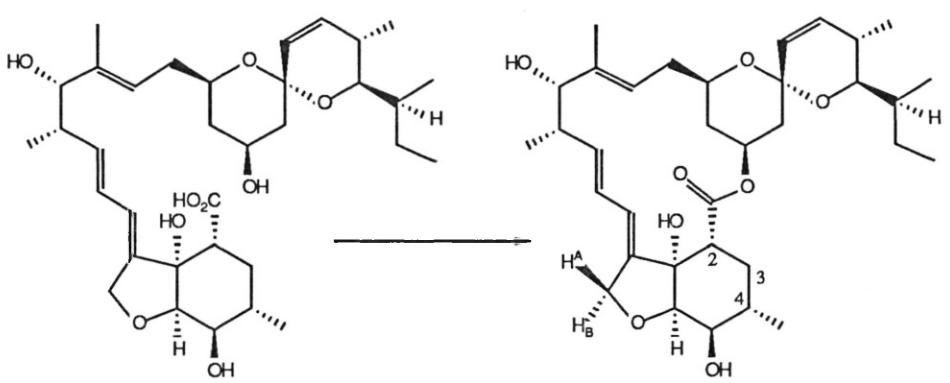


(118) (117)

The α-ester (118) (0.-075 g, 0.0855 mmol) in DME (0.6 ml) at 0°C was treated with aqueous potassium hydroxide solution (1.0M, 0.403 ml, 0.403 mmol) and the solution heated at 60°C for 8h. The mixture was cooled to 0°C and 6M HCl was added dropwise until the solution was at pH2. Solid sodium chloride was added and the mixture extracted with ether. The combined organics were passed through a pad of celite and evaporated *in vacuo*. Flash chromatography (94:5:1, ethyl acetate : methanol : acetic acid) afforded the hydroxy acid (117) (0.039 g, 80%) as a foam. ν_{max}(film) 3386, 2959, 2922, 3000-2100, 1583, 1452, 1261, 1017 and 801 cm^{-1}; δ (500 MHz) 6.20-5.87 (1H, v.br.,CO_2H), 5.90 (1H, dt, J 11.0 and 2.0 Hz, 9-H), 5.81 (1H, dd, J 15.0 and 11.0 Hz, 10-H), 5.71 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.60 (1H, dd, J 15.0 and 8.5 Hz, 11-H), 5.52 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.28 (1H, br.t, J 6.0 Hz, 15-H), 4.59 (2H, 2xdd, J 14.0 and 2.0 Hz, 8_{α}-H_2), 4.19 (1H, J 11.0 and 4.5 Hz, 19-H), 3.83-3.79 (2H, obs.m, 13-H, 17-H),

3.78 (1H, d, J 3.5 Hz, 6-H), 3.48 (1H, dd, J 11.0 and 3.5 Hz, 5-H), 3.40 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.58 (1H, dd, J 13.0 and 3.0 Hz, 2-H), 2.43 (1H, m, 12-H), 2.34 (1H, m, 24-H), 2.24-2.17 (2H, obs.m, $16H_2$), 2.00-1.93 (2H, obs.m, 3-H, $20\text{-}H_e$), 1.81-1.76 (3H, obs.m, 4-H, $18\text{-}H_e$, 5-OH), 1.62-1.52 (3H, obs.m, 20-Ha, $27\text{-}H_2$), 1.16 (3H, d, J 6.5 Hz, 12-Me), 1.10 (3H, d, J 7.0 Hz, 4-Me),0.89 (3H, t, J 7.5 Hz, $28\text{-}H_3$), 0.88 (3H, d, J 7.0 Hz, 24-Me), 0.85 (3H, d, J 7.0 Hz, 26-Me); m/z 604 (M^+), 586 ($M^+\text{-}H_2O$), 568 ($M^+\text{-}2H_2O$), 550 ($M^+\text{-}3H_2O$), 532 ($M^+\text{-}4H_2O$); (Found: C, 67.35; H, 8.62. $C_{34}H_{52}O_9$ requires C, 67.5; H, 8.7%).

28. Preparation of 3,4-dihydro-avermectin B_{1a} aglycone (120).

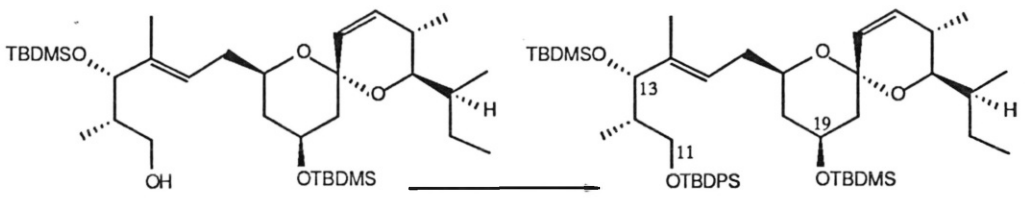


(117) (120)

To a refluxing solution of 1-methyl-2-chloropyridinium iodide (0.059 g, 0.232 mmol) in dry acetonitrile (7 ml), was continuously and uniformly added, by a syringe pump, a solution of the hydroxy acid (117) (0.035 g, 0.0580 mmol) and

triethylamine (0.065 ml, 0.464 mmol) in dry acetonitrile (3.5 ml) over 8h, and the reaction was refluxed for a further 4h after addition was completed. The solvent was evaporated *in vacuo* and flash chromatography of the residue (50% ethyl acetate-petrol) afforded the macrocyclic triol (120) (47%, 0.016 g) as a glass. ν_{max}(film) 3455, 2958, 2930, 1701, and 999 cm^{-1}; δ (500 MHz) + COSY+ C-H COSY, 5.76 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.75-5.65 (3H, obs, 9-H, 10-H, 11-H), 5,55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.41 (1H, tt, J 11.5 and 5.0 Hz, 19-H), 5.30 (1H, br.d, J 10.0 Hz, 15-H), 4.63 (1H, dd, J 14.0 and 2.0 Hz, 8_{α}-H_B), 4.63 (1H, s, 7-OH), 4,56 (1H,dd. J 14.0 and 2.0 Hz, 8_{α}-H_A), 3.99 (1H, br.s, 13-H), 3.87 (1H, m, 17-H), 3.82 (1H, d, J 3.5 Hz, 6-H), 3.51 (1H, dd, J 11.0, 9.0 and 3.5 Hz, 5-H), 3.46 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.45 (1H, dd, J 9.5 and 6.5 Hz, 2-H), 2.50 (1H, m, 12-H), 2.33-2.24 (3H, obs.m, 16-H_2, 24-H), 1.91 (1H, ddd, J 12.0, 5.0 and 2.0 Hz, 20-H_e), 1.80 (1H, d, J 9.0 Hz, 5-OH), 1.75-1.69 (2H, obs.m, 4-H, 18-H_e), 1.65-1.43 (6H, obs.m, 3-H_2, 26-H, 27-H_2, 13-OH), 1.50 (3H, s, 14-Me), 1.45 (1H, obs.m, 20-H_a), 1.17 (3H, d, J 7.0 Hz, 12-Me), 1.07 (3H, d, J 7.0 Hz, 4-Me), 0.96 (3H, t, J 7.0 Hz, 28-H_3), 0.91 (3H, d, J 7.0 Hz, 24-Me), 0.89 (3H, d, J 7.0 Hz, 26-Me), 0.84 (1H, q, J 12.0 Hz, 18-H_a) ; m/z 586 (M^+), 568 (M^+-H_2O), 550 (M^+-$2H_2O$), 500, 305, 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$), 169; (Found: C, 69.51, H, 8.38; $C_{34}H_{50}O_8$ requires C, 69.6; H, 8.6%).

29. Preparation of 13,19-di-^{t}butyldimethylsilyloxy-11-^{t}butyldiphenylsilyloxy-avermectin B_{1a} aglycone northern hemisphere (106).

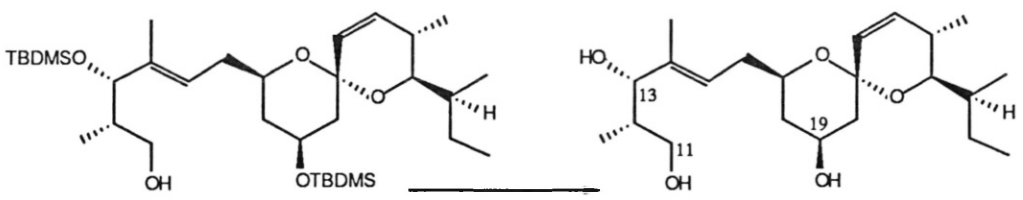


(88) (106)

TBDPSCl (0.021 ml, 0.0766 mmol), was added to a solution of disilyl alcohol (88) (0.039 g, 0.0638 mmol), imidazole (0.009 g, 0.134 mmol), and DMAP (0.0005 g, cat.) in dry (0.2 ml) under argon and stirred for 40 min. at r.t. The mixture was then poured into ether/water, extracted with ether and the combined organics washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (Gradient elution 2-5% ether-petrol) afforded the trisilyl derivative (106) (0.033 g, 62%) as a white foam. ν_{max}(film) 2957, 2935, 2883, 2858, 1653, 1464, 1383, 1254, 1158, 1113, 1072, 1005 and 872 cm^{-1}; δ (500 MHz) 7.75-7.35 (10H, m, Ph_2), 5.69 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.24 (1H, br.t, J 7.0 Hz, 15-H), 4.10 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 3.84 (1H, dd, J 10.0 and 4.0 Hz, 11-H), 3.75 (1H, obs.m, 17-H), 3.73 (1H, d, J 9.0 Hz, 13-H), 3.52 (1H, dd, J 10.0 and 7.0 Hz,11-H), 3.41 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.33 (1H, m, 16-H), 2.23 (1H, m, 24-H), 2.13 (1H, m, 16-H), 1.88-1.84 (2H, obs.m, 20-H_e, 12-H), 1.76 (1H, m, 18-H_e), 1.59-1.35 (4H, obs.m, 20-H_a, 26-H, 27-H_2),1.17 (1H, q, J 12.0 Hz, 18-H_a), 1.07 (9H, s,

$^{t}BuSiPh_2$), 0.94-0.86 (9H, 24-Me, 26-Me, 28-H_3), 0.87 (9H, s, $^{t}BuSiMe_2$), 0.76 (9H, s, $^{t}BuSiMe_2$), 0.055, 0.050 (6H, 2xs, $SiMe_2$), -0.10, -0.11 (6H, 2xs, $SiMe_2$); m/z 866 ($M+NH_4^+$), 791 (M^+-^{t}Bu), 734 (M^+-$2^{t}Bu$), 717 (M^++H-TBDMSOH), 585 (M^++H-2TBDMSOH), 329 (M^++H-2TBDMSOH-TBDPSOH), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$); (Found: see Appendix).

30. Preparation of 11,13,19-trihydroxy-avermectin B_{1a} aglycone northern hemisphere (107).

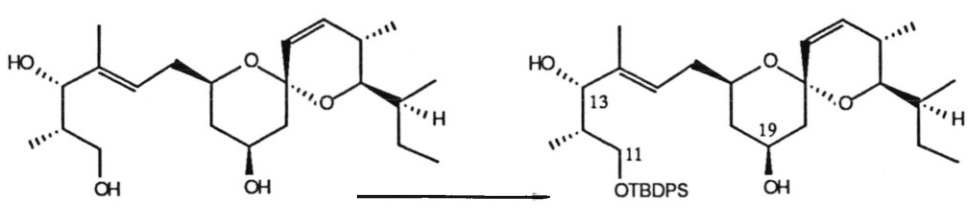


(88) (107)

TBAF (0.054 ml, 1.0M solution in THF) was added to a solution of disilyl alcohol (88) (11 mg, 0.018 mmol) in dry THF (0.1 ml) under argon at r.t. The mixture was stirred at r.t. for 1h. (t.l.c analysis showed an equal amount of 13-monosilyl derivatiuve and triol), and then heated at 50°C for 30 min. (T.l.c.analysis at this point, showed complete conversion to triol). The mixture was poured into ethyl acetate/water and extracted with ethyl acetate (x4). The combined organics were washed with brine, passed through a pad of florisil, evaporated *in vacuo* and dried over P_2O_5 *in vacuo*, to give the triol (107) (7 mg, 100%) as a clear

glass.(Column chromatography was not necessary as purity was confirmed by high field n.m.r.) ν_{max}(film) 3319, 2960, 2874, 1653, 1457, 1380, 1149, 1035, 983, 882 and 736 cm^{-1}; δ (500 MHz) + D_2O shake, 5.72 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.54 (1H, dd, J 10.0 and 3.0 Hz, 23-H),5.38 (1H, br.t, J 7.0 Hz, 15-H), 4.20 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 3.88 (1H, d, J 9.0 Hz, 13-H),3.78 (1H, m, 17-H), 3.72, 3.62 (2H, 2xdd, 11-CH_2), 3.36 (1H, dd, 25-H), 3.20 (1H, br, OH), 2.32 (1H, m, 16-H), 2.24-2.20 (2H, obs.m, 24-H, 16-H), 2.02-1.90 (4H, obs.m, 12-H, 18-H_e, 20-H_e, OH), 1.61 (3H, s, 14-Me), 1.55(1H, obs.m, 26-H), 1.48-1.32 (4H, obs.m, 20-H_a, OH, 27-H_2), 1.12 (1H, q, J 12Hz, 18-H_a), 0.90 (3H, t, J 7.0 Hz, 28-H_3), 0.88, 0.85 (6H, 2xd, J 7.0 Hz, 24-Me, 26-Me), 0.70 (3H, d, J 7.0 Hz, 12-Me); m/z CI/ammonia: 400 ($M+NH_4^+$), 382 ($M+NH_4^+$-H_2O), 365, 329, 299, 239 ($C_{14}H_{20}O_2+NH_4^+$), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$); (Found: M, 382.2719. $C_{22}H_{40}O_4N$ requires M^+, 382.2712).

31. Preparation of 11-^{t}butyldiphenylsilyloxy-13,19-dihydroxy-avermectin B_{1a}-aglycone northern hemisphere (108).

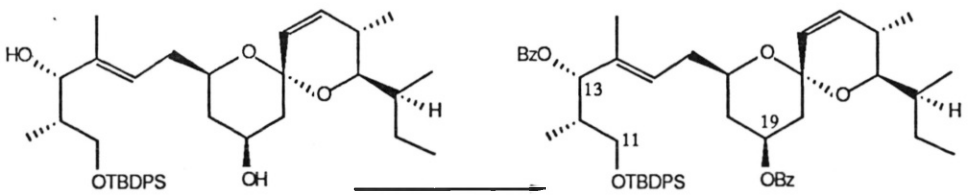


(107) (108)

Triethylamine (0.035 ml, 0.248 mmol), followed by TBDPSCl (0.059 ml,

0.227 mmol) was added to the triol (107) (0.079 g, 0.207 mmol) in dry DCM (8 ml) under argon at r.t., and stirring continued for 8h. The mixture was poured into DCM/water and extracted with DCM (x3). Salt was added to the aqueous phase to saturate it and reextracted with ethyl acetate. The combined organics were washed once with brine, and evaporated *in vacuo*. Flash chromatography (20% ethyl acetate- petrol) afforded the diol (108) (0.117 g, 91%) as a clear glass. ν_{max}(film) 3415, 2963, 2929, 2866, 1744, 1657, 1462, 1431, 1382, 1264, 1153, 1115, 1076, 1000 and 826 cm^{-1}; δ (500 MHz) 7.79-7.40 (10H, m, Ph_2), 5.70 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.56 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.40 (1H, br.t, J 7 Hz, 15-H), 4.11 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 3.92 (1H, d, J 9.0 Hz, 13-H), 3.78 (2H, obs.m, 17-H, OH), 3.78 (1H, dd, J 10.0 and 4.0 Hz, 11-H), 3.66 (1H, dd, J 10.0 and 8.0 Hz, 11-H), 3.40 (1H, m, 16-H), 2.25-2.18 (2H, obs.m, 24-H, 16-H), 1.99 (2H, obs.m, $20H_e$, $18\text{-}H_e$), 1.91 (1H, m, 12-H), 1.62 (3H, s, 14-Me), 1.60 (1H, m, OH), 1.55-1.35 (4H, obs.m, $20\text{-}H_a$, 26-H, $27\text{-}H_2$), 1.13 (1H, q, J 12.0 Hz, $18\text{-}H_a$), 1.06 (9H, s, ^tBu), 0.91 (3H, t, J 7.0 Hz, $28\text{-}H_3$), 0.88, 0.85 (6H, 2xd, J 7.0 Hz, 24-Me, 26-Me), 0.66 (3H, d, J 7.0 Hz, 12-Me); m/z 602 ($M^+\text{-}H_2O$), 584 ($M^+\text{-}2H_2O$), 566, 545 ($M^+\text{-}H_2O\text{-}^tBu$), 361, 221 ($C_{14}H_{20}O_2^+$), 183; (Found: C, 73.16; 9.17. $C_{38}H_{56}O_5Si$ requires C, 73.5; H, 9.1%)).

32. Preparation of 13,19-dibenzoyloxy-11-^{t}butyldiphenylsilyloxy-avermectin B_{1a} aglycone northern hemisphere (109).

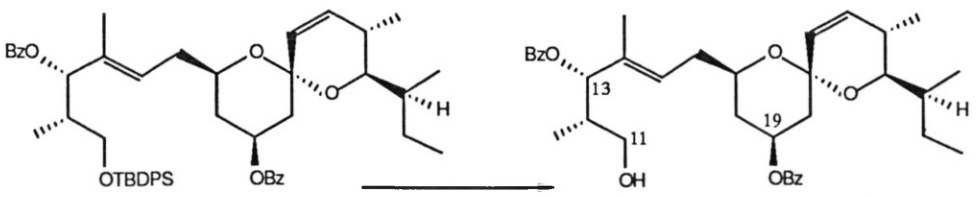


(108) (109)

Benzoyl chloride (0.058 ml, 0.467 mmol) was added to a solution of diol (108) (0.116 g, 0.186 mmol) and DMAP (0.0023 g, 0.019 mmol) at 0°C under argon. After stirring at r.t. for 17h, it was cooled to 0°C, 3-dimethylaminopropyjamine (0.053 ml, 0.425 mmol) was added and the mixture stirred at r.t. for 30 min. It was then poured into 1M HCl and extracted with ether. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate, brine dried (MgSO4) and evaporated *in vacuo*. Flash chromatography (5% ethyl acetate-petrol) afforded the dibenzoyl derivative (109) (0.140 g, 92%) as a white foam. $[\alpha]_D^{20}$ +68.4° (c=0.51, $CHCl_3$); ν_{max}(film) 3069, 2961, 2930, 1717, 1601, 1450, 1380, 1313, 1274, 1161, 1111, 1069, 1040, 1026, 997 and 969 cm^{-1}; δ (500 MHz) 8.01-7.91 (4H, 2xapp.d, Bz(o)), 7.64-7.13 (16H, obs.m, Bz(m),(p), Ph_2Si), 5.72 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.65 (1H, br.t, J 7.0 Hz, 15-H), 5.54 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.44 (1H, tt, J 11.5 and 5.0 Hz, 19-H), 5.32 (1H, d, J 10.0 Hz, 13-H), 3.95 (1H, m, 17-H), 3.67 (2H, obs.m, 11-H_2), 3.43 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.36 (1H, m,

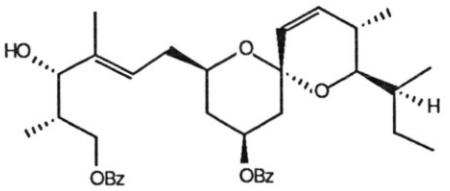
16-H), 2.26-2.12 (5H, obs.m, 12-H, 16-H, 18-H_e, 20-H_e, 24-H), 1.63 (3H, s, 14-Me), 1.60-1.40 (4H, obs.m, 20-H_a, 26-H, 27-H_2), 1.36 (1H, q, J 12 Hz, 18-H_a), 1.01 (9H, s, ^tBu), 1.05 (3H, obs.d, 12-Me), 0.93-0.86 (9H, obs.m, 24-Me, 26-Me, 28-H_3); m/z 771 (M^+-^tBu), 706 (M^+-$PhCO_2H$), 649 (M^+-$PhCO_2H$-^tBu), 584 (M^+-$2PhCO_2H$), 527 (M^+-$2PhCO_2H$-^tBu), 457, 303, 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$), 122($PhCO_2H^+$); (Found: C, 75.16; H, 7.63. $C_{52}H_{64}O_7Si$ requires C, 75.3; H, 7.8%).

33. Preparation of 13,19-dibenzoyloxy-11-hydroxy-avermectin B_{1a} aglycone northern hemisphere (84) and 11,19-dibenzoyloxy-13-hydroxy-avermectin B_{1a} aglycone northern hemisphere (86).



(109) (84)

1 : 9



(86)

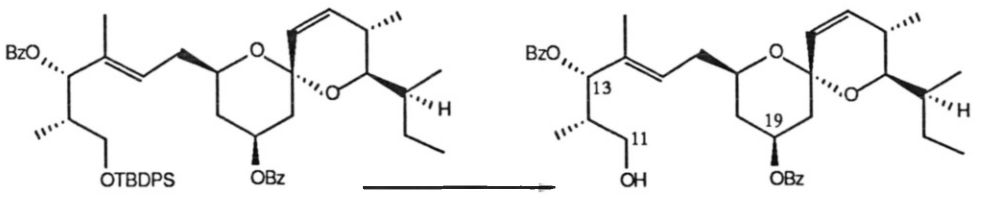
TBAF (0.017 ml, 0.017 mmol, 1.0M solution in THF) was added to a

solution of the silyl derivative (109) (0.012 g, 0.0145 mmol) in dry THF (0.5 ml) under argon. After 5 min. t.l.c. analysis showed the formation of the 13-OH compound (84) with a trace of the required 11-OH compound (86),.[(86) R_f=0.35, (84) R_f=0.30 in 20% ethyl acetate-petrol]. A further portion of TBAF (0.017 ml, 0.017 mmol) was added after 1h. and the reaction stirred for a further 1h. It was then poured into ether/water, extracted with ether (x3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (15% ethyl acetate-petrol) afforded the less polar C-13 alcohol (86) (5.2 mg, 61%) and the more polar C-11 alcohol (84) (0.6 mg, 9%) (ratio 9:1).

Less polar (86): ν_{max}(film) 3502, 3033, 2963, 1717, 1602, 1584, 1450, 1380, 1314, 1276, 1217, 1162, 1070, 1026, 997 and 916 cm^{-1}; δ (500 MHz) 8.05-7.42 (10H, m, Ph), 5.76 (1H, dd, J 10.0 and 1.8 Hz, 22-H), 5.60 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.49-5.40 (2H, obs.m, 15-H, 19-H), 4.50 (1H, dd, J 11.0 and 4.5 Hz, 11-CH), 4.45 (1H, dd, J 11.0 and 4.0 Hz, 11-CH), 3.96 (1H, m, 17-H), 3.89 (1H, d, J 9.0 Hz, 13-H), 3.44 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.38 (1H, m, 16-H), 2.30-2.11 (5H, obs.m, 12-H, 16-H, 18-H_e, 20-H_e, 24-H), 1.66 (3H, s, 14-Me), 1.60-1.45 (5H, obs.m, 13-OH, 20-H_a, 26-H, 27-H_2), 1.39 (1H, q, 12 Hz, 18-H_a),0.96-0.91 (12H, obs.m, 12-Me, 24-Me, 26-Me, 28-H_3); m/z 608($M+NH_4^+$), 573 ($M+H^+-H_2O$), 486 ($M+NH_4^+-PhCO_2H$), 305 ($C_{20}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$); (Found: C, 73.35; H, 7.95. $C_{36}H_{46}O_7$.requires C, 73.2; H, 7.8%).

More polar (84): Identical in all respects to previous sample obtained by ozonolysis .

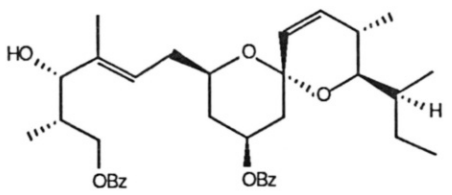
34. Preparation of 13,19-dibenzoyloxy-11-hydroxy-avermectin B_{1a} aglycone northern hemisphere (84) and 11,19-dibenzoyloxy-13-hydroxy-avermectin B_{1a} aglycone northern hemisphere (86).



(109) (84)

3 : 1

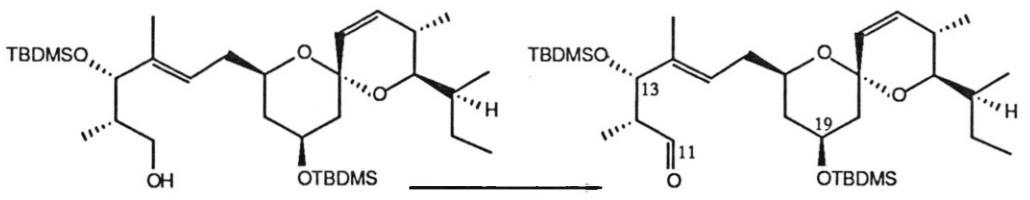
+



(86)

TsOH (10 mg, excess) was added to a solution of the silyl derivative (109) (2 mg, 0.00241 mmol) and water (2drops) in acetone (0.5 ml) at r.t . The mixture was stirred for 50h. after which time t.l.c. analysis showed 60% conversion to the C-11 alcohol (84) and C-13 alcohol (86) in a ratio of 3 :1.

35. Preparation of 13,19-di-^{t}butyldimethylsilyloxy-11-formyl-avermectin B_{1a}-aglycone northern hemisphere (110).

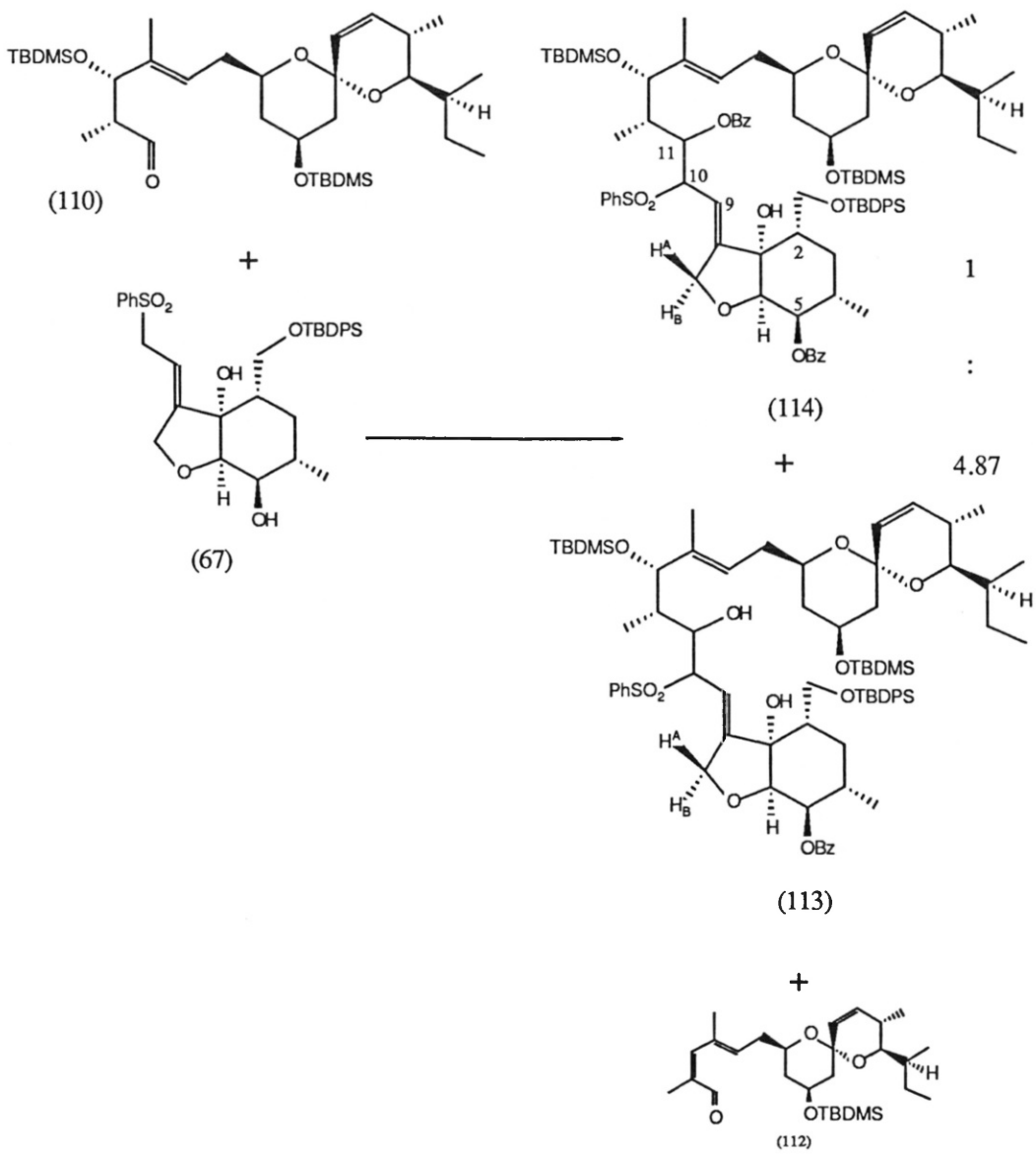


(88) (110)

DMSO (0.047, 0.667 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.029 ml, 0.333 mmol) in dry DCM (1.1 ml) under argon, at -60°C. After 10 min., the alcohol (88) (0.097 g, 0.159 mmol) in dry DCM (1.8 ml) was added dropwise. (After one half of the alcohol had been added a white precipitate was seen.) After a further 30 min. at -60°C, triethylamine (0.111 ml, 0.794 mmol) was added. The mixture was allowed to warm to r.t., poured into water and extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (8% ether-petrol) afforded the aldehyde (110) (0.089 g, 92%) as a clear viscous oil.$[\alpha]_D^{20}$ +40.9° (c=0.44, $CHCl_3$); ν_{max}(film) 2956, 2931, 2857, 1726, 1459, 1382, 1254, 1213, 1155, 1117, 1069, 999, 918, 872 and 775 cm^{-1}; δ (500 MHz) 9.75 (1H, d, J 3.0 Hz, 11-H), 5.69 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.54 (1H, dd, J 10.0 and 3.0 Hz, 23-H), 5.38 (1H, t, J 7.0 Hz, 15-H), 4.10 (1H, obs.tt, J 11.0 and 5.0 Hz, 19-H), 4.09 (1H, d, J 8.5 Hz, 13-H), 3.77 (1H, m, 17-H), 3.38 (1H, dd, J 10.0 and 2.0 Hz, 25-H), 2.55 (1H, m, 12-H), 2.31 (1H, m, 16-H), 2.22 (1H, obs.m, 24-H), 2.18 (1H, obs.m, 16-H), 1.87 (1H, ddd, J 13.0, 4.0 and 2.0 Hz, 20-H_e), 1.81

(1H, m, 18-H_e), 1.59 (3H, s, 14-Me), 1.55 (1H, obs.m, 26-H), 1.42-1.35 (3H, obs.m, 20-H_a, 27-H_2), 1.18 (1H, q, J 12.0 Hz, 18-H_a), 0,94-0.85 (12H, obs.m, 12-Me, 24-Me, 26-Me, 28-H_3), 0.88, 0.86 (2x9H, 2xs, ^tBu), 0.05, 0.045, 0.02, -0.03 (2x6H, 4xs, $SiMe_2$); m/z 593 (M^+-Me), 551 (M^+-^tBu), 419, 353, 221 ($C_{14}H_{20}O_2^+$); (Found: C, 66.91; H, 10.83. $C_{34}H_{64}O_5Si_2$ requires C, 67.0; H, 10.6%).

36. Preparation of 1-^{t}butyldiphenylsilyloxy-2α–3,4-dihydro-5,11-dibenzoyloxy-10-phenylsulphonyl-13,19-di^{t}butyldimethylsilyoxy-avermectin B_{1a} aglycone (114) , 1-^{t}Butyldiphenylsilyloxy-2α–3,4-dihydro-5-benzoyloxy-11-hydroxy-10-phenylsulphonyl-13,19-di^{t}butyldimethylsilyoxy-avermectin B_{1a}-aglycone (113) and 19-^{t}butyldimethylsilyloxy-13-deoxy-12-dehyro-11-formyl-avermectin B_{1a} aglycone nothern hemisphere (112).



The diol sulphone (67) (0.054 g, 0.0879 mmol), was dissolved in dry THF (1.5 ml) under argon at -78°C. ^{t}BuLi (0.163 ml of a 1.7M pentane solution, 0.276 mmol) was added dropwise over 1min. Dry HMPA (0.2 ml) was added to the very viscous, deep orange mixture at -78°C. The solution became a clear orange colour, and was stirred for 10 min. The aldehyde (110) (0.051 g, 0.0837 mmol) in dry THF (0.6 ml) was added dropwise at -78°C, over 2 min. and stirring continued for 35 min. at -78°C. The mixture was warmed to -50 °C and stirred for a further 30 min.. Saturated ammonium chloride was added and the mixture allowed to come to r.t. It was poured into 10% HCl/ether, and the ether layer was washed with saturated aqueous sodium hydrogen carbonate, brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (Gradient elution 5%, 25% and60% ethyl acetate-petrol) afforded recovered unepimerised aldehyde (110) (0.0328 g) $[\alpha]_D^{20}$ = +36.3° (c=3.3, $CHCl_3$); enone (112) (0.0081 g, 20%), ν_{max}(film) 2958, 2928, 2856, 1681, 1617, 1462, 1381, 1258, 1155, 996 and 872 cm^{-1}; δ (500 MHz) 9.49 (1H, s, 11-H), 6.74 (1H, bs.s, 13-H), 5.94 (1H, br.t, J 7,0 Hz, 15-H), 5.72 (1H, dd, J 10.0 and 1.8 Hz, 22-H), 5.56 (1H, dd, J 10.0 and 23-H), 4.13 (1H, tt, J 11.0 and 4.5 Hz, 19-H), 3.85 (1H, m, 17-H), 3.37 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2,42, 2.37 (2H, m, 16-H_2), 2.23 (1H, m, 24-H), 1.95 (3H, d, J 3.0 Hz, 14-Me),1.89 (1H, ddd, J 5.0 and 2.0 Hz, 20-H_e), 1.82 (1H, m, 18-H_e), 1.56 (3H, s, 12-Me), 1.54 (3H, obs.m, 26-H), 1.45-1.35 (3H, obs.m, 20-H_a, 27-H2), 1.27 (1H, obs.q, 18-H_a), 0.59-0.58 (18H, obs.m+s, 24-Me, 26-Me, 28-H_3, ^{t}Bu), 0.06, 0.05 (6H, 2s, Me_2Si); m/z 476 (M^+), 419 (M^+-^{t}Bu), 390, 353, 253, 221 ($C_{14}H_{20}O_2^+$), 199; hydroxy sulphones (0.0284 g, 28%) and recovered diol sulphone (67) (0.0225 g).

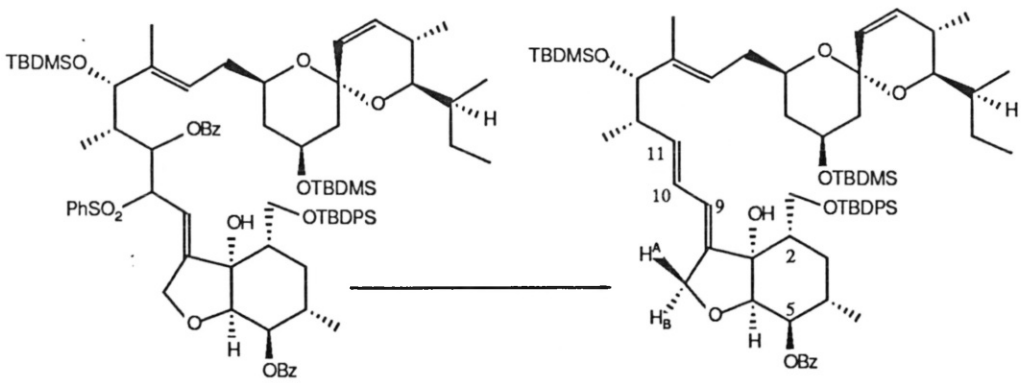
Benzoyl chloride (0.053 ml, 0.461 mmol) was added to the hydroxy sulphones (0.028 g, 0.023 mmol) and DMAP (0.002 g, 0.016 mmol) in dry pyridine (3 ml) under argon at 0°C. After stirring at room temperature for 15 h at r.t., 3-dimethylaminopropylamine (0.05 ml) was added at 0°C and the mixture stirred at r.t for 15 min. It was poured into 1M HCl/ether, the ether layer washed with saturated sodium hydrogencarbonate, brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography afforded the benzoyloxy sulphone (114) (0.0048 g, 15%) and hydroxy sulphone (113) (0.0016 g, 73%) as white foams.

Less polar (114): ν_{max}(film) 3451, 2959, 2930, 1719, 1659, 1642, 1521, 1382, 1261, 1179, 1142, 1071 and 999 cm^{-1}; δ (500 MHz) + COSY, 8.09 (2H, dd, J 8.0 and 1.5 Hz, PhCO(o)), 7.95 (2H, dd, J 8.0 and 1.5 Hz, PhCO(o)), 7.61-7.34 (21H, m, $PhSO_2$, PhSi, Ph(m), Ph(p)), 5.61 (1H, J 10.0 and 1.5 Hz, 22-H), 5.43 (1H, J 10.0 and 2.5 Hz, 23-H), 5.22-5.19 (1H, dd, J 11.0 and 3.0 Hz, 5-H), 4.78 (1H, app.d, J 9.5 Hz, 11-H), 4.26 (1H, dd, 14.0 and 2.5 Hz, 8_α-H), 4.07 (1H, tt, J 11.0 and 4.5 Hz, 19-H), 4.01 (1H, br.d, J 10.5 Hz, 1-H), 3.92 (1H, d, J 9.5 Hz, 13-H), 3.835 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H), 3.68 (1H, m, 17-H), 3.64 (1H, d, J 3.5 Hz, 6-H), 3.545 (1H, dd, J 11.0 and 9.5 Hz, 10-H), 3.51 (1H, br.d, J 10.5 Hz, 1-H), 3.31 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.31 (1H, m, 12-H), 2.21-2.13 (3H, obs.m, 16-H_2, 4-H), 2.05 (1H, M, 24-H), 1.88 (1H, q, J 13-Hz, 3-H_B), 1.83, 1.79 (2H, obs.m, 18-H_e. 20-H_e), 1.56 (3H, s, 14-Me), 1.53 (1H, obs.m, 3-H_e), 1.36-1.26 (4H, obs.m, 20-Ha, 26-H, 27-H_2), 1.13 (1H, q, J 12.0 Hz, 18-H_a), 1.05 (9H, s, ^{t}BuDPS), 0.95 (3H, d, J 6.5 Hz, 4-Me), 0.92 (9H, s, ^{t}BuDMS), 0.87-0.82 (9H, obs.m, 24-Me, 26-Me, 28-H_3), 0.87 (9H, s, ^{t}BuDMS), 0.39 (3H, d, J 7.0 Hz, 12-Me), 0.11, 0.07, 0.04,-0.03 (12H, 4xs, Me_2Si); m/z FAB 1187, 1132, 721, 703, 551, 221 ($C_{14}H_{20}O_2^+$); (Found: see

Appendix).

More polar (113): ν_{max}(film) 3450(s), 2958, 2858, 1719, 1655, 1588, 1511, 1428, 1383, 1270, 1178, 1146, 1115,1069 and 997 cm^{-1}; δ (500 MHz) + COSY 8.06 (2H, dd, 8.0 and 1.5 Hz, PhCO(o), PhCO(m),(p), $PhSO_2$), 5.93 (1H, dt, J 10.5 and 2.5Hz, 9-H), 5.68 (1H, dd, J 10.0 and 1.5, 22-H), 5.58 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.32 (1H, br.t, 7.0 Hz, 15-H), 5.16 (1H, s, 7-OH), 5.14 (1H, dd, J 12.0 and 3.5 Hz, 5-H), 4.905 (1H, br.m, 11-H), 4.25 (1H, dd, J 14.5 and 2.0 Hz, 8a-H), 4.095 (1H, tt, J 11.0 and 4.5, 19-H), 4.05 (1H, dd, J 10.5 and 2.0, 1-H), 3.95 (1H, d, J 7.5, 13-H), 3.78 (1H, d, J 3.5 Hz, 6-H), 3.77 (1H, dd, J 14.5 and 2.0 Hz, 8a-H), 3.75 (1H, obs.m, 17-H), 3.57-3.49 (2H, obs.m, 10-H, 1-H), 3.355 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.01 (1H, br.s, 11-OH), 2.35-2.12 (5H, obs.m, 4-H, 12-H, 16-H_2, 24-H), 1.92 (1H, q, J 13.0 Hz, 3-Ha), 1.85 (2H, obs.m, 3-H_e, 20-H_e), 1.67 (1H, m, 18-H_e), 1.48 (1H, s, 14-Me, 1.43-1.34 (4H, obs.m, 20-H_a, 26-H, 27-H_2), 1.11 (9H, s, ^{t}BuDPS), 0.99 (3H, s, 4-Me), 0.89 (9H, s, ^{t}BuDMS), 0.87 (9H, s, ^{t}BuDMS), 0.92-0.85 (12H, obs.m, 24-Me, 26-Me, 28-H_3), 0.090, 0.045, 0.040, -0.015 (12H, 4xs, $SiMe_2$); m/z FAB 773, 673, 633, 524, 470, 409, 199; (Found: see Appendix).

37 Preparation of 1-^{t}butyldiphenylsilyloxy-2α–3,4-dihydro-5-benzoyloxy-13,19 di^{t}butyldimethylsilyloxy-avermectin B_{1a} aglycone (115).

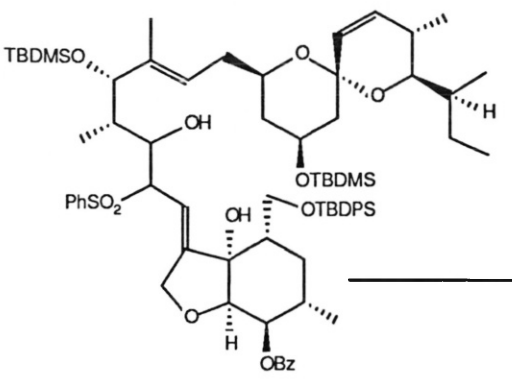


(114) (115)

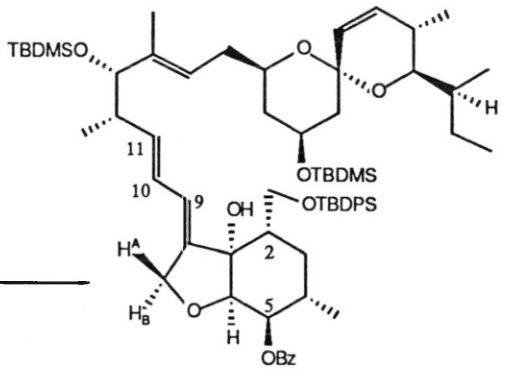
Powdered 6% sodium amalgam (0.011 g, 0.028 mmol), was added to a vigorously stirred slurry of potassium dihydrogen orthophosphate (0.038 g, 0.280 mmol), and benzoyloxy sulphone (114) (0.004 g, 0.0028 mmol) in THF:methanol, 3:1, (0.4 ml) under argon at -40°C. After 2h, a further portion of powdered 6% sodium amalgam (0.011 g, 0.028 mmol) was added. After 5h more, t.l.c. showed complete consumption of starting material. The mixture was cooled to -60°C, ethyl acetate (5 ml) and powdered ammonium chloride were added, and the cold mixture filtered through a pad of ammonium chloride and silica gel. The filtrate was evaporated *in vacuo*. Flash chromatography (8% ethyl acetate-petrol) afforded the *E,E*-diene (115) (0.001 g, 31%), as a glass. ν_{max}(film) 3460, 2927, 2856, 1719, 1589, 1459, 1380, 1269, 1187, 1113, 1069, 966 and 872 cm^{-1}; δ (500 MHz) 8.11 (2H, app.d, J 7.0 Hz, Bz(o)), 7.70 (4H, 2app.d, J 7.0 Hz, PhSi (o)), 7.54-7.40 (9H, m, PhSi (m), (p), Bz (m), (p)), 6.00 (1H, dt J dt, 11.0 and 2.0 Hz, 9-H),

5.80 (dd, J 15.0 and 11.0 Hz, 10-H), 5.69 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.58 (1H, dd, J 15.0 and 8.0 Hz, 11-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.27 (1H, br.t, J 6.0 Hz, 15-H), 5.22 (1H, dd, J 11.0 and 3.5 Hz, 5-H), 4.99 (1H, s, 7-OH), 4.60, 4.47 (2H, 2xdd, J 14.0 and 2.0 Hz, 8_{α}-H_2), 4.19 (1H, dd, J 11.0 and 2.0 Hz, 1-H), 4.12 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 3.91 (1H, d, J 3.5 Hz, 6-H), 3.76 (1H, m, 17-H), 3.63 (1H, dd, J 11.0 and 2.0 Hz, 1-H), 3.58 (1H, d, J 8.5 Hz, 13-H), 3.41 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.35-2.15 (4H, obs.m,. 12-H, 16-H_2, 24-H), 2.02 (1H, obs.m, 20-H_e), 1.96 (1H, q, J 13.0 Hz, 3-H_a), 1.86 (2H, obs.m, 3-H_e, 18-H_e), 1.55 (3H, 14-Me), 1.60-1.20 (5H, obs.m, 18-H_a, 20-H_a, 26-H, 27-H_2),1.12 (3H, d, J 7.0 Hz, 4-Me), 1.12 (3H, s, ^{t}BuDPS), 1.02 (3H, d, J 7.0 Hz, 12-Me), 0.94-0.82 (9H, obs.m, 24-Me, 26-Me, 28-H_3), 0.88, 0.76 (18H, 2xs, ^{t}BuDMS), 0.07, 0.07, -0.09, -0.11 (12H, 4xs, Me_2Si); m/z 1160 (M^+), 1143 (M^+-OH), 1104 (M^+-C_4H_8), 1086 (M^+-C_4H_8-H_2O), 981, 966, 934, 889, 775, 695, 551, 419, 352, 199, 122 ($PhCO_2H$).

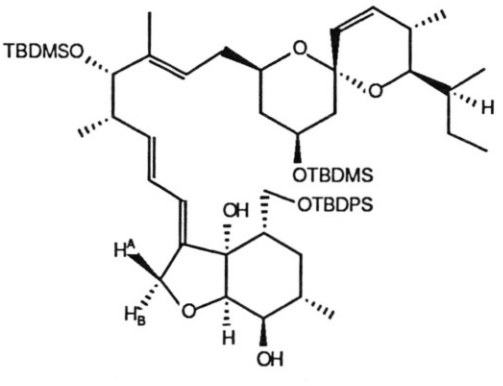
38. Preparation of 1-^{t}butyldiphenylsilyloxy-2α–3,4-dihydro-5-benzoyloxy-13,19 di^{t}butyldimethylsilyloxy-avermectin B_{1a} aglycone (115) and 1-^{t}butyldiphenylsilyloxy-2α–3,4-dihydro-5-hydroxy-13,19-di^{t}butyldimethylsilyloxy-avermectin B_{1a} aglycone (116).



(113)



(115)



(116)

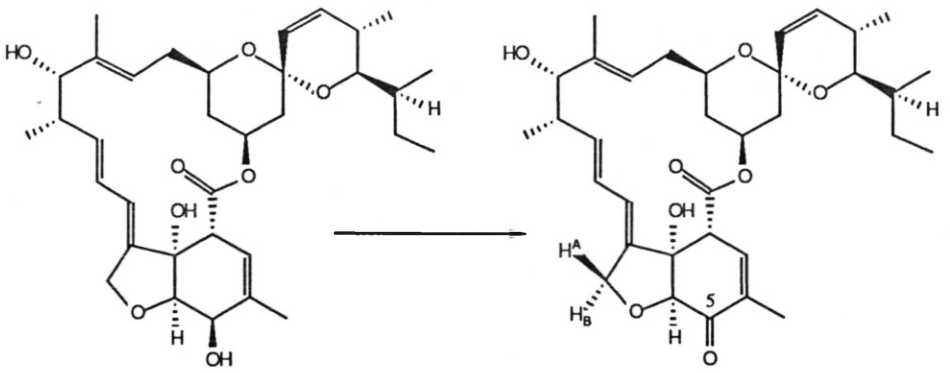
Powdered 6% sodium amalgam (0.0205 g, 0.0535 mmol), was added to a vigorously stirred slurry of potassium dihydrogen orthophosphate (0.029 g, 0.214 mmol), and hydroxy sulphone (113) (0.0065 g, 0.00492 mmol) in THF:methanol, 3:1, (0.8 ml) under argon at -40°C. After 30 min, a further portion of powdered 6% sodium amalgam (0.0010 g, 0.026 mmol) was added. After 40 min. more, t.l.c.

showed complete consumption of starting material. The mixture was cooled to -60°C, ethyl acetate (2 ml) and powdered ammonium chloride were added, and the cold mixture filtered through a pad of ammonium chloride and silica gel, washing with ethyl acetate. The filtrate was evaporated *in vacuo*. Flash chromatography (Gradient elution 8%, 10% and 25% ethyl acetate-petrol) afforded the *E,E*- 5-benzoyloxy diene (115) (0.00211 g, 43%), and *E,E*- 5-hydroxy diene (116) (0.00191g, 37%) as clear glasses.(Total yield of diene products is 80%.) Overall yield of Julia is 18% (49% based on recovered aldehyde).

Less polar (115): Identical in all respects to previously obtained sample.

More polar (116): ν_{max}(film) 3461, 2928, 2855, 1735, 1461, 1380, 1255, 1155, 1113, 1068, and 999 cm^{-1}; δ (500 MHz) 7.69-7.36 (10H, m's, Ph), 5.99 (1H, dt, J 11.0 and 2.5 Hz, 10-H), 5.695 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.58 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.28 (1H, br.t, J 7.0 Hz, 15-H), 5.08 (1H, s, 7-OH), 4.61, 4.43 (2H, 2xdd, J 14.0 and 2.5 Hz, 8a-H), 4.17 (1H, dd, 11.0 and 2.5 Hz, 1-H), 3.76 (1H, m, 16-H), 3.75 (1H, d, 3.5 Hz, 6-H), 3.60 (1H, dd, 11.0 and 2.5 Hz, 1-H), 3.59 (1H, d, 8.5 Hz, 13-H), 3.57 (1H, m, 5-H), 3.41 (1H, dd, 10.0 and 1.5 Hz, 25-H), 2.35-2.22 (5H, obs.m, 2-H, 12-H, 16-H_2, 12-H), 2.15 (1H, m, 20-H_e), 1.86-1.76 (3H, obs.m, 3-H_e, 3-H_a, 18-H_e), 1.54 (3H, s, 14-Me), 1.46-1.35 (4H, obs.m, 20-H_a, 26-H, 27-H_2), 1.15 (1H, obs.q, 18-H_a), 1.10 (9H, s, ^{t}BuDPS), 1.10 (3H, obs.d, 12-Me), 0.95-0.87 (12H, obs.m, 4-Me, 24-Me, 26-Me, 28-H_3), 0.89 (9H, s, ^{t}BuDMS), 0.75 (9H, s, ^{t}BuDMS), 0.08 to -0.014, 4xs, Me_2Si); m/z 1039 (M^+-H), 1022 (M^+-H_2O), 1021 (M^+-H-H_2O), 982 (M^+-H-C_4H_9), 965 (M^+-H_2O-C_4H_9), 935, 889, 832 (889-C_4H_9), 775, 619, 551, 419, 353, 199.

39. Preparation of 5-oxo-avermectin B_{1a} aglycone (122).

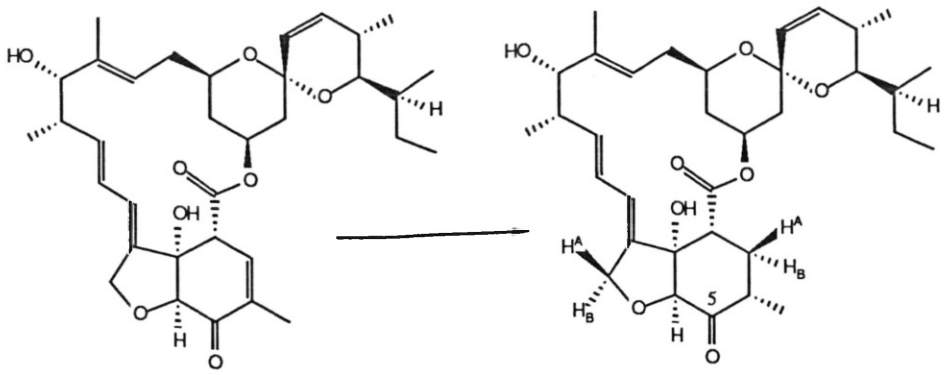


(81) (122)

Manganese dioxide (4.46g, 51.3 mmol) was added to a solution of aglycone (81) (1.00g, 1.71 mmol) in dry DCM (20 ml) under argon and vigorously stirred for 15 min at r.t. (t.l.c. showed no aglycone present). Ethyl acetate (30 ml) was added stirring continued for 10 min. and the mixture filtered through a pad of florisil. The filtrate was evaporated *in vacuo* and flash chromatography (30% ethyl acetate-petrol) afforded the enone (122) (60%, 0.597 g) as a foam. [Decomposes slightly on silica].$[\alpha]_D^{20}$ +85.8° (c=0.66, $CHCl_3$); ν_{max}(film) 3480, 2962, 2927, 1714, 1680, 1539, 1450, 1338, 1183, 1160, 1037, 997, 907 and 733 cm^{-1}; δ (500 MHz) 6.57 (1H, m, 3-H), 5.90 (1H, dt, J 11.0 and 2.5 Hz, 9-H), 5.76 (3H, m, 10-H, 11-H, 22-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.42 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 5.34 (1H, m, 15-H), 4.76 (1H, dd, J 14..0 and 2.5 Hz, 8_α-H_B), 4.71 (1H, J 14.0 and 2.5 Hz, 8_α-H_A), 4.02 (1H, obs.m, 17-H), 3.85 (1H, s, 7-OH), 3.56 (1H, m, 2-H), 3.47 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.53 (1H, m, 12-H), 2.33-2.25 (2H, m, 16-H_2, 24-H), 2.03 (1H,m ddd, J 12.0 and 5.0 and 1.5 Hz,

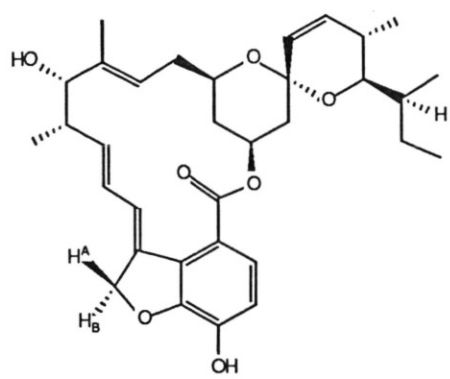
20-H_e), 1.88 (3H, m, 4-Me), 1.79 (1H, m, 18-H_e), 1.63 (1H, br.s, 13-OH), 1.61 (1H, obs.m, 20-H_a), 1.58 (1H, obs.m, 26-H), 1.53 (3H, s, 14-Me), 1.49 (2H, m, 27-H_2), 1.18 (3H, d, J 7.0 Hz, 12-Me), 0.97 (3H, t, J 7.5 Hz, 28-H_3), 0.92 (3H, d, J 7.0 Hz, 26-Me), 0.92 (3H, d, J 7.0 Hz, 24-Me), 0.90 (1H, q, J 12.0 Hz, 18-H_a); m/z 582 (M^+), 564 (M^+-H_2O), 496, 456 ($C_{29}H_{42}O_5^+$), 305 ($C_{20}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{14}H_{20}O_2^+$),, 169 ($C_{10}H_{20}O_2^+$), 123, 111 ($C_6H_6O_2^+$); (Found M, 582.3198. $C_{34}H_{46}O_8$ requires M^+, 582.3192)

40. Preparation of 3,4(*R*)-dihydro-5-oxo-avermectin B_{1a} aglycone (121),



(122) (121)

+



(124)

To a mixture of enone (122) (0.051 g, 0.0875 mmol), sodium ditionate (0.137 g, 0.788 mmol) and sodium hydrogen carbonate (0.132 g, 1.58 mmol) in benzene:water, 1:1, (2 ml) under argon was added Aliquat ® (0.012 ml, 0.0263 mmol). The vigorously stirred two-phase system was refluxed for 10 min.(no enone by t.l.c). The mixture was brought to r.t. and poured into ether/water. The aqueous phase was extracted with ether and the combined organics washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. Rapid flash chromatography on florisil (20% ethyl acetate-petrol) afforded the 5-ketone (121) (48%, 0.244 g) and aromatic aglycone (124) (8%, 0.0040g) as foams.

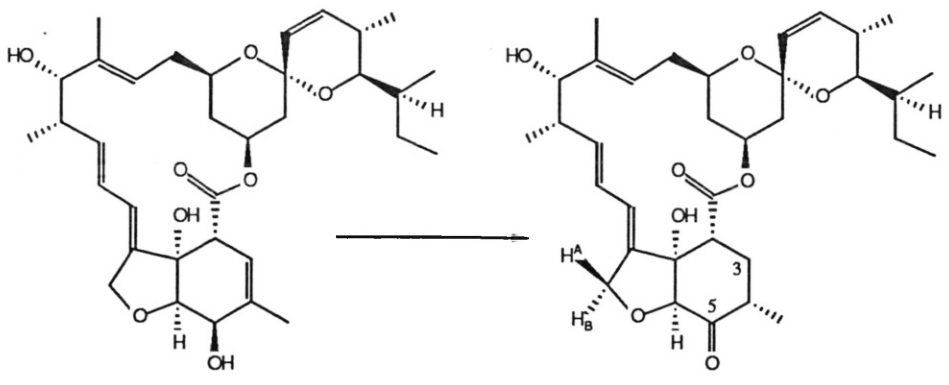
Less polar: (121) $[\alpha]_D^{20}$ +189.5° (c=0.57, $CHCl_3$); ν_{max}(film) 3472, 3029, 2962, 2930, 1721(r), 1453, 1379, 1350, 1180, 1161, 1073 and 997 cm^{-1}; δ (500 MHz) 5.82-5.72 (4H, obs.m, 9-H, J 10-H, 11-H, 22-H), 5.64 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.42 (1H, tt, J 11.5 and 5.0 Hz, 19-H), 5.31 (1H, m, 15-H), 4.76 (1H, dd, J 14.0 and 2.5 Hz, 8_α-H_B), 4.65 (1H, dd, J 14.0 and 2.5 Hz, 8_α-H_A), 4.55 (1H, s, 7-OH), 4.00 (1H, br.s, 13-H), 3.89 (1H, m, 17-H), 3.76 (1H, s, 6-H), 3.46 (1h, dd, J 10.0 and 1,5 Hz, 25-H), 3.01 (1H, dd, J 13.0 and 4.0 Hz, 2-H), 2.79 (1H, m, 4-H), 2.51 (1H, m, 12-H), 2.34-2.24 (3H, obs.m, 16-H_2, 24-H), 2.07 (1H, q, J 13.0 Hz, 3-H_B), 2.03 (1H, obs.m, 3-H_A), 1.93 (1H, ddd, J 12.0, 5.0 and 1.5 Hz, 20-H_e), 1.75 (1H, m, 18-H_e), 1.62-1.45 (5H, obs.m, 13-OH, 20-H_a, 26-H, 27-H_2), 1.52 (3H, s, 14-Me), 1.17 (3H, d, J 7.0 Hz, 12-Me), 1.09 (3H, d, J 7.0 Hz, 14-Me), 0.96 (3H, t, J 7.5 Hz, 28-H_3), 0.91 (3H, d, J 7.0 Hz, 26-Me), 0.90 (3H, d, J 7.0 Hz, 24-Me), 0.85 (1H, q, J 12.0 Hz, 18-H_a); m/z 584 (M^+), 566 (M^+-H_2O), 4978, 305, ($C_{20}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 193

($C_{13}H_{19}O^+$), 169 ($C_{16}H_{17}O_2^+$), 151, 135, 123, 119, 105, 74; (Found: M, 584.3358. $C_{34}H_{48}O$ requires M^+, 584.3349,).

More polar: (124): Very U.V. active; ν_{max}(film) 3451, 2962, 2926, 1708 (br), 1610, 1507, 1452, 1347, 1125, 1073 and 996 cm^{-1}; δ (500 MHz) 7.06 (1H, s, 3-H), 6.26 (1H, dt, J 12.0 and 2.5 Hz, 9-H), 5.88 (1H, dd, J 15.0 and 12.0 Hz, 10-H), 5.74 (1H, dd, J 10.0 and 2.5 Hz, 22-H), 5.72 (1H, dd, J 15.0 and 10.0 Hz, 11-H), 5.52 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.47 (1H, m, 19-H), 5.42 (1H, m, 15-H), 5.24 (2H, m, 8_α-H_2), 5.09 (1H, br.s, 5-OH), 4.10 (1H, br.s, 13-H), 4.01 (1H, m, 17-H), 3.49 (1H, dd, J 10 and 1.5 Hz, 25-H), 2.63 (1H, m, 12-H), 2.38-2.22 (4H, obs.m, 16-H_2, 20-H_a, 24-H), 2.22 (3H, s, 4-Me), 2.06 (1H, m, 18-H_e), 1.64-1.42 (5H, obs.m, 13-OH, 20-H_a, 26-H, 27-H_2), 1.55 (3H, s, 14-Me), 1.21 (3H, d, J 7.0 Hz, 12-Me), 1.04 (1H, q, J 12.0 Hz, 18-H_a), 0.99-0.90 (9H, obs.m, 24-Me, 26-Me, 28-H_3).

41. Preparation of 3,4(*R*)-dihydro-5-oxo-avermectin B_{1a} aglycone (121).

IMPROVED PROCEDURE.

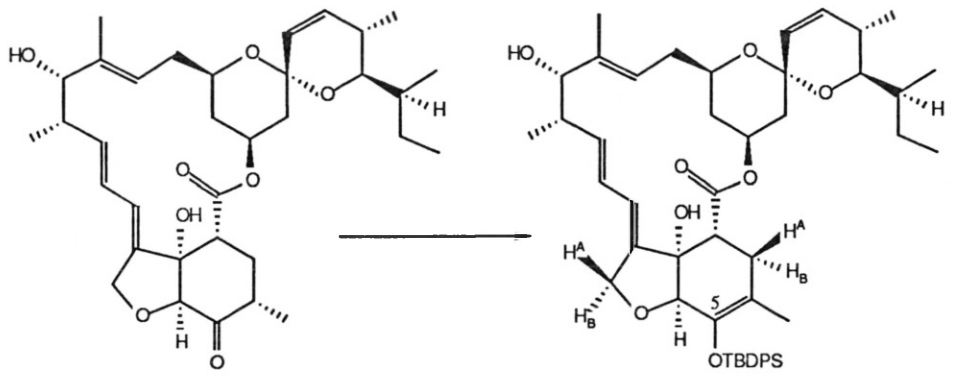


(81) (121)

Manganese dioxide (2.54 g, 29.2 mmol) was added to a solution of aglycone (81) (0.57 g, 0.975 mmol0, in dry DCM (10 ml) under argon and vigorously stirred for 15 min. at r.t. (T.l.c. showed no aglycone present). Ethyl acetate (30 ml) was added and stirring continued for 10 min. and the mixture filtered through a pad of florisil. The filtrate was evaporated in vacuo to give the crude enone (122) (0.422 g) as a yellow foam. To a mixture of enone (122) (0.422 g, 0.724 mmol), sodium ditionate (1.133 g, 6.51 mmol) and sodium hydrogen carbonate (1.094 g, 13.03 mmol) in benzene: water, 1:1, (18 ml) under argon was added Aliquat ® (0.099 ml, 0.217 mmol). The vigorously stirred two-phase system was refluxed for 10 min (no enone by t.l.c.), brought to r.t. and poured into ether/water. The aqueous phase was extracted with ether and the combined organics washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography on florisil (20 % ethyl acetate-petrol) afforded the less polar 5-ketone (121) (40%, 0.185) and the more polar

aromatic aglycone (124) (10%, 0.055 g), as white foams. Both were identical in all respects to previously obtained samples.

42. Preparation of 5-^{t}butyldiphenylsilyloxy-3-hydro-Δ^{4}-avermectin B_{1a} aglycone (123).

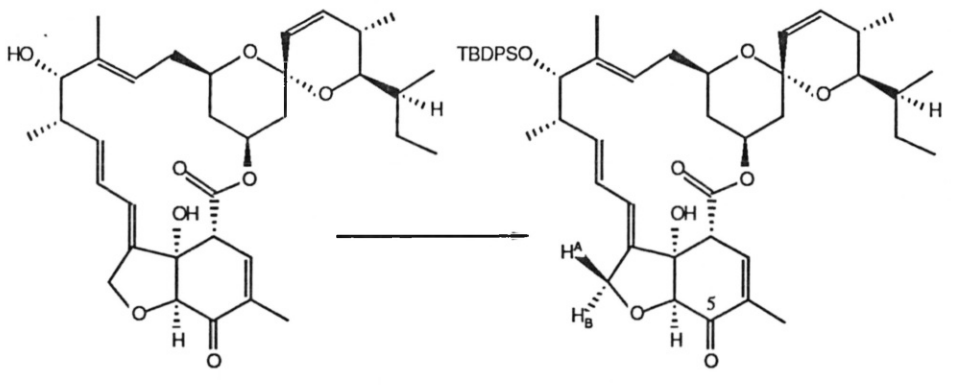


(121) (123)

^{t}Butyldiphenylsilylchloride (0.147 ml, 0.564 mmol) was added to a stirred solution of the alcohol (121) (0.165 g, 0.282 mmol), imidazole (0.077 g, 1.128 mmol) and DMAP (0.007 g, 0.056 mmol) in dry DMF (0.5 ml), under argon, at r.t.. After 13h. more ^{t}butyldiphenylsilylchloride (0.147 ml, 0.564 mmol), imidazole (0.077 g, 1.128 mmol) and DMAP (0.007 g, 0.056 mmol) was addd and the mixture stirred for a further 8h. It was then poured into water an extracted with ether. The combined organic extracts were dried (Na_2SO_4), and evaporated *in vacuo*. Flaash chromatoraphy (15% ethyl acetate-petrol) afforded the silyl enol ether (123) (74%, 0.171 g) as a foam. ν_{max}(film) 3489, 2926, 2854, 1707 (br), 1458, 1427, 1377, 1320, 1236, 1113, 1037, 999 and 965 cm^{-1}; δ (500 MHz) 7.70-7.32 (10H, m, Ph), 5.75 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.71)1H, m, 9-H), 5.60

(2H, m, 10-H, 11-H), 5.54 (1H, dd, J 10.0 an d2.5 Hz, 23-H), 5.39 (1H, tt, J 12.0 and 5.0 Hz, 19-H), 5.27 (1H, m, 15-H), 4.39 (1H, dd, J 14.5 and 2.0 Hz, 8_{α}-H), 4.02 (1H, s, 7-OH), 3.96 (1H, dd, J 14.5 and 2.0 Hz, 8_{α}-H),3.96 (1H, br.s, 13-H), 3.85 (1H, m, 17-H), 3.54 (1H, br.s, 6-H), 3.45 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.62 (1H, dd, J 12.0 and 5.0 Hz, 2-H), 2.51 (1H, dd, J 16.0 an d12.0 Hz, 3-H_B), 2.44 (1H, m, 12-H), 2/30-2.20 (3H, m, 16-H2, 24-H), 2.05 (1H, dd, J 16.0 and 5.0 Hz, 3-H_A), 1.87 (1H, ddd, J 12.0, and 5.0 and 2.0 Hz, 20-H_e), 1.71 (1H, m, 18-H_e), 1.60 (3H, s, 4-Me), 1.55 (1H, s, 13-OH), 1.48 (3H, s, 14-Me), 1.54-1.42 (4H. obs.m, 20-H_a, 26-H, 27-H2), 1.12 (3H, t, J 7.0 Hz,12-Me), 1.10 (9H, s, ^{t}Bu), 0.94 (3H, t, J 7.0 Hz, 28-H_3), 0.89 (6H, 2xd, J 6.0 Hz, 24-Me, 26-Me), 0.80 (1H, q, J 12.0 Hz, 18-H_a); m/z 823 (M^+), 805 (M^+-H_2O), 747 (M^+-H_2O-^{t}Bu), 579, 459, 305 ($C_{20}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$), 169 ($C_{10}H_{17}O_2^+$); (Found: C, 72.97; H,8.26. $C_{50}H_{66}O_8Si$ requires C, 72.96; H, 8.1%)

43. Preparation of 13-^{t}Butyldiphenylsilyloxy-5-oxo-avermectin B_{1a} aglycone (122b).

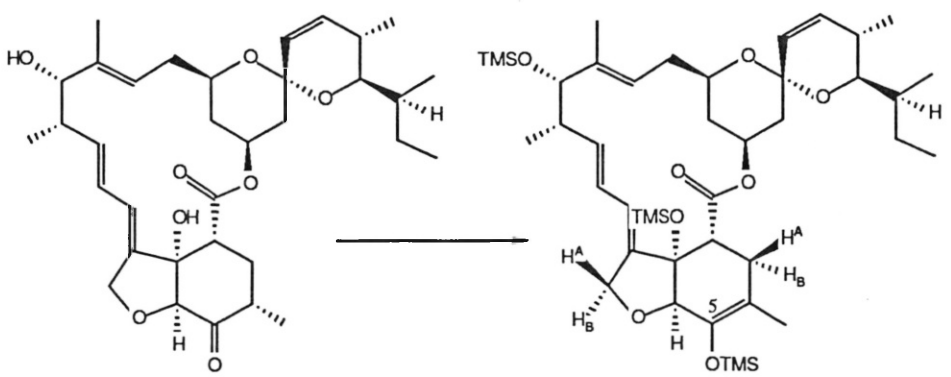


(122) (122b)

^{t}Butyldiphenylsilylchloride (0.025 ml, 0.0961 mmol) was added to a stirred solution of the alcohol (122) (0.028 g, 0.048 mmol), imidazole (0.0105 g, 0.154 mmol) and DMAP (0.001 g, 0.096 mmol) in dry DMF (0.6 ml), under argon, at r.t.. After 17h. the deep orange solution was poured into water and extracted with ether. The combined organic extracts were dried (Na_2SO_4), an evaporated *in vacuo*. Flash chromatography (21% ethylacetate-petrol) afforded the enone (122b) (37%, 0.015 g) as a foam. ν_{max}(film) 3497, 2930, 1696, 1660, 1581, 1462, 1378, 1311, 1156, 1072, 1038 and 997 cm^{-1}; δ (500 MHz) 7.22-7.35 (10H, m, Ph), 6.35 (1H,s, 3-H), 6.22 (1H, dt, J 10.0 and 2.5 Hz, 9-H), 5.76 (1H, dd, J 10.0 and 2.0 Hz, 22-H), 5.70-5.60 (2H, obs.dd, 10-H, 11_H), 5.561 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.27 (1H, m, 15-H), 5.24 (1H, m, 19-H), 4.16 (1H, dd, J 14.0 and 2.5 Hz, 8_{α}-H_B), 3.98 (1H, dd, J 14.0 and 2.5 Hz, 8_{α}-H_A), 3.95 (1H, br.s, 13-H), 3.90 (1H, m, 17-H), 3.86 (1H, s, 6-H), 3.74 (1H, s, 2-H), 3.46 (1H, dd, J

10.0 and 1.5 Hz, 25-H), 2.44 (1H, m, 12-H), 2.30-2.22 (2H, m, 16-H_2, 24-H), 1.94 (1H, dd, J 12.0, 5.0 and 1.5 Hz, 20-H_e), 1.88 (1H, br.d, J 12.0 Hz, 18-H_e), 1.82 (3H, s, 4-Me), 1.62-1.56 (2H, m, 20-H_a, 26-H), 1.50-1.45 (2H, m, 13-OH, 27-H_2), 1.46 (3H, s, 14-Me), 1.13 (3H, d, J 7.0 Hz, 12-Me), 1.11 (9H, s, ^{t}Bu), 0.94 (3H, t, J 7.5 Hz, 28-H_3), 0.91, 0.89 (6H, 2d, J 7.0 Hz, 24-Me, 26-Me), 0.67 (1H, q, J 12.0, 18-H_a); m/z 820 (M^+), 802 (M^+-H_2O), 767, 727 (M^+-H_2O-^{t}Bu), 305 ($C_{20}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 199, 169 ($C_{10}H_{17}O_2^+$); (Found: M^+, 820.4340; $C_{50}H_{64}O_8Si$ requires M, 820.4370).

44. Preparation of 5,7,13- tris-trimethylsilyloxy-3-hydro-Δ^4-avermectin B_{1a}-aglycone (126).



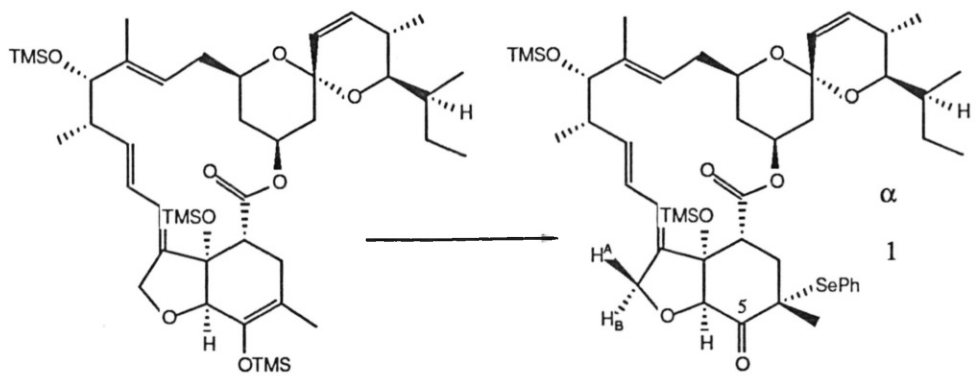
(121) (126)

Triethylamine (0.715 ml, 5.13 mmol) followed by trimethylsilyltriflate (0.04 ml, 0.205 mmol) was added to the ketone (121) (20 mg, 0.0342 mmol) in dry DCM (6 ml) under argon at 0°C. After 1h there was no starting material by t.l.c., but the

less polar 13-OTMS (137) (major) and 13,7-OTMS (138) (minor) respctively (see Experimental Appendix for data), were clearly evident on t.l.c. After a further 30 min. more trimethylsilyltriflate (0.08 ml, 0.410 mmol) was added and the solution stirred for a further 4h. It was then cooled to 0°C, saturated sodium hydrogen carbonate was added and the aqueous phase extracted with DCM (x3). The combined organics were evaporated down (ca. 5 ml), passed through a pad of florisil and the filtrate was evaporated *in vacuo* Flash chromatography on florisil (5% ethyl acetate-petrol) afforded the trisilyloxy enol ether (126) as a stable white foam. $[\alpha]_D^{20}$ +86.9° (c=0.213, $CHCl_3$); ν_{max}(film) 2957, 1740, 1685, 1456, 1376, 1250, 1158, 1035, 874, 843 and 754 cm^{-1}; δ (500 MHz) 5.80 (1H, dt, J 11.0 and 2.0 Hz, m, 9-H), 5.72 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.68 (1H, dd, J 15.0 and 11.0 Hz, 10-H), 5.52 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.24 (1H, obs.tt, 19-H), 5.21 (1H, obs.m, 15-H), 5.47 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B), 4.49 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_A), 3.90 (1H, br.s, 13-H), 3.83 (1H, m, 17-H), 3.68 (1H, s, 6-H), 3.48 (1H, dd, J 10.0 and 1.0 Hz, 25-H), 2.69 (1H, dd, J 16.0 and 12.0 Hz, 3-H_B), 2.57 (1H, dd, J 12.0 and 5.0 Hz, 2-H), 2.43 (1H, m, 12-H), 2.24 (3H, obs.m, 16-H_2, 24-H), 1.96 (1H, ddd, J 12.0, 5.0 and 2.0 Hz, 20-H_e), 1.91 (1H, dd, J 16.0 and 5.0 Hz, 3-H_A), 1.77 (1H, m, 18-H_e), 1,60 (3H, s, 4-Me), 1.49 (3H, s, 14-Me), 1.58-1.35 (4H, obs.m, 20-H_a, 26-H, 27-H_2), 1.06 (3H, d, J 7.0 Hz, 12-Me), 0.95 (3H, t, J 7.0 Hz, 28-H_3), 0.90 (3H, d, J 7.0 Hz, 24-Me), 0.89 (3H, d, J 7.0 Hz, 26-Me), 0.76 (1H, q, 12.0 Hz, 18-H_a), 0.18 (9H, s, Si Me_3), 0.11 (9H, s, Si Me_3), 0.08 (9H, s, Si Me_3),; m/z 800 (M^+), 710 (M^+-TMSOH), 617, 406, 377, 287 (377-TMSOH), 221 ($C_{14}H_{20}O_2^+$), 207, 193 ($C_{13}H_{19}O^+$), 185, 169 ($C_{10}H_{17}O_2^+$), 73 (TMS^+); (Found: M, 800.4512.

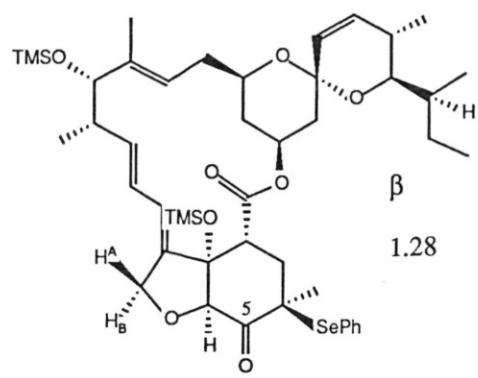
$C_{43}H_{72}O_8Si_3$ requires M^+, 800.4535).

45. Preparation of 4α-benzeneselenyl-7.13-bis-trimethylsilyloxy-3-hydro-5-oxo-avermectin B_{1a} aglycone (129) and 4β-benzeneselenyl-7.13-bis-trimethylsilyloxy-3-hydro-5-oxo-avermectin B_{1a} aglycone (128).



(126) (129)

+



(128)

To a solution of the enol ether (126) (62 mg, 0.0744 mmol) in dry DCM (4 ml) under argon at -78°C was added benzeneselenyl chloride (16.3 mg, 0.0851 mmol) in dry DCM (0.5 ml) dropwise. After stirring the yellow solution for 1h. at -

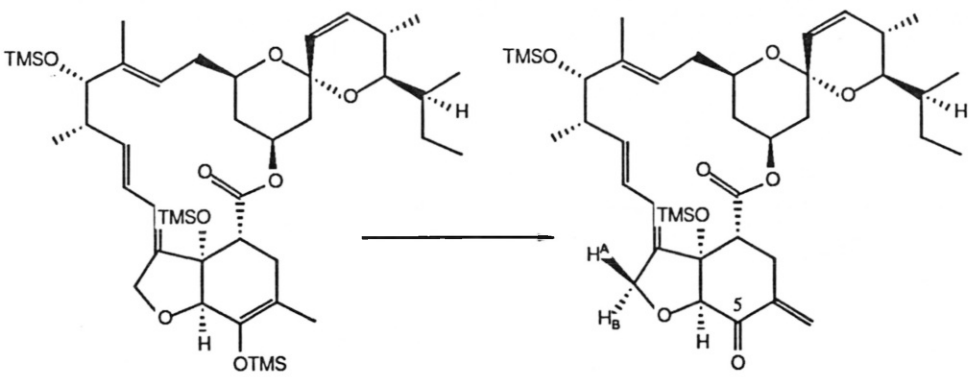
78°C, saturated sodium hydrogen carbonate was added and the mixture allowed to come to 0°C. The cold solution was poured into DCM and the aqueous phase extracted with more DCM (x3). The combined organics were passed through a pad of florisil and evaporated *in vacuo*. Flash chromatography afforded the β-seleno ketone (128) (more polar than s.m.) (25.1 mg, 37%) and α-selenoketone (129) (most polar) (19.7 mg, 29%) as clear glasses. [A very minor product (6 mg) of intermediate polarity between (128) and (129) was isolated and tentatively assigned from the n.m.r. as arising from addition of PhSeCl across then 22,23-double bond].

Less polar (128) β: ν_{max}(film) 2959, 2252, 1741(ester),,1696 (ketone), 1455, 1375, 1253, 1209, 1159, 1101, 1083, 1037, 996, 884 and 736 cm^{-1}; δ (500 MHz) + nOe (see Appendix) + decoupling, 7.52-7.30 (5H, m, PhSe), 5.79 (1H, obs.m, 9-H), 5.76 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.78-5.66 (2H, obs.dd, J 10-H, 11-H), 5.56 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.28 (1H, br.t, J 8.0 Hz, 15-H), 5.15 (1H, tt, J 11.0 and, 5.0 Hz, 19-H), 4.82, 4.65 (2H, 2xdd, J 14.0 and 2.5 Hz, 8_{α}-H_2), 3.93 (1H, br.s, 13-H), 3.87 (1H, s, 6-H),. 3.85 (1H, m, 17-H), 3.50 (1H, dd, J 10.0 and 2.0 Hz, 25-H), 3.35 (1H, dd, J 13.0 and 3.0 Hz, 2-H), 2.59 (1H, J dd, 15.0 and 13.0 Hz, 3-HB), 2.50 (1H, m, 12-H), 2.29-2.25 (3H, obs.m, 16-H_2, 24-H), 2.10 (1H, ddd, J 12.0, 5.0 and 2.0 Hz, 20-H_e), 2.01 (1H, dd, J 15.0 and 3.0 Hz, 3-H_A), 1.81 (1H, m, 18-H_e), 1.60-1.40 (4H, obs.m, J 20-Ha, 26-H, 27-H2), 1.51 (3H, s, 14-Me), 1.44 (3H, s, 4-Me), 1.06 (3H, d, J 7.0 Hz, 12-Me), 0.96 (3H, t, J 7.0 Hz, 28-H_3), 0.92, 0.91, (6H, 2xd, J 7.0 Hz, 24-Me, 26-Me), 0.84 (1H, q, J 12.0 Hz, 18-H_a), 0.12 (9H, s, $SiMe_3$), 0.06 (9H, s, $SiMe_3$); m/z(M^+) ;(Found: see Appendix).

Most polar (129) α: ν_{max}(film) 2959, 1741(ester), 1710 (ketone), 1455,

1375, 1252, 1158, 1103, 1036, 996, 874, 842 and 741 cm^{-1}; δ (500 MHz) +nOe (see Appendix) +decoupling, 7.48-7.29 (5H, m, PhSe), 5.85 (1H, tt, J 10.0 and 2.0 Hz, 9-H), 5.76-5.68 (3H, 22-H, 10-H, 11-H), 5.51 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.28 (1H, br.dd, J 11.0 and 5.0 Hz, 15-H), 5.22 (1H, tt, J 11.0 and 19-H), 5.03 (1H, s, 6-H), 4.65, 4.46 (2xdd, J 13.0 and 2.5 Hz, 8_{α}-H_2), 3.91 (1H, br.s, 13-H), 3.84 (1H, m, 17-H), 3.48 (1H, J dd, 10.0 and 1.0Hz, 25-H), 2,89 (1H, J dd, 15.0 and 14.0 Hz, 3-H_B), 2.49 (1H, m, 12-H), 2.29 (3H, J dd, 13.0 and 2-H), 2.25-2.21 (1H, obs.m, 16-H_2, 24-H), 2.10 (1H, dd, J 15.0 and 3.0 Hz, 3-H_A), 1.99 (1H, obs.m, 20-H_e), 1.78 (1H, m, 18-H_e), 1.60-1.35 (4H, obs.m, 20-H_a, 26-H, 27-H_2), 1.46 (3H, s, 14-Me), 1.41 (3H, s, 4-Me), 1.16 (3H, d, J 7.0 Hz, 12-Me), 0.96 (3H, t, J 7.0 Hz, 28-H_3), 0.91, 0.90 (6H, 2xd, J 7.0 Hz, 24-Me, 26-Me), 0.77 (1H, q, J 12.0 Hz, 18-H_a), 0.22 (9H, s, $SiMe_3$), 0.11 (9H, s, $SiMe_3$); m/z(M^+); (Found: see Appendix).

46. Preparation of 7,13-bis-trimethylsilyloxy-3-hydro-4-methylene-5-oxo-avermectin B_{1a} aglycone (127).

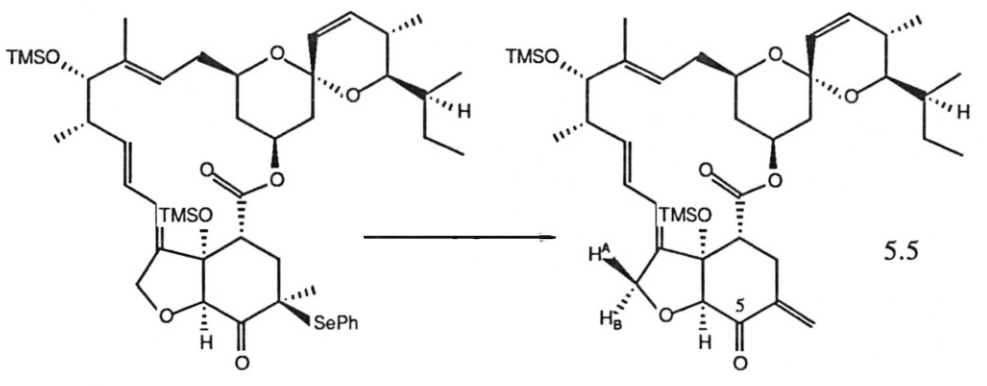


(126) (127)

$Pd(OAc)_2$ (7 mg, 0.0312 mmol) p-benzoquinone (3.4 mg, 0.0312 mmol) and silyl enol ether (126) (5mg, 0.0062 mmol) in dry acetonitrile (0.1 ml) under argon was heated at 50°C for 22 h. Saturated sodium hydrogen carbonate was added at room temperature, an dthe mixture extracted with ethyl acetate. The combined organics were passed through a pad of florisil and the filtrate evaporated *in vacuo*. FGlash chromatography (15% ether-petrol) afforded the *exo*cyclic enone (127) (0.9 mg, 20%), as a clear glass. δ (500 MHz) 6.19 (1H, m, 4-CH), 5.85 (1H, m, J 9-H), 5.74 (1H, dd, J 10.0 and 2.0 Hz, 22-H), 5.69 (2H, obs.m, 10-H, 11-H), 5.53 (1H, J dd, 10.0 and 2.5 Hz, 23-H), 5.42 (1H, m, 4-CH), 5.24 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 5.12 (1H, m, 15-H), 4.65-4.60 (2H, 2xdd, J 14.0 and 2.5 Hz, 8_{α}-H_2), 3.90 (2H, br.s+s, 13-H, 6-H), 3.84 (1H, m, 17-H), 3.48 (1H, dd, J 10.0 and 1.0 Hz, 25-H), 3.25 (1H, ddt, J 16.0, 13.0 and 2.0 Hz, 3-H_B), 2.73 (1H, dd, J 13.0 and 3.0 Hz, 2-H), 2.61 (1H, app.dd, J 16.0 and 3.0 Hz, 3-H_A), 2.46 (1H, m, 12-H), 2.35-2.25 (3H, obs.m, 16-H2, 24-H), 2.05 (1H, obs.m, 20-H_a), 1.79

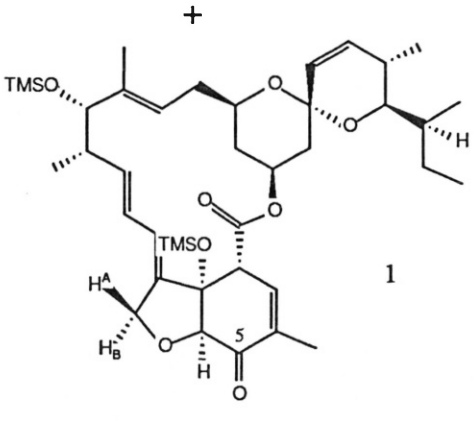
(1H, m, 18-H_e), 1.60-1.40 (4H, obs.m, 20-He, 26-H, 27-H_2), 1.60 (3H, s, 14-Me), 1.07 (3H, d, J 7.0 Hz, 12-Me), 0.95 (3H, t, J 7.0 Hz, 28-H_3), 0.88, 0.87 (6H, 2xd, J 7.0 Hz, 24-Me, 26-Me), 0.75 (1H, q, J 12.0 Hz, 18-H_a), 0.14 (9H, s, $SiMe_3$), 0.06 (9H, s, $SiMe_3$).

47. Preparation of 7,13-bis-trimethylsilyloxy-5-oxo-avermectin B_{1a} aglycone (131) and 7,13-bis-trimethylsilyloxy-3-hydro-4-methylene-5-oxo-avermectin B_{1a} aglycone (132).



(128) (132)

+



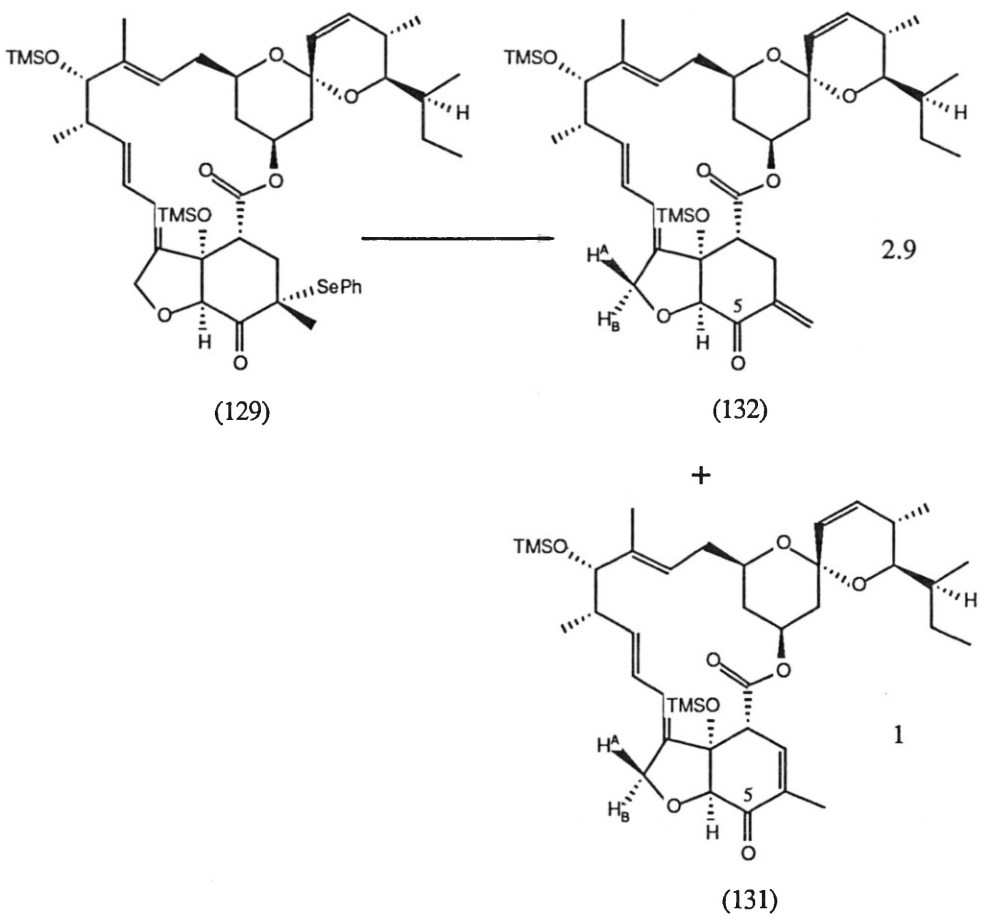
(131)

The oxaziridine (130) (1mg, 0.0033 mmol) was added to a solution of the β-seleno ketone (128) (1mg, 0.001 mmol) in deuterochloroform (1 ml) in an n.m.r. tube at r.t. The reaction was monitored by n.m.r. Reaction was complete within 25 min. at r.t.

Inspection of the crude 500 MHz n.m.r. showed the ratio of *exo* (132) to

endo (131) enone as 5.5 : 1. Characteristic resonance of (131) at δ 6.81 (3-H) and of (132) at δ 6.18 (br.s,4-CH), δ 5.42 (br.s, 4-CH).

48. Preparation of 7,13-bis-trimethylsilyloxy-5-oxo-avermectin B_{1a} aglycone (131) and 7,13-bis-trimethylsilyloxy-3-hydro-4-methylene-5-oxo-avermectin B_{1a} aglycone (132).

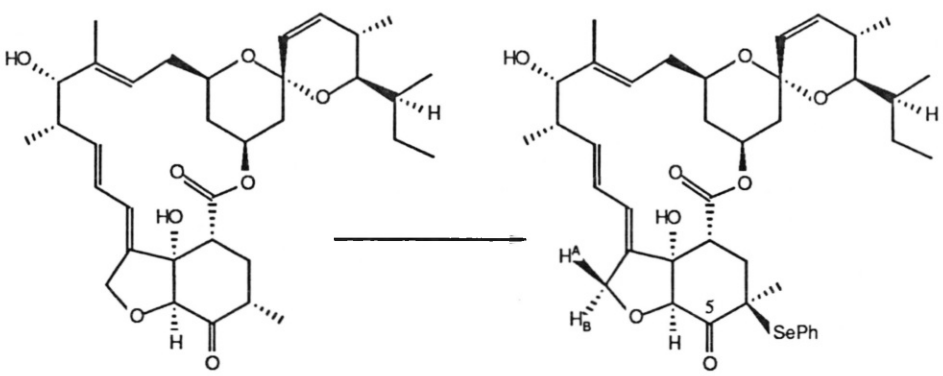


The oxaziridine (132) (0.5 mg, 0.0016 mmol) was added to a solution of the α-seleno ketone (129) (0.5 mg, 0.0005 mmol) in an n.m.r. tube at r.t. The reaction

was monitored by n.m.r. and was complete after 25 min.

Inspection of the crude 500 MHz n.m.r. showed the ratio of *exo* (132) to *endo* (131) enone as 2.9 : 1. Characteristic resonance of (131) at δ 6.81 (3-H) and of (132) at δ 6.18 (br.s,4-CH), δ 5.42 (br.s, 4-CH).

49. Preparation of 4β-benzeneselenyl-3-hydro-5-oxo-avermectin B_{1a} aglycone (133).



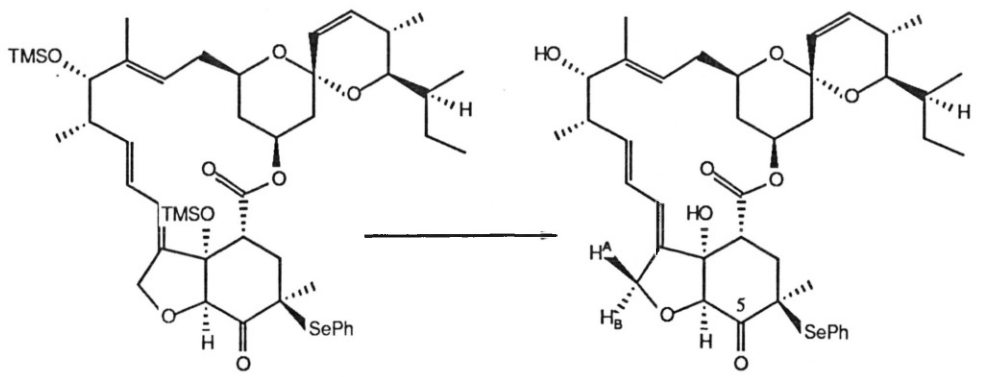
(121) (133)

To freshly prepared KDA (0.624 mmol, 70 mg, KO^tBu; 0.086 ml DIPA, 0.416 ml of 2.5 M hexane solution of ^nBuLi) in THF (2 ml) at -78°C under argon was added the ketone (121) (30 mg, 0.0513 mmol) in THF (1 ml). The clear, pinkish red solution was stirred for 3h. at -78°C, after which time benzeneselenyl chloride (196 mg, 0.0125 mmol) in THF (0.6 ml) was added dropwise. The colour discharged to give a deep yellow solution (no, change in R_f by t.l.c.).After stirring at -78°C for 1h30min saturated sodium hydrogen carbonate was added at -78°C and

`the mixture allowed to come to r.t. Extraction with ethyl acetate was followed by evaporation *in vacuo*. Flash chromatography on florisil (18% ethyl acetate-petrol) afforded a mixture of the β-selenoketone (133) and co-running starting ketone (121) (17 mg, n.m.r. of the mixture showed that 44% of this was the starting ketone. Thus the yield of (133) is 20%),

(133) and (121) were separated by reversed phase HPLC [10% water-methanol. Analytical column. R_t (121) ketone 12 min, Rt (133) β-seleno ketone B_{1a} 18-19 min, R_t (133b) β-seleno ketone B_{1b} 20-24 min. (See Appendix). The B_{1a} homologue is separable from the B_{1b} under these HPLC conditions.], affording the β-seleno ketone (133) (20%) as a pale yellow foam. ν_{max}(film) 3478, 2924, 1713, 1453, 1377, 1273, 1160, 997 and 738 cm^{-1}; δ (500 MHz) 7.55-7.32 (5H, m, PhSe), 5.85 (1H, m, 9-H), 5.79 (1H, dd, J 10.0 and 2.0 Hz, 22-H), 5.75 (2H, obs.m, 10-H, 11-H), 5.60 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.46 (1H, m, 19-H), 5.32 (1H, br.m, 15-H), 4.87 (1H, dd, J 14.0 and 2.5 Hz, 8_α-H_B), 4.69 (1H, dd, J 14.0 and 2.5 Hz, 8_α–H_A), 4.50 (1H, br.s, 7-OH), 4.01 (1H, br.s, 13-H), 3.90 (1H, m, 17-H), 3.84 (1H, s, 6-H), 3.51 (1H, dd, J 13.0 and 3.0 Hz, 2-H), 3.48 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.55 (1H, dd, 15.0 and 13.0 Hz, 3-H_a), 2.54 (1H, m, 12-H), 2.34-2.26 (3H, m, 24-H, 16-H_2), 2.04 (1H, dd, J 15.0 and 3.0 Hz, 3-H_e), 1,96 (1H, ddd, 20-H_e), 1.79 (1H, br.d, 18-He), 1.60-1.40 (4H, obs.m, 26-H, 27-H_2, 13-OH), 1.53 (3H, s, 14-Me), 1.19 (3H, d,J 7.0 Hz, 12-Me), 0.97 (3H, t, J 7.5 Hz, 28-H_3), 0.95-0.87 (7H, obs.m, 26-Me, 24-Me, 18-Ha); m/z 721 (M^+-H_2O), 565 (M^+-H_2O-PhSe), 305 ($C_{20}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O_2^+$); (Found: C, 65.17; H,7.29. $C_{40}H_{52}O_8Se$ requires C, 64.9; H,7.1%).

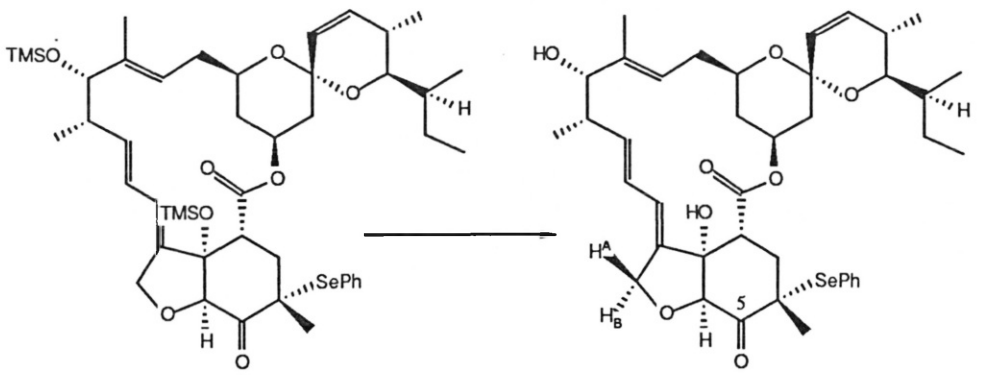
50. Preparation of 4β-benzeneselenyl-3-hydro-5-oxo-avermectin B_{1a} aglycone (133).



(128) (133)

Aqueous HF (40% solution, 7 drops) was added to a solution of the diTMS seleno ketone (128) (5 mg, 0.0056 mmol) and pyridine (0.05 ml), in acetonitrile (2 ml) at 0°C. A cloudiness in the reaction , which persists, was observed. The mixture was left stirring at r.t. for 4h. (T.l.c. monitor in 30% ethyl acetate-petrol; mono 7-TMS and complete consumption of s.m. is observed after 5 min. at 0°C). Additional aliquots of pyridine and aq. HF were added during the reaction by adding pyridine before further aq. HF. Saturated aqueous sodium hydrogen carbonate was added cautiously. The mixture was extracted with ethyl acetate (x4), the combined organics filtered through a pad of florisil and then evaporated *in vacuo*. Flash chromatography (18% ethyl acetate-petrol) afforded the β-seleno hydroxy ketone (133) (4 mg, 96%) as a clear glass. (R_f 0.5 in 30% ethyl acetate-petrol) Identical in all respects to previously obtained sample by KDA/PhSeCl method.

51. Preparation of 4α-benzeneselenyl-3-hydro-5-oxo-avermectin B_{1a} aglycone (135).

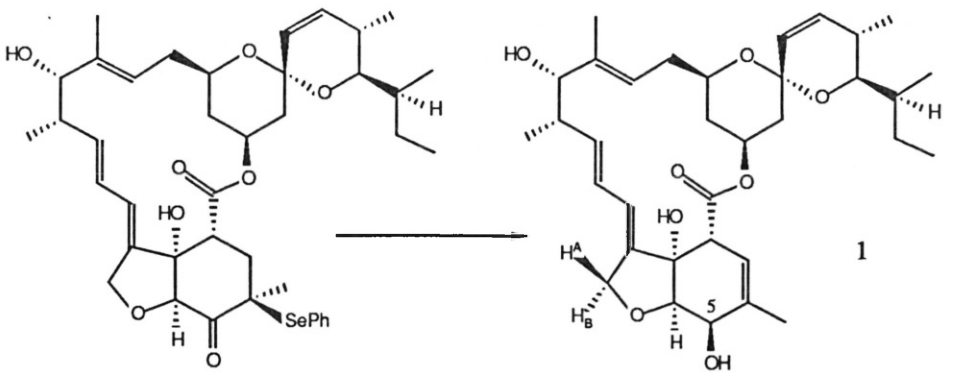


(129) (135)

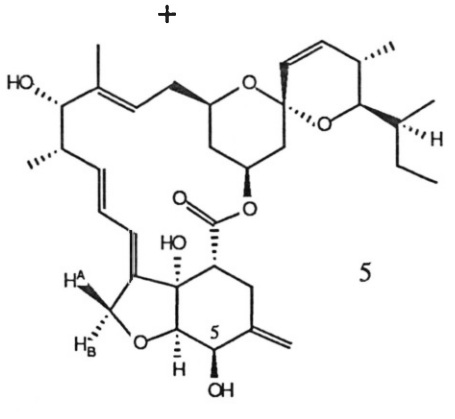
Aqueous HF (40% solution, 7 drops) was added to a solution of the diTMS seleno ketone (129) (4.5 mg, 0.00509 mmol) and pyridine (0.05 ml), in acetonitrile (2 ml) at 0°C. A cloudiness in the reaction , which persists, was observed. The mixture was left stirring at r.t. for 3h. (T.l.c. monitor in 30% ethyl acetate-petrol; mono 7-TMS and complete consumption of s.m. is observed after 5 min. at 0°C). Additional aliquots of pyridine and aq. HF were added during the reaction by adding pyridine before further aq. HF. Saturated aqueous sodium hydrogen carbonate was added cautiously. The mixture was extracted with ethyl acetate (x4), the combined organics filtered through a pad of florisil and then evaporated *in vacuo*. Flash chromatography (18% ethyl acetate-petrol) afforded the α-seleno hydroxy ketone (135) (2.2 mg, 60%) (R_f 0.35 in 30% ethylacetate-petrol) as a yellow glass.[A product of R_f 0.5 was also isolated in 15% yield. From the n.mr. it contained the β-seleno hydroxy ketone (133) and deselenated hydroxy ketone (121) in an equal

ratio] (135) ν_{max}(film) 3462, 2923, 1706, 1453, 1376, 1262, 1160, 1039, 802, 735 and 664 cm^{-1}; δ (500 MHz) 7.49-7.30 (5H, m, PhSe), 5.98 (1H, m, 9-H), 5.78-5.73 (3H, obs.m, 22-H, 10-H, 11-H), 5.54 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.42 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 5.31 (1H, br.d, 11.0 Hz, 15-H), 4.85 (1H, s, 6-H), 4.68, 4.51 (2H, 2xdd, J 14.0 and 2.5 Hz, 8_{α}-H_2), 4.38 (1H, s, 7-OH), 4.01 (1H, br.s, 13-H), 3.88 (1H, m, 17-H), 3.46 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.85 (1H, dd, 15.0 and 13.0 Hz, 3-H_B), 2.52 (2H, dd+obs.m, J. 13.0 and 4.0 Hz, 2-H, 12-H), 2.34-2.24 (3H, obs.m, 16-H_2, 24-H), 2.10 (1H, dd, J 15.0 and 4.0 Hz, 3-H_A), 1.90 (1H, ddd, 12.0, 10.0 and 2.0 Hz, 20-H_e), 1.76 (1H, m, 18-H_e), 1.60-1.46 (5H, obs.m, 13-OH, 20-H_a, 26-H, 27-H_2), 1.50 (3H, s, 14-Me), 1.46 (3H, s, 4-Me), 1.18 (3H, d, J 7.0 Hz, 12-Me), 0.96 (3H, t, J 7.0 Hz, 28-H_3), 0.91 (6H, 2xd, J 7.0 Hz, 24-Me, 26-Me), 0.81 (1H, q,.J 12.0 Hz, 18-H_a); m/z (M^+); (Found:see appendix).

52. Preparation of Avermectin B_{1a} aglycone (81) and 3-hydro-4-methylene-avermectin B_{1a} aglycone (134).



(133) (81)



(134)

The oxaziridine (130) (3 mg, 0.0098 mmol) was added to a stirred solution of the β-seleno ketone (133) (2.6 mg, 0.00351 mmol) in deuterochloroform (1 ml) in an n.m.r. tube at r.t. The reaction was monitored by n.m.r. After 30 min., the reaction was poured into cold methanol at 0°C containing cerium (III) chloride heptahydrate. After 5 min., sodium borohydride was added portion wise at, 0°C until t.l.c. indicated consumption of the enones. After 15 min. saturated ammonium

chloride was added and the mixture extracted with ethyl acetate. The organic extracts were washed with brine, combined, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (40% ethyl acetate-petrol) afforded a 1 : 5 ratio (from 500 Hz ^1H n.m.r.) of the aglycone (81) and *exo* aglycone (134) (mixture: 1.5 mg, 73%).

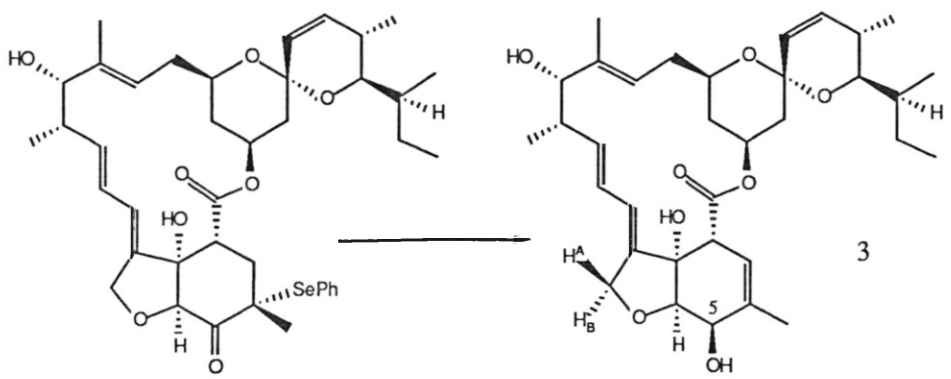
(81) was separated from (134) by reversed phase HPLC [gradient elution: 25% water-methanol (5 min), then 25% water-methanol to 10% water-methanol (over 5 min.), then 10% water-methanol (15 min): R_t (81) = 13 min, R_t (134) = 14 min.], affording the alcohols as fluffy white solids after freeze drying.

More polar (81): Identical in all respects to sample obtained by hydrolysis of sugars from avermectin B_{1a}.

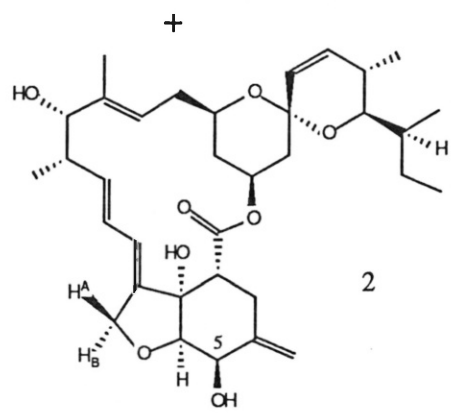
Less polar (134): $[\alpha]_D^{20}$ +135° (c=0.02, $CHCl_3$); ν_{max}(film) 3581, 2922, 2852, 1715, 1653, 1596, 1456, 1377, 1160, 1121, 1075 and 997 cm^{-1}; δ (500 MHz) 5.78-5.70 (4H, obs.m, 9-H, 10-H, 11-H, 22-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.42 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 5.31 (1H, br.d, J 10.0 Hz, 15-H), 5.20 (1H, br.m, 4-CH), 5.03 (1H, br.m, 4-CH), 4.66 (1H, s, 7-OH), 4.59 (2H, m, 8_α-H_2), 4.45 (1H, m, 5-H) 4.00 (1H, br.s, 13-H) 3.92 (1H, d, 4.5 Hz, 6-H), 3.87 (1H, m, 17-H), 3.47 (1H, d, J 10.0 and 1.5 Hz, 25-H), 2.63 (1H, t, J 14.0 and 13.0 Hz, 3-H_B), 2.55 (1H, dd, J 14.0 and 3.0 Hz, 3-H_A), 2.50 (1H, m, 12-H), 2.39 (1H, dd, J 13.0 and 3.0 Hz, 2-H), 2.32-2.24 (3H, obs.m, 16-H2, 24-H), 2.12 (1H, d, J 3.5 Hz, 5-OH), 1.94 (1H, ddd, J 12.0, 5.0 and 2.0 Hz, 20-H_e), 1.72 (1H, m, 18-He), 1.50 (3H, s, 14-Me), 1.60-1.45 (5H, obs.m, 13-OH, 20-H_a, 26-H, 27-CH_2), 1,17 (3H, d, J 7.0 Hz, 12-Me), 0.96 (3H, t, J 7.0 Hz, 28-H_3), 0.91, 0.90 (6H, 2xd, J 7.0 Hz, 24-Me, 26-Me), 0.85 (1H, q, J 12.0 Hz, 18-H_a); m/z 584 (M^+), 566 (M^+-H_2O), 541 (M^+-H_2O), 305 ($C_{30}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 169 ($C_{10}H_{17}O_2^+$); (Found: M, 584.3358. $C_{34}H_{48}O_8^+$ requires

M^+, 584.3349).

53. Preparation of Avermectin B_{1a} aglycone (81) and 3-hydro-4-methylene-avermectin B_{1a} aglycone (134).



(135) (81)



(134)

The oxaziridine (130) (3 mg, 0.0098 mmol) was added to a stirred solution of the α-seleno ketone (135) (2 mg, 0.00270 mmol) in deuterochloroform (1 ml) in an n.m.r. tube at r.t. The reaction was monitored by n.m.r. After 30 min., the reaction

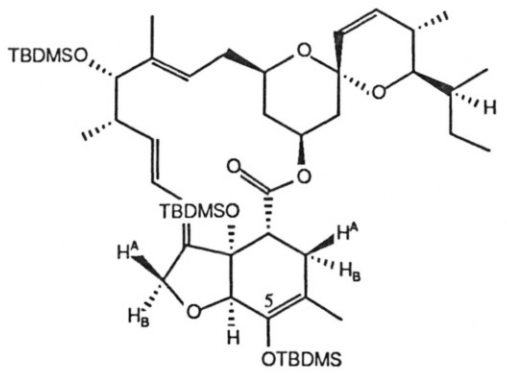
was poured into cold methanol at 0°C containing cerium (III) chloride heptahydrate. After 5 min., sodium borohydride was added portion wise at, 0°C until t.l.c. indicated consumption of the enones. After 15 min. saturated ammonium chloride was added and the mixture extracted with ethyl acetate. The organic extracts were washed with brine, combined, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography (40% ethyl acetate-petrol) afforded a 3 : 2 ratio (from 500 Hz ^1H n.m.r.) of the aglycone (81) and *exo* aglycone (134) (mixture: 1.5 mg, 95%).

(81) was separated from (134) by reversed phase HPLC [gradient elution: 25% water-methanol (5 min), then 25% water-methanol to 10% water-methanol (over 5 min.), then 10% water-methanol (15 min): R_t (81) = 13 min, R_t (134) = 14 min.], affording the alcohols as fluffy white solids after freeze drying.

More polar (81): $[\alpha]_D^{20}$ +70.0° (c=0.1, $CHCl_3$), {lit. $[\alpha]_D^{20}$ +65.5° (c=0.595, $CHCl_3$) [59] ; rotation for aglycone obtained from acid hydrolysis of oleandrosyl residues from avermectin B_{1a}/B_{1b} (94:6) was $[\alpha]_D^{20}$ +88.7° (c=3.8, $CHCl_3$)} Identical in all respects to sample obtained by hydrolysis of sugars from avermectin B_{1a}.

Less polar *exo* aglycone (134): Identical in all respect to previously obtained sample.

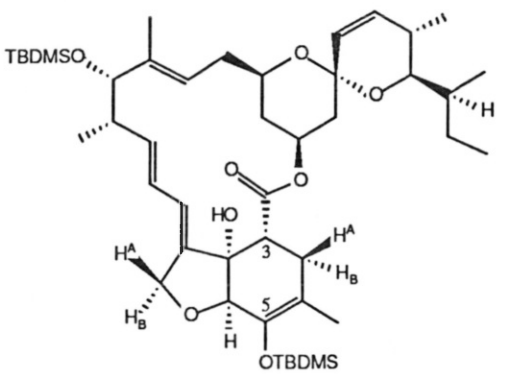
Appendix for Experimental Data.



(125)

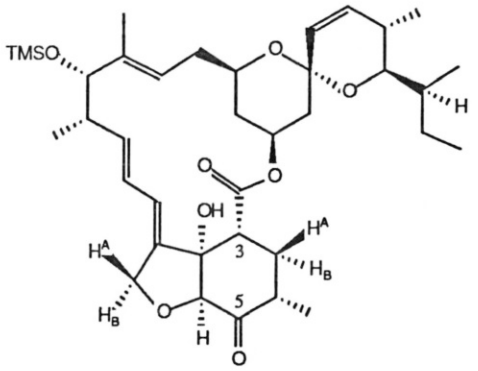
1) (125), White foam: $[\alpha]_D^{25}$ +103.4° (c=0.203, $CHCl_3$); ν_{max}(film) 2930, 2857, 1739, 1681, 1462, 1375, 1317, 1259, 1107, 998 and 838 cm^{-1}; δ (500 MHz) 5.80 (1H, dt, J 11.5 and 2.5 Hz, 9-H), 5.72 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.65 (1H, dd, J 15.0 and 11.5, 10-H), 5.54 (1H, dd, J 15.0 and 10.0 Hz, 11-H), 5.52 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.26 (1H, obs.m, 15-OH), 5.24 (1H, tt, J 11.0 and 4.0 Hz, 19-H), 4.57-4.46 (2H, 2xdd, J 14.0 and 2.5 Hz, 8_α-H_2), 3.88 (1H, br.s, 13-H), 3.83 (1H, m, 17-H), 3.62 (1H, s, 6-H), 3.48 (1H, dd, 10.0 and 1.5 Hz, 25-H), 2.71 (1H, dd, J 16.0 and 12.0 Hz, 3-H_B), 2.62 (1H, dd, J 12.0 and 4.5 Hz, 2-H), 2.41 (1H, m, 12-H), 2.26-2.20 (3H, obs.m, J 16H_2, 24-H), 1.97 (1H, obs.m, 20-H_e), 1.94 (1H, dd, 16.0 and 4.5 Hz, 3-H_A), 1.76 (1H, m, 18-H_e), 1.61 (3H, s, 4-Me), 1.58-1.35 (4H, obs.m, 20-H_a, 26-H, 27-CH2), 1.46 (3H, s, 14-Me), 1.07 (3H, d, J 7.0 Hz, 12-Me), 0.95, 0.93, 0.92 (3x9H, 3xs, 3x^{t}Bu), 0.95-0.88 (9H, 0bs.m, 28-H_3, 26-Me, 26-Me), 0.75 (1H, q, 12.0 Hz, 18-H_a), 0.85, 0.81; 0.75, 0.74; -0.015, -0.025 (3x6H, 3xs, TMS); m/z

926 (M^+), 869 (M^+-^{t}Bu), 840, 794 (M^+-TBDMSOH), 701, 507, 491, 287, 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$); (Found: M, 926.5958. $C_{52}H_{90}O_8Si$ requires M^+, 926.5944).



2) Clear glass: ν_{max}(film) 3498, 2926, 2855, 1736, 1707, 1635, 1460, 1377, 1322, 1252, 1159, 1116, 1034, 997, 963 and 869 cm^{-1}; δ (500 MHz) 5.83 (1H, br.d, 9.5 Hz, 9-H), 5.75 (1H, dd, J 10.0 and 1.5 Hz, 22-H), 5.68-5.65 (2H, obs.m, 10-H, 11-H), 5.55 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.48 (1H, tt, J 11.0 and 5.0 Hz, 19-H), 5.24 (1H, br.t, J 7.0 Hz, 15-H), 4.61, 4.54 (2H, dd, J 14.0 and 2.0 Hz, 8a-H2), 4.23 (1H, s, 7-OH), 3.86 (1H, br.s, 13-H), 3.84 (1H, m, 17-H), 3.73 (1H, s, 6-H), 3.48 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 2.70 (1H, dd, J 11.0 and 5.0 Hz,2-H), 2.62 (1H, dd, 16.0 and 11.0 Hz, 3-H_B), 2.40 (1H, m, 12-H), 2,.28-2.22 (1H, obs.m, 16-H_2, 24-H), 2.08 (3H, dd, J 16.0 and 5.0 Hz, 3-H_A), 1.90 (1H, ddd, J 12.0, 5.0 and 2.0 Hz, 20,-H_e), 1.76 (1H, m, 18-H_e) 1.66 (3H, s, 4-Me), 1.6-1.45 (4H, obs.m, 20-Ha, 26-H, 27-H_2), 1.47 (3H, s, 14-

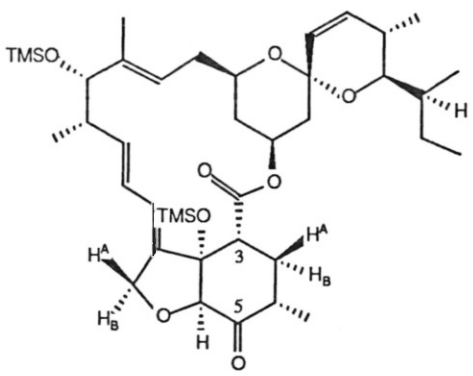
Me), 1.05 (3H, d, J 7.0 Hz, 12-Me), 0.95, 0.93 (2x9H, 2xs, ^{t}Bu), 0.93-0.90 (9H, obs.m, 28-H_3, 24-Me, 26-Me), 0.82 (1H, q, J 12 Hz, 18-H_a), 0.15, 0.13 (2x6H, 4xs, TMS); m/z 812 (M^+), 794 (M^+-H_2O), 755 (M^+-^{t}Bu), 726, 419, 287, 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$); (Found: M, 812.5090. $C_{46}H_{76}O_8$ requires M^+, 812.5079).



(137)

3) (137),Clear glass: ν_{max}(film) 3468, 2958, 2930, 1721, 1451, 1379, 1249, 1213, 1161, 1076, 1037, 997 and 893 cm^{-1}; δ (500 MHz) 5.80 (1H, dt, J 10.0 and 11.0 Hz, 9-H), 5.77 (1H, dd, 10.0 and 2.0 Hz, 22-H), 5.74 (1H, dd, 15.0 and 10.0 Hz, 5.66 (1H, dd, J 15.0 and 11.0 Hz, 10-H), 5.57 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.44 (1H, tt, J 12.0 and 5.0 Hz, 19-H), 5.21 (1H, br.t, J 7.0 Hz, 15-H), 4.75, 4.65 (1H, 2xdd, J 14.0 and 2.5 Hz, 8a-H2), 4.54 (1H, s, 7-OH), 3.88 (1H, s, 13-H), 3.85 (1H, m, 17-H), 3.76 (1H, s, 6-H), 3.50 (1H, dd, J 10.0 and 1.5 Hz, 25-H), 3.02 (1H, dd, J.13.0 and 4.0 Hz, 2-H), 2.79 (1H, m, 4-H), 2.43 (1H, m, 12-H), 2.26 (3H, obs.m, 16-H_2, 24-H), 2.07 (1H, d, J 13.0 Hz, 3-H_B),

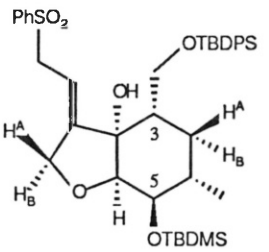
2.03 (1H, obs.m, 3-H_A), 1.94 (1H, ddd, J 12.0 and 5.0 and 2.0 Hz, 20-He), 1.74 (1H, m, 18-He), 1.47 (3H, obs.m, 20-H_a, 26-H, 27-H_2), 1.60-1.46 (3H, s, 14-Me), 0.11 (3H, d, 7.0 Hz, 12-Me), 0.15 (3H, d, 7.0 Hz, 4-Me), 0.95 (3H, t, J 7.0 Hz, 28-H_3), 0.91 (6H, 2xdd, J 7.0 Hz, 24-Me, 26-Me), 0.86 (1H, q, J 12.0 Hz, 18-Ha), 0.09 (9H, 3xs, TMS); m/z 656 (M^+), 638 (M^+-H_2O), 552, 482, 377, 359, 305, ($C_{20}H_{31}O_3^+$), 221 ($C_{13}H_{19}^+$); (Found: M, 728.4139. $C_{40}H_{64}O_8Si_2$ requires M^+, 728.4146).



(138)

4) (138), Clear glass: ν_{max}(film) 3431, 2925, 2854, 1735, 1457, 1375, 1251, 1159, 1075, 1036, 996 and 842 cm^{-1}; δ (500 MHz) 5.75-5.68 (4H, obs.m, 9-H, 10-H, 11-H, 22-H), 5.53 (1H, dd, J 10.0 and 2.5 Hz, 23-H), 5.30 (1H, m, J 15.0 Hz, 15-H), 5.05 (1H, tt, J 11.0 and 4.5.Hz, 19-H), 4.72 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_B),4.62 (1H, dd, J 14.0 and 2.0 Hz, 8_α-H_A), 3.93 (1H, br.s, 13-H), 3.85 (1H, m, 17-H), 3.79 (1H, s, 6-H), 3.48 (1H, dd, J 10.0 and 1.0 Hz, 25-H), 2.92 (1H, dd, J 13.0 and 3.0 Hz, 2-H), 2.76 (1H, m, 4-H), 2.49 (1H, m, 12-H),

2.30-2.24 (3H, obs.m, 16-H2, 24-H), 2.10-2.00 (2H, obs.m, 3-H_2), 1.94 (1H, J 12.0, 5.0 and 2.0 Hz, 20-He), 1.79 (1H, m, 18-H_e), 1.60-1.45 (4H, obs.m, 20-H_a, 26-H, 27-H_2), 1.54 (3H, s, 14-Me), 1.08 (3H, d, J 7.0 Hz, 12-Me), 1.07 (3H, d, J 7.0 Hz, 4-Me), 0.96-0.88 (9H, obs.m, J 7.0 Hz, 4-Me), 0.96-0.88 (9H, obs.m, 28-H_3, 24-Me, 26-Me), 0.82 (1H, q, 12 Hz, 18-Ha), 0.18 (9H, s, TMS), 0.11 (9H, s, TMS); m/z, CI ammonia: 729 ($M+H^+$), 655 (M^+-TMS), 627, 582, (M^+-2TMS), 537, 305 ($C_{20}H_{31}O_3^+$), 221 ($C_{14}H_{20}O_2^+$), 193 ($C_{13}H_{19}O^+$); (Found: 728.4139. $C_{40}H_{64}O_8Si_2$ requires 728.4146).



5) White foam: ν_{max}(film) 3449, 2930, 2857, 1587, 1462, 1427, 1388, 1321, 1321, 1307, 1251, 1149, 1112, 1021 and 963 cm^{-1}; δ (500 MHz) 7.80-7.40 915H, m, Ph), 5.46 (1H, tt, J 8.0 and 2.5 Hz, 9-H), 5.17 (1H, s, 7-OH), 4.05 (1H, dd, J 11.0 and 2.0 Hz, 1-H), 3.88 (1H, dd, J 15.0 and 2.0 Hz, 8_α-H_B), 3.79 (1H, dd, J 15.0 and 2.5 Hz, 8_α-H_A), 3.73 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 3.58 (1H, dd, J 14.0 and 8.0 Hz, 10-H), 3.52 (2H, dd, 5-H+1-H), 3.40 (1H, d, J 3.0 Hz, 6-H), 1.80 (1H, m, 4-H), 1.77 (1H, q, J 12.0 Hz, 3-H_B), 1.35 (1H, m, 2-H), 1.24 (1H, m, 3-HA), 1.10 (9H, s, ^{t}BuDPS), 0.99 (3H, d, J 6.0 Hz, 4-Me), 0.90 (9H, s, ^{t}BuDMS)0.10 (3H, s, Me), 0.07 (3H, s, Me) ; m/z 705 (M^+-Me), 663 (M^+-Me-

C_4H_9), 521, 503, 199, 173, 57; (Found: M, 663.2632 $C_{36}H_{47}O_6Si_2S$ requires M^+, 663.2617).

Re: Experimental.

Awaiting mass spectral results from School of Pharmacy, University of London.

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S. Trahanovsky, "Oxidation in Oraganic Chemistry", Ch.1 H.J. Reich p.96, *5C*, 197. Academic Press.

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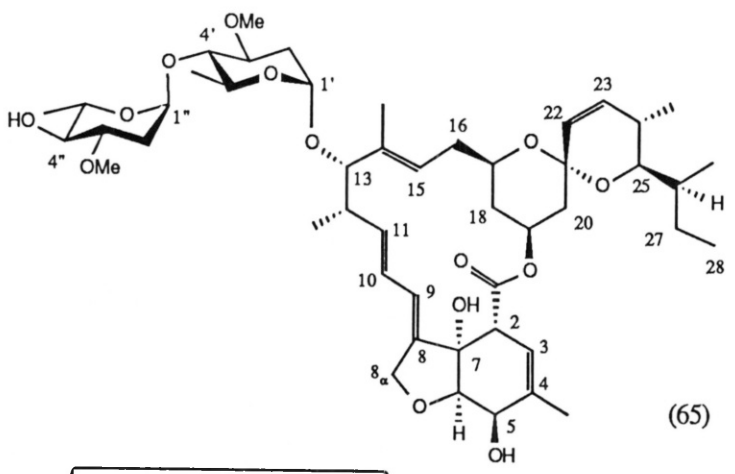
86. Reductive cleavage of Selenides with Nickel Boride: T.G. Back, V.I. Briss,

M. Edwards and M.V. Krishna, *J. Org. Chem.*, 1988, 53, 3815.

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88. S.N. Lewis, J.J. Millo, *J. Org. Chem*, 1972, *37*, 1478.

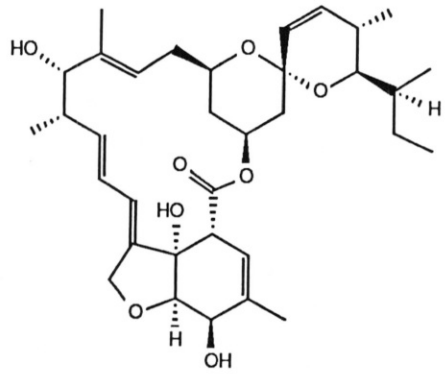
Appendix



(65)

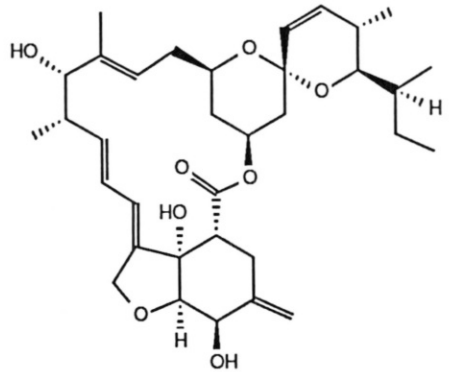
Avermectin B_{1a}

Avermectin B_{1a} Aglycone



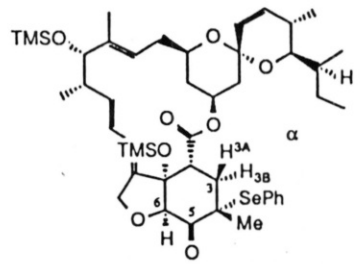
(81)

Avermectin B_{1a} *Exo*-Aglycone



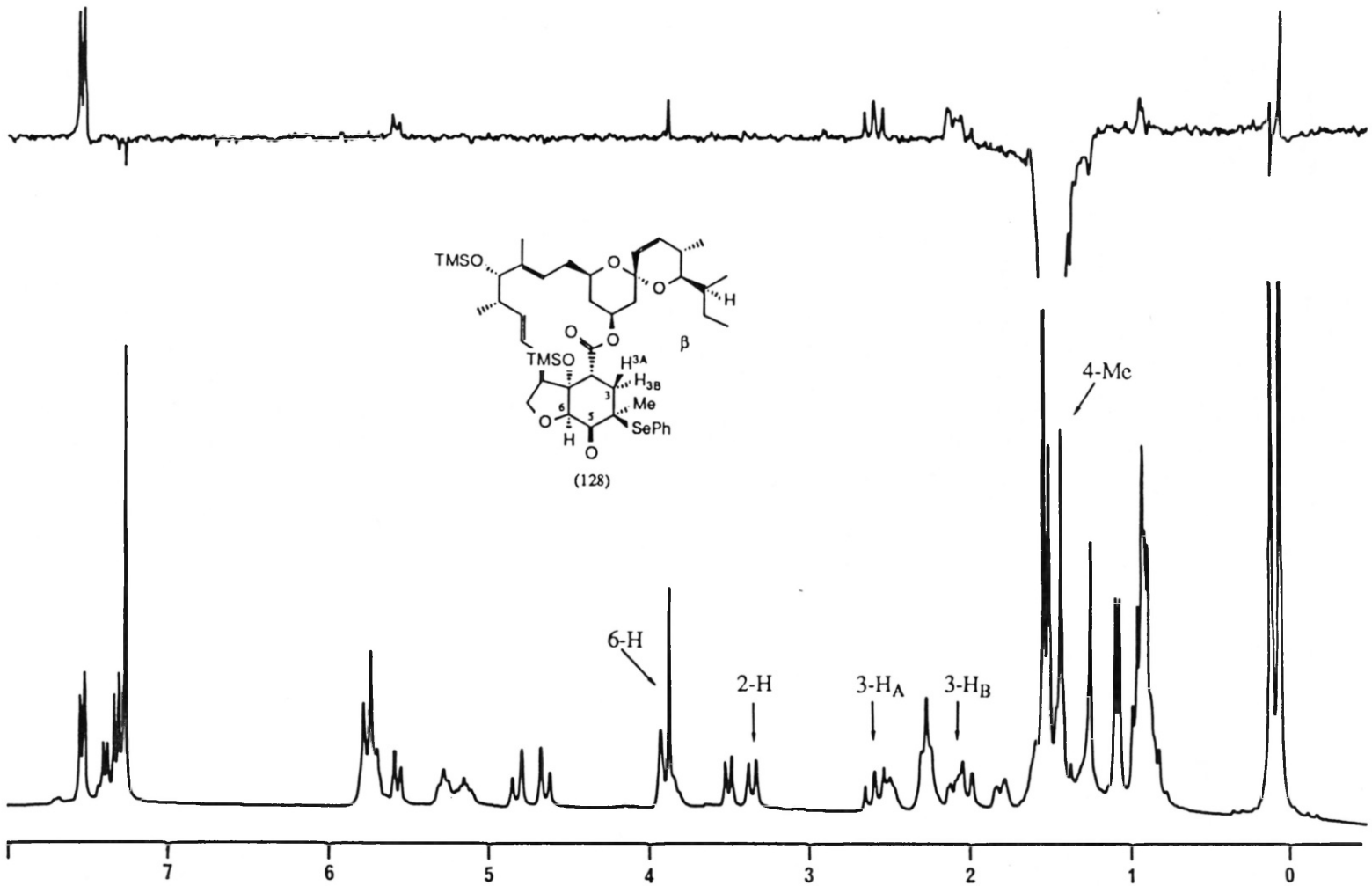
(134)

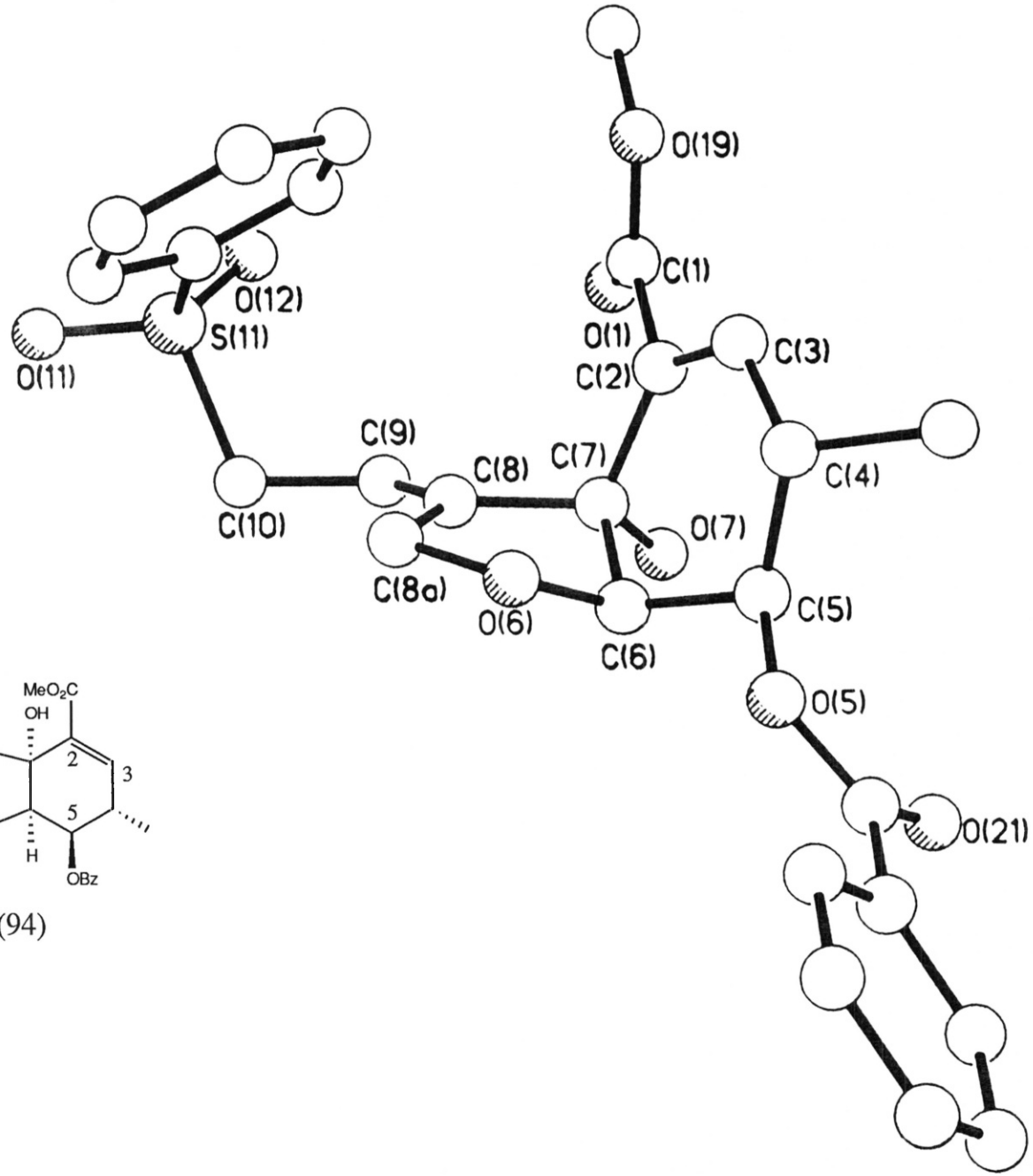
n.O.e. Difference Spectra of (129), with irradiation of H-6 and CH_3-4



(129)

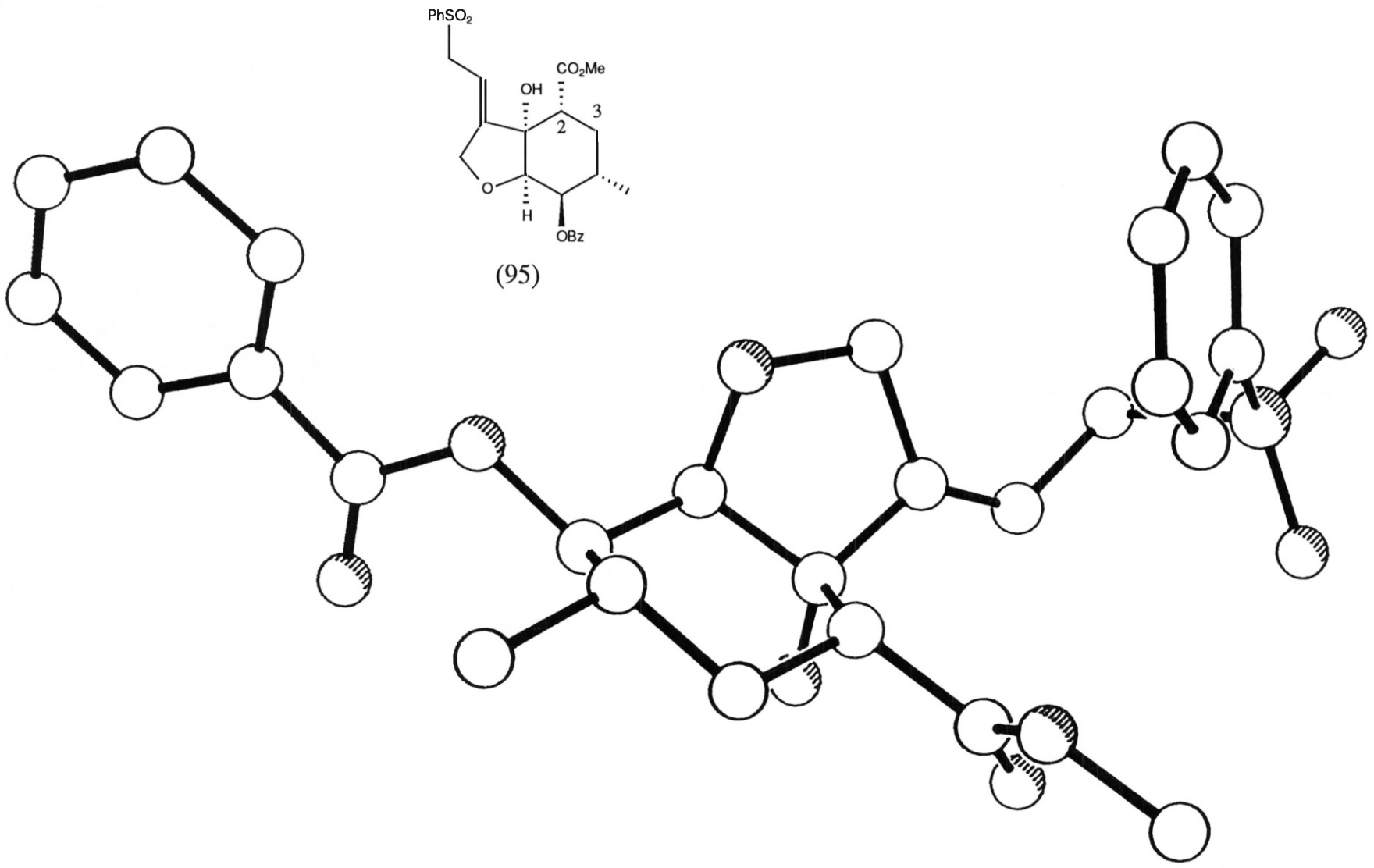
n.O.e. Difference Spectrum of (128), with irradiation of CH_3-4




O(19)
C(1)
O(12)
S(11)
O(1)
C(3)
O(11)
C(2)
C(9)
C(8)
C(7)
C(4)
C(10)
O(7)
C(8a)
O(6)
C(5)
C(6)
O(5)
O(21)

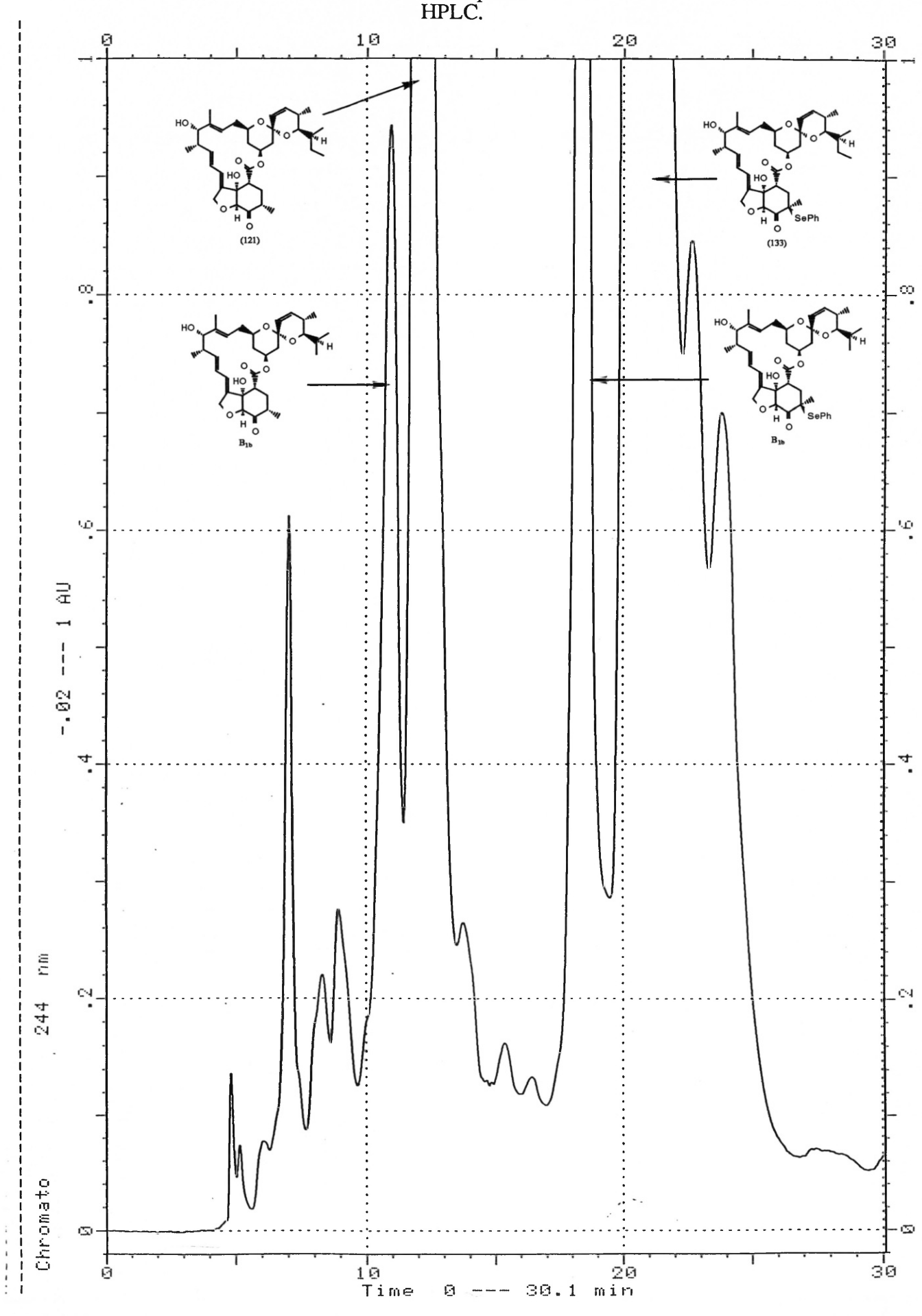
PhSO2
10
MeO2C
OH
2
3
5
O
H
OBz

(94)



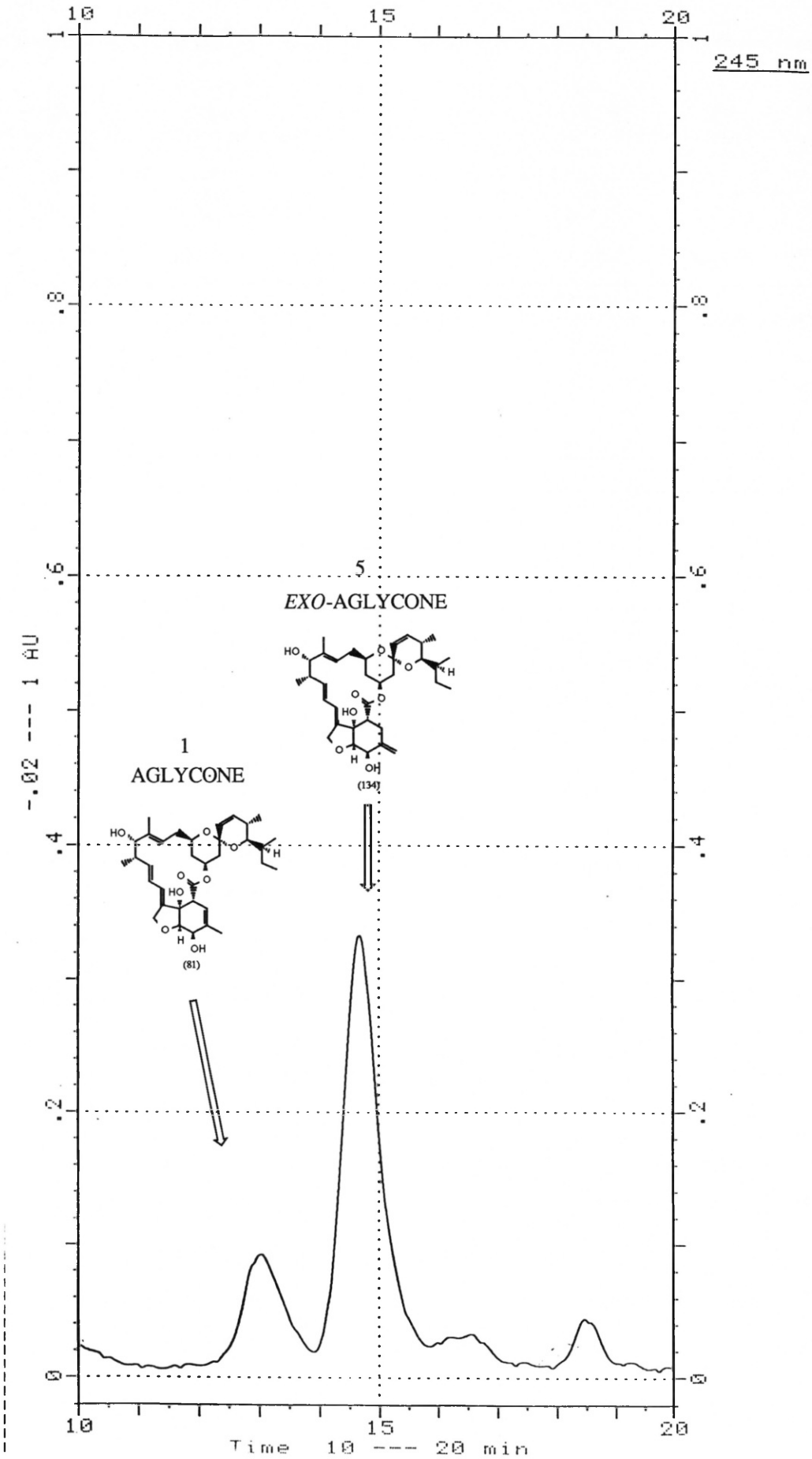
(95)

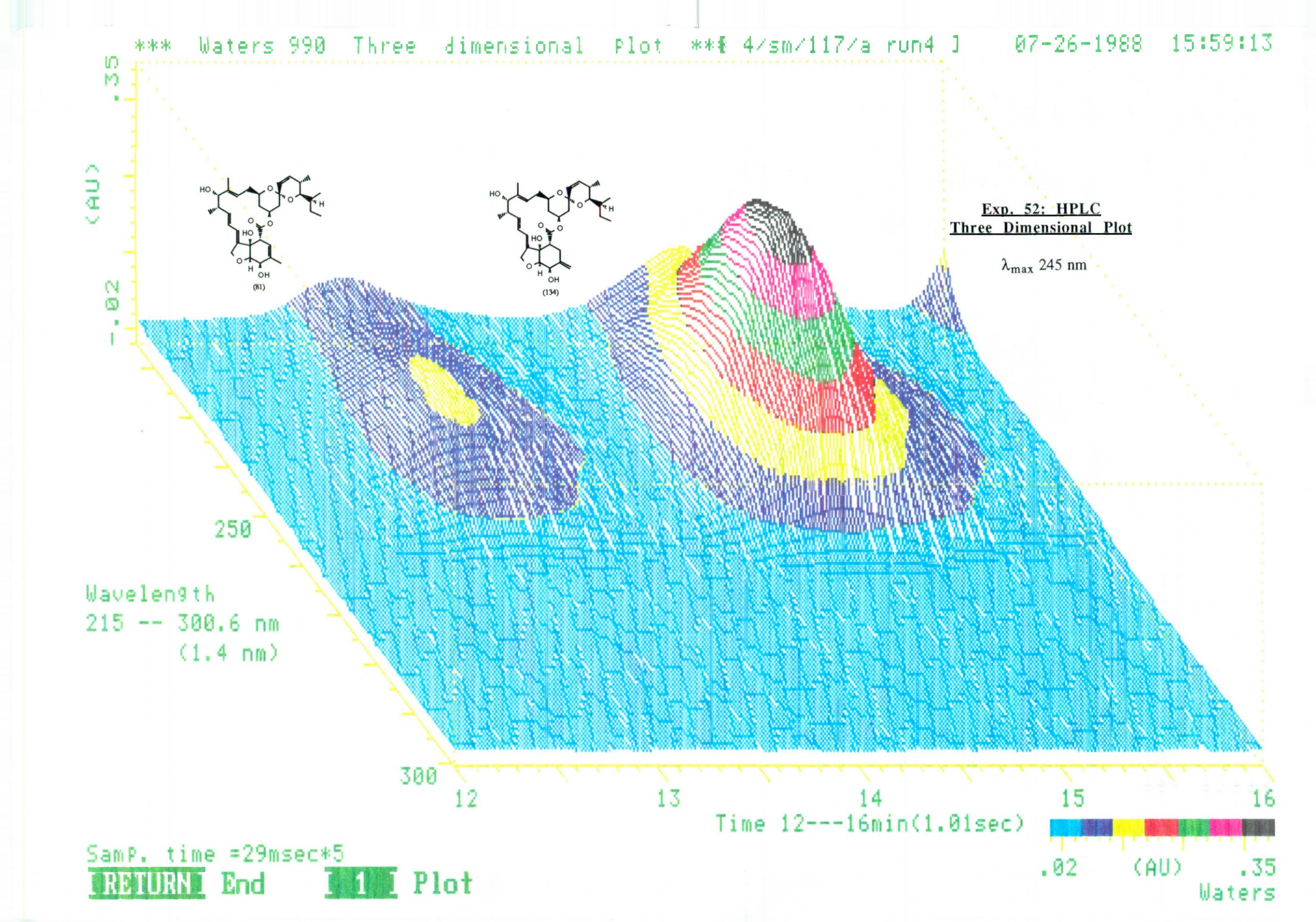
Experiment 49
Reversed phase
HPLC.



Waters 21508 7101 Waters

Experiment 52
Reversed phase
HPLC.




*** Waters 990 Three dimensional Plot *** 4/sm/117/a run4] 07-26-1988 15:59:13
.35
(AU)
.02
(81)
(134)
Exp. 52: HPLC
Three Dimensional Plot
λmax 245 nm
250
Wavelength
215 -- 300.6 nm
(1.4 nm)
300
12
13
14
15
16
Time 12---16min(1.01sec)
.02 (AU) .35
Waters
Samp. time =29msec*5
RETURN End 1 Plot