SYNTHESIS OF THE MILBEMYCIN SOUTHERN HEMISPHERE

A Thesis Presented By

NEVILLE JOHN ANTHONY

In Partial Fulfilment of the Requirements
for the Award of the Degree of

DOCTOR OF PHILOSOPHY

of the

UNIVERSITY OF LONDON

WHIFFEN LABORTORY,
DEPT. OF CHEMISTRY,
IMPERIAL COLLEGE,
LONDON SW7 2AY.

APRIL 1988

Abstract

This thesis is divided into two sections. The first begins with an overview of the biological properties of the milbemycins and avermectins. This is followed by a review of the synthetic strategies to these natural products.

The second section describes work towards the synthesis of the southern hemisphere of milbemycin β_1. Initial efforts to develop a suitable C-1, C-7 cyclohexyl fragment are described. Subsequent elaboration of this unit to southern hemisphere synthons and their subsequent sulphone mediated coupling to northern hemisphere C-11 aldehydes is described. Finally, dehydrogenation - via selenoxide *syn*-elimination - of a macrocyclic ketone and further manipulation resulted in the synthesis of an isomer of milbemycin β_1. NMR evidence is provided to support the proposal that this material is an atropo isomer.

Contents

	Page
Abstract	2
Acknowledgements	4
List of Abbreviations	5
Introduction	7
Review - Strategies to Milbemycin and Avermectin Synthesis	12
Results and Discussion	41
Synthesis of Southern Hemisphere Synthons	
Approaches to the Milbemycin α Series	
Optically Active Subunit Synthesis	
Experimental	100
References	223
Appendix	236
Macromodel Calculations	
NMR Spectra	
X-ray Structures	

Acknowledgements

I would like to thank Professor Steve Ley for his inspiration, friendship and enthusiastic support during the course of this work. My thanks go to my colleagues - both past and present - of the Whiffen and Perkin labs for providing such a unique and stimulating atmosphere in which to work and play. In particular, I would like to thank Dr. Howard Broughton for his inexhaustible creative influence and for performing numerous molecular mechanics and MNDO calculations. Special thanks also go to Dr. Donald Craig for his expert advice and to Graham, Pete, Subha and Jim, whose willingness to run NMR's at virtually any time is greatly appreciated. I would also like to thank Pete, Alan, Howard and Graham for their invaluable proof reading and Luiza for typing the manuscript. Similarly, I would like to acknowledge the contributions that Dr. Peter Grice and Dr. A.Brian Jones have made to this work.

I am indebted to the technical staff of Imperial College who include Mr. J.N. Bilton for mass spectra, Mr K.I.Jones and his microanalytical staff and Mr. Dick Sheppard for NMR services. Thanks also go to Dr. D.J.Williams and Ms. A.M.Z Slawin for the X-ray structure determinations,

Finally, I would like to thank my wife Vivienne for her love, understanding and patience and my parents for their continual love and support.

Abbreviations

Ac	Acetyl
acac	acetyacetonate
BBN	Borabicyclo[3.3.1]nonan-9-yl
Bn	Benzyl
Bz	Benzoyl
DATMP	Diethylaluminium tetramethylpiperidide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DHP	Dihydropyran
DIBAL-H	Diisobutylaluminium Hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethylsulphoxide
Ether	Diethyl ether
HMPA	Hexamethyl phosphoramide
Hplc	High performance liquid chromatography
Im	Imidazole
IPA	Isopropyl alcohol
IPC	Isopinocampheyl

KDA	Potassium Diisopropylamide
mCPBA	*m* - Chloroperoxybenzoic acid
MoOPH	Oxodiperoxymolbdenium (pyridine) hexamethyl phosphoramide
NCS	N- Chlorosuccinimide
Oxone	Potassium peroxymonosulphate
PDC	Pyridinium dichromate
Pv	Pivaloyl
Py	Pyridine
Petrol	40-60° Petroleum ether
r.t.	Room temperature
TBAF	Tetra-n-butylammonium fluoride
TBS	t-Butyldimethylsilyl
TBDPS	t-Butyldiphenylsilyl
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
TMS	Trimethylsilyl
THP	Tetrahydro-2*H*-pyran-2-yl
Tr	Trityl

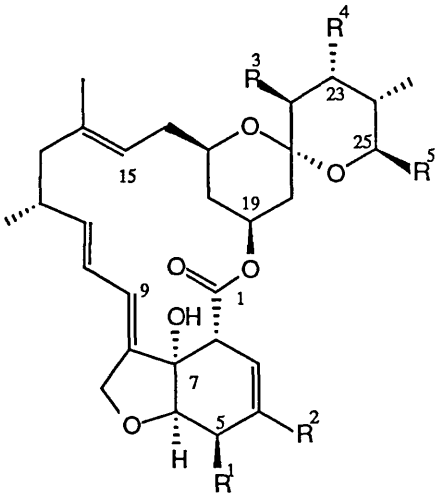
Introduction

In 1974, isolation and characterisation of the biocidal components from a Japanese soil extract revealed a new class of macrocyclic lactones - the milbemycins[1]. Later, a related family of compounds - the avermectins - was isolated from another Japanese soil extract by workers at Merck Sharp and Dohme.[2] An X-ray crystallographic study of the 4-bromourethane derivative of milbemycin β_1[3] allowed gross structural assignment of the milbemycin and avermectin groups.[4] Absolute stereochemical assignment followed from an X-ray analysis[5] of avermectin B_{1a}, in which the disaccharide residue had been shown to be derived from α-L-oleandrose through degradative studies. A similarity in the solid and solution conformation is suggested by comparison of X-ray and NMR data. The absolute configuration 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]

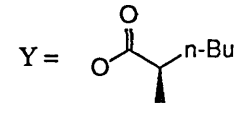
Figures 1 and 2 depict the structures of representative members of the milbemycin and avermectin families, respectively. The only consistent difference between the two groups is the absence of C-13 oxygenation in the milbemycins.

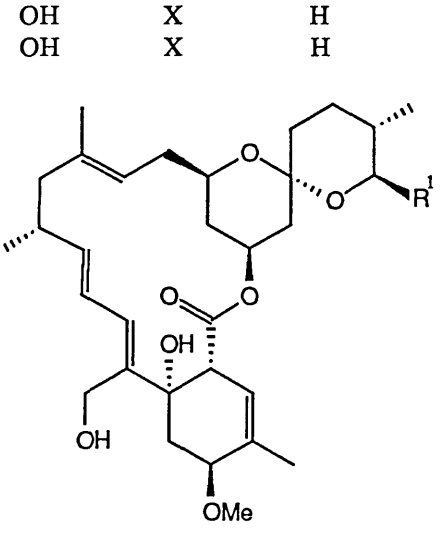
^{13}C-NMR analysis of the avermectin A_{1a}, A_{2a}, B_{1a} and B_{2a} produced by streptomyces avermitilis culture 5192 after [1-^{13}C]- acetate and propionate feeding

experiments showed that the carbon distribution of the macrolide ring was consistent with a biosynthetic

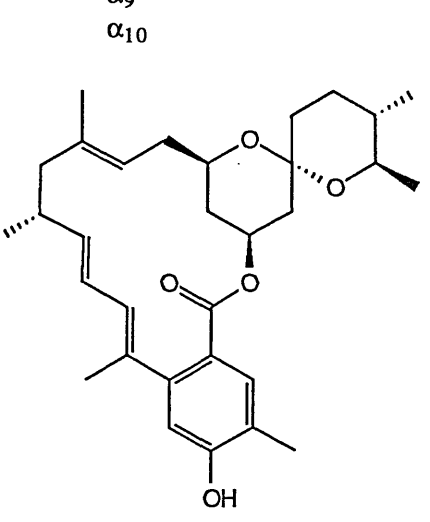


R^1	R^2	R^3	R^4	R^5	Milbemycin
OH	Me	H	H	Me	α_1
OMe	Me	H	H	Me	α_2
OH	Me	H	H	Et	α_3
OMe	Me	H	H	Et	α_4
OH	Me	OH	Y	Me	α_5
OMe	Me	OH	Y	Me	α_6
OH	Me	OH	Y	Et	α_7
OMe	Me	OH	Y	Et	α_8
OH	X	H	H	Me	α_9
OH	X	H	H	Et	α_{10}



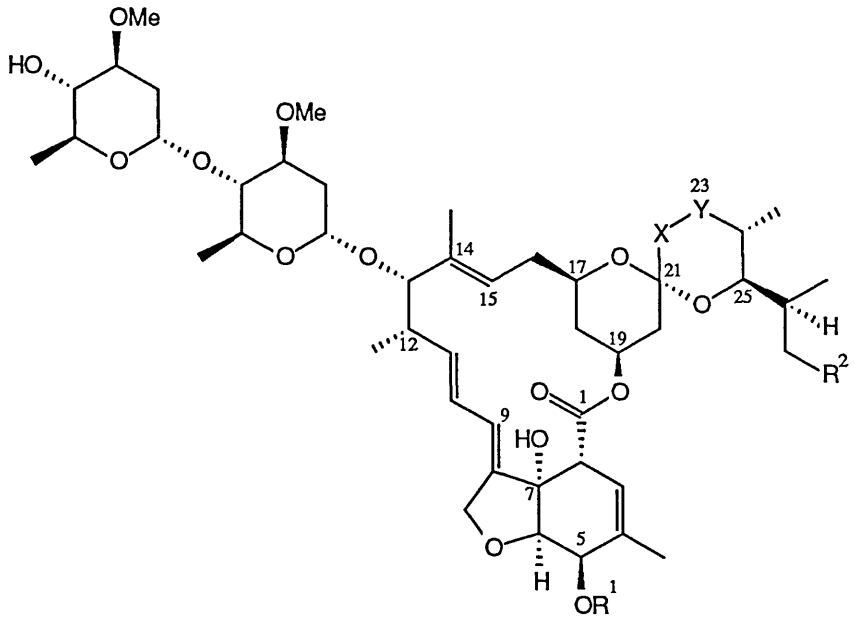


β_1 R^1 = Me
β_2 R^1 = Et



β_3

Figure 1. The Structures of the Principal Milbemycins



X - Y	R^1	R^2	Avermectin
CH=CH	Me	Me	A_{1a}
CH=CH	Me	H	A1b
CH=CH	H	Me	B1a
CH=CH	H	H	B1b
CH_2–CH(OH)	Me	Me	A2a
CH_2–CH(OH)	Me	H	A2b
CH_2–CH(OH)	H	Me	B2a
CH_2–CH(OH)	H	H	B2b

Figure 2. The Structures of the Principal Avermectins

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 hydroxyl 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 that the milbemycins are infact 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 at the C-14 methyl group.

The milbemycins and avermectins are highly potent against two major classes of parasite[9] - nematodes (round worms) and arthropods (insects, ticks, mites, lice). The milbemycins are generally regarded as rather less potent biocides than the avermectins. However the distinction is not clear cut. Studies with infected Sheep[10] showed that the activity of 22,23 dihydroavermectin B_1 was virtually equal to that of its parent. Hydrolytic cleavage of one of the sugars resulted in a four fold decrease in activity, while the corresponding aglycone retained only one thirtieth of the original potency. In contrast, complete C-13 deoxygenation - giving a milbemycin nucleus - restored activity to high levels.[9]

Structure - activity studies have largely concerned the avermectin family.[10] Generally the B series - those containing a C-5 hydroxyl group - are more potent than the A series. Hydrogenation of the C-3, C-4 double bond results in substantially decreased activity. The differences between the 1 and 2 series are found to be slight and often dependent on the particular parasite. There is apparently no difference

between the activities of the a and b series.

The above results imply the involvement of a significant portion of the gross structure in binding to the biological receptor(s). This appears to be substantiated by the lack of observed activity of simple analogues containing spiroacetal[11] and macrolide moieties.[12]

The action of the milbemycins and avermectins appears to involve interference with γ-aminobutyric acid (GABA) mediated neurotransmission.[9] They are not GABA antagonists as they do not compete with GABA for its receptor sites. Instead, they seem to stimulate the release of GABA from the presynaptic membrane and enhance the binding of GABA to its receptors. These receptors are found on the post-synaptic membrane of an excitatory motorneuron in nematodes and on the post-junction membrane of a muscle cell in arthropods. The enhanced GABA binding, causes an irreversible opening of chloride ion channels, which results in an increased flow of chloride ions into the cell. Hyperpolarisation of the cell results and the terminal becomes unresponsive to further neurotransmission - paralysis and often death follows.

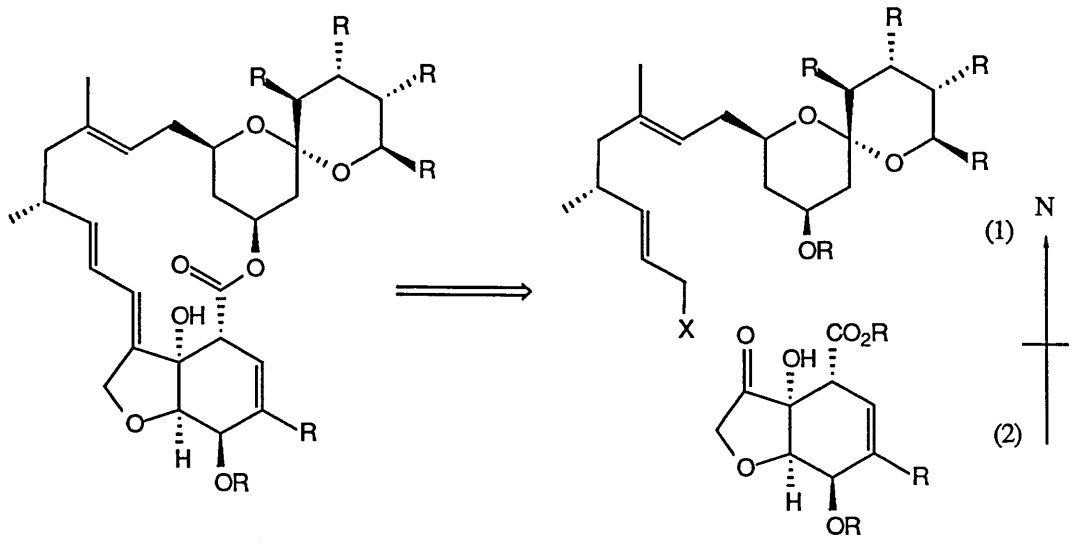
The milbemycins and avermectins are inactive against cestodes (tapeworms) and trematodes (flukes) as GABA independent neurotransmission is utilized by these organisms. GABA dependent nerves in mammals only occur within the central nervous system. The avermectins and milbemycins do not readily cross the blood-brain barrier[9] and consequently these compounds are not toxic to mammals at

therapeutic concentrations.

As a result of the extreme potency of the avermectins, Ivermectin [9,10] was introduced as an antiparasitic drug in 1981. Typically a dose of 0.2-0.3 mg/kg is recommended for the treatment of a variety of infected animals. Additionally, trials in man against the filarial worm *Onchoceus Volvulus* - the agent responsible for river blindness - have proved successful. A single oral dose of 0.1-0.2 mg/kg resulted in almost complete disappearance of microfilariae from the skin for six to twelve months.[9] The reduced incidence and severity of side effects in these trials relative to those produced by present day treatments is notable.

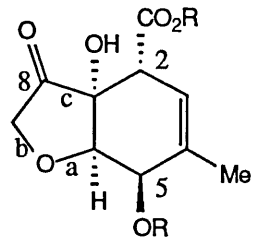
Strategies to Milbemycin and Avermectin Synthesis

The structurally complex milbemycins and avermectins pose major challenges to the synthetic chemist. Convergent approaches to the synthesis of these classes of natural products have invariably led to dissection of the target molecules into two major units - the northern (1) and southern hemispheres (2).

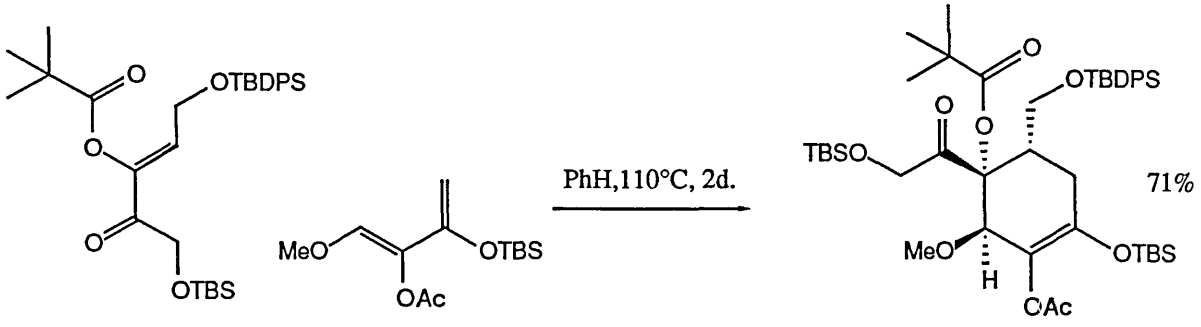


In this section an overview of the methods adopted to synthesise various non aromatic southern hemisphere fragments is presented. The coupling strategy employed in successful syntheses of various members of these macrolide families is subsequently discussed.

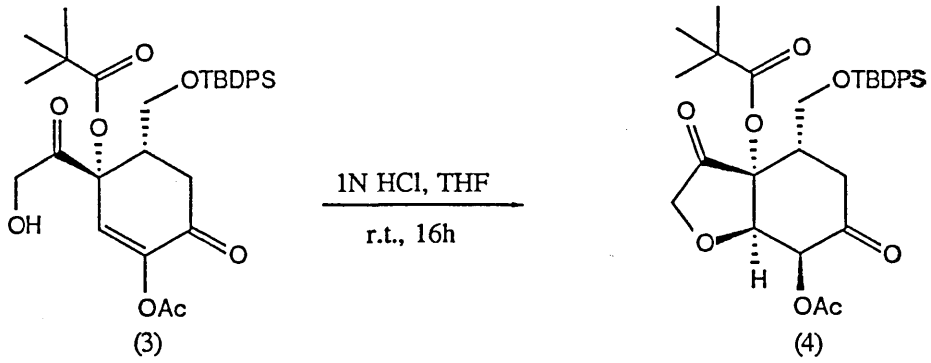
The construction of the hexahydrobenzofuran ring system of the avermectins and milbemycins has been a popular theme of recent publications. The most common entry into this unit has involved tetrahydrofuran ring closure subsequent to cyclohexyl ring synthesis i.e. formation of bonds (a), (b), or (c).



Formation of bond (a) has been achieved by Ireland,[13] who elegantly constructed the cyclohexyl moiety through the application of Diels Alder chemistry.

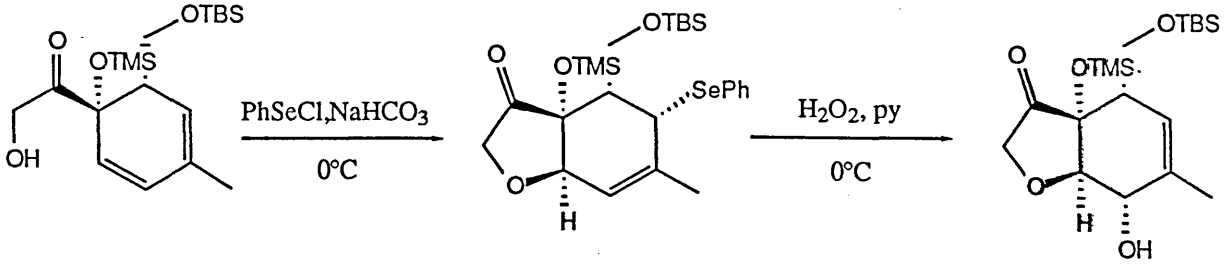


The furan ring was closed upon acid treatment of silyl ether (3) in a reversible intramolecular Michael reaction, which predominantly afforded the equatorial acetate (4).



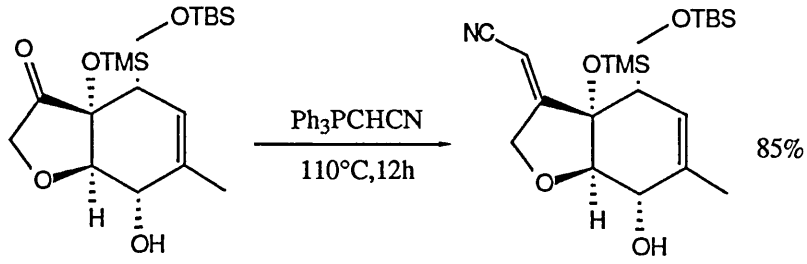
(3) (4)

Crimmins[14] has analogously demonstrated that facile bond (a) formation may be induced by electrophilic selenium.



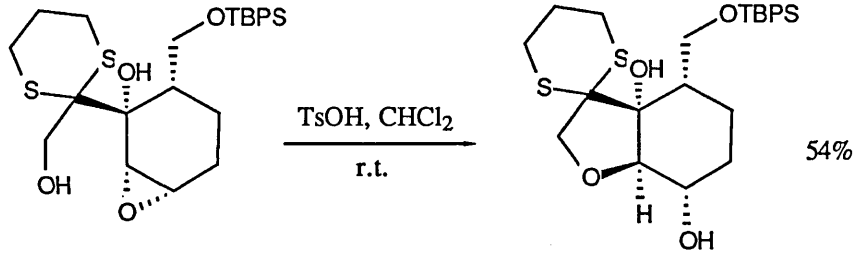
Suprafacial [2,3] sigmatropic rearrangement of the corresponding selenoxides simultaneously introduced C-3, C-4 unsaturation and C-5 α-hydroxylation. Correction of C-5 stereochemistry was achieved upon subsequent oxidation and reduction. Two carbon homologation of the C-8 ketone[15] (5) by Wittig reaction was

also shown to be viable.

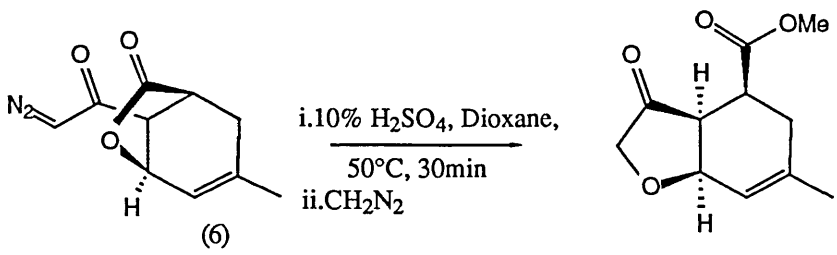


(5)

Barrett[16] has similarly used bond (a) formation - via an intramolecular epoxide opening reaction - to secure the benzofuran nucleus of avermectin A_{2b}.

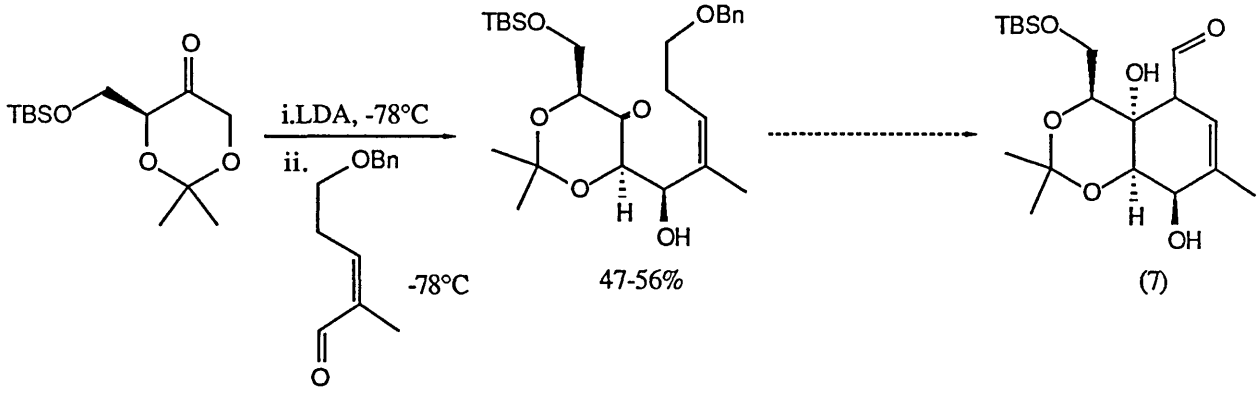


In contrast a strategy involving bond (b) closure has been adopted by White[17]. Diels-Alder chemistry was central to cyclohexyl ring preparation. The formation of the furan ring was achieved by utilization of the nucleophilic C-6 oxygen atom in the displacement of nitrogen from the α-diazoketone (6).

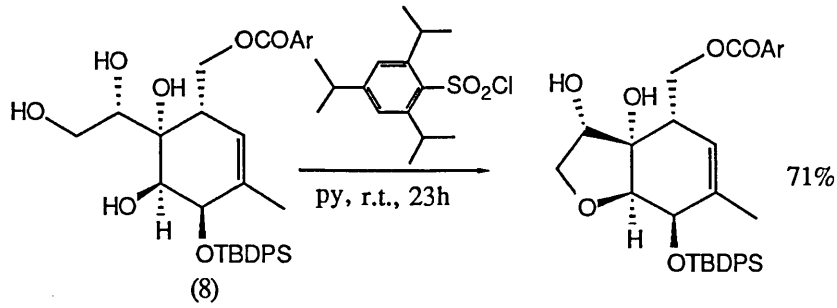


(6)

Hirama[18] has made good use of two aldol reactions to construct the cyclohexyl portion of the avermectins.

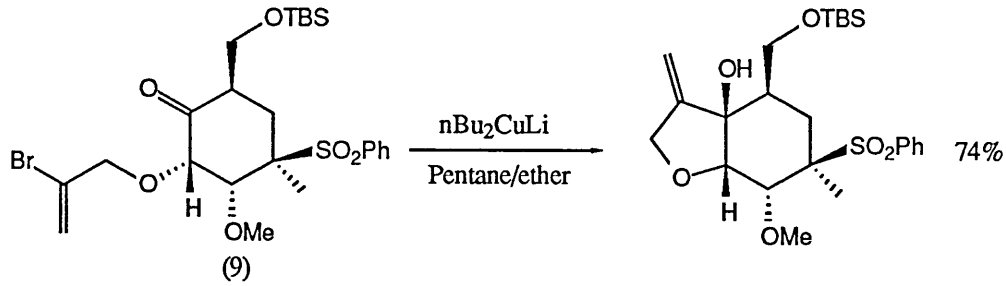


A tendency for the C-3, C-4 double bond to migrate to the more stable C-2, C-3 position[19] was halted by reduction of the aldehyde (7) to the corresponding alcohol. Bond (b) closure occurred on selective sulphonylation of tetraol (8).



(8)

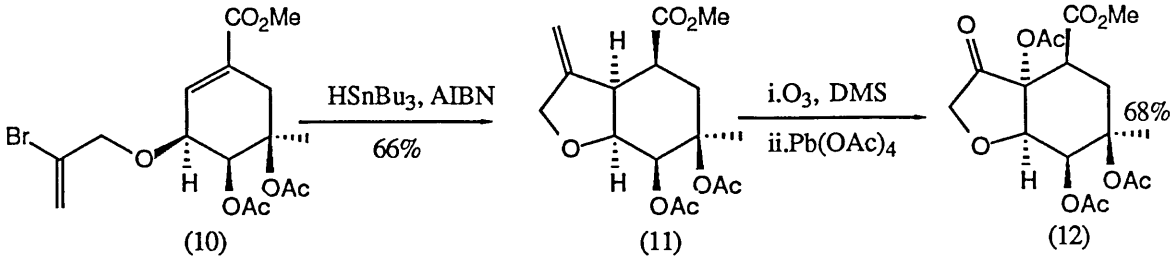
Three related approaches utilizing bond (c) connection of the furan ring have been reported. In the first Kozikowski[20] demonstrated that intramolecular nitrile oxide cycloaddition chemistry may be applied to cyclohexanone synthesis. Intramolecular cyclisation to afford the furan ring occurred on exposure of vinyl bromide (9) to di n-butyl copper lithium.



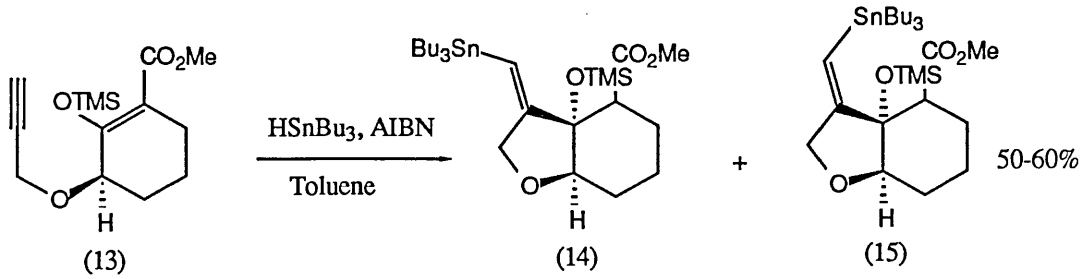
(9)

Unfortunately initial experiments have indicated that the phenylsulphone moiety is not the group of choice for introducing C-3, C-4 unsaturation.

Intramolecular free radical cyclisation of vinyl bromide (10) - available in eleven steps from (-)quinic acid - has been shown by Hanessian[21] to afford the bicyclic acetate (11).

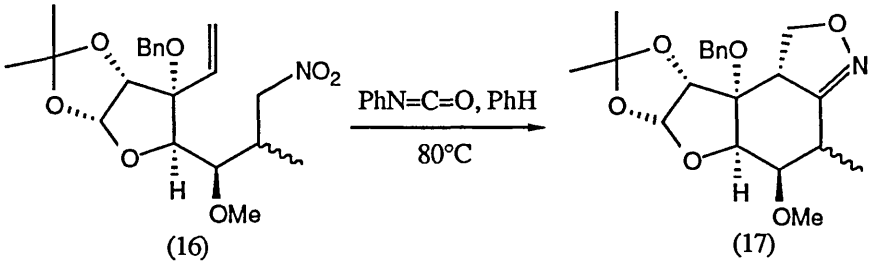


α-Acetoxylation occurred regio- and stereoselectively on treatment of the corresponding C-8 ketone with lead tetracetate to afford the triacetate (12). However, further manipulation of this intermediate i.e. C-8 homologation and/or introduction of the C-3, C-4 double bond, was not reported. More recently, Julia[22] has shown that tributyl tin radical addition to acetylene (13) is accompanied by intramolecular bond (c) formation, to afford a 30:70 mixture of bicyclic ethers (14) and (15), in moderate yield.



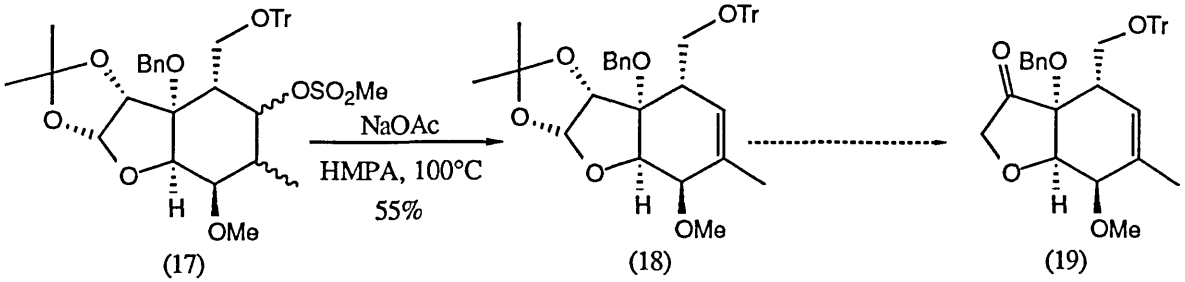
Perhaps a more successful general strategy to the milbemycin and avermectin benzofuran ring system involves the construction of an appropriate furan derivative with subsequent cyclohexyl ring formation.

This approach was first adopted by Fraser-Reid[23], who incorporated the furanose form of D-glucose into the avermectin benzofuran unit. Closure of the cyclohexyl ring followed upon treatment of the nitroalkenes (16) with phenyl isocyanate.



(16) (17)

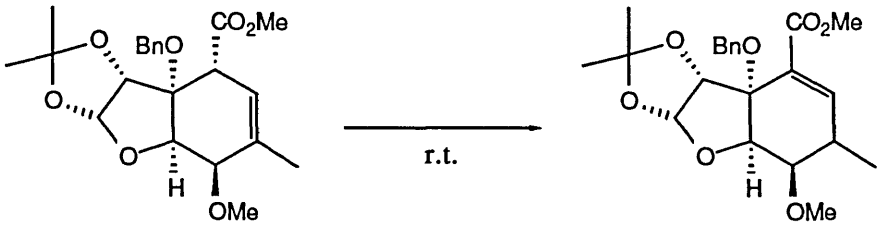
Regioselective introduction of the C-3, C-4 double bond was achieved in moderate yield on prolonged treatment of the mesylates (17) with sodium acetate in hot HMPA.



(17) (18) (19)

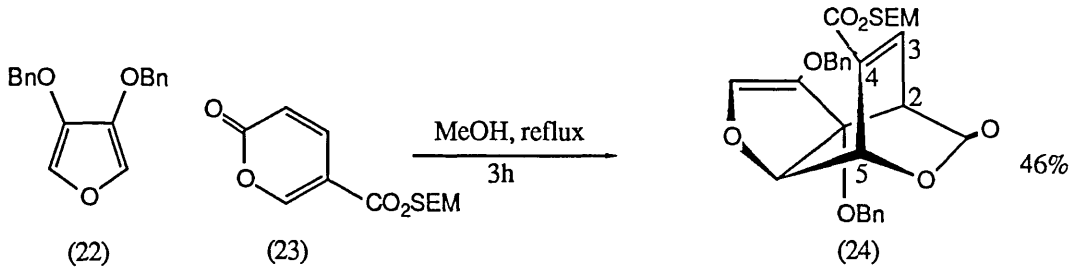
Unfortunately direct reductive cleavage of the glycosidic bond in (18) was unsuccessful, and use of a more lengthly reaction sequence was necessary to secure the required oxidation state in the furanose ring (19).

Further studies[19] revealed that the carboxylic derivative (20) underwent conjugation to give (21) upon standing at room temperature. This led Fraser-Reid to surmise that C-3,C-4 alkenes such as (20) "must be regarded as unreliable synthons" for southern unit synthesis.



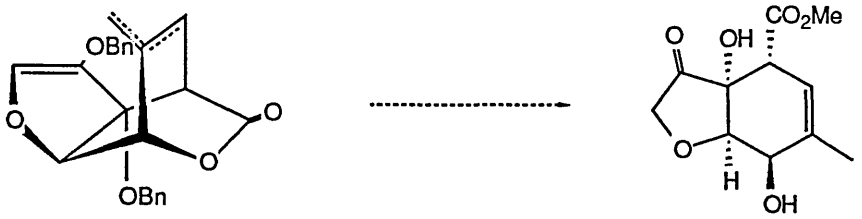
(20) (21)

Jung[24] has utilized an inverse electron demand Diels-Alder strategy to fuse cyclohexyl (23) and furan (22) rings together.



(22) (23) (24)

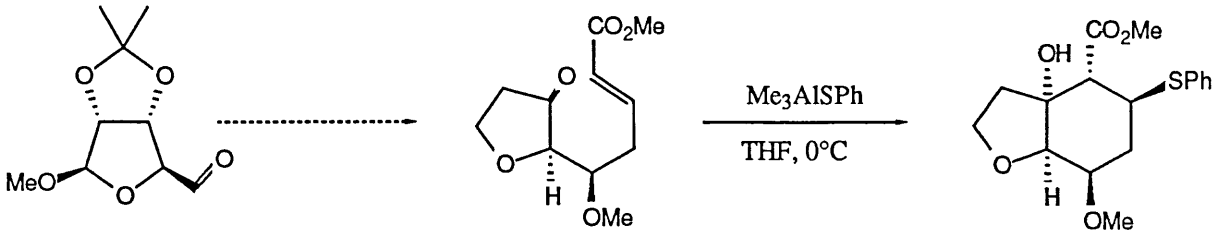
The endo adduct (24) constitutes the entire benzofuran carbon selection. Reduction of the C-4 ester to the required methyl group was achieved efficiently via sodium trimethoxyborohydride reduction of the corresponding chloromethyl derivative. This process was, however, complicated by partial S_N2' by hydride to give a 82:18 mixture of endo- and exocyclic double bond isomers (25).



(25) (26)

Correction of C-5 stereochemistry was accomplished via an oxidation-reduction protocol. Reductive cleavage of the benzyl protecting groups served to complete the synthesis of (26).

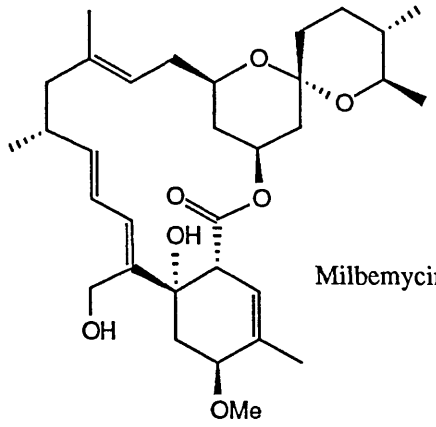
Finally Danishefsky[25] has utilized the D-Ribose derivative (27) as an intermediate for avermectin synthesis. In this case the cyclohexyl ring was closed in an intramolecular Nozaki reaction.



(27) (28)

Oxidative syn-elimination of the sulphoxides derived from (28), afforded the C-2, C-3 alkene. This methodology has since been successfully used in a key step in avermectin A_{1a} total synthesis.[26] The introduction of C-3, C-4 unsaturation was achieved *via* a deconjugation-equilibration process (vide infra).

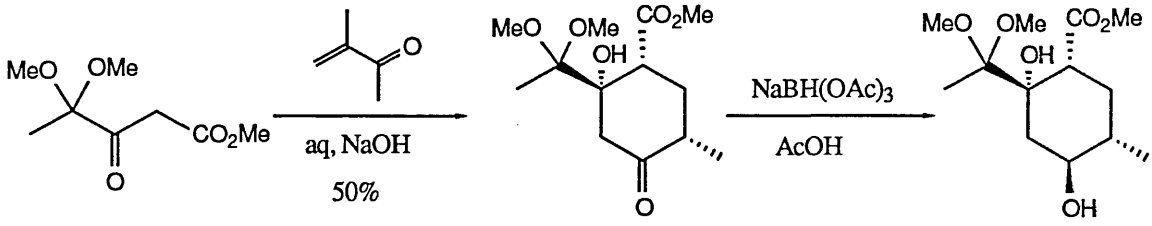
In contrast to the previous section, preparation of the structurally simpler cyclohexyl portions of non-aromatic milbemycins - such as milbemycin β_1 (29) - have received relatively little attention.



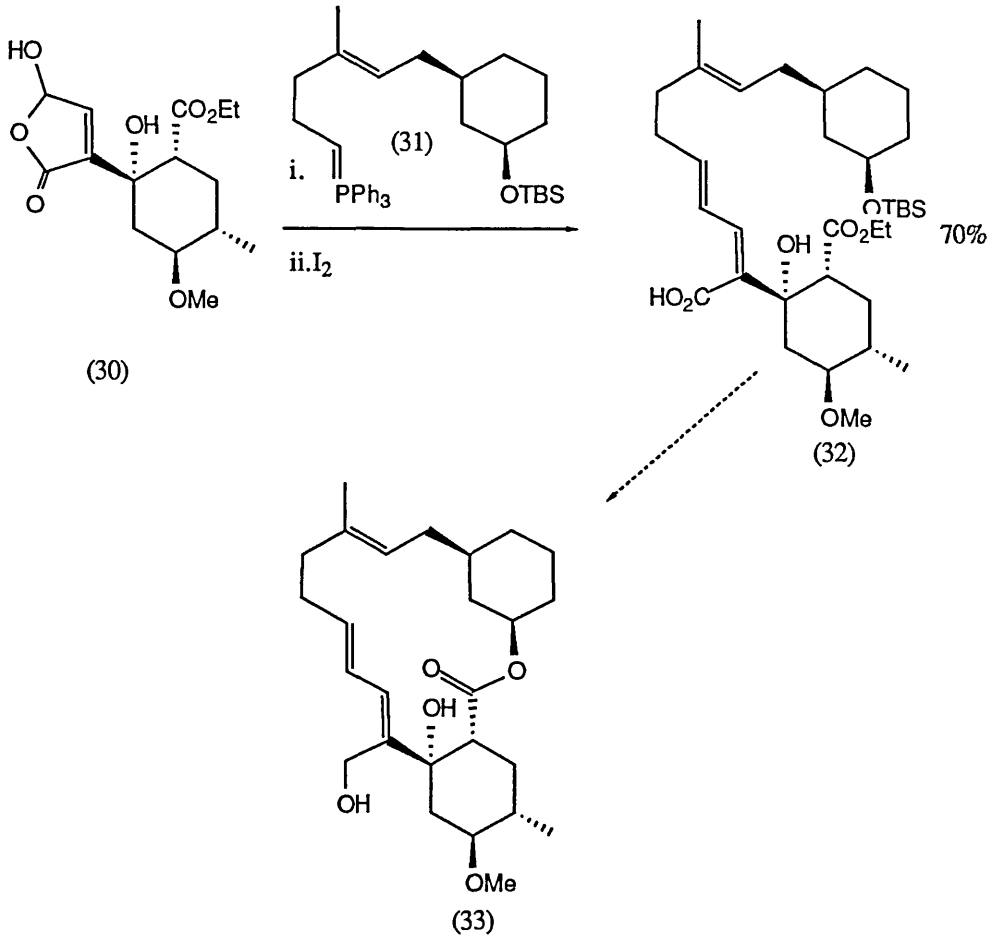
Milbemycin β_1

(29)

Turnbull[27] has shown that such a ring system can be rapidly constructed in the Michael-Aldol reaction sequence shown overleaf.

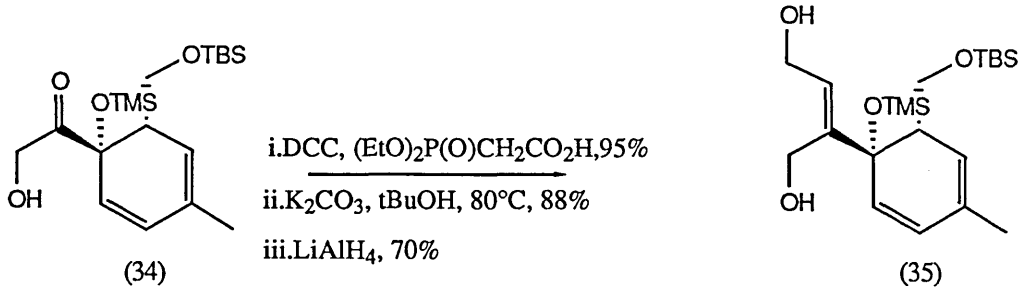


Stereospecific hydroxyl directed reduction of the ketone has been used to secure C-5 stereochemistry. Turnbull and Thomas[12] have since prepared the more advanced intermediate (30) with this methodology.



Wittig coupling of the ylide (31) and lactol (30) afforded mostly a Z,Z diene. Isomerisation by treatment with a catalytic amount of iodine gave the more stable E,Z olefin (32) in good yield. This was subsequently used to prepare the simple milbemycin analogue (33).

Crimmins[14] in his work directed towards the benzofuran ring system of milbemycin D demonstrated that the ketone (34) could be homologated via an intramolecular Wittig reaction to give the diol (35) which resembles the southern zone of milbemycin β_1.

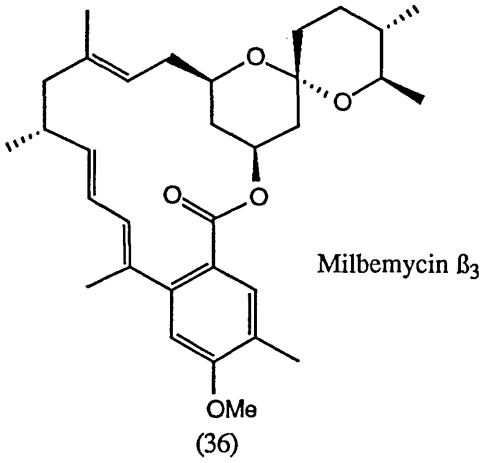


(34) (35)

Presumably the intermolecular version of this reaction was less efficient.

Total Syntheses of Milbemycin β3.

To date eight syntheses of milbemycin β_3 (36) - the simplest member of the milbemycin family - have been reported.

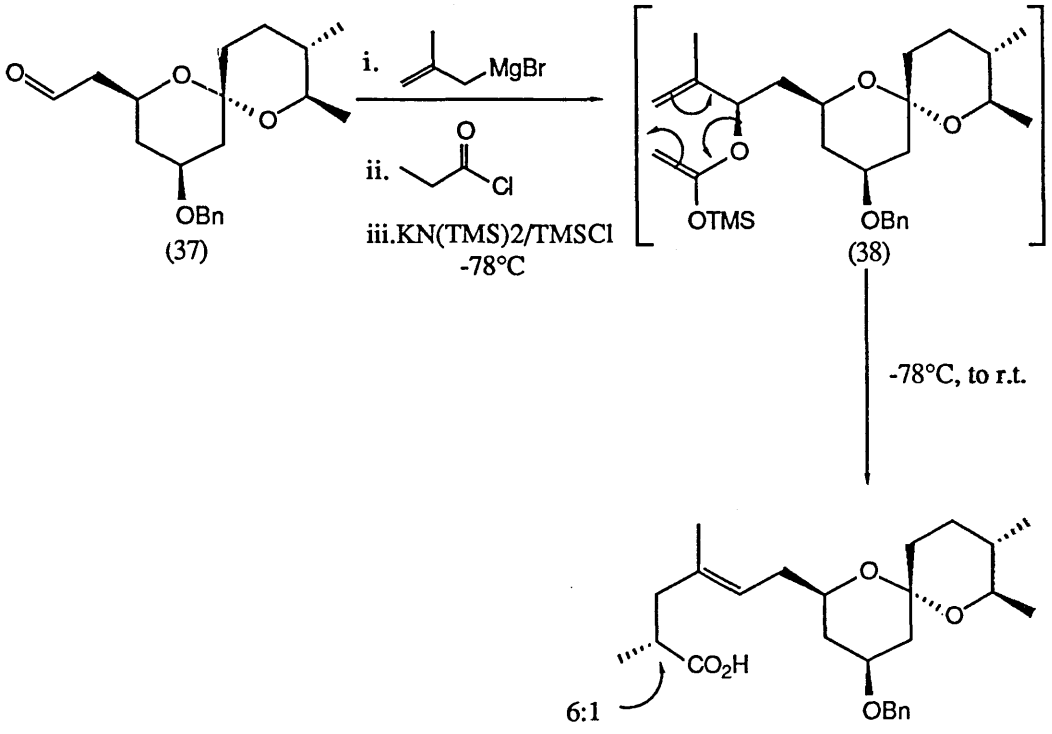


Milbemycin β_3

(36)

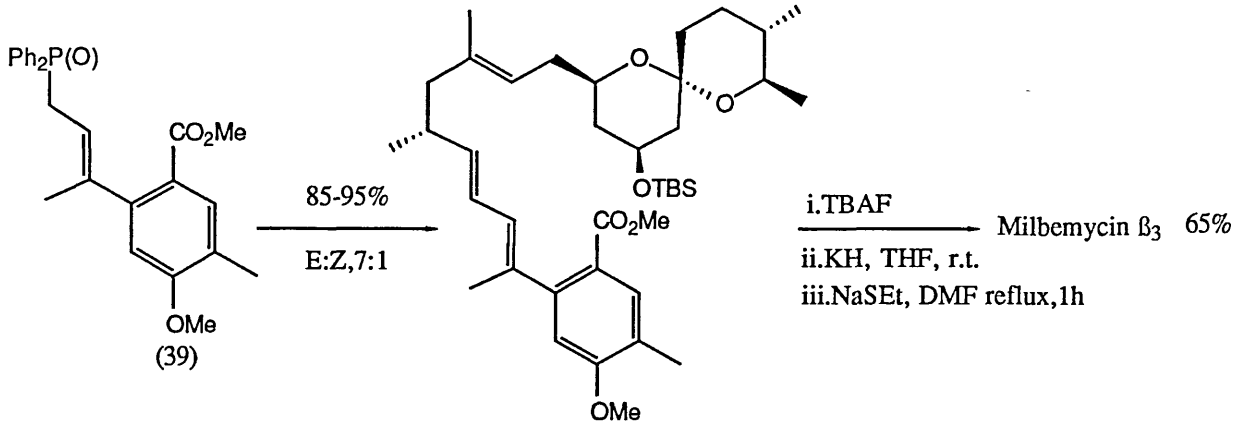
This section describes the strategy and reactions employed in the convergent coupling of the various milbemycin fragments rather than subunit synthesis itself.

The first total synthesis of racemic milbemycin β_3 was reported in 1982 by Smith.[28] Chain elongation of aldehyde (37) was achieved by sequential Grignard addition (minor isomer depicted below) and stereoselective Claisen rearrangement via the Z- ketene acetal (38). In this way concomitant control of both the trisubstituted double bond geometry and the stereochemistry of the remote C-12 methyl group was achieved.



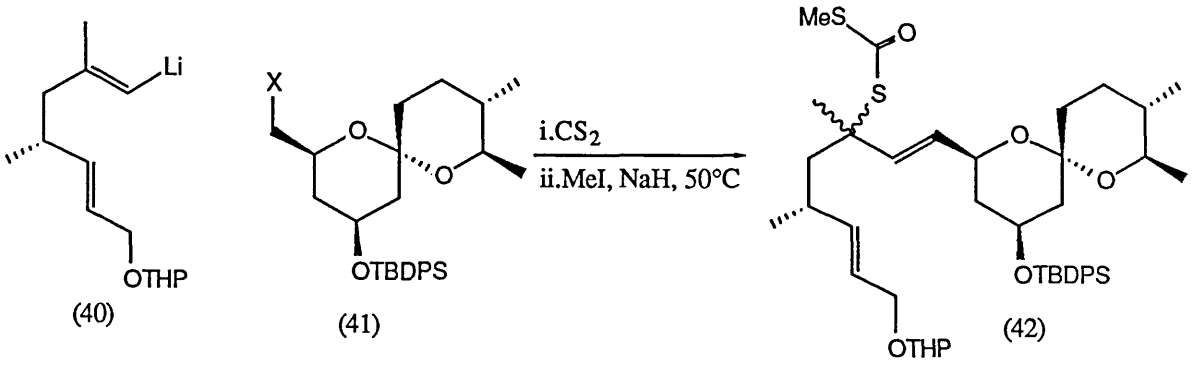
Trans selective Horner-Emmons reaction of the vinylogous phosphine oxide (39)

effected union of the northern and southern hemispheres.



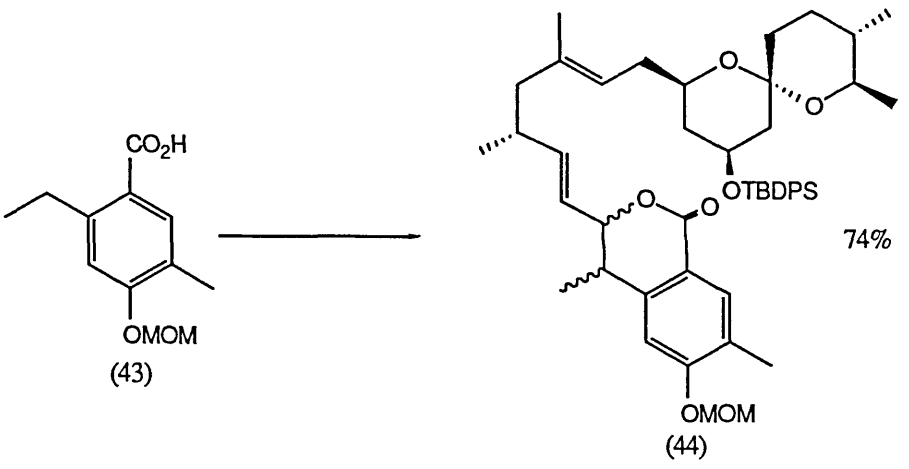
After silyl ether cleavage, macrolactonisation occurred simply on exposure of the hydroxy ester to potassium hydride. Demethylation of the arylmethyl ether gave (±) milbemycin β_3 in good yield. A semi-synthetic avermectin/milbemycin hybrid[29] has since been prepared in an analogous manner.

In the same year Williams[30] achieved the first asymmetric synthesis of milbemycin β_3. It was intended that Negishi's carboalumination of acetylenes would serve to control the C-14, C-15 double bond geometry. However, coupling of the two optically active units (40) and (41) could not be achieved by nucleophilic displacement reactions.

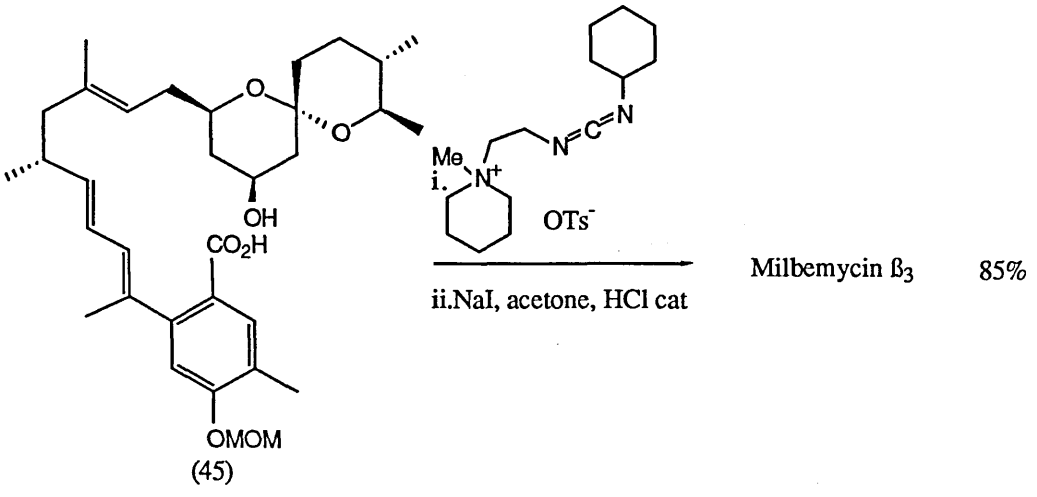


Addition to the more reactive aldehyde (41) (X=O) was successful, however, the now necessary deoxygenation was complicated by [3,3] sigmatropic rearrangement of the corresponding xanthates to give the dithiocarbonates (42). Reduction of these derivatives gave a mixture of isomeric olefins, of which the major component (75%) was shown to be the desired trans C-14, C-15 alkene.

Unison of the southern and northern hemispheres, in contrast to Smith's procedure, involved C-8, C-9 double bond formation. Thus, addition of the requisite aldehyde to the benzylic lithiodianion derived from (43) afforded the diastereomeric lactones (44) upon acid workup.

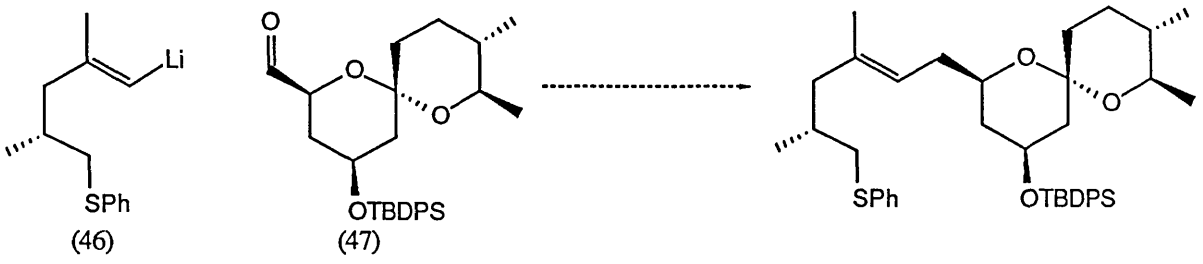


The silyl ether was subsequently cleaved and treatment with excess potassium hydride gave a single dienyl carboxylic acid (45) in 85% yield.

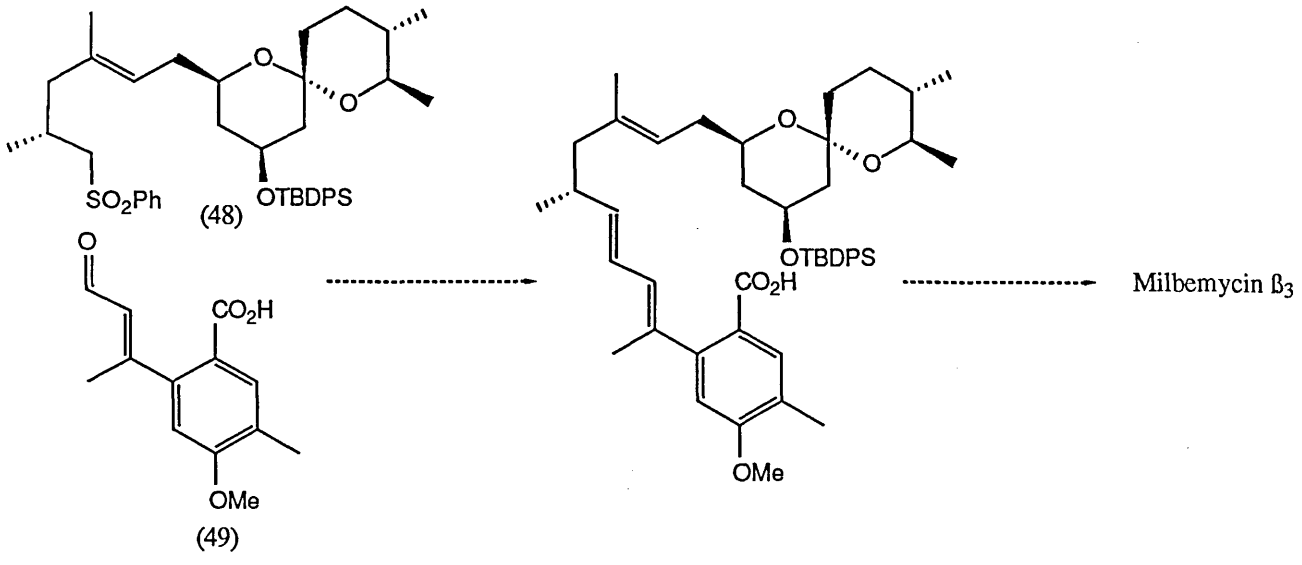


Efficient macrolactonisation and deprotection of the MOM ether completed the synthesis.

Baker's[31] synthesis of milbemycin β_3 followed Williams' problematic strategy, coupling vinyl lithium (46) with the aldehydic spiroacetal (47).

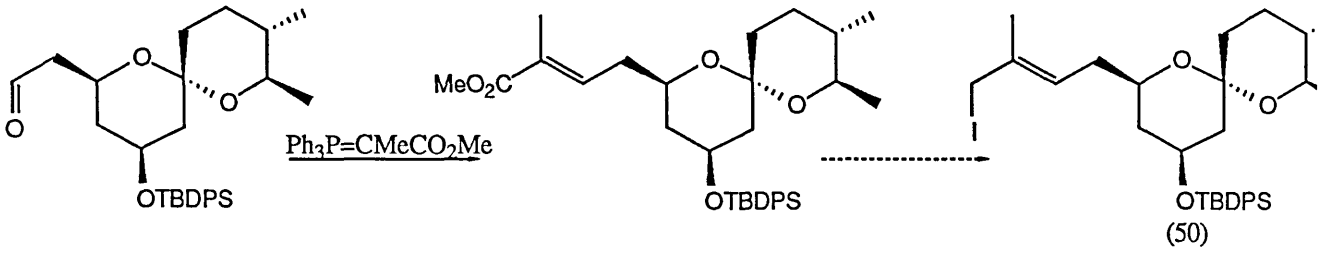


The trans selective Julia reaction was employed to efficiently (70-80%) couple the northern (48) and southern hemispheres (49), no mention of Z olefin formation was made.



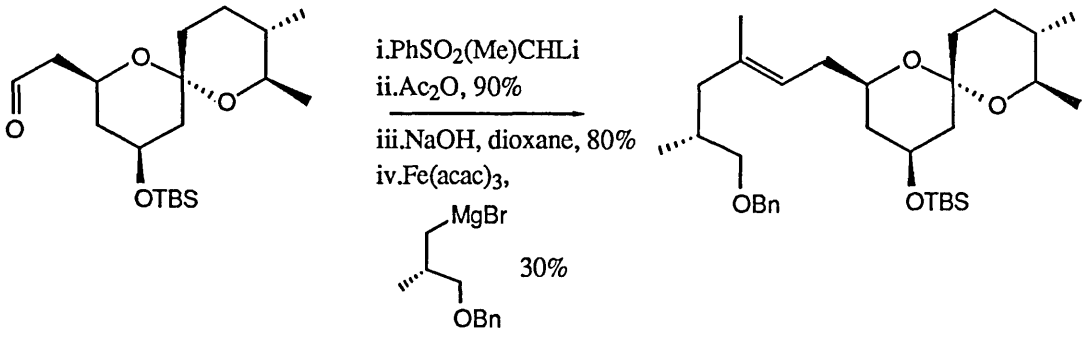
A modification of Smith's protocol afforded the natural product.

Baker[32] has since utilized stabilised Wittig methodology for C-14, C-15 olefination. Absolute stereochemistry at C-12 was controlled by Evans alkylation of the requisite allylic iodide (50).

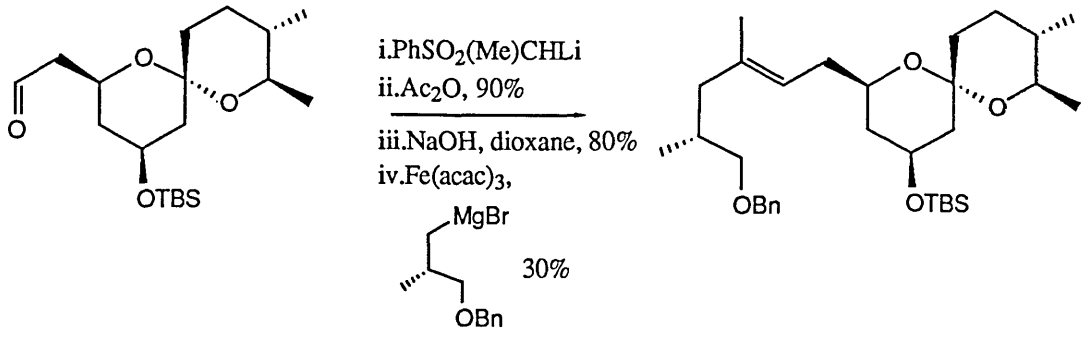


(50)

Kocienski[33] applied the iron(III) mediated trisubstituted alkene synthesis developed by Julia to the problem of C-14, C-15 bond formation.

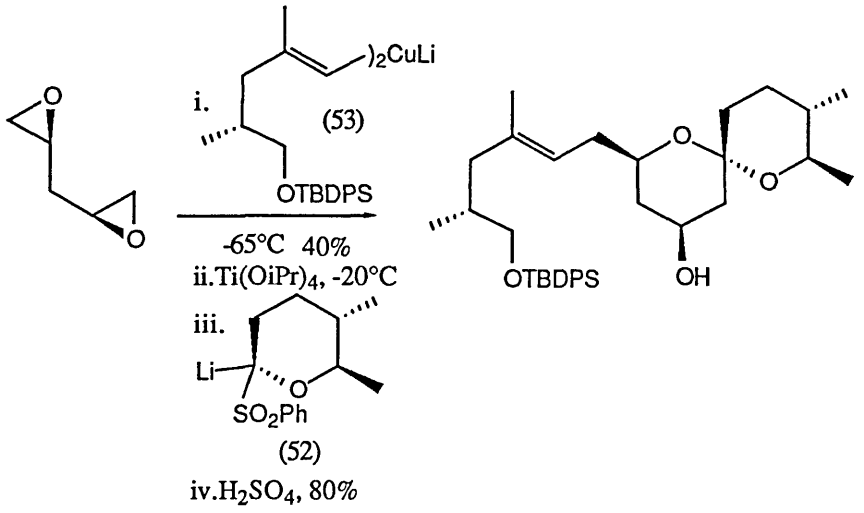


Kocienski[33] reversed the polarity of Baker's[31] C-10, C-11 Julia olefination by incorporating the sulphone moiety into the southern zone (51).



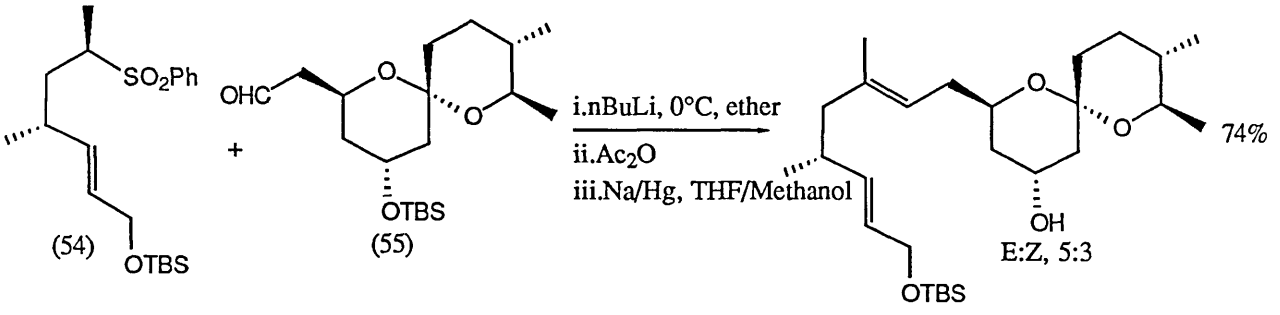
Interestingly, this process was less efficient than Baker's in terms of both chemical yield and trans selectivity, perhaps indicating that problems are encountered in reduction of a sulphone attached to a highly conjugated system. Again, adoption of Smith's methodology served to complete the synthesis.

Ley[34] elegantly coupled east (52) and west (53) portions in a highly convergent manner. In contrast to previous approaches (vide supra), the full potential of a zirconium catalysed carboalumination reaction was realized in controlling C-14, C-15 olefin geometry.



Kocienski[35] has utilized a similar Negishi reaction epoxide opening protocol to improve his first northern hemisphere synthesis.

In Barrett's synthesis of milbemycin β_3 [35] Julia methodology was used to couple the optically active sulphone (54) and aldehyde (55).



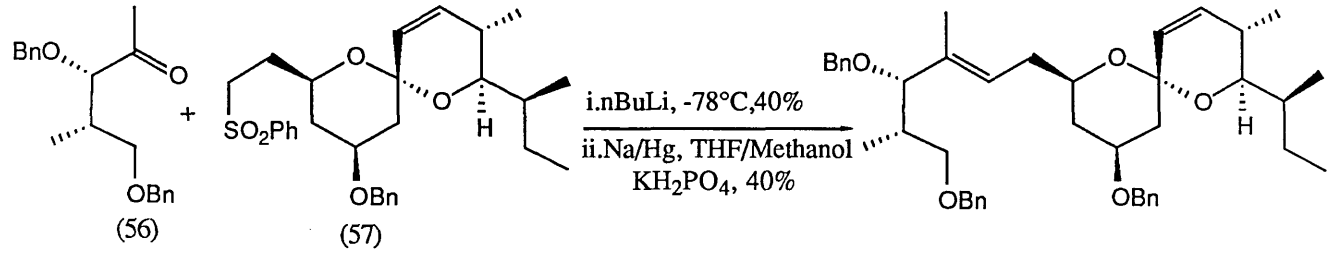
The poor trans selectivity probably reflects the influence of the methyl group in counteracting non-bonded interactions in the transition state which usually produce good trans selectivity in 1,2, disubstituted alkene formation. The remaining coupling of the northern and southern hemispheres paralleled that of Williams (*vide supra*). Closure of the macrolactone under Mitsunobu conditions corrected C-19 stereochemistry and final demethylation afforded (+) milbemycin β_3.

Crimmins[37] has recently reported a synthesis of Williams'[30] northern hemisphere in which the trisubstituted double bond geometry was controlled by Wittig methodology analogous to that of Baker.[32]

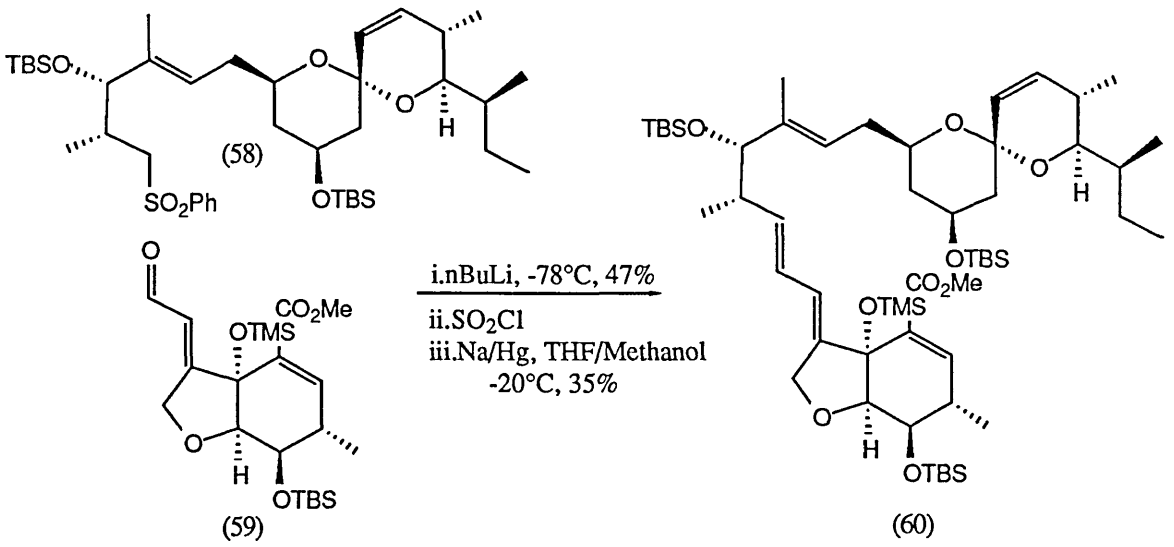
Avermectin Synthesis

Hanessian[38] has reported a semi synthesis of avermectin B_{1a} in which Julia olefination reactions played a central role in achieving geometric control of both C-10, C-11 and C-14, C-15 double bonds.

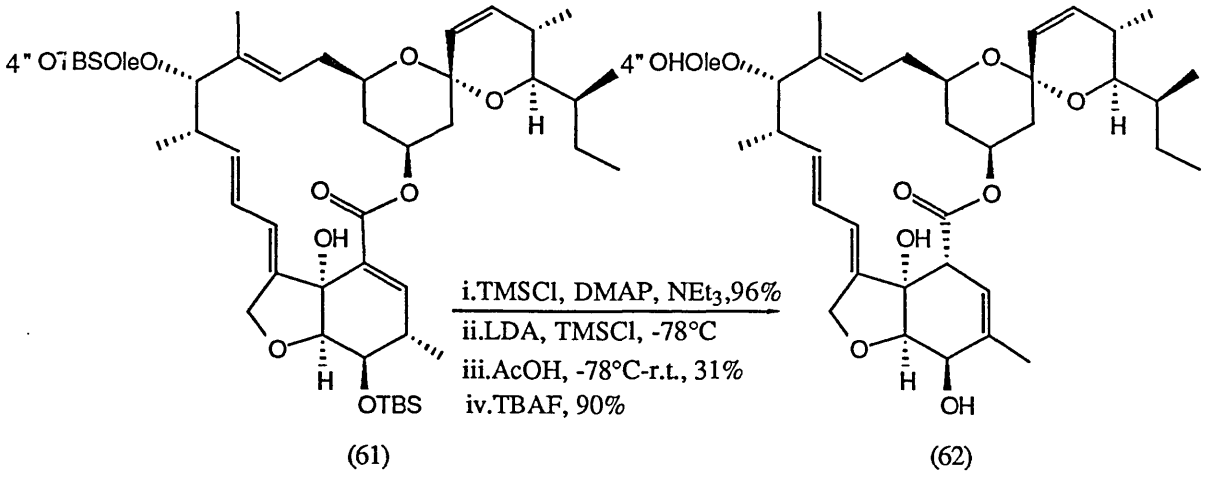
Coupling of the synthetic sulphone (57) and ketone (56) units was achieved in 16% overall yield, (38% on recovered sulphone) Reversibility of the initial anionic addition may explain the inefficiency of this process[39].



In coupling synthetic northern hemisphere (58) with naturally derived enal (59) only the trans alkene (60) was detected.



Further manipulation, DCC mediated macrolactonisation, attachment of the L-oleandrose disaccharide residue and protecting group adjustment afforded the α,β unsaturated lactone (61).

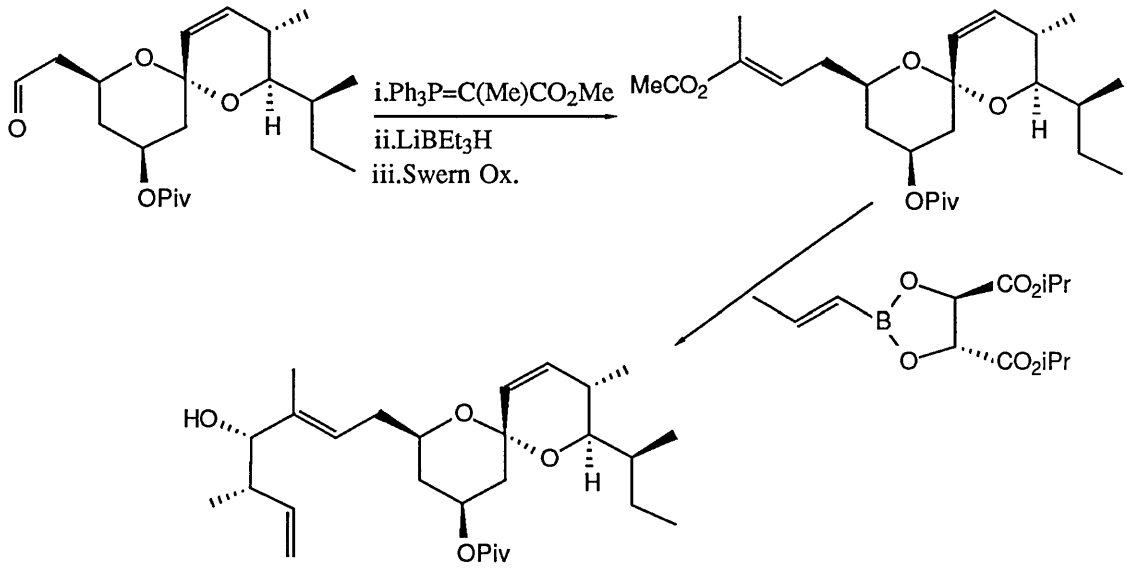


The critical deconjugation experiment was performed as follows. The C-7 hydroxyl group was protected to block the α-face of the bicycle. Ketene acetal formation followed by careful acidification and subsequent desilylation gave

avermectin B_{1a} (62).

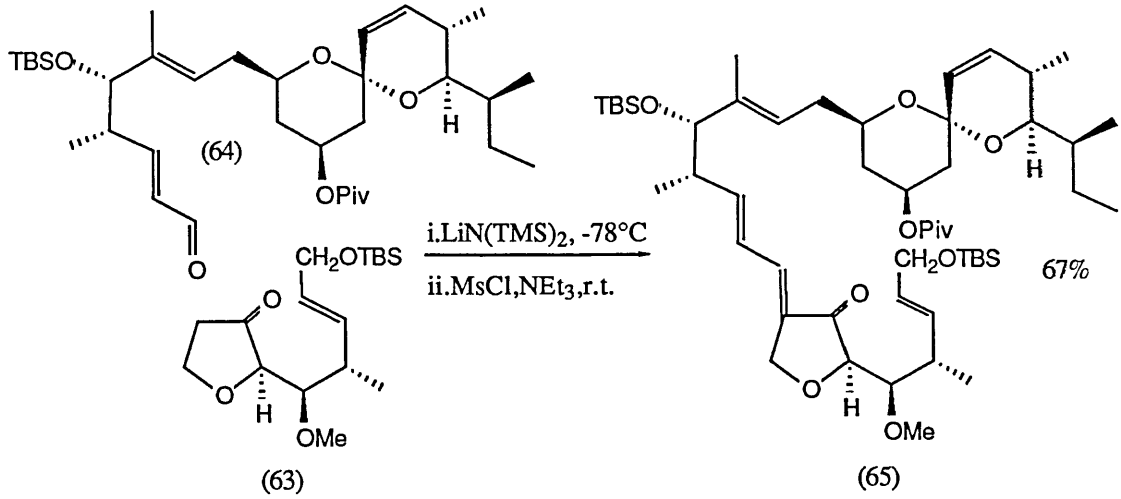
However, the stereochemical outcome of this deconjugation sequence has been fiercely contested by Fraser-Reid[19]; who under Hanessian's reported conditions obtained the C-2 epi macrolide, resulting from kinetic protonation of the convex-α-face of the benzofuran ring system.

Finally, the efforts of Danishefsky[26] have culminated in the first total synthesis of a member of the avermectin family. 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.

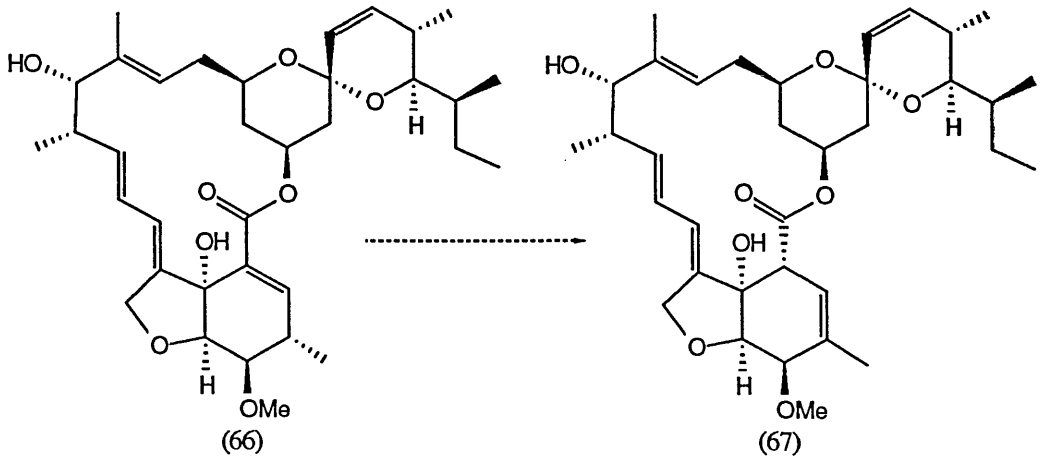


Danishefsky chose to couple southern and northern units via C-8, C-9 connection. A classical crossed aldol condensation/dehydration sequence elegantly achieved this end. Thus the lithium enolate of ketone (63) reacted with enal (64), and sulphonylation of

the intermediate adduct afforded the enone (65) in good yield.



Employment of an intramolecular Nozaki reaction[25] (vide supra) served to complete the benzofuran nucleus. Macrolactonisation (67%) using Mukaiyama's technology occurred smoothly and liberation of the C-13 hydroxyl group afforded the conjugated Δ^2 tautomer (66) of avermectin A_{1a} aglycone.



The deconjugation of (66) was accomplished through the action of LDA in THF at -78°C followed by an aqueous HCl quench, which afforded the C-2 epi derivative (67) in 75% yield. Reaction of this lactone with a concentrated solution of imidazole in refluxing benzene afforded an equilibrium mixture comprised of (67) 33%, (66) 21% and avermectin A_{1a} aglycone 32%. The total synthesis was completed by attachment of a synthetic L-oleandrose disaccharide residue[26,38,40].

Conclusion

The widespread success of milbemycin β_3 total synthesis has yet to be achieved within the more structurally elaborate non - aromatic milbemycin and avermectin series. This may be primarily attributed to the differculties that are encountered during the synthesis of the southern zone of these natural products.

In particular, two recurring problems have plagued the efforts of synthetic chemists.

Although the preparation of southern units containing C-8 ketone functionality has proven popular, the pausity of publications regarding C-8 ketone elaboration and the fact that such ketones are flanked by two ß oxygen substituents suggest that these ketones are only weakly electrophillic. In contrast, C-10, C-11 attachment has been demonstrated as a successful strategy for effecting northern and southern hemisphere union.

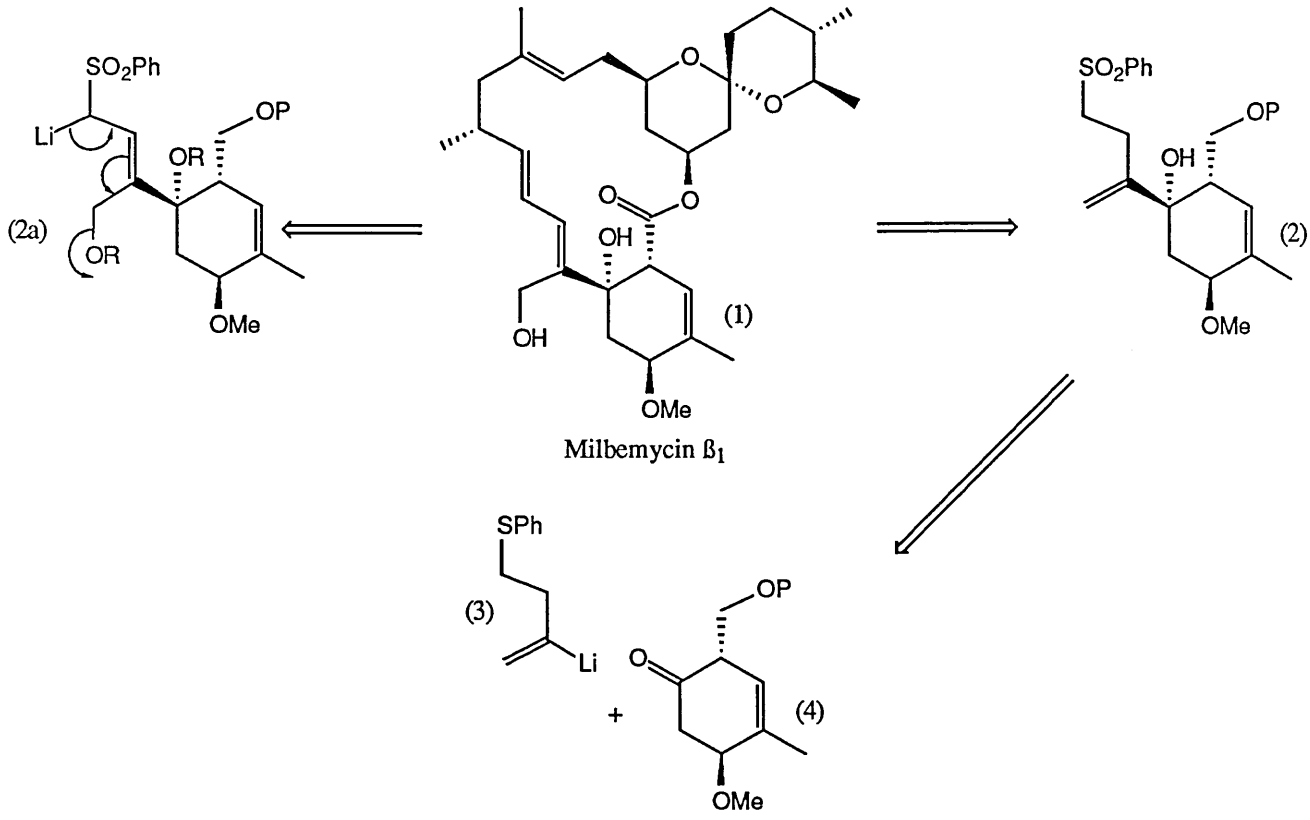
The regioselective introduction of the C-3, C-4 olefin has been achieved. However its regio-instability - particularly in non - macrocyclic intermediates - has proven problematic. The recent development of a deconjugation / equilibration protocol constitutes the first solution of this problem. However, efforts to discover more direct methods of introducing this functionality are required and will surely follow[47].

Results and Discussion

Milbemycin β_1[3] (1) was chosen as the initial focus of our ongoing efforts to develop a general synthetic strategy towards the avermectin and milbemycin families[7] of natural products.

We considered that a Julia[39] olefination reaction would be an attractive method of effecting the unison of northern and southern hemisphere subunits.[42] However, the application of this methodology to trisubstituted olefin synthesis was known to be poorly trans selective and often capricious. Thus, we were dissuaded from the adoption of C_8-C_9 olefination strategy. In contrast, the control of C-10, C-11 double bond geometry was expected to be particularly amenable to such a sulphone based coupling procedure. In particular, the presence of α-branching[39] at C-12 was expected to enhance the intrinsic E-selectivity of the olefination process.

Incorporation of the sulphone moiety into the southern hemisphere synthon (2) was chosen to avoid vinylogous elimination of the potential leaving groups at C-7 and C-8 of the anionic intermediate (2a). After coupling, simultaneous introduction of the C-8' hydroxyl substituent and the trans C-8, C-9 double bond was envisaged via a C-7-hydroxyl-directed epoxidation[43]/ epoxide ring opening[44] sequence.



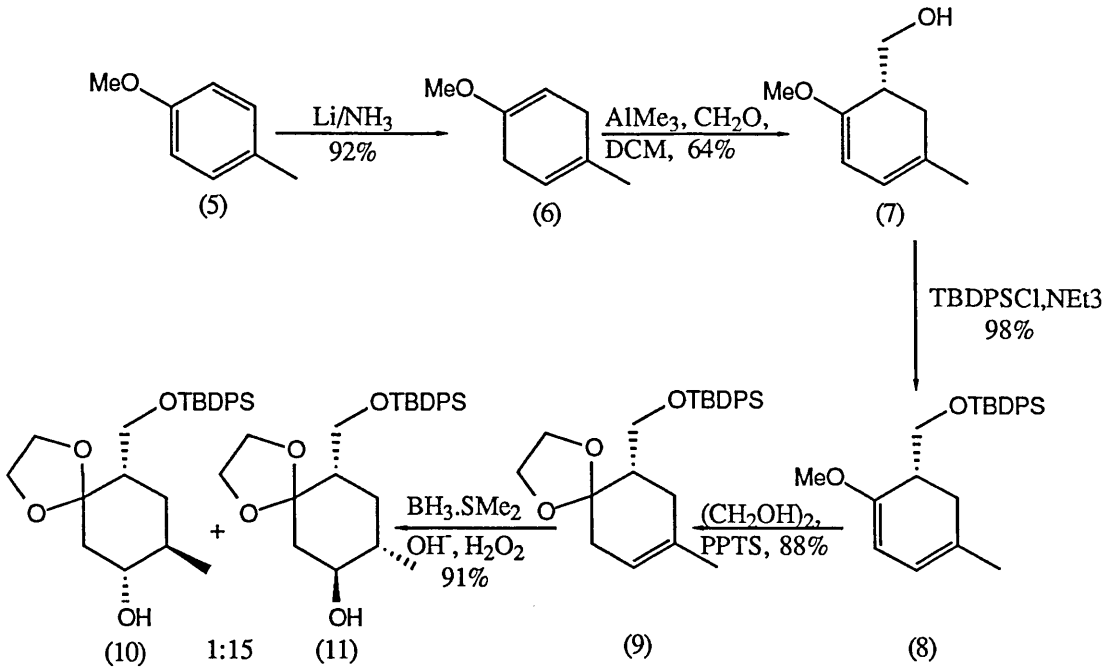
Retro-analysis of the sulphone (2) indicated that it should be available through the stereocontrolled addition of the vinyl anion (3) to the least hindered face of the corresponding C-7 ketone (4). Clearly the successful synthesis of this requisite ketone would require the discovery of a mild and regiocontrolled method for introducing C-3, C-4 unsaturation.

The results reported here pertain to the synthesis of milbemycin β_1 southern hemisphere synthons, their coupling to northern fragments and their subsequent elaboration to macrocycles. Additionally the manipulation of some milbemycin β_1 intermediates have allowed some progress to be made towards the milbemycin α series[7] of natural products.

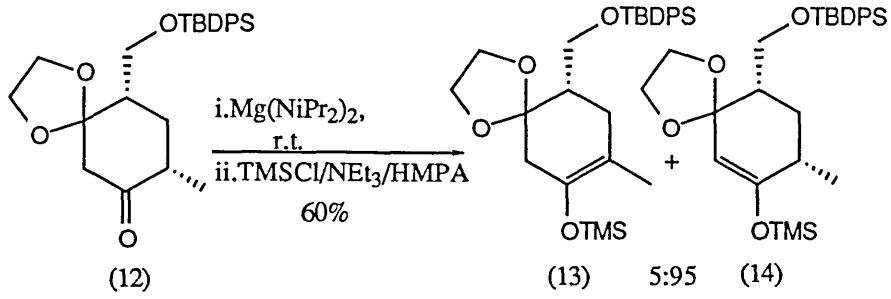
Synthesis of Southern Hemisphere Synthons.

A four step procedure[45] - involving only one chromatographic separation - allowed the alkene (9) to be prepared on a one mole scale. Thus, 4-methylanisole (5) was reduced with lithium in liquid ammonia to afford the dihydro derivative (6) in 92% yield. The enol ether (6) prepared in this way was of sufficient purity to be used in the next step without purification. Trimethylaluminium mediated Prins[46] reaction with paraformaldehyde gave the hydroxymethylated material (7) in good yield. Protection of this primary alcohol as its corresponding TBDPS[47] ether (8) served to prevent its acid catalysed fragmentation via retro-aldolisation. The enol ether (8) was subsequently converted to the dioxolane[47] (9) in a single step and without isomerisationof the C-4, C-5 double bond.

Regio- and stereoselective hydroboration[48] of this alkene with borane dimethyl sulphide complex gave the chromatographically separable diastereomeric alcohols (10) and (11) in a respective ratio of 1:15 The preferred formation of the β alcohol (11) presumably reflected the fact that the approach of the electrophilic reagent had occured from the least-hindered face of the olefin.



Attempted PDC oxidation of the intermediate organoboranes[49] failed to effect ketone formation. However, Swern[50] oxidation of the alcohols (10 and (11) afforded a single crystalline ketone (12) in excellent yield. A method by which C-3, C-4 unsaturation could be introduced was promptly sought. Direct methods[51] of dehydrogenating the ketone (12) proved unsatisfactory. Thus, the regioselective[52] preparation of the C-4, C-5 silylenol ether (13) was investigated. Subjection of the ketone (12) to the published conditions of Krafft[53] gave upon work-up, a mixture of silyl enolethers (13) and (14) in which the desired product was the minor component.

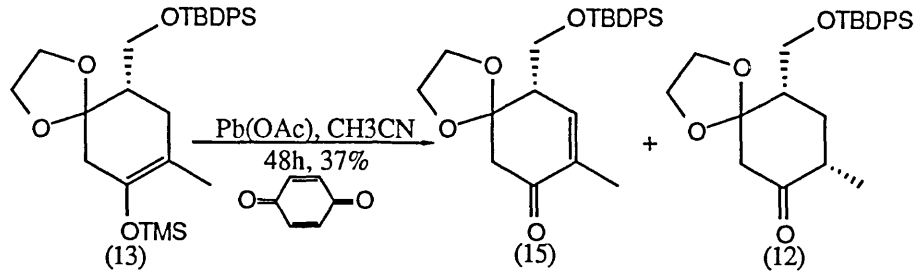


(12) (13) 5:95 (14)

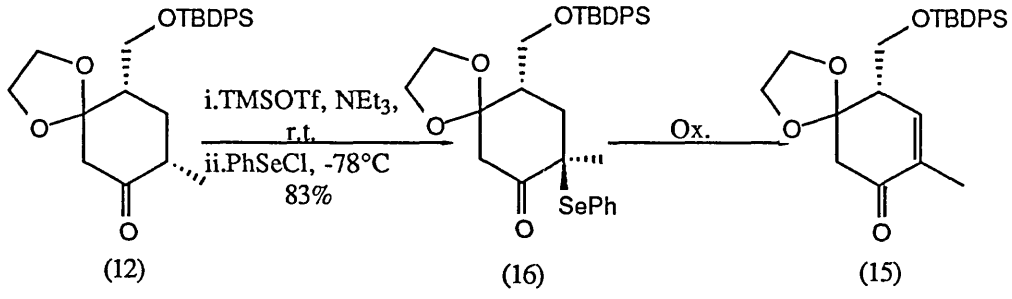
The unexpected regiochemistry of the process may be attributed to the participation of the dioxolane oxygen lone pairs[45,54] coordinating a magnesium cation and directing the nitrogen base to the more exposed C-6 proton. This disappointing result was however, of further interest. Stereoselective oxidation of silyenol ether (14) was envisaged to allow access to C-6 hydroxylated products, thereby providing a possible entry to the milbemycin α series[7] (*vide infra*).

In contrast, treatment of the ketone (12) with trimethylsilyltriflate under thermodynamic conditions[55] allowed the preparation of the desired, more substituted silylenol ether (13) to the virtual exclusion of its isomer (14) in 69% yield.

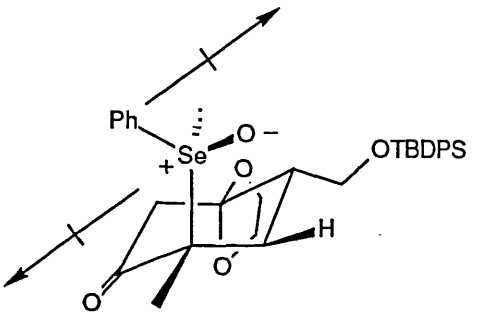
Palladium II catalysed dehydrogenation[56] of this silylenol ether (13) was complicated by silylenol ether hydrolysis. However an inseparable mixture of the ketone (12) and the desired endocyclic enone (15) was obtained though, in low yield.



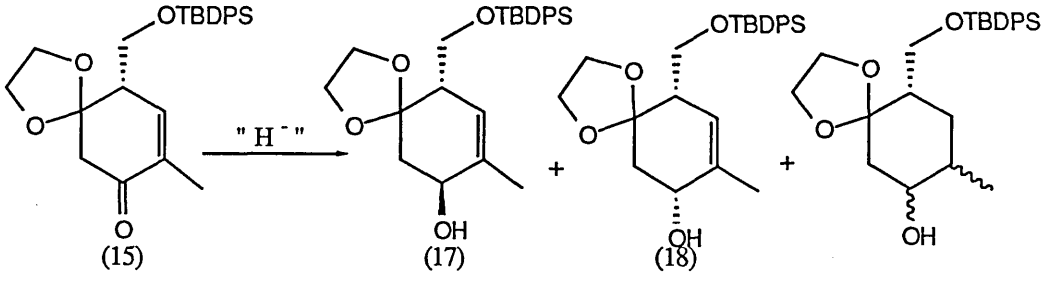
Encouraged by this result, alternative dehydrogenation methods were examined. The most successful of these involved stereoselective, low temperature selenenylation[58] of the crude enol ether (13).



Oxidation of the selenide (16) to the corresponding selenoxides with oxone or more conveniently with hydrogen peroxide, followed by room temperature *syn*-elimination, gave the desired endocyclic enone (15) as the sole product. The regioselectivity 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 favours endocyclic proton abstraction.[59]



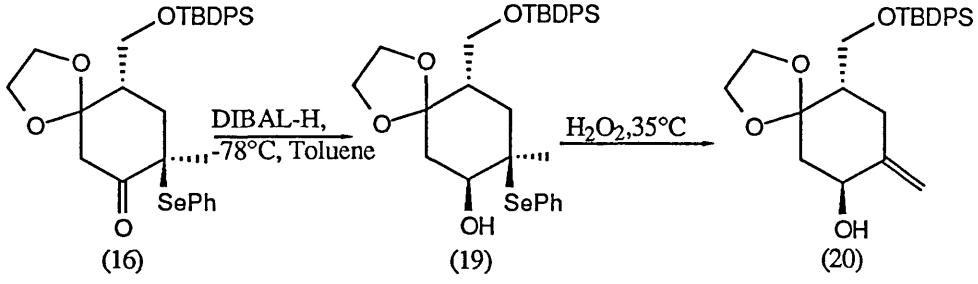
An efficient preparation of enone (15) had now been achieved and methods for its stereoselective reduction to the required equatorial allylic alcohol (17) were examined. The results of this study are tabulated below.



H^-	Combined Yield	Ratio	Ref.
Al $(OiPr)_3$, iPrOH	54%	26 : 74 : 0	60
BH_3, THF, 0°C- r.t.	60%	34 : 56 : 0	61
9BBN, THF, reflux	N.R.	- - -	62
L. Selectride, THF, -78°C	80%	13 : 87 : 45	63
DIBAL-H, toluene, -78°C	98%	15 : 85 : 0	64
$Zn(BH_4)_2$, ether, r.t.	N.R.	- - -	65
$NaBH_4$, MeOH, r.t.	90%	39 : 61 : 10	66
$NaBH_4$, $CeCl_3$, MeOH, r.t.	53%	45 : 55 : 0	67

H^-	Combined Yield	Ratio	Ref.
$NaBH_4$, $CeCl_3$, MeOH, -20°C	51%	46 : 54 : 0	67

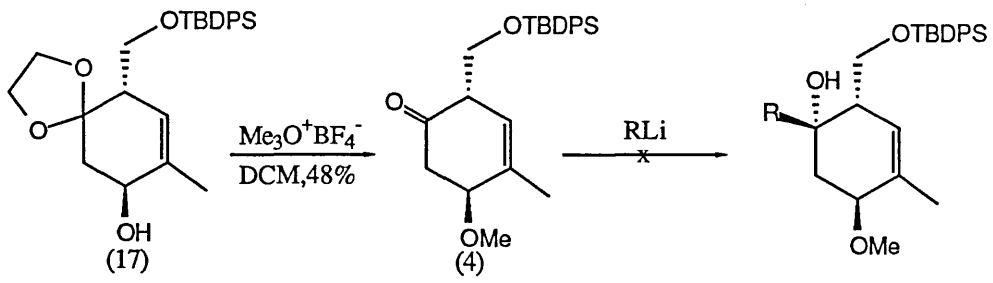
In contrast to these unselective hydride reductions, reduction of the α-selenenylketone (16) to the corresponding alcohol was expected to proceed stereoselectively due to the presence of the sterically demanding phenylselenenyl substituent.



Indeed, DIBAL-H[64] reduction of the α-selenenyl ketone (16) at -78°C occurred with complete stereocontrol to give the corresponding β alcohol (19). Oxidative *syn*-elimination of the selenide, however, furnished only the undesired exocyclic

allylic alcohol (20). The outcome of this reaction was unresponsive to variation in solvent, temperature or the nature of the oxidant. The smaller dipole moment[68] of an hydroxyl group relative to that of a carbonyl group may offer an explanation for this dramatic change in regioselectivity. Thomas[69] has subsequently reported some results analogues to the above.

Despite the disappointing nature of these results the lanthanide mediated sodium borohydride reductions provided sufficient quantities of the equatorial alcohol (17) for further study. Treatment of this alcohol with a large excess of trimethyl oxonium tetrafluoroborate effected both 5-O-methylation and deketalisation to afford the corresponding ketone (4) in modest yield.[70]

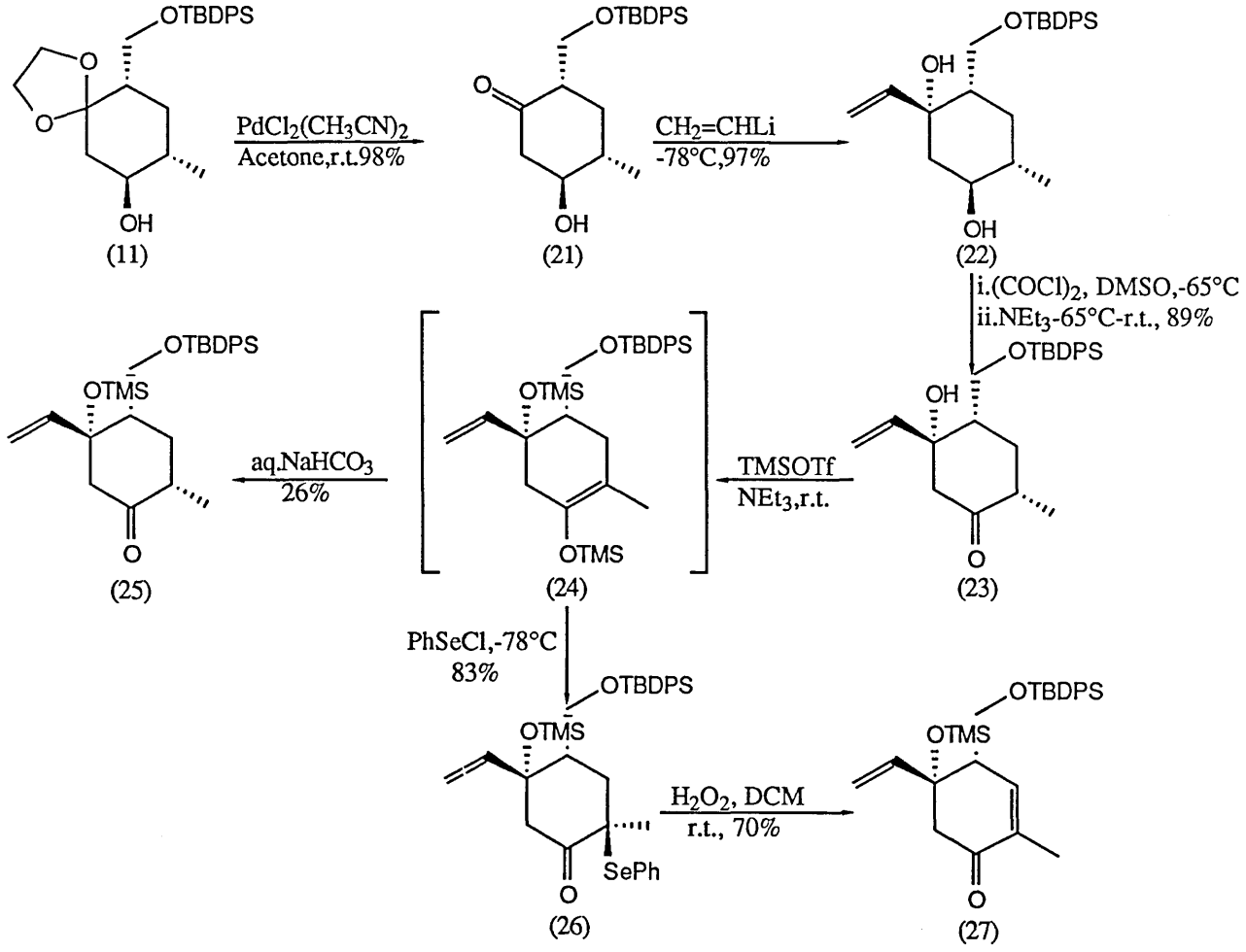


Unfortuately, this ketone failed to participate electrophilically in coupling reactions with a variety of organolithio species[70], presumably due to the acidic nature of the C-2 proton.

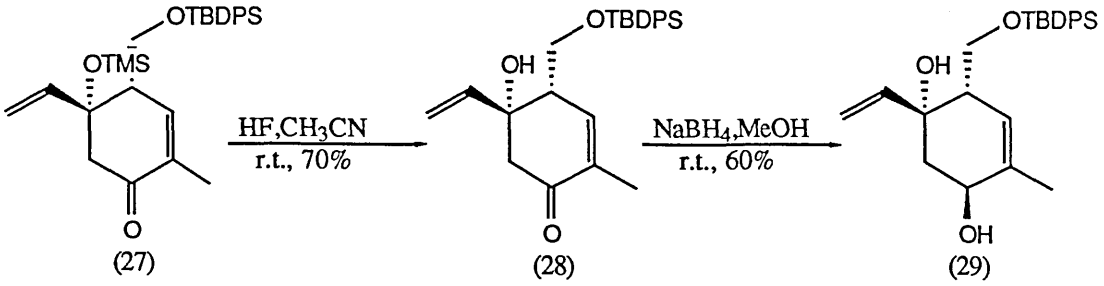
These results suggested that the coupling of an appropriate C-8', C-10 organolithium species with a C-7 ketone should be attempted prior to the introduction of C-3, C-4 unsaturation. In this way the acidity of the C-2 proton

would be reduced. Later, the newly introduced C-7 α-hydroxyl group could be usefully employed to control C-5 stereochemistry via an hydroxyl-directed 1,2 reduction of the corresponding enone.

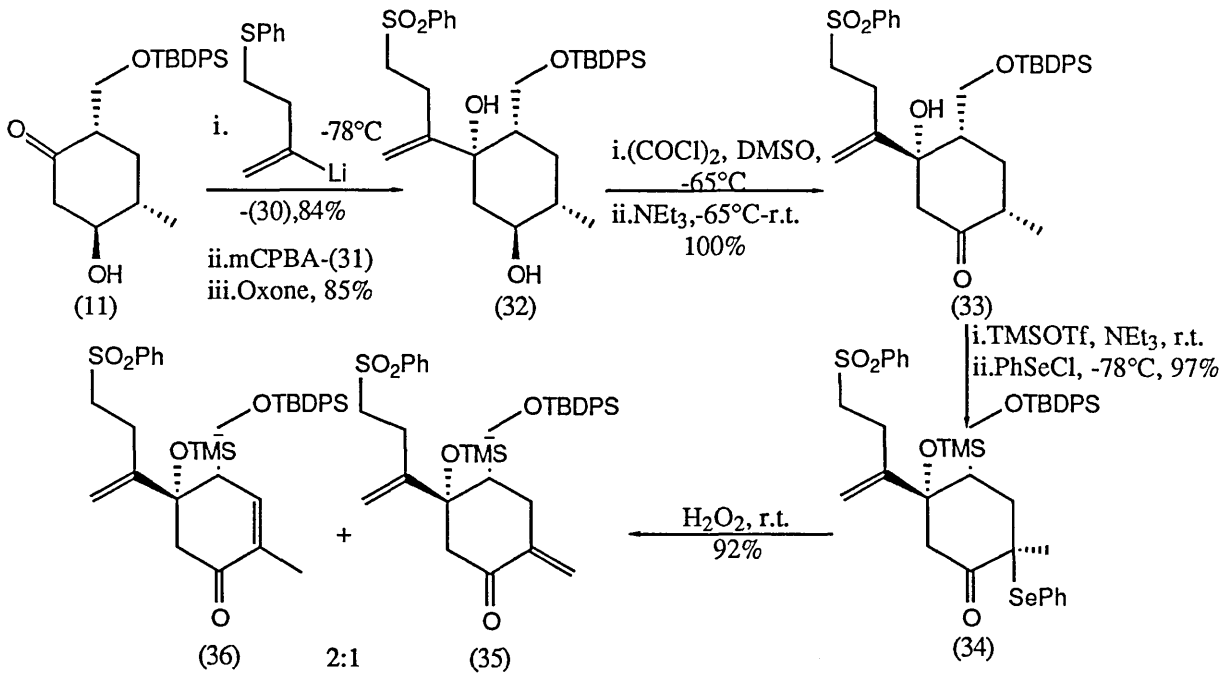
Palladium II catalysed transacetalisation[71] of the dioxolane (11) with acetone avoided the acid catalysed β-elimination of the silylether and hydroxyl groups encountered with conventional deprotection methods.[47,72] Addition of the ketone (21) to an excess of vinyl-lithium[73] at low temperature gave excellent and reproducible yields of the vinyl adduct (22). The sterically demanding nature of the silyloxy group, as anticipated[45], controlled the virtual complete diastereoselectivity (> 95:5) of the process. Swern oxidation[50] of the alcohol (22) to the ketone (23) was straightforward. However, attempts to isolate the enol ether (24) were met with hydrolysis to give the C-7 trimethylsilylether (25).



This complication was avoided by simply treating the crude silylenol ether at low temperature with phenylselenenyl choride. In this way the selenide (26) was obtained as a single diastereoisomer in excellent yield. Oxidation and subsequent selenoxide *syn*-elimination afforded the endocyclic enone (27) exclusively. Selective TMS ether cleavage occurred smoothly and without aromatisation upon treatment with aqueous hydrofluoric acid.

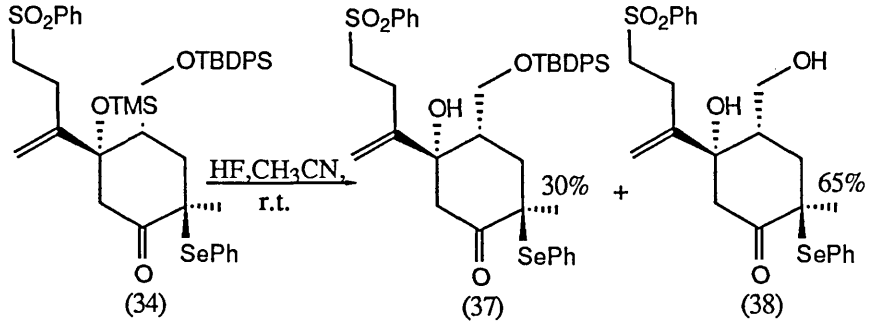


1,2 Reduction of the enone with sodium borohydride in methanol occurred stereoselectively to give the desired equatiorial alcohol (29) in 60% yield. As determined by coupling constant analysis of the geminal C-6 protons (C_{6eq} 2.15 ppm dd, J 13.0 and 6.5 Hz; C_{6ax} 1.60 ppm ddd, J 13.0, 9.0 and 1.5 Hz). The success of this methodology prompted its application to the synthesis of the southern hemisphere synthon (2). The addition of vinyl lithium (3) (Prepared from the corresponding bromide[74] via lithium bromide exchange with one equivalent[75] of t-butyllithium) to the hydroxy ketone (21) occurred with complete diastereoselectivity, to afford the corresponding diol (30) in reproducibly high yields.

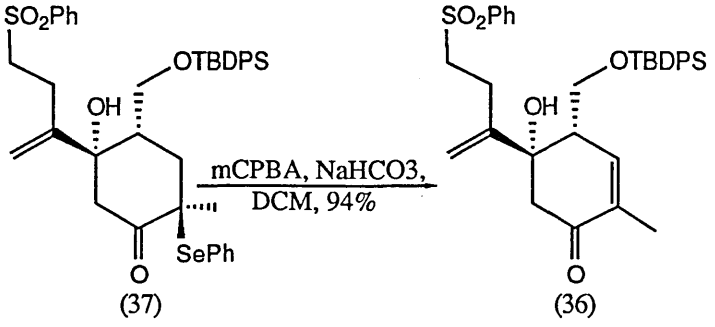


Oxidation of the sulphide to the sulphone was most conveniently achieved via the sulphoxides (31). In this way epoxidation and prolonged exposure of the silylether to the acidic oxone[76] oxidation conditions was avoided. Swern oxidation of the alcohol (32) to the ketone (33) followed by one pot selenenylation afforded the diastereoisomerically pure selenide (34) in excellent yield. However, oxidative *syn*-elimination of the corresponding selenoxides, in contrast to the previous examples, afforded a chromatographically inseparable 2:1 mixture of endocyclic (36) and exocyclic (35) enones. The product ratio was invariant with respect to changes in temperature, solvent or mode of oxidation. Consequently, it was decided to examine the effect of selective TMS ether cleavage upon the regioselectivity of the elimination and methods were sought to achieve this transformation.

Treatment of the silyether (34) with hydrofluoric acid[47] under our previously successful conditions was complicated by accompanying TBDPS ether cleavage. It is interesting to note that a free C-7 alcohol appears to labilise the TBDPS ether to fluoride mediated deprotection (vide infra) this is perhaps a consequence of its ability to hydrogen bond to fluoride ion.

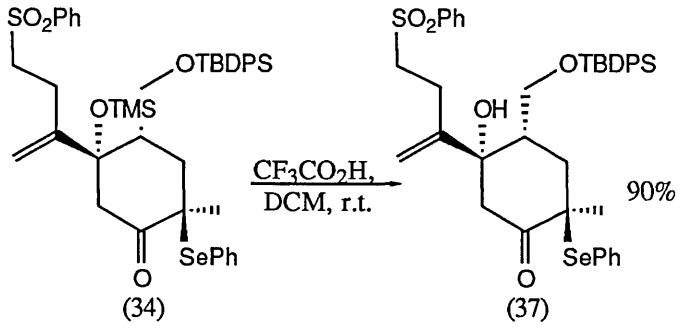


To our delight room temperature oxidation of the selenide (37) with hydrogen peroxide afforded the desired endocyclic enone (36) in excellent yield.

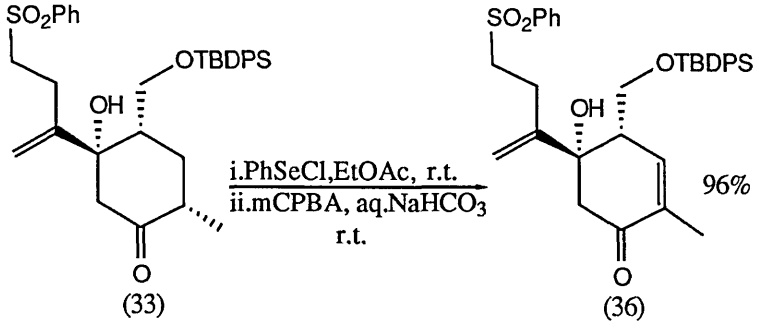


The excellent regioselectivity of the elimination reaction prompted a more thorough investigation into achieving the selective cleavage of the trimethylsilylether. In contrast to traditional methods[47], treatment of the silyl derivative (34) with excess

trifluoroacetic acid in DCM at room temperature resulted in virtually quantitative cleavage of the trimethylsilylether with no detectable diol (38) formation.



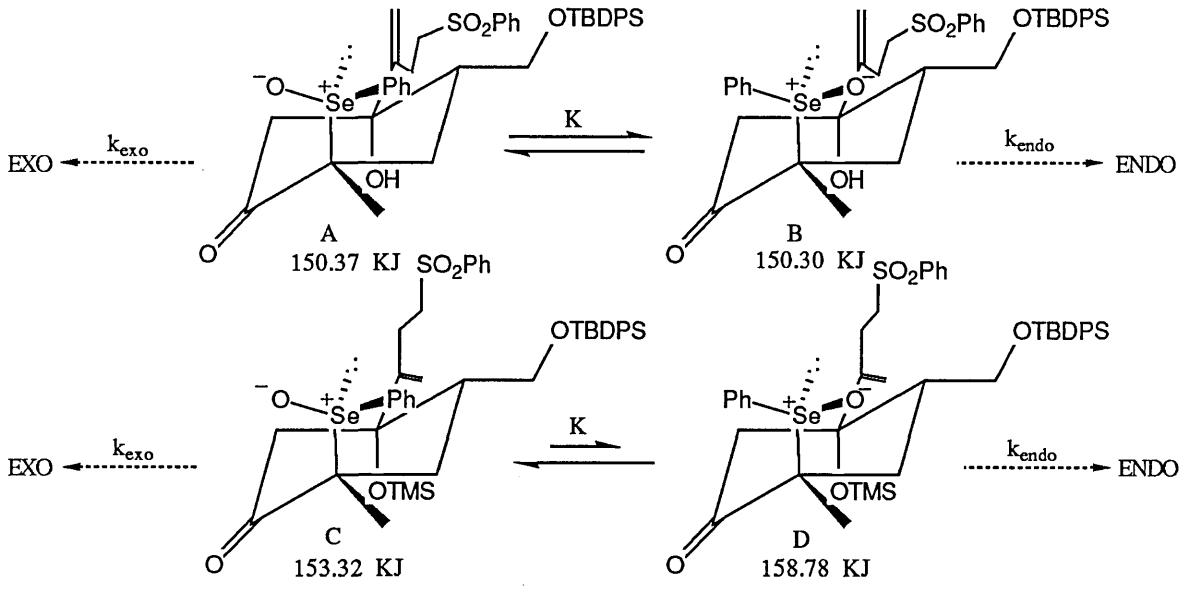
Subsequently it was found that the regioselective selenenylation / oxidative elimination procedure of Sharpless[77] could be efficiently employed to convert the ketone (33) to the corresponding enone (36) in excellent yield.



The effect of 7-O-silylation on the regiochemical course of these selenoxide *syn*-elimination processses is intriguing and requires explanation. Selenoxides are known to be configurationally unstable in the presence of aqueous acid or base[78]. Therefore, if the elimination step is rate determining, an equilibrium will exist between the diastereomeric selenoxides. Calculations using W.C. Still's macromodel program[79,80] were performed on the corresponding sulphoxides (as

the required selenoxide force field parameters were unavailable). The lowest energy conformers of each diastereoisomer are shown below.

The calculated energies of the hydroxy selenides (A) and (B) suggest that, at equilibrium, they will be present in essentially equal amounts ie K≈1. Additionally, it may be noted that the preferred conformations of the selenoxides (A) and (B) are analogous to transition state geometries which correspond to exo- and endocyclic

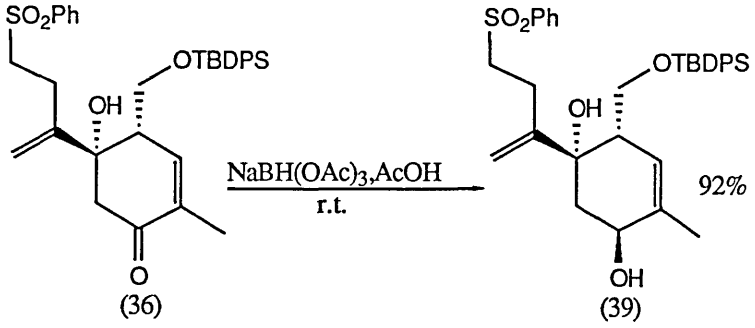


elimination processes respectively. The sole formation of the endocyclic enone would indicate that the rate constant for endocyclic elimination, k_{endo} , is considerably larger than that for exocyclic elimination k_{exo}.

The conformation change that accompanies O-7-silyation is predicted to destabilise the selenoxide (D) relative to its diastereosiomer (C). Therefore, selenoxide (C) is expected to be the major species present at equilibrium (K = 0.106

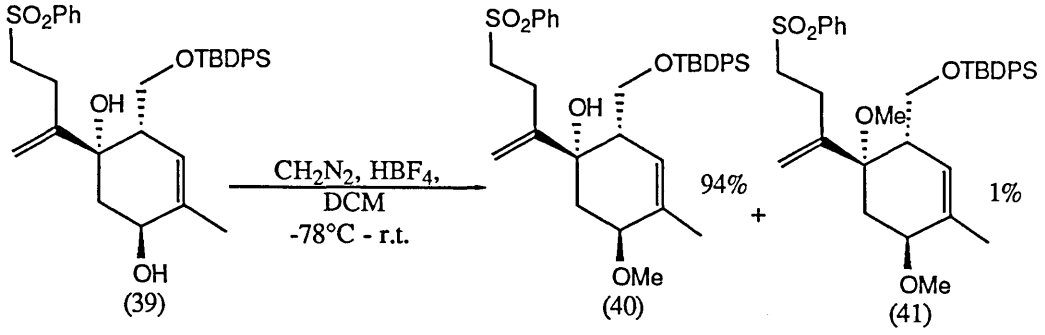
at 20°C). The observed decrease in the endoselectivity of the elimination reaction (endo: exo, 2:1) is consistent with this model. The rate constant for the endocyclic elimination (k_{endo}) clearly remains larger than that for the exocyclic process (k_{exo}), but the increased amount of selenoxide (C) present in the equilibrium mixture results in competitive exocyclic elimination.

Stereospecific reduction of the enone (36) to the desired allylic alcohol (39) was achieved in excellent yield with sodium triacetoxyborohydride[81] in acetic acid. Attendent aromatisation was not observed despite the acidic nature of the solvent.



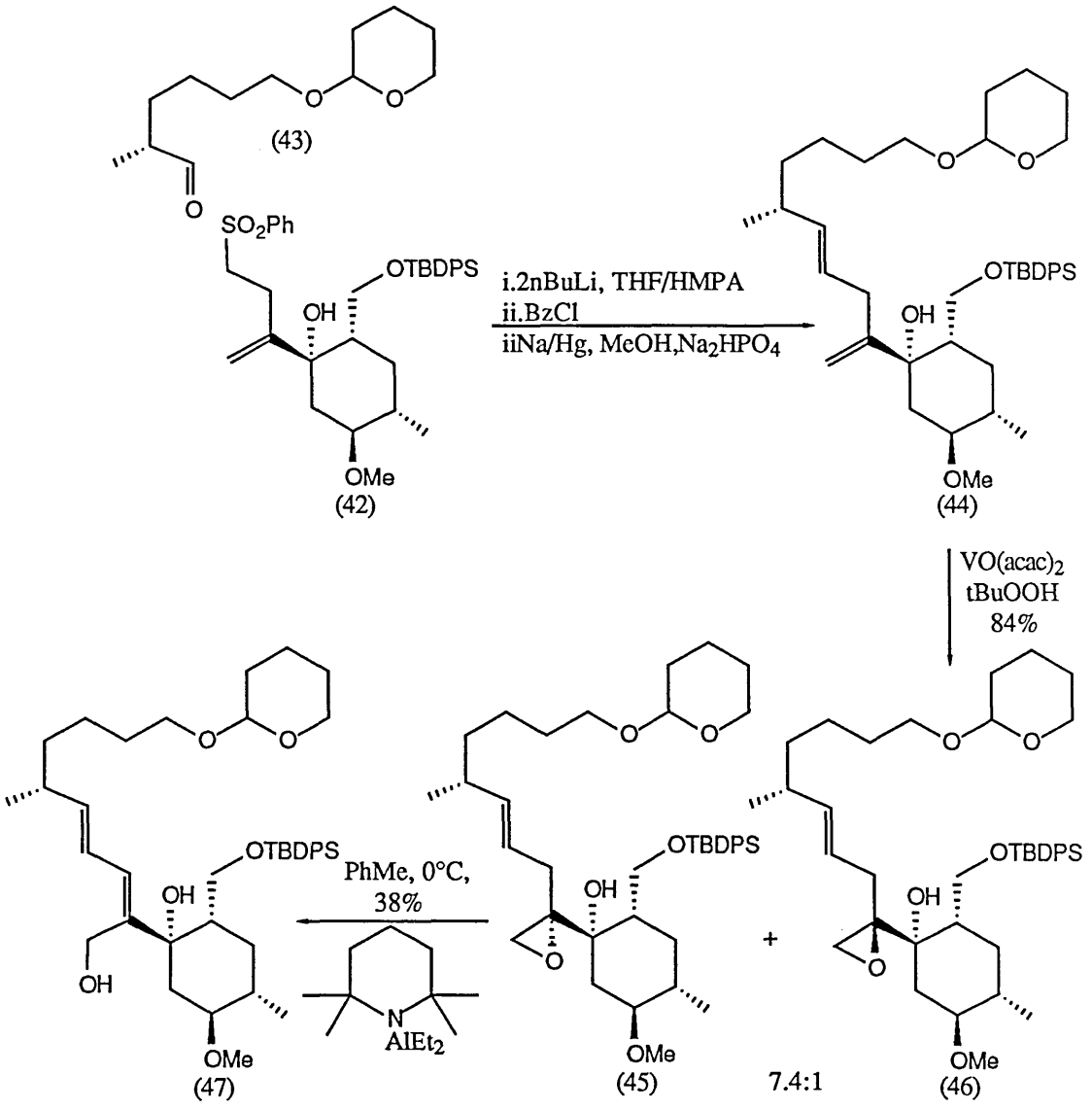
The integrity of C-5 relative stereochemistry was implied by coupling constant analysis J_{aa} 9.0 Hz and J_{ae} 6.0 Hz and confirmed by a single crystal X-ray analysis. (Appendix)

Attempts to methylate the secondary hydroxyl by conventional methods proved to be inefficient[82] or unselective.[83] However, acid catalysed methylation with diazomethane afforded excellent yields of the desired methyl ether (40) and only trace amounts of the dimethylated material (41).

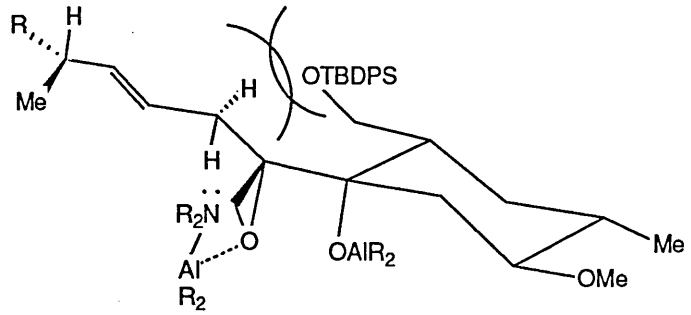


The synthesis of the required southern hemisphere synthon (40), with mild and regioselective introduction of C-3, C-4 unsaturation and control of all three stereocentres had been achieved in twelve steps from 4-methylanisole.

Our desire to test the viability of our planned epoxide ring opening approach to C-8, C-9 double bond construction, prompted a model study. Julia coupling[39] of the racemic sulphone (42) with the chiral aldehyde (43) afforded the adducts (44) in good yield as a mixture of diastereoisomers. Regiospecific hydroxyl directed epoxidation[43] of the allylic olefin (44) gave the separable diastereomeric epoxides (45) and (46) in good yield. Treatment of the major epoxide (45) with an excess of diethylaluminium tetramethylpiperidide (DATMPD) gave the diene (47) in moderate yield.

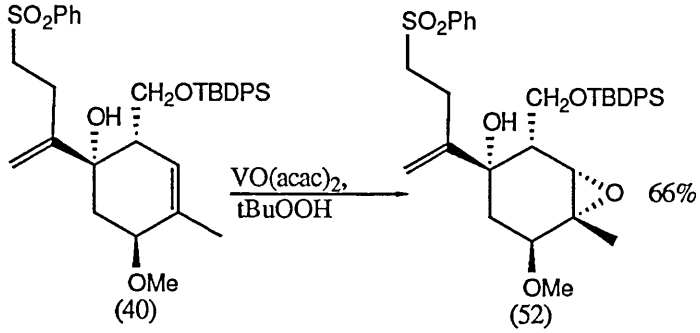


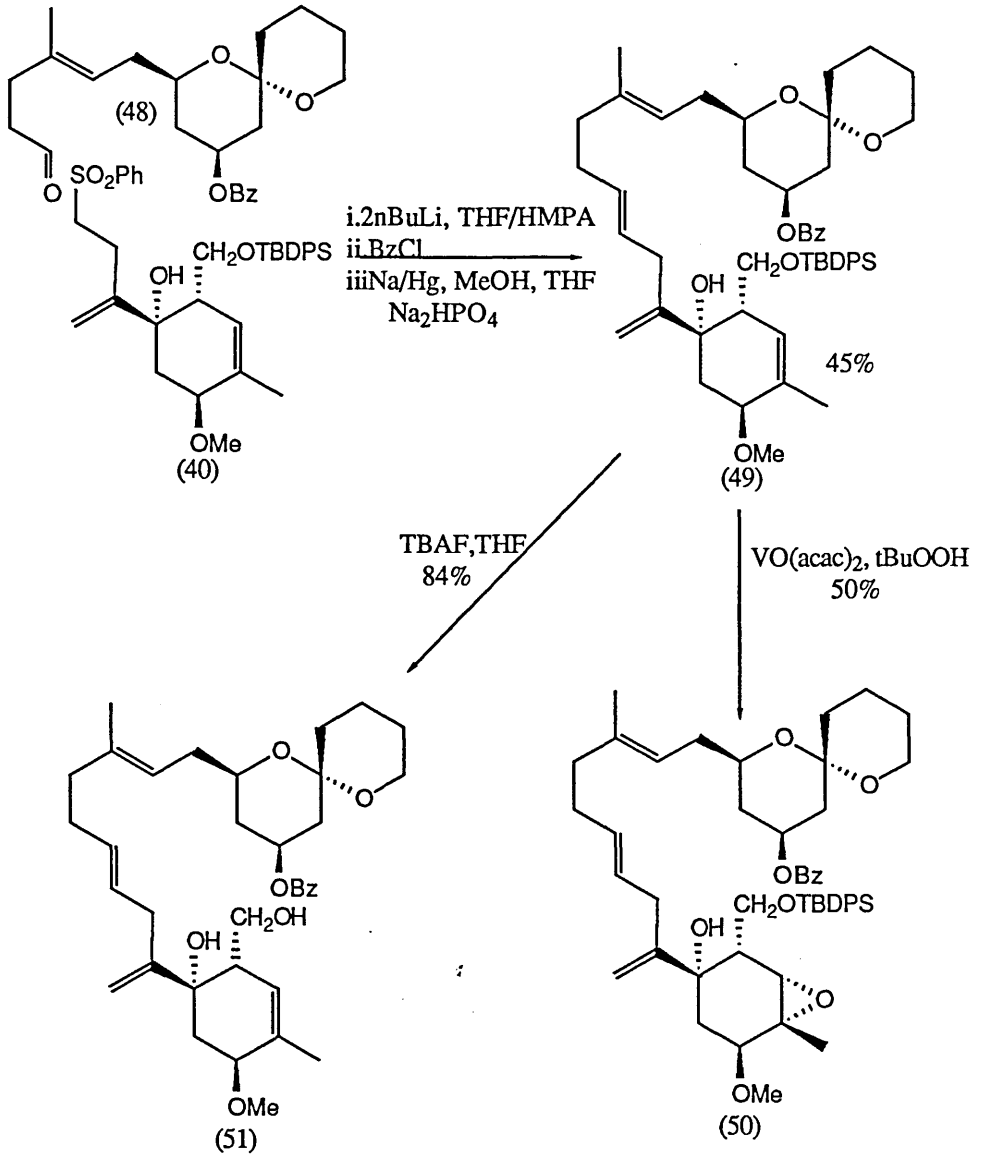
It was expected that steric interactions between the bulky silyloxy and alkyl groups would be minimised in the transition state that produces the E-C-8, C-9 double bond isomer (47).



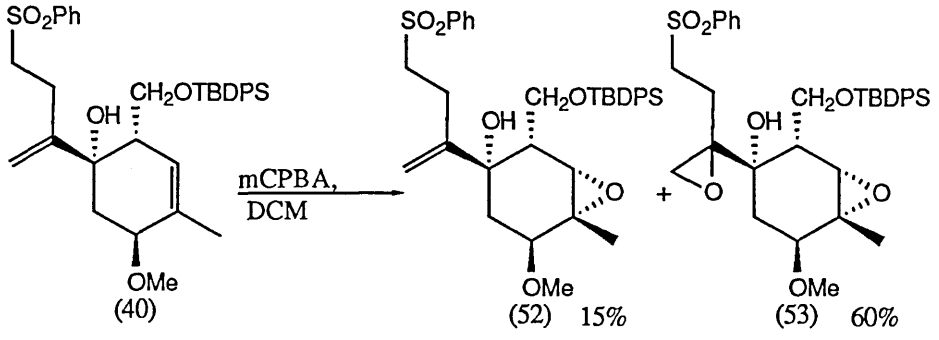
This methodology was subsequently applied to a more advanced model system illustrated overleaf. The Julia coupling reaction was moderately efficient. However, hydroxyl directed epoxidation of the allylic olefin did not occur. Instead, selective monoepoxidation of the endocyclic homallylic double bond was observed.

Similar results were obtained upon epoxidation of the diene (40).



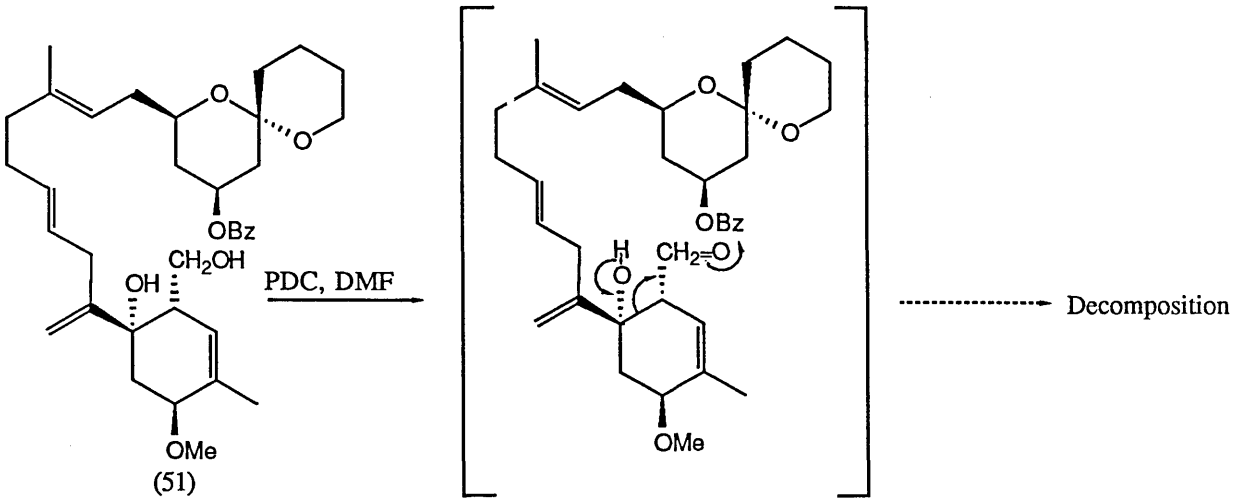


Use of mCPBA as oxidant gave a mixture of mono- and diepoxides (52) and (53).

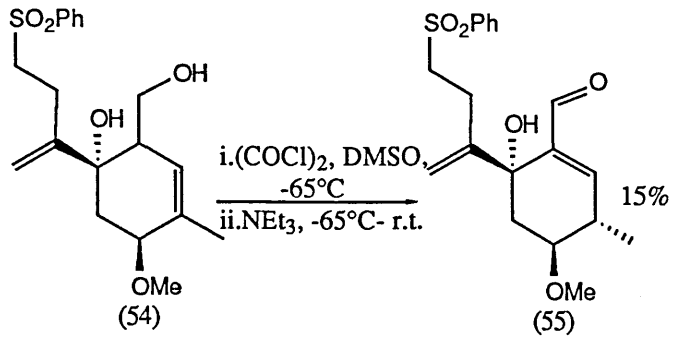


It was suspected that the presence of C-3, C-4 unsaturation would not compatible with our strategy. Attention was therefore turned towards achieving the correct oxidation state at C-1 so that macrolactonisation studies could commence. Thus, the silyl ether was cleaved with TBAF to give the diol (51). However, attempts to oxidise this alcohol to the corresponding acid[86] resulted in starting material degradation.[87]

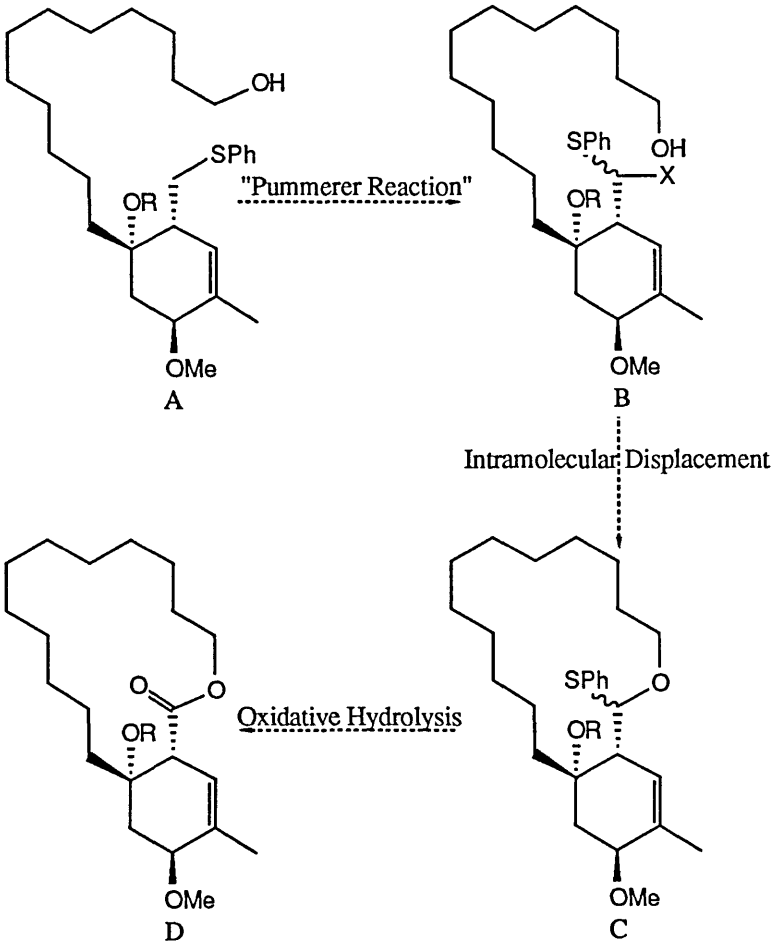
The instability of the intermediate aldehyde to the retro-aldol fragmentation shown below was suspected.



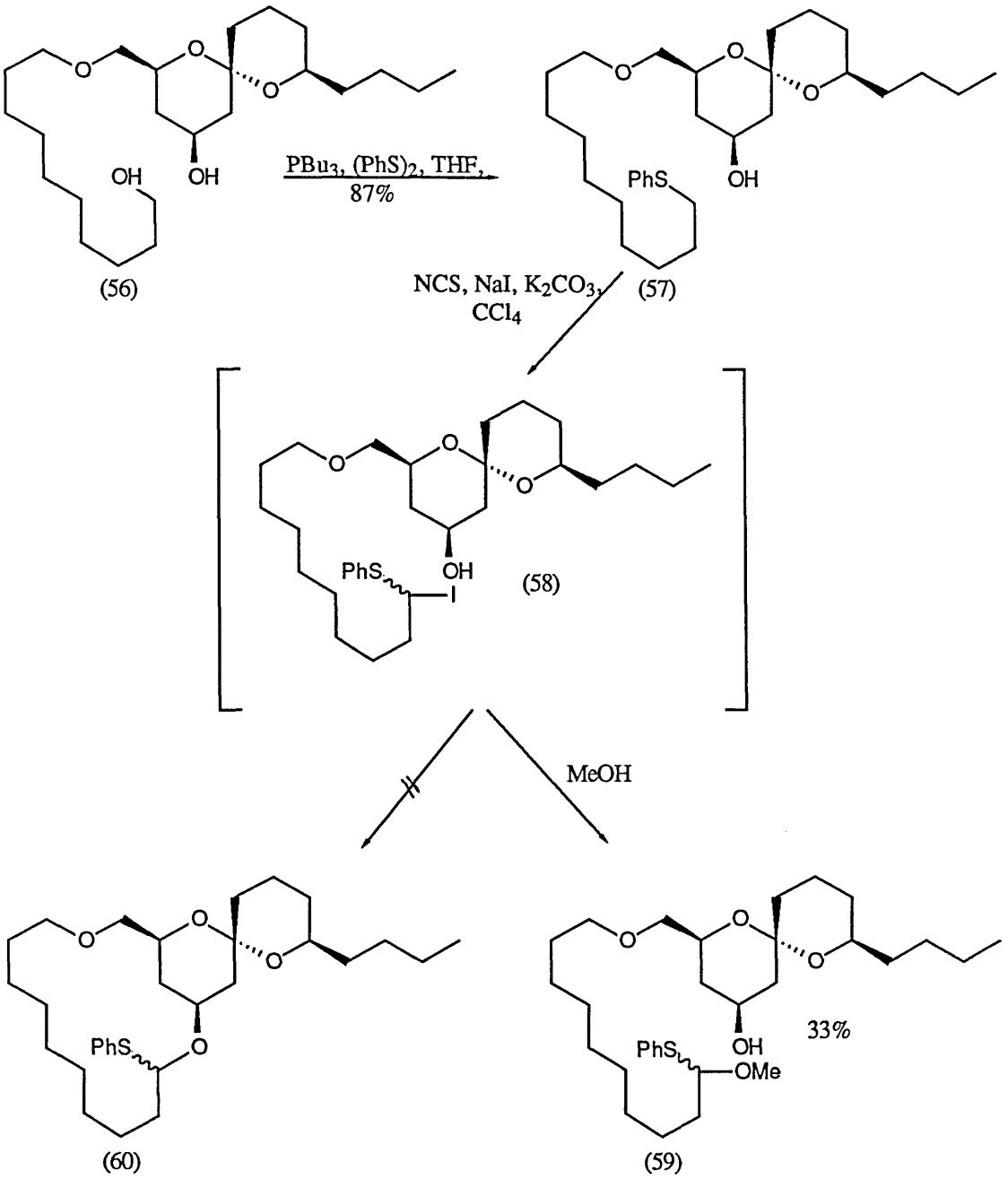
Support for this hypothesis was provided by the observation that Swern oxidation[50] of the alcohol (54) afforded only the enal (55). From which such fragmentation is considered unlikely.



Literature precedent suggested that a Pummerer reaction of an appropriate C-1 phenylsulphide (A) may be followed by an intramolecular displacement of the newly introduced leaving group X (X = Cl, OAc etc). In this way simultaneous C-1 oxidation and macrocyclisation was envisaged.

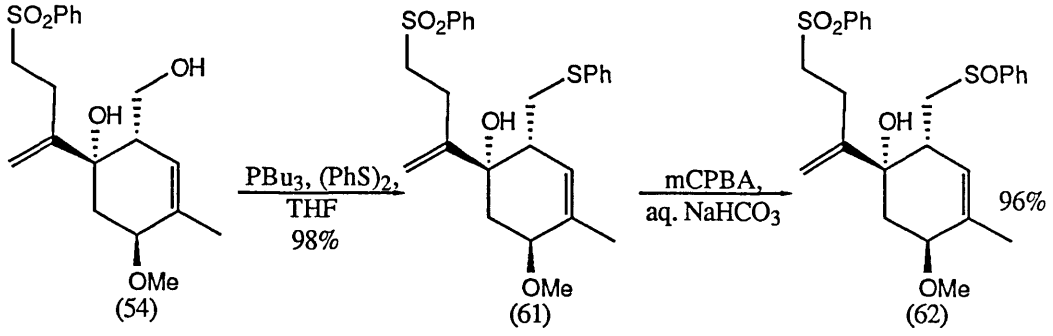


Oxidative hydrolysis[90] of the hemithioacetal (C) to give (D) would constiute a novel macrolide synthesis. Thus, a model investigation of this process was initiated. The primary alcohol (56) was selectively and efficiently converted to the corresponding phenylsulphide[91] (57). Successful conversion of the sulphide (57) to the reactive α iodo derivative[92] (58) was indicated by the formation of the hemithioacetal (59) upon methanolysis.

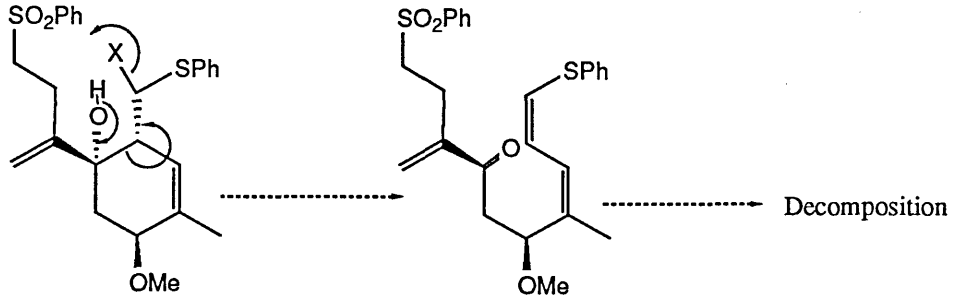


However, various attempts to achieve intramolecular iodide[92] or chloride[93] displacement failed. Despite this result the simplistic nature of the model system and the success of the oxidation step encouraged us to apply this methodology to C-1 oxidation. Thus the alcohol (54) was efficiently converted to its corresponding

sulphide (61) and sulphoxide (62) derivatives.



However, Pummerer reaction of the sulphide[92] or sulphoxides[94] followed by methanolysis led only to degraded material, presumably via a fragmentation pathway[95]analogous to that suspected for the corresponding aldehyde.

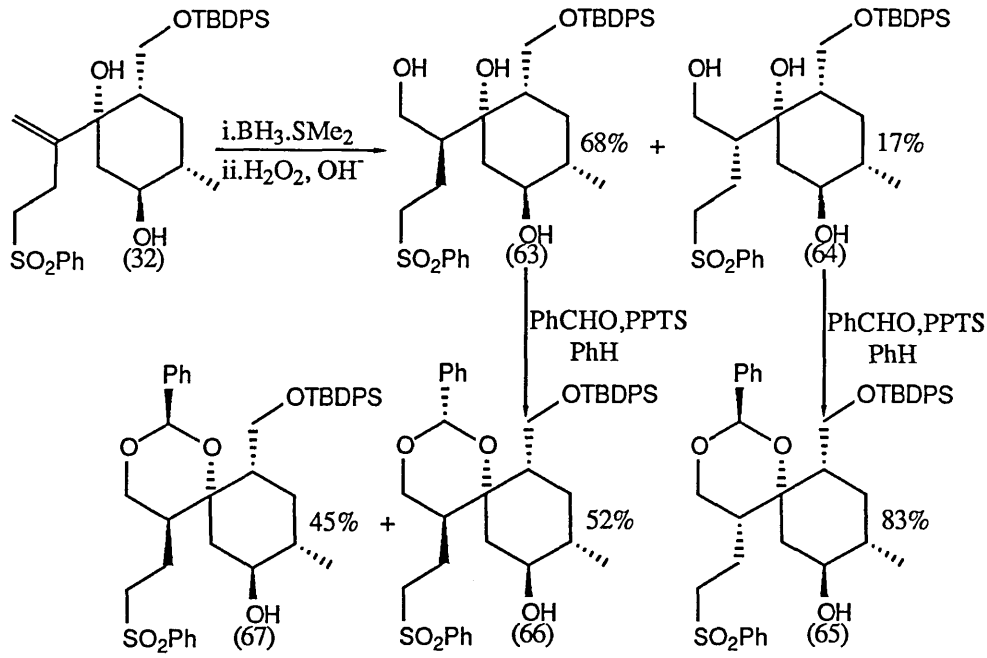


An attempt to retard this competitive fragmentation process by preparing the corresponding C-7 methyl ether was unsuccessful.

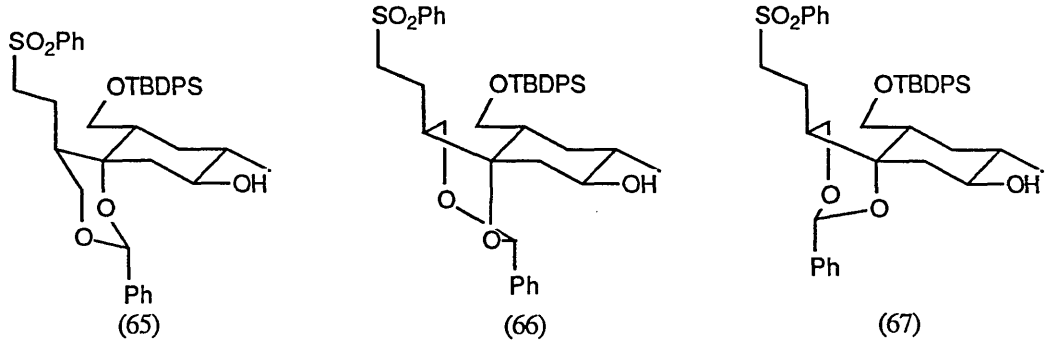
These results indicated that C-3, C-4 unsaturation was indeed incompatible with the synthetic stratergy we had pursued. In particular, selective hydroxyl-directed epoxidation of the C-8, C-8' olefin was impossible in the presence of the C-3, C-4 double bond. Additionally, the C-3, C-4 olefin was considered capable of vinylogously stabilising the intermediates produced in the apparent retro-aldo

fragmentation that occurred during C-1 oxidation. Evidence had also been obtained suggesting that the C-3, C-4 olefin had a tendency to migrate into conjugation with a carbonyl group at C-1[96].

A possible method of avoiding these problems would be to introduce C-3, C-4 unsaturation after side chain elaboration and macrolactonisation. This approach was expected to be additionally advantageous as the C-3, C-4 double bond was known to be regiochemically more stable when the C-1 carboxyl group was incorporated into a macrocyclic structure[97]. In the interests of covergency we decided to introduce the C-8', hydroxymethyl substituent prior to Julia coupling.[98] Attempts to achieve this transformation via an expoxidation / ring opening protocol failed.[70] Therefore the olefin (32) was hydroborated to give a readily separable mixture of the triols (63) and (64) in good yield. Treatment of the separated triols (63) and 64) with benzaldehyde in the presence of an acid catalyst effected their conversion to the corresponding cyclic acetals (66), (67) and (65). The relative stereochemistry of the acetals (66) and (67) was indicated in a crystallographic study of a methane sulphonate derivative of the alcohol (67) (Appendix). The stereochemical assignment of the remaining benzylidene acetal

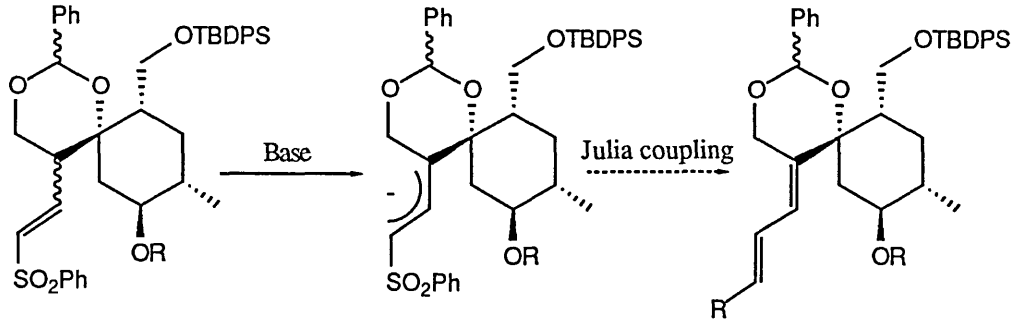


(65) was based on the known preference for such acetals to adopt a chair conformation in which the majority of substituents adopt the energetically favoured equatorial positions[99]. The predicted solution conformations of the three benzylidene acetals are depicted below.

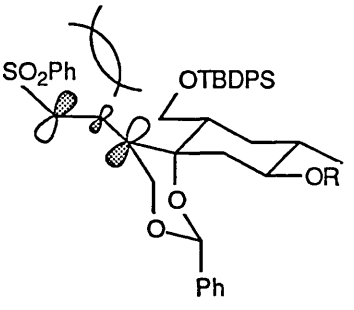


It was anticipated that simaltaneous construction of the C-8, C-9 and C-10, C-11 double bonds could be achieved by a novel reaction sequence involving deprotonation of a vinyl sulphone and alkylation of the resulting allyl anion α to the

sulphone moiety.



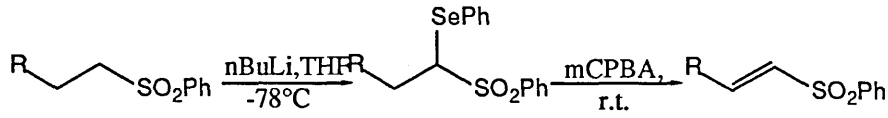
Vinylogous elimination of benzaldehyde from this type of anion was thought to be more difficult than in an analogous acyclic structure. The benzylidene ring was expected to geometrically constrain the allyl-anion HOMO and C-O σ orbitals in such a way that antiperiplanar orbital overlap[100] could not readily be achieved.



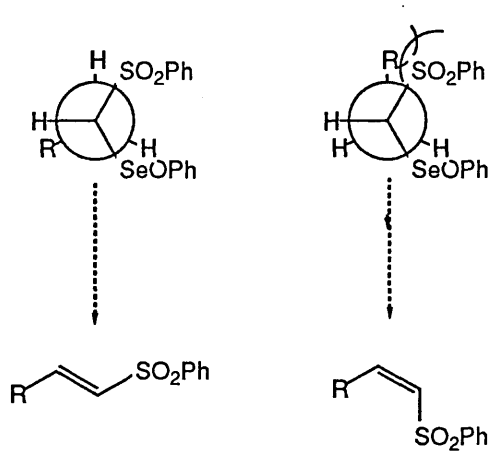
Additionally it was hoped that a minimisation of non-bonded interactions between the bulky phenyl sulphone and TBDPS groups would result in the preferential formation of the desired trans C8, C-9 double bond geometry.

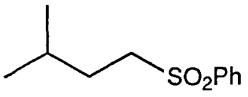
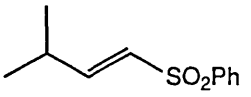
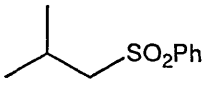
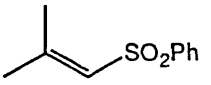
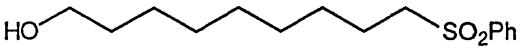
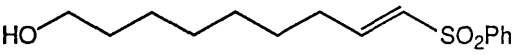
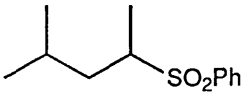
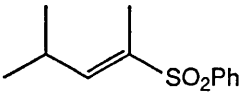
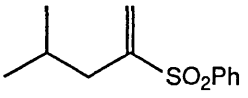
A method of dehydrogenating a sulphone to the corresponding vinyl sulphone derivative was promptly sought. The selenylation of a sulphone anion and subsequent selenoxide formation and elimination proved to be a novel and efficient

method of achieving this transformation.

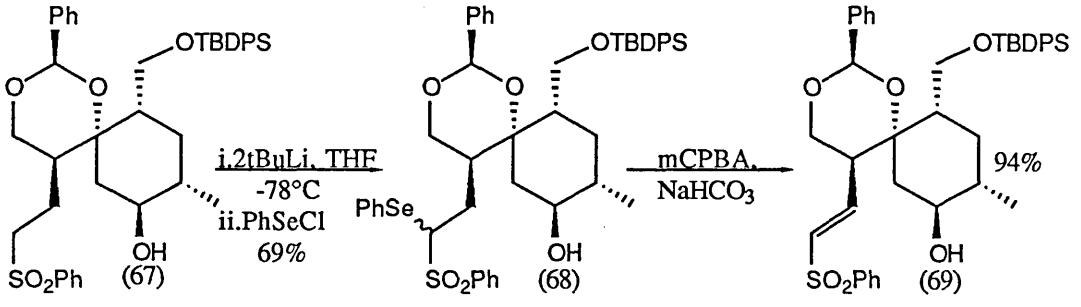


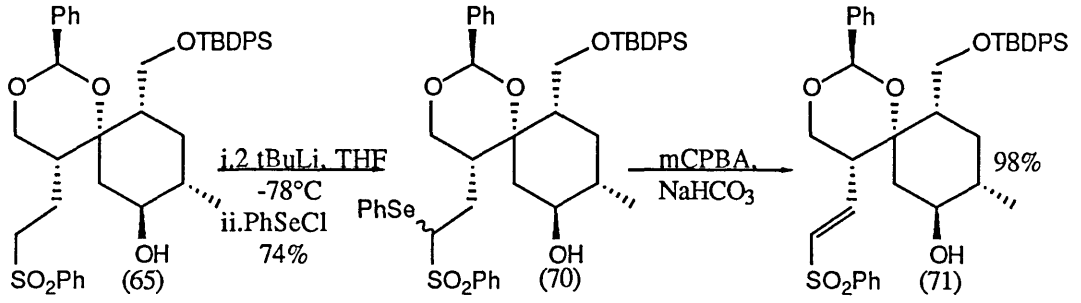
The unoptimised results[101] presented below indicate that this two-step procedure is general. The trans selectivity of the method is noteable and is a probably a consequence of non bonded interactions between the phenyl sulphone and the alkyl chain R which occur in the transiton state that leads to the cis alkene.



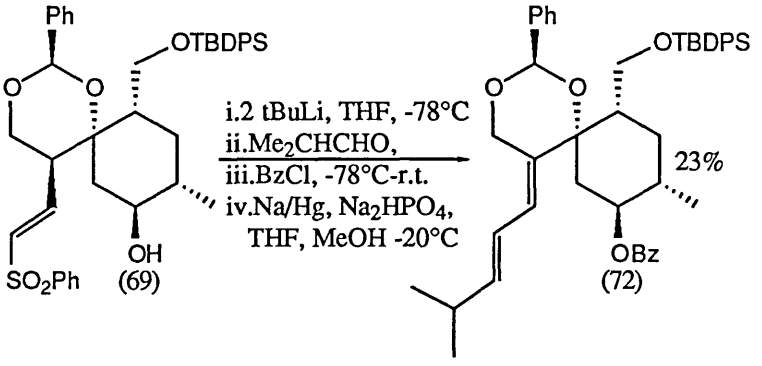
Sulphone	Base	Vinyl Sulphone
	nBuLi	 36%
	nBuLi	 62%
	nBuLi, 3LiCl	 82%
	nBuLi	 57%  20%

This new methodology was subsequently applied to the bicyclic sulphones (67) and (65).

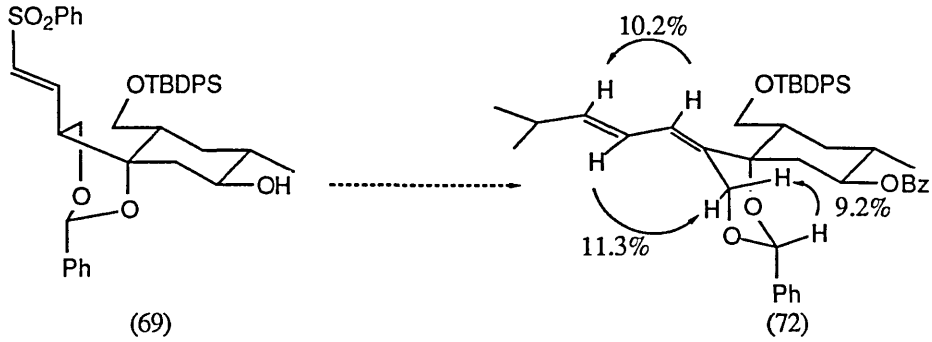




Deprotonation of the vinyl sulphone (69) was achieved with two equivalents of t-butyllithium. Addition of isobutyraldehyde to the bright yellow allyl-anion, *insitu* benzoylation and subsequent reductive elimination of the corresponding benzoxysulphones afforded the diene (72) in moderate yield.

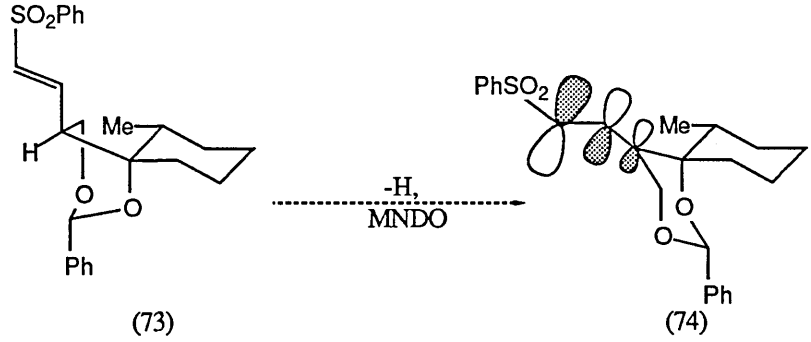


NOE experiments indicated that the desired trans-trans diene had been obtained. These NMR experiments also demonstrated that the dienyl product - in contrast to the starting sulphone - preferred to adopt a chair-chair conformation.



(69) (72)

The properties of the allyl anion (73) were calculated by an MNDO method[102] in an attempt to explain the apparent stability of the benzyldene acetal towards benzaldehyde expulsion.



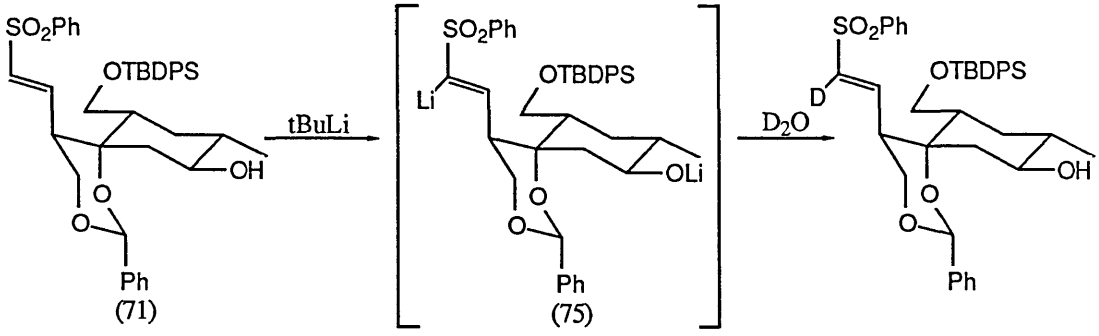
(73) (74)

These calculations indicate that the molecule prefers to adopt a chair-chair conformation in which the anion was shown to be delocalised over sp^2 hybridised atoms at C-8, C-9 and C-10. A negative change of 0.79 units was found to reside on the carbon atom α to the phenyl sulphone. This may be compared with the smaller negative change of 0.41 units on the C-8 carbon atom. Additionally, the calculations indicated that the symmetry of the allyl-anion HOMO was perturbed.

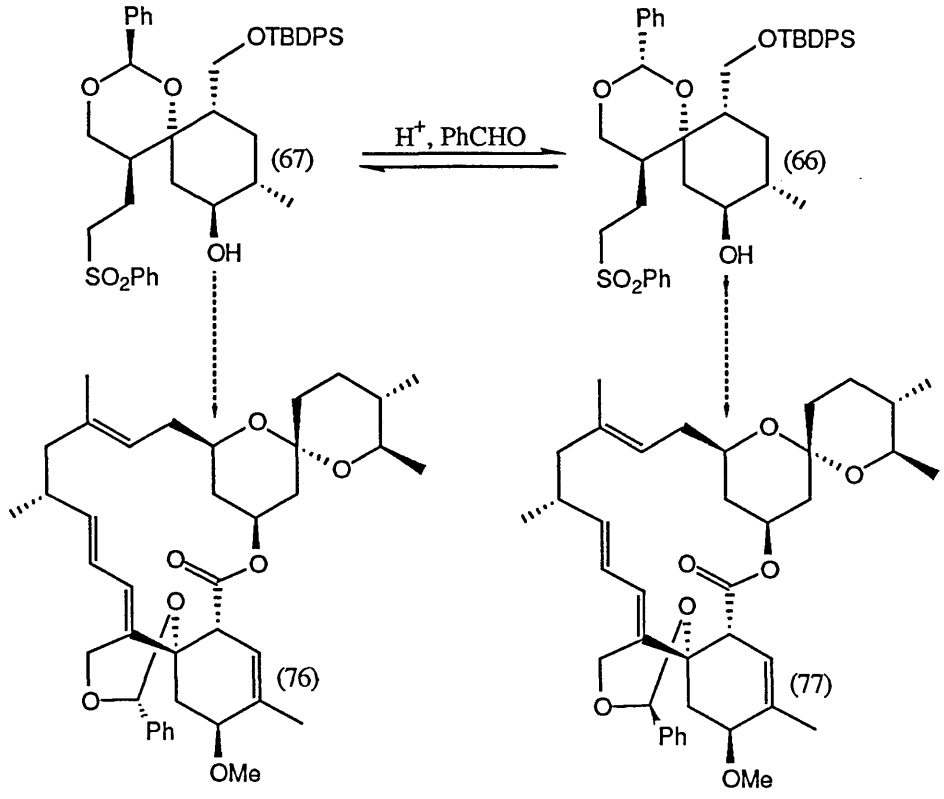
The largest HOMO coefficient occurs on the carbon atom α to the phenyl sulphone while the smallest HOMO coefficient occurs on C-8. These results indicated that alkylation of the allyl anion would be both coulombically and orbitally favoured to occur at C-10.[103]

The benzylidene acetal was not expected to fragment by C-O bond cleavage as only a slight lengthening of the relevant C-O bonds (0.2A) is predicted to occur upon deprotonation. This small distortion is probably a consequence of both the small HOMO coefficient at C-8 and the poor alignment of the allyl-anion HOMO and the C-O σ* orbitials. Preferential formation of the transoid C-8, C-9 olefin was also predicted to be energetically favoured. This is probably due to a reduction of the non-bonded interaction between the sterically demanding phenyl sulphone and the equatorial methyl group of the cyclohexyl ring.

Analoguous deprotonation of the diastereomeric vinyl sulphone (71) was expected to furnish the same allyl-anion. However treatment of the sulphone (71) with t-butyl lithium at -78°C did not produce the characteristic bright yellow colour of the allyl anion. Instead a D_2O anion quench[104] indicated that the sulphone had undergone deprotonation at the more exposed α position to yield the corresponding vinyl anion[105] (75).



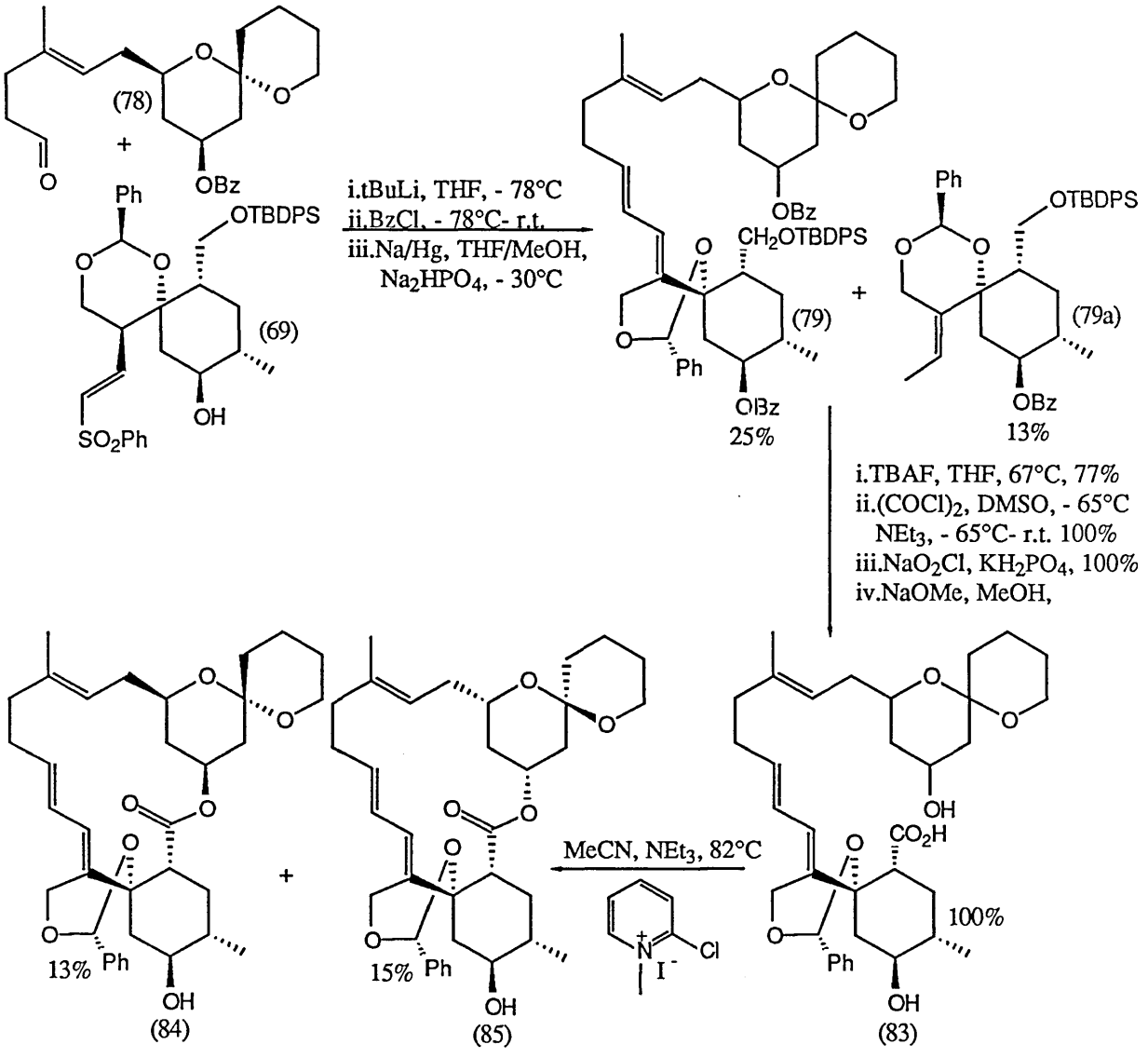
Before our novel coupling methodology was applied to a more advanced model system (vide infra), macromodel calculations[106] were performed on the macrolides (76) and (77) which are derivatives of the interconvertiable benzylidene acetals (67) and (66).



The calculations indicated that the macrolide derived from the acetal (67) would be of lowest energy. Therefore, the acetal (66) was converted to its isomer

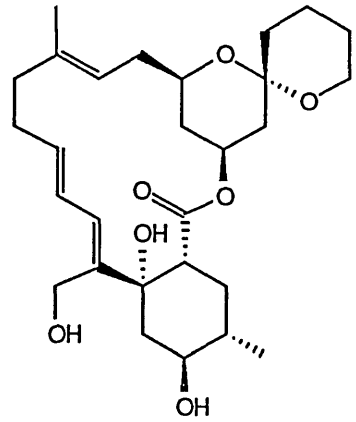
(67).

The racemic vinylsulphone (69) underwent Julia coupling with the racemic aldehyde (78) to afford the diastereomeric E,E Dienes (79). A small amount of the desulphonylated material (79a) was also obtained.



Despite the moderate yield of the coupling reaction, no isomeric olefins could be detected in significant amounts. Deprotection of the silyl ether with TBAF[47] - in contrast to the case where the C-7 hydroxyl was group present - was slow and

required reflux in THF to proceed at an acceptable rate. The resulting primary alcohols (80) were oxidised under Swern[50] conditions to the aldehydes (81). These were then further oxidised to the corresponding acids (82) in excellent yield with buffered sodium chlorite[107]. The benzoyl esters were removed upon basic methanolysis and the crude hydroxy acids (83) were macrolactonised[108]. The macrocyclic products (84) and (85) were obtained as a separable 1:1 mixture of diastereoisomers in 28% yield from the acids (82). Trifluoroacetic acid mediated hydrolysis of the benzylidene acetal (84) occurred cleanly[109] and completed a synthesis of the model milbemycin derivative (86).

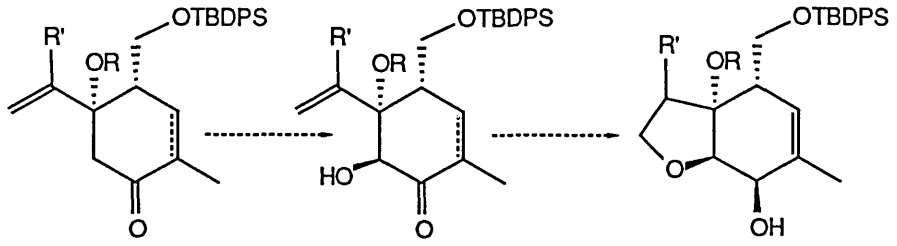


(86)

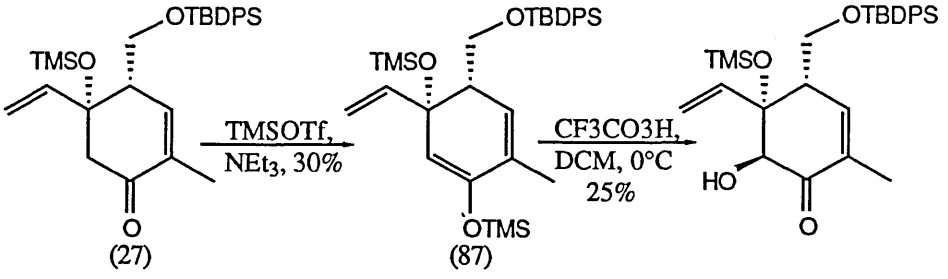
Approaches to the Milbemycin α Series

At the outset of our work towards the synthesis of milbemycin β_1 we envisaged that the stereocontrolled C-6 hydroxylation of a suitable ketone would

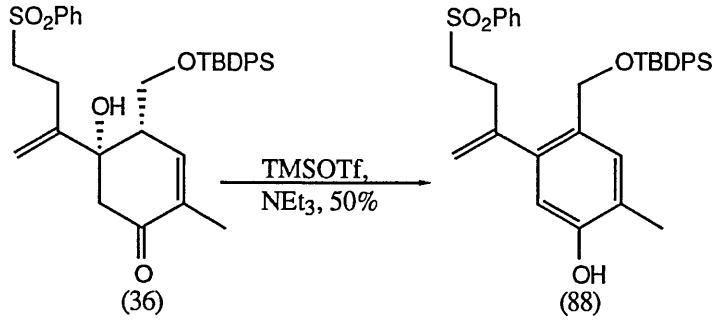
provide an entry to the milbemycin α series[7] of natural products.



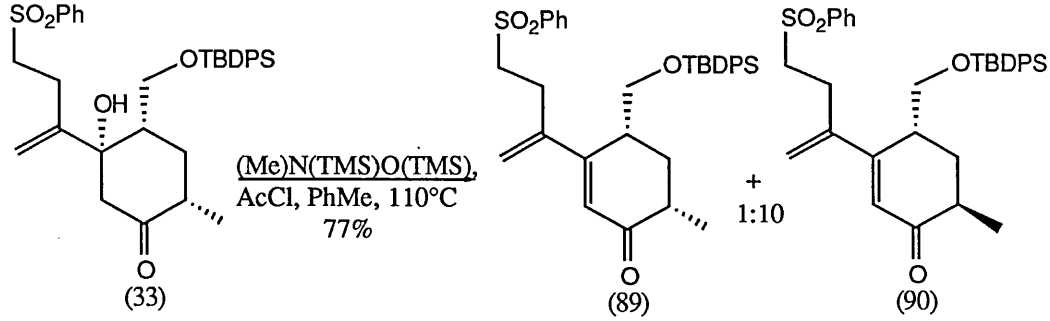
In an effort to test the viability of this approach the enone (27) was converted to the unstable dienylenol ether (87) in moderate yield. Successful stereoselective C-6 oxidation of this silylenol ether could be achieved by its treatment with pertrifluoroacetic acid[110].



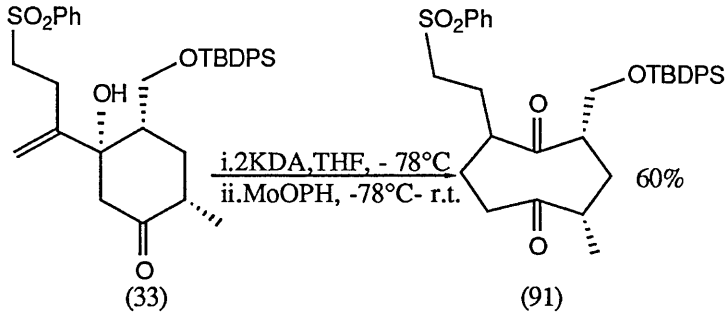
Disappointingly, facile aromatisation was observed upon analogous treatment of the enone (88) with TMS triflate.



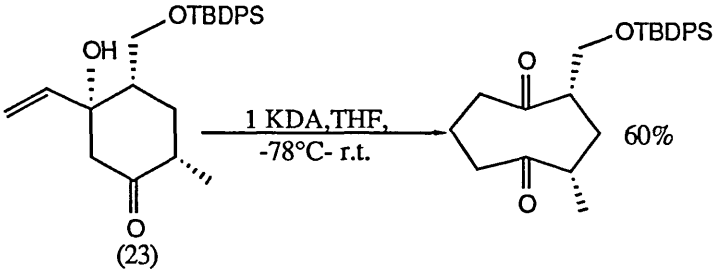
Attempted C_6 acetoxylation[113] of the ketone (33) also led to β elmination of the tertiary hydroxyl group.



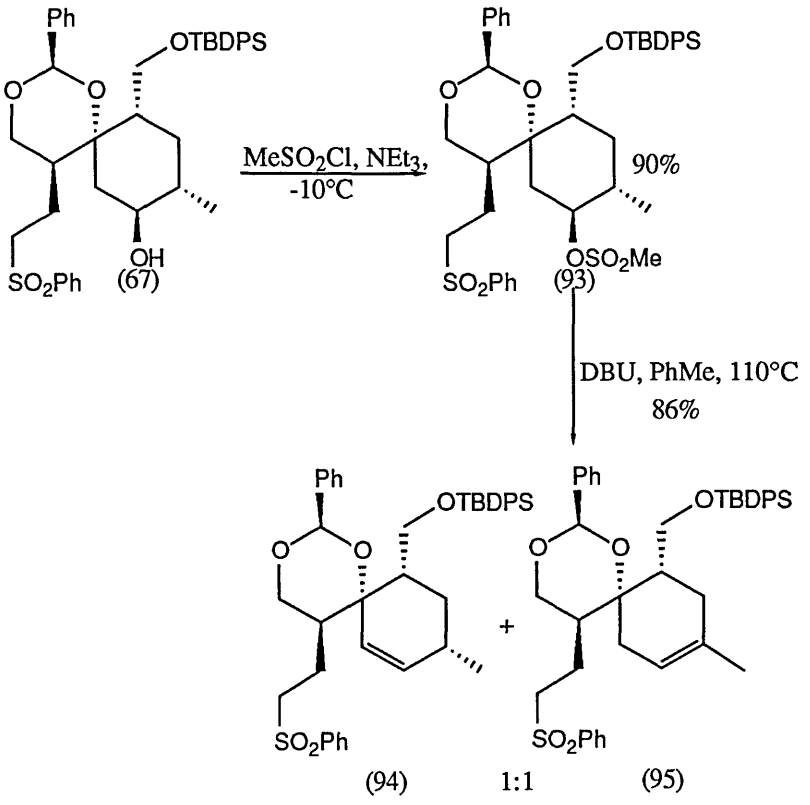
The cyclooctanone (91) was formed in a surprising two carbon ring expansion reaction, when the ketone (33) was treated with two equivalents of KDA[111].



T.L.C. analysis of the anion indicated that the rearrangement occurred within a five minute period and prior to the introduction of the MOOPH[112] reagent. Whether the ring expansion occurs via a stepwise or concerted mechanism is unknown. However the rearrangement appears to be general - at least within this structural series - as an analogous ring expansion occurs upon exposure of the simpler hydroxy ketone (92) to 1 equivalent of KDA[57].



The failure of the above attempts to efficiently α-hydroxylate ketone derivatives prompted the decision to seek a method by which a C-5, C-6 olefin could be regioselectively prepared. Cis hydroxylation of such an olefin would provide an alternative synthesis of C-6 hydroxylated products. Thus, the alcohol (67) was converted into its corresponding methane sulphonate derivative[114] (93).

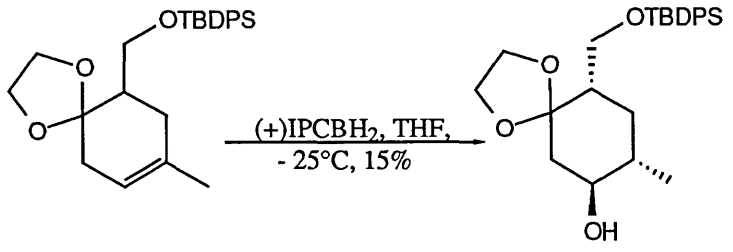


Treatment of this mesylate with DBU[115] in refluxing toluene gave the two regioisomeric olefins (94) and (95) as an inseparable 1:1 mixture. The proportion of the desired olefin (94) could be increased if the mesylate (93) was treated with basic alumina at room temperatue. Under these conditions the C-5, C-6 olefin (94) constituted 75% of the product mixture. Attempts to elaborate this and related olefins to the hexahydrobenzofuran moiety of the milbemycin α series are currently being examined in our laboratories[116].

Optically Active Subunit Synthesis

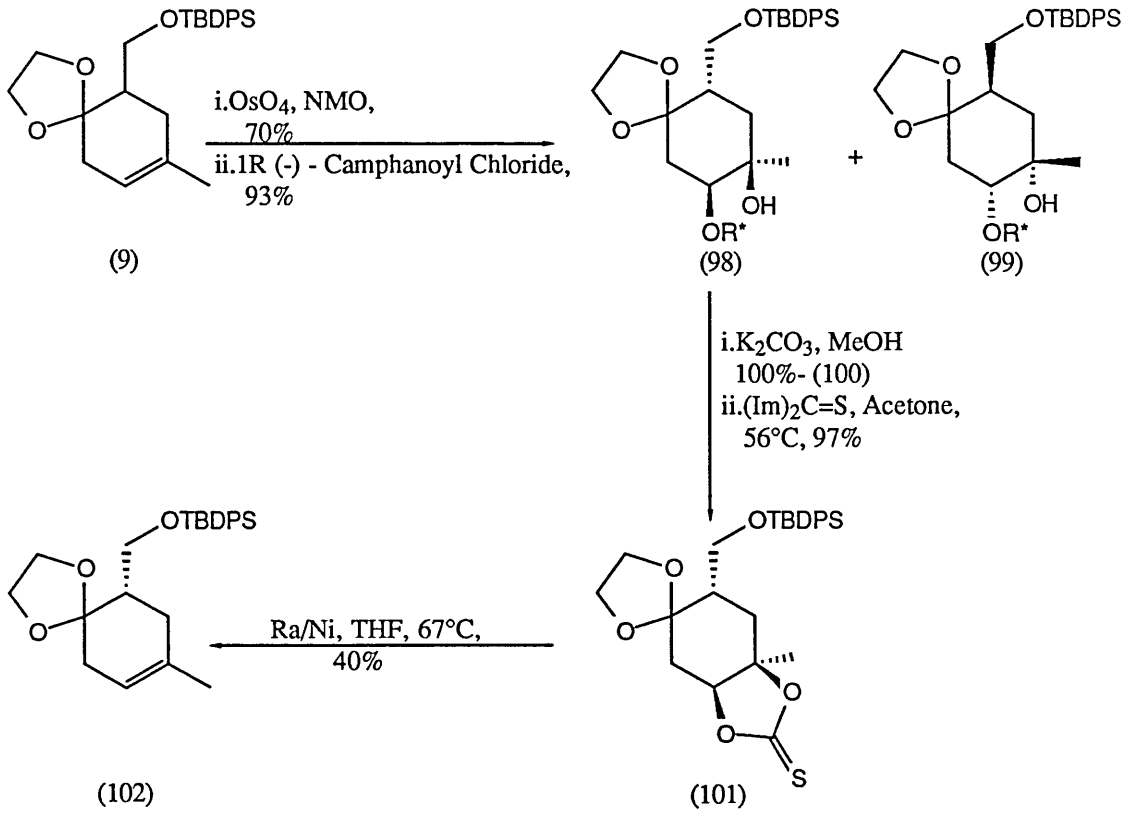
All the work discussed above pertains to the use of racemic compounds to

establish a methodology by which the synthesis of milbemycin β_1 could be achieved. Our wish to synthesise milbemycin β_1 in optically active form required the resolution of one of our synthetic intermediates. The attractive possibility of harnessing the power of an asymmetrical hydroboration reaction to simultaneously effect C-5 hydroxylation and kinetic resolution of alkene (9) demanded examination.



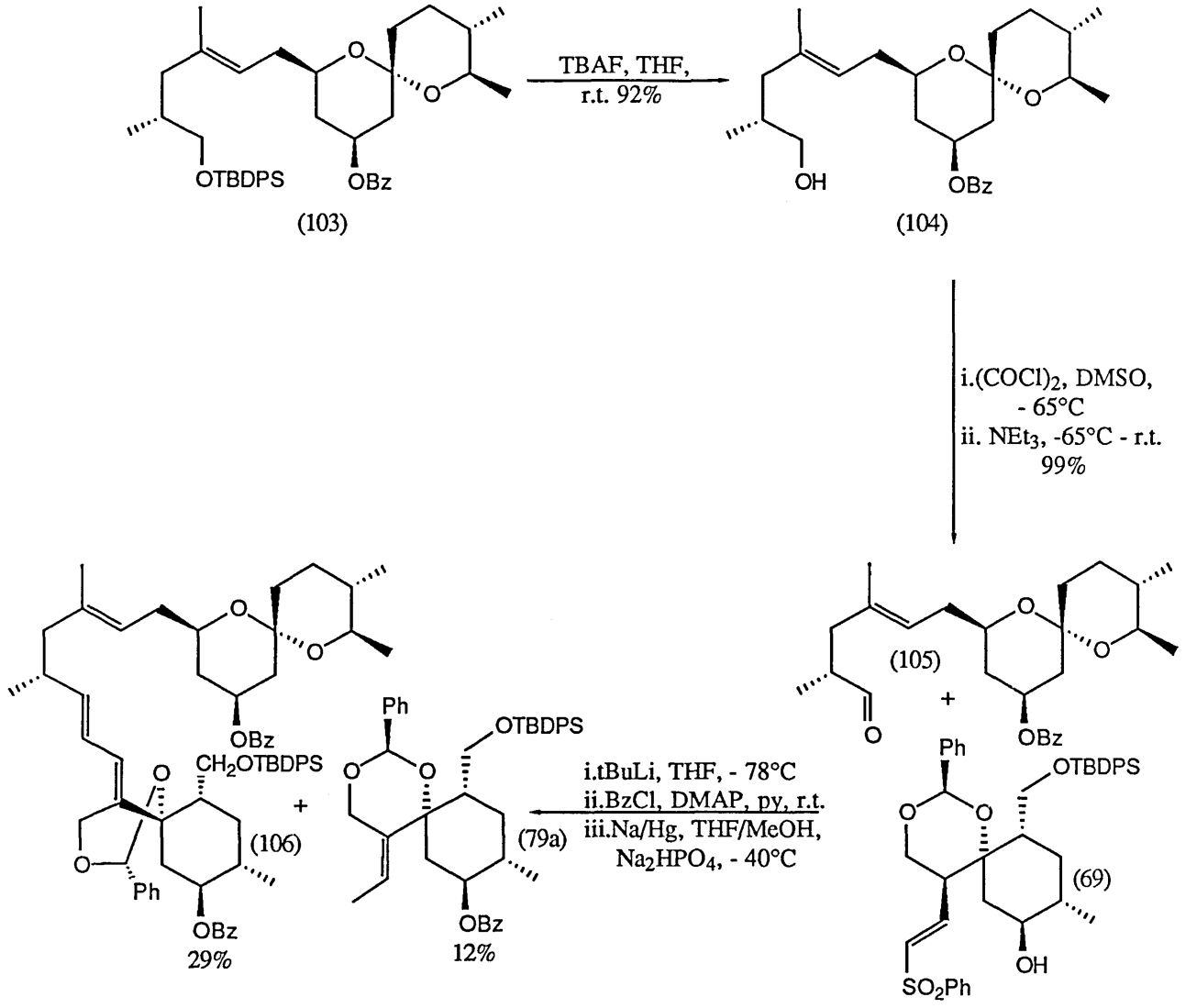
(9) (97)

Thus hydroboration of the olefin (9) with (+)IPCBH$_2$ under Brown's conditions[117] gave the product alcohol in an enantiomeric excess of 50% - as determined by 1H NMR analysis of the corresponding diastereomeric Mosher ester deriviatives.[18] An attempt to increase the enantioselectivity of this process by conducting the reaction at lower temperature (-40°C) was thwarted by a prohibitively slow rate of reaction. Alternative methods for achieving this kinetic resolution were not pursued, instead the olefin was resolved by the somewhat lengthy sequence indicated below.

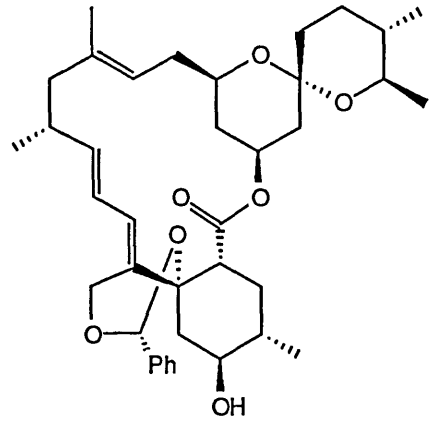


Catalytic and stereoselective osmylation of the olefin (9) gave the corresponding enantiomeric diols. These upon treatment with 1R-(-)-camphanic acid chloride gave the readily separable diastereomeric esters[70] (98) and (99). Efficient methanolysis of the desired ester[70] (98) gave the diol (100) which was converted to the thiocarbonate derivative[120] (101) in excellent yield. Raney nickel mediated fragmentation of this thiocarbonate afforded the optically pure olefin (102). This route was modified[70] to improve the efficiency of the last step.

Now that an efficient synthesis of the optically active sulphone (69) had been achieved the TBDPS protected northern hemisphere fragment[121] (103) was cleaved with TBAF[122] to afford the alcohol (104).

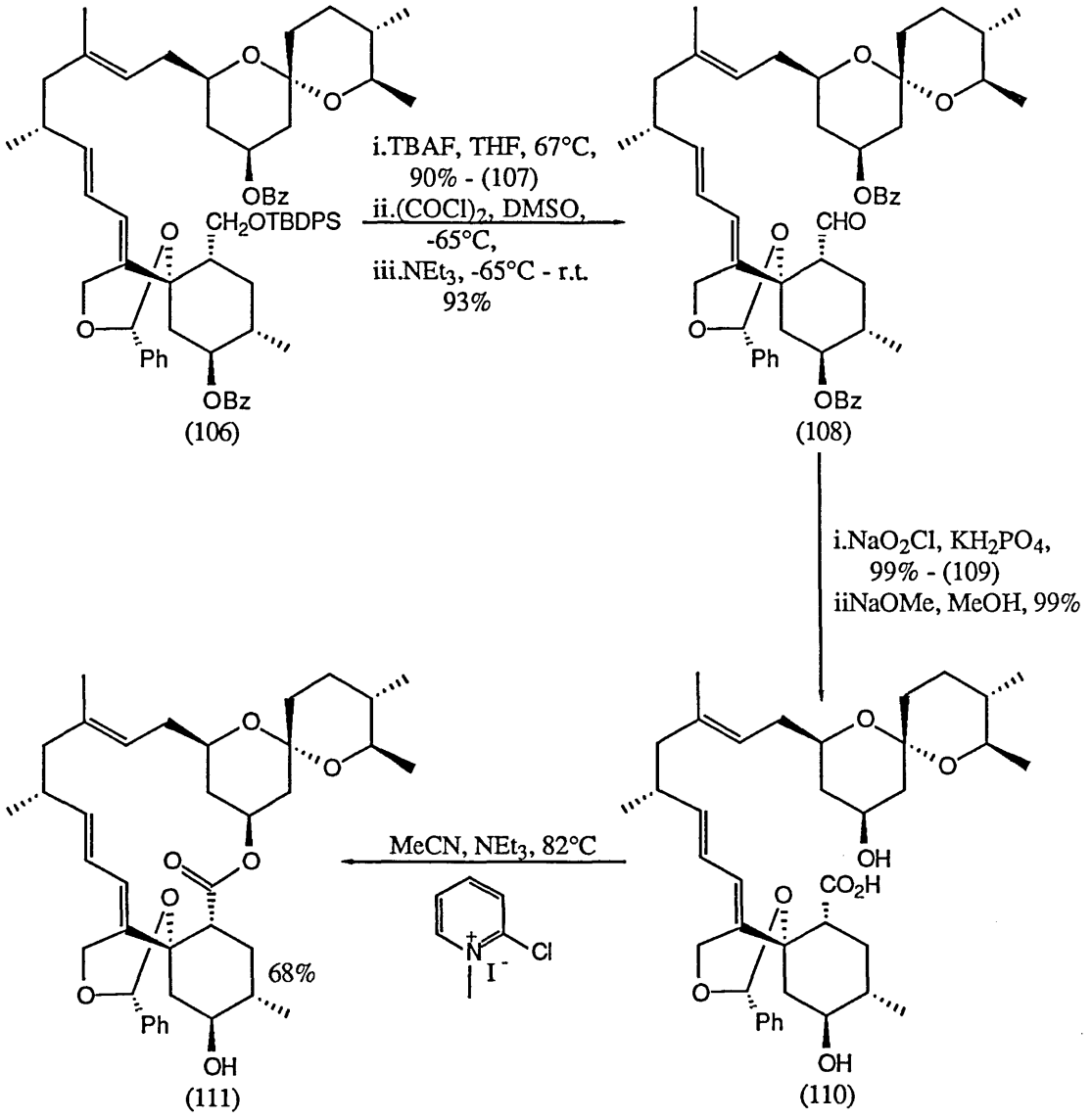


Use of a two fold excess of Swern[50] reagent resulted in the clean formation of the aldehyde (105). Julia coupling[39] and simultaneous 5-O benzoylation occurred in 29% yield. The formation of a small amount of the reduced uncoupled product (106) probably results from the use of a small excess of the sulphone (69) in the coupling reaction. The diene (106) was elaborated to the macrolide (111) in a manner analogous to that used in the previous model study.

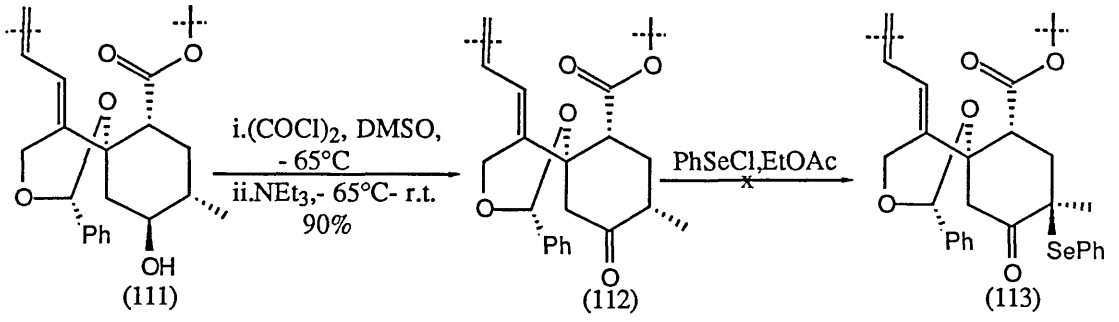


(111)

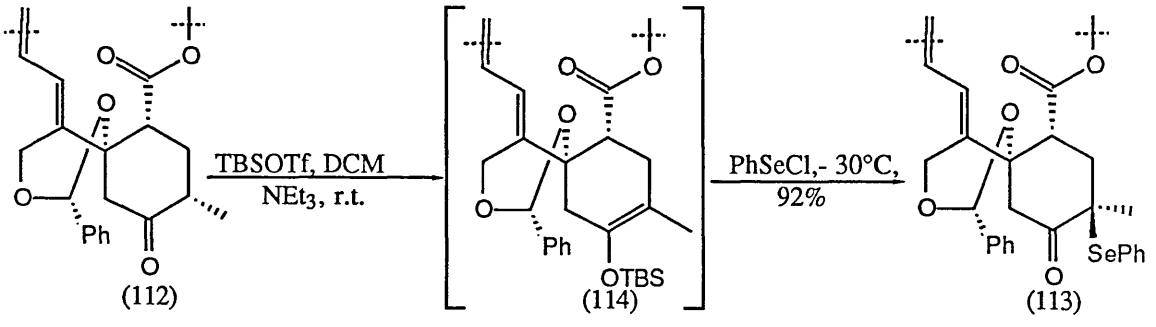
Thus, fluoride mediated deprotection[122] of the silyl ether (106) gave the alcohol (107) in good yield. The primary alcohol was converted first to the aldehyde (108) and then to the acid (109) by sequential Swern[50] and sodium chlorite[107] oxidations. This acid (109) was not purified but was subjected to basic methanolysis which on anhydrous workup afforded the hydroxy acid (110). Subsequent macrolactonisation[108] of this seco acid afforded the macrocyclic lactone (111) in excellent overall yield.



Now that an efficent route to the macrolide (111) had been developed, the introduction of C-3, C-4 unsaturation required examination .The C-5 hydroxyl group was cleanly oxidised to the corresponding ketone (112).



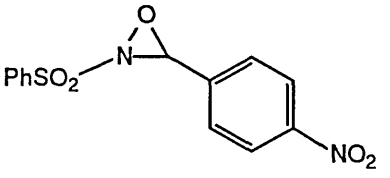
However α-selenenylation of this ketone (112) under the previously successful conditions of Sharpless[77] failed due to competitive addition of electrophillic selenium to the diene. Conversion of the ketone to the trimethylsilyl enol ether with TMS triflate[55] was complicated by side reactions, perhaps a consequence of the Lewis acidity of this reagent. However *insitu* selenenylation of the crude product mixture afforded the selenide (113) in 30% yield. Consequently, it was found that treatment of the ketone with the less powerfully Lewis acidic reagent TBS triflate effected the smooth formation of the isolable TBS enol ether (114).



In situ selenenylation of the TBS enol ether (114) occurred readily at -30°C and the selenide (113) was obtained as a single diastereoisomer in virtually

quantitative yield.

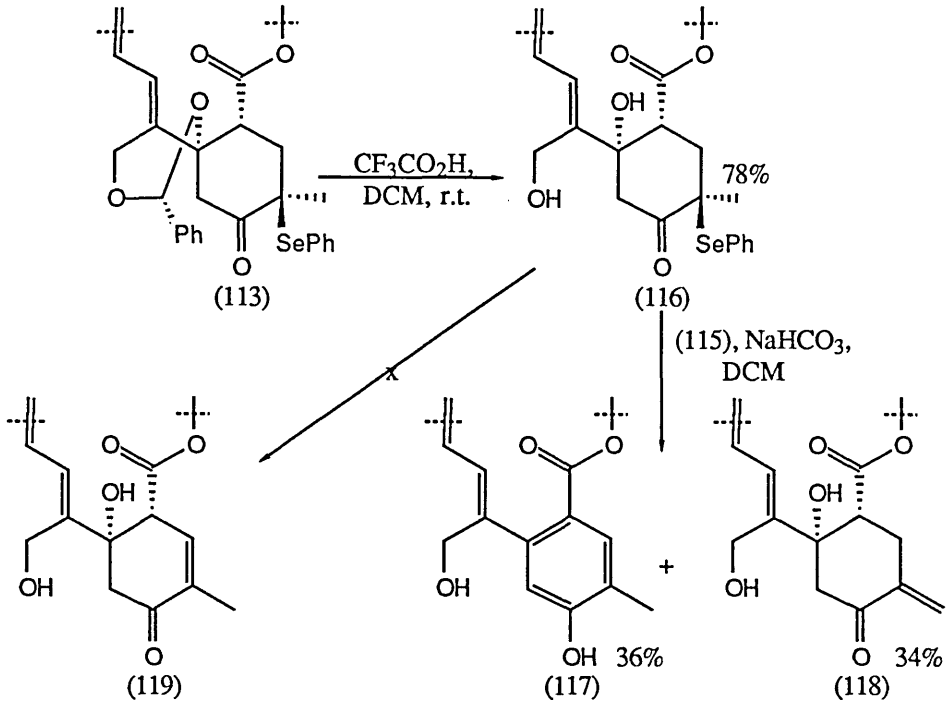
However treatment of the selenide with hydrogen peroxide, mCPBA or the oxaziridine[123] (115) resulted only in starting material degradation.



(115)

Palladium II catalysed dehydrogenation[56] of the TBS enol ether (114) was also unsuccessful. No reaction was observed even upon prolonged exposure of the silylenol ether to stoichiometric quantities of the reagent in refluxing acetonitrile.

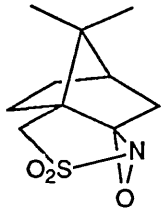
The benzylidene acetal was removed in an attempt to improve selenoxide formation and *syn*-elimination.



Treatment of the selenide (116) with the oxaziridine (115) in the presence of aqueous sodium hydrogencarbonate afforded the exocyclic enone (118) and the phenol (117) in essentially equal amounts. The aromatic material was considered to be derived from the desired endocyclic enone (119) by simple elimination of a molecule of water. Thus, the reaction was repeated in an NMR tube in the absence of aqueous base. A new olefinic resonance at 6.41ppm was observed in addition to those of the exocyclic enone. These resonances increased with time as the starting material was consumed. Integration of the olefinic signals indicated that the endo- and exocyclic enones were produced in a ratio of 6:5 respectively. Attempts to increase the amount of endocyclic product by varying the temperature and reaction solvent were unsuccessful.

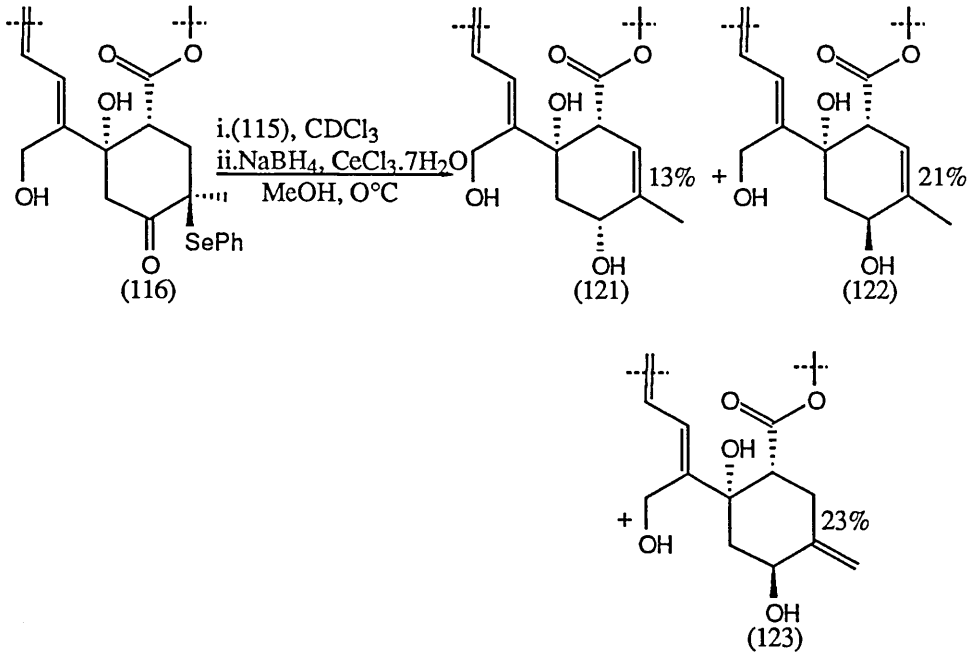
The use of a chiral oxaziridine[124] (120) as oxidant also failed to alter the

product distribution.

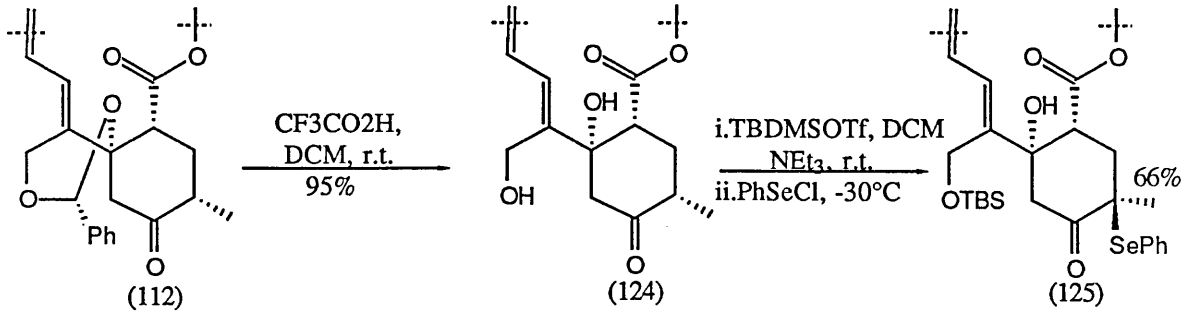


(120)

Attempts to reduce the crude enones with acid free sodium[81] or tetramethylammonium[125] triacetoxyborohydride reagents were met with attendent aromatisation. Presumably, the complexation of the tertiary alcohol - a prerequisite to ketone reduction - was sufficient to labilise it towards β elimination. In contrast, lanthanide assisted[67] intermolecular reduction of the crude enone mixture with sodium borohydride in methanol afforded a separable mixture of the allylic alcohols (121), (122) and (123) in moderate yield. However, the allylic alcohol (122) did contain the correct stereochemical array of functionality required to complete milbemycin β_1 synthesis.



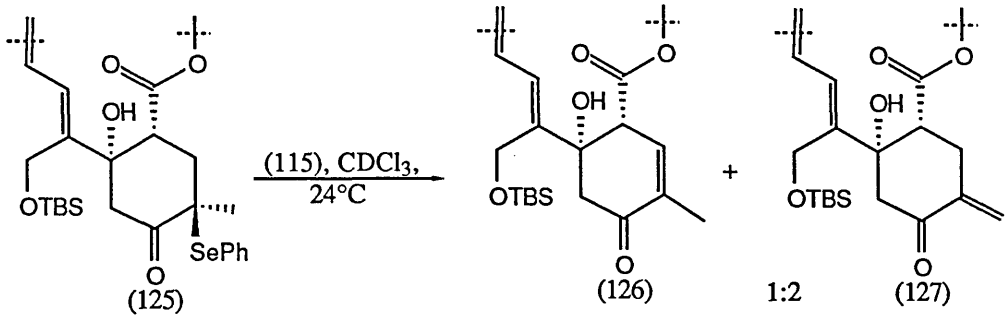
The disappointing endocyclic selectivity of the dehydrogenation processes prompted a brief investigation into the effect of protecting the primary alcohol of the selenide (116) as the corresponding TBS ether. This material was best prepared in the manner illustrated below.



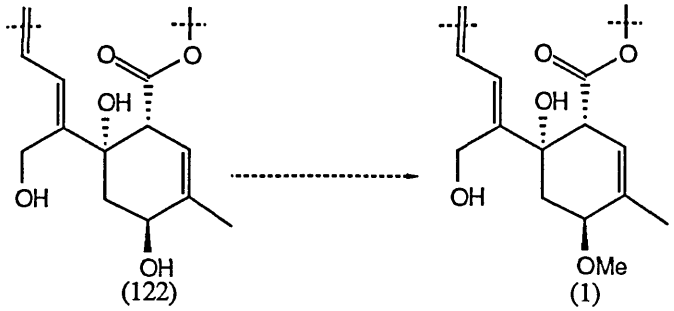
The benzylidene acetal was hydrolysed under acidic conditions in virtually quantitative yield. Simultaneous primary alcohol silylation and silyl enol ether

formation was achieved by treating the hydroxy ketone (124) sequentially with triethylamine and TBS triflate. The silyl enol ether was not isolated, but selenenylated *in situ*, to provide the selenide (125) in good overall yield.

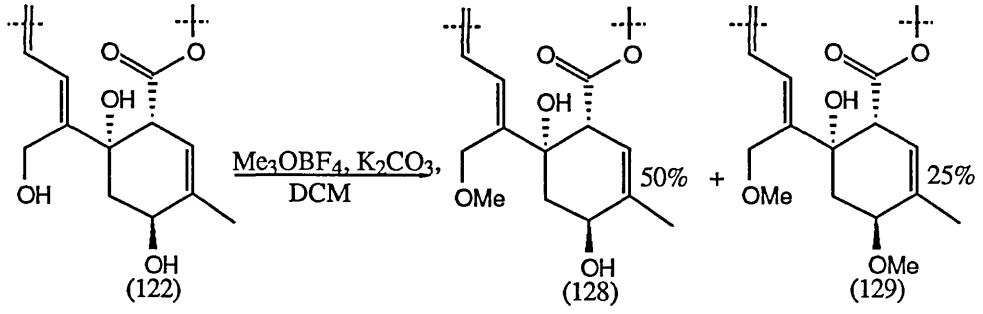
Unfortunately, oxidative elimination of the selenide (125) afforded a 2:1 mixture of the enones (127) and (126), in which the endocyclic product could be identified as the minor component.



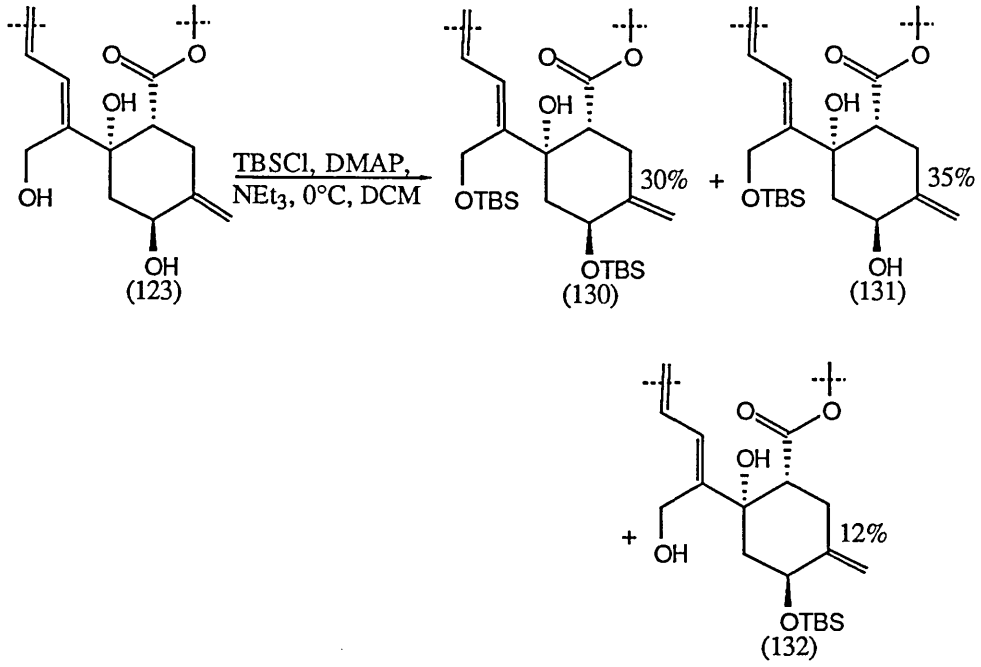
Further efforts to improve the endocyclic selectivity of these elimination processes were abandoned, and our attention was focused on conversion of the allylic alcohol (122) to milbemycin β_1 (1).



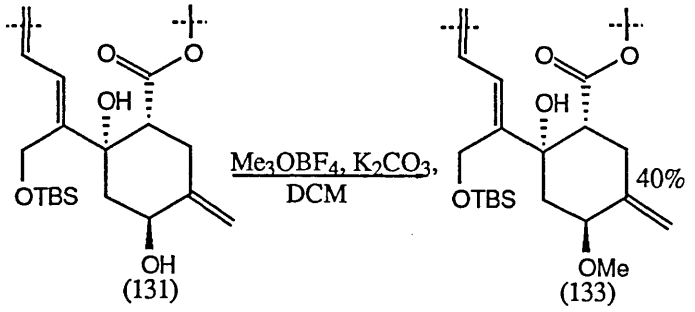
An attempt to directly methylate the secondary allylic alcohol of the triol (122) was unsuccessful. Instead, preferential methylation of the primary alcohol occurred.



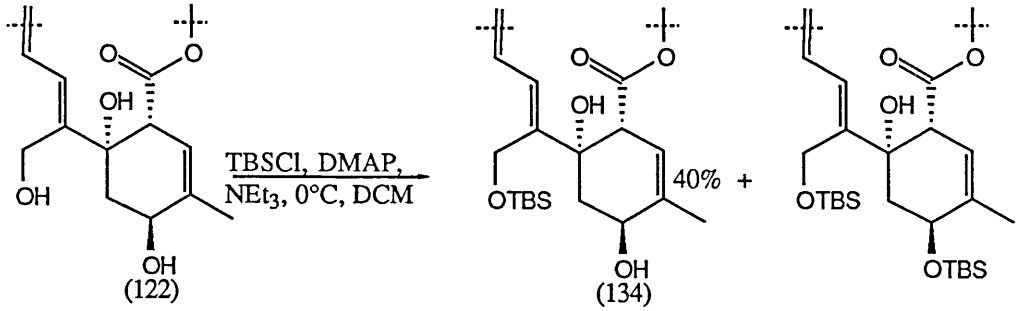
Clearly selective protection of the primary alcohol was necessary and the viability of this process was investigated by treatment of the exo-allylic alcohol (123) with TBS chloride under nucleophilic catalysis.



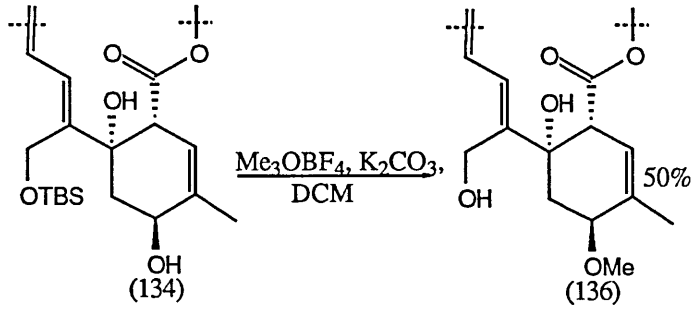
Methylation of the allylic alcohol (131) with buffered methyl Meerweins reagent was complicated by silyl ether cleavage. However, the desired methyl ether (133) could be isolated in moderate yield.



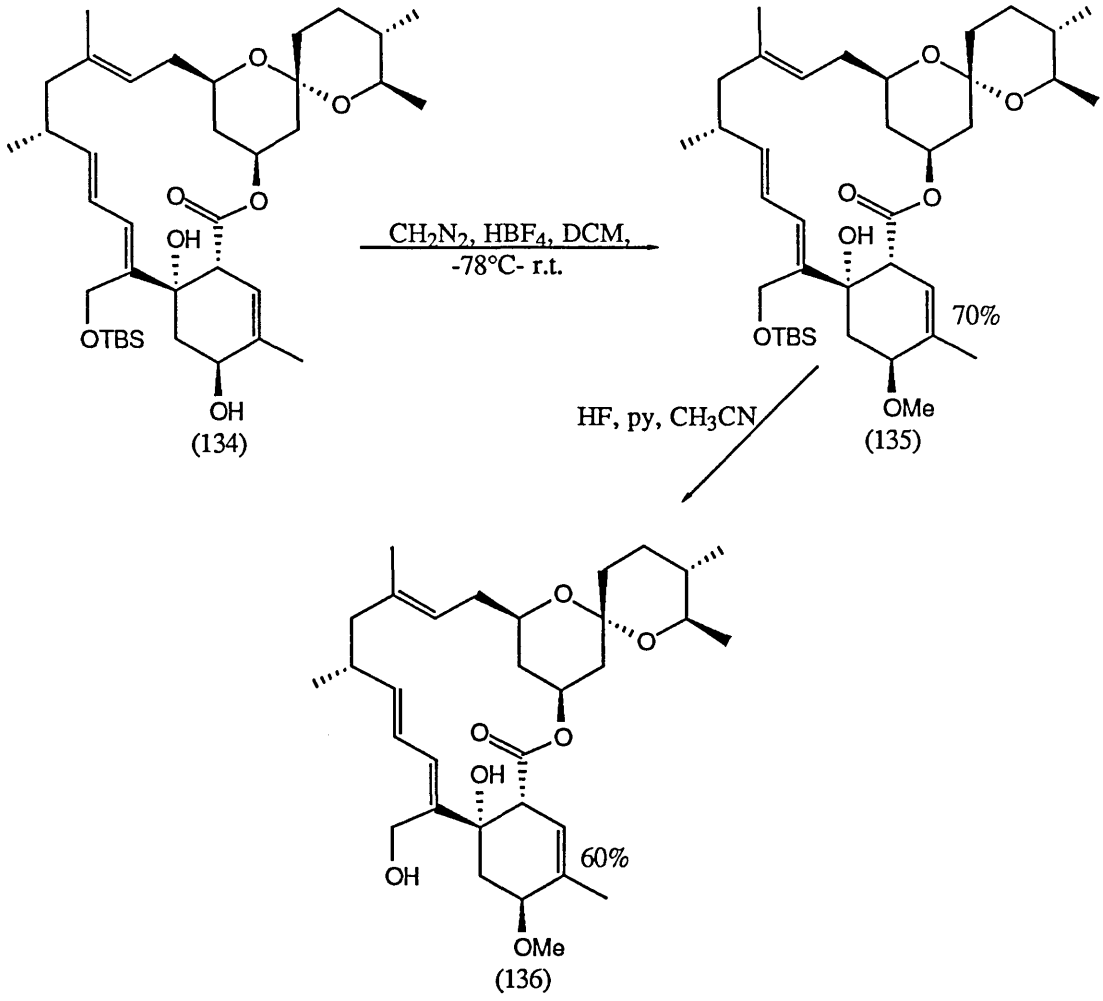
The success of this methodology demanded that it be applied to the allylic alcohol (122). Thus, the alcohol underwent smooth silylation to afford a separable mixture of mono (134) and disilylated derivatives.



Methylation of the monosilyl ether (134) with buffered methyl Meerweins reagent occurred with concomitant silylether cleavage to yield the desired 5-O-methoxy derivative (136).

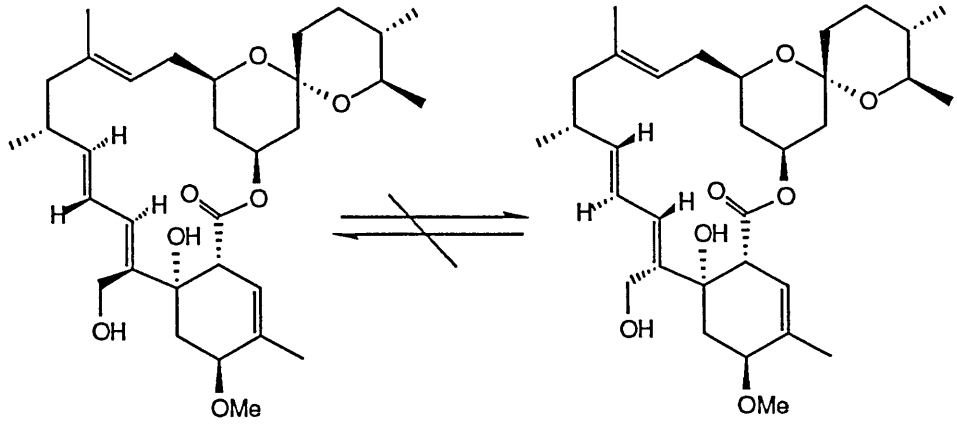


As an alternative to this procedure the silylether (134) could be methylated with diazomethane in the presence of an acid catalyst[84] to afford the methyl ether (137) in good yield.



The silyl ether was cleaved cleanly upon treatment with hydrofluoric acid. To our dismay comparison of the NMR and mass spectra of our synthetic milbemycin β_1 (136) with authentic data[126] showed that the natural and synthetic materials were isomeric.

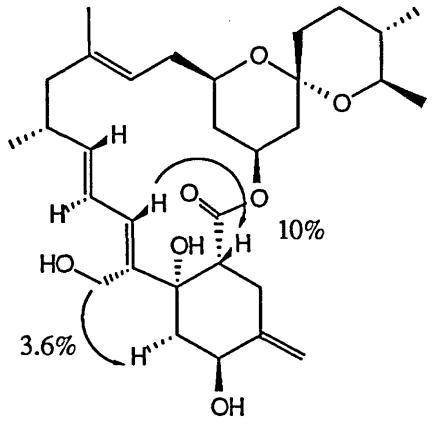
A consideration of the three dimensional molecular array of the natural macrolide indicates that it can adopt two low energy conformations (A) and (B).



A B

Molecular dynamics studies indicated that thermal interconversion of these conformations is strongly disfavoured since rotation of the diene system about the C-7, C-8 and C-11, C-12 bonds generates prohibitively large transannar non-bonded interactions. Therefore atropoisomerism is possible. X-ray studies of avermectin β indicate that conformer A is adopted by this series of natural products. Comparable X-ray data of milbemycin β_1 derivatives has not been published. Therefore, information about the conformation of milbemycin β_1 was unavailable to us.

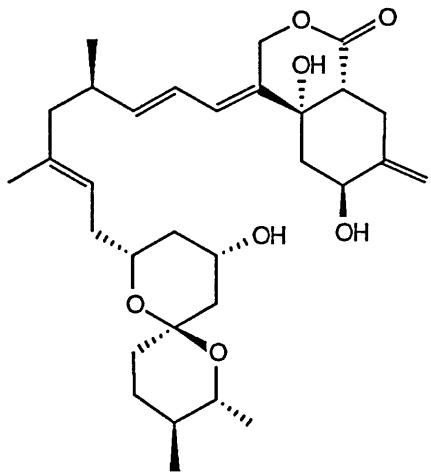
In order to determine which atropoisomer we had synthesised a series of nOe experiments were conducted. The 4-exomethylene derivative (123) was used because we had prepared insufficient quantities of synthetic milbemycin β_1(136) for this study. Irradiation of the C-9 proton was accompanied by an enhancement (7.4%) of the C-11 proton. This indicated that the E,E diene was indeed intact. Additionally, a strong



(123)

Observed nOe enhancements

enhancement (10%) of the axial C-2 proton was observed, indicating that the C-9 and C-2 protons reside on the β-face of the macrolide ring. Irradiation of the methylene pair at C-8' resulted in strong enhancement (10.3%) of the diene proton at C-10 and, more significantly, 3.6% enhancement of the α (equatorial) proton at C-6. These results are clearly consistant with conformation B. Attempted thermal isomerisation of this atropoisomer resulted merely in formation of δ lactone (137).



(137)

In retrospect the synthesis of atropomilbemycin β_1 is a logical consequence of constraining the C-7 and C-8' oxygen atoms within a benzylidene acetal , during the macrolactonisation. This suggests that a simple modification of our synthetic strategy - lactonising a suitable seco-acid in which the C-7 and C-8' hydroxyl groups are seperately proctected - should allow successful synthesis of milbemycin β_1. This approach is currently under investigation in our laboratories.

We have demonstrated that introduction of C-3, C-4 unsaturation subsequent to macrocyclisation is feasible. Additonally, the increased regio-stability of this olefin has been shown to allow straightforward elaboration of late synthetic intermediates.

Experimental

I.r. spectra were recorded on a Perkin Elmer 983G Infrared Spectrophotometer. 1H NMR spectra 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 microanalyses 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. These solvents were distlled prior to use. Other solvents and reagents were purified by standard procedures as necessary. Petrol refers to light petroleum ether, b.p. 40-60 °C, and was redistilled proir to use. Ether refers to diethyl ether. Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F254) 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.

1. Preparation of 2,5-Dihydro-1-methoxy-4-methylcyclohexa-1,4-diene (6)



(6)

Freshly cut lithium pieces (5.28g, 0.75 mol) were added to a vigorously stirred solution of 4-methyl anisole (30 g, 0.25 mol) in ether (60 ml) and liquid ammonia (200 ml) over 20 min. The resulting blue solution was stirred for 30 min, methanol 60 ml added dropwise, and after the blue colour was discharged the ammonia allowed to evaporate. The residue was cautiously treated with water (200 ml) and extracted with ether, each extract was washed with brine and the combined extracts were dried ($MgSO_4$). Solvent evaporation *in vacuo* at (O°C) gave the enol ether (5) (27.8g, 92%) as a colourless oil, ν_{max} (film) 2994, 2824, 1697, 1665, and 1217 cm^{-1}; δ (60 MHz) 5.35 (1H, m, 5-H), 4.60 (1H, m, 2-H), 3.59 (3H, s, 1-OMe), 2.70 (4H, m), and 1.70 (3H, s, 4-Me); m/z 124 (M^+).

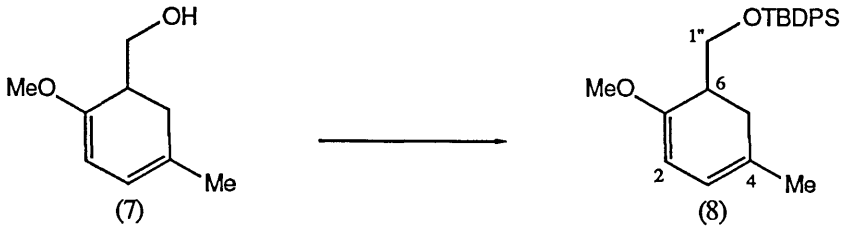
2. Preparation of (±)(6S) 6-Hydroxymethyl-1-methoxy-4-methyl-cyclohexa-1,3-diene (7).



(6) (7)

Trimethyl aluminium (707 ml of a 2.0M solution in hexane, 1.41 mol) was added dropwise to a stirred mixture of parafurmaldehyde (42.40 g 1.41 mol) and the enol ether (6) (87.5 g 0.705 mol) in DCM (1l) at 0°C under argon. The solution was stirred at this temperature for 1 hr. The solution was diluted with ether, (1l) and cautiously treated with water (400 ml). The aqueous phase was exhaustively extracted with ether, each extract was washed with brine. The combined organic extracts were dried ($MgSO_4$), and evaporated *in vacuo*. Rapid column chromatography (30% ether-petrol) gave the alcohol (7) (129.5 g, 64%) as a colourless oil, ν_{max} (film) 3378, 2930, 1661, 1610 and 1216 cm^{-1}; δ (250 MHz) 5.51 (1H, m, 3-H), 4.93 (1H, d, J 5.7 Hz, 2-H), 3.70-3.50 (2H, m, 1"-H_2), 3.57 (3H, s, OMe), 2.52 (1H, m, 6-H), 2.33 (1H, m, 5-H), 2.14 (1H, m, 5-H), 2-05 (1H, br s, 1"-OH), 1.72 (3H, d, J 1.4 Hz, 4-Me); m/z 154 (M^+).

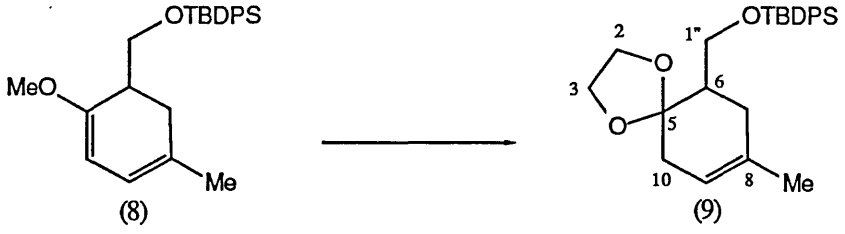
3. Preparation of (±)(6S) 6-t-Butyldiphenylsilyloxymethyl-1-methoxy-4-methyl cyclohexa-1,3-diene (8).



^{t}Butyldiphenylsilyl chloride (16.87 ml, 64.86 mmol) was added to a stirred solution of the alcohol (7) (10.0g 64.86 mmol), DMAP (317 mg, 2.6 mmol) and

triethylamine (10.85 ml 77.8 mmol) in DCM (200 ml), under argon, at O°C. After 18 h, the reaction was poured into water and extracted with DCM. The combined organic extracts were dried ($MgSO_4$), and evaporated *in vacuo*. Rapid column chromatography (3% ether- petrol) of the residue afforded the silyl ether (8) (24.9 g 98%) as a colourless oil, ν_{max} 3071, 2931, 1663, and 1610 cm^{-1}; δ (250 MHz), 7.80-7.30 (10H, m, Ph), 5.51 (1H, m, 3-H), 4.87 (1H, d, J 6.5 Hz, 2-H), 3.70-3.56 (2H, m, 1"-H), 3.48 (3H, s, OMe), 2.51 (1H, m, 6-H), 2.48-2.36 (2H, m, 5-Hz), 1.75 (3H, s, 4-Me) and 1.07 (9H, s, ^tBu) m/z 392 (M^+).

4. Preparation of (±)(6S) 6-t-Butyldiphenylsilyloxymethyl-8-methyl-1,4-dioxaspiro-[4.5]-dec-8-ene (9).

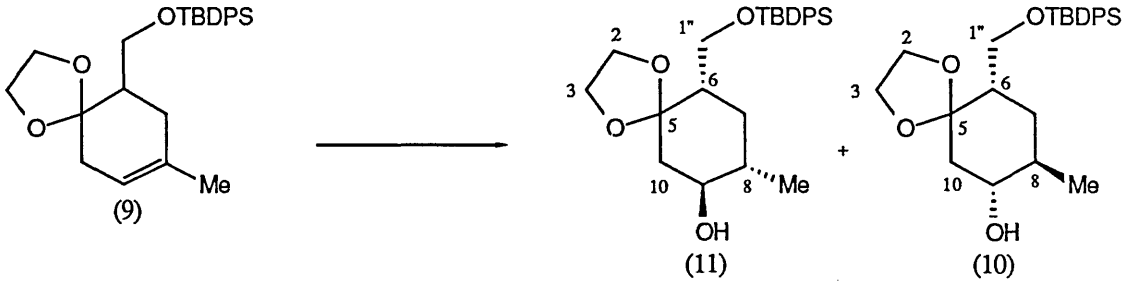


(8) (9)

A solution of the methyl enol ether (8) (1.0g 2.54 mmol) ethylene glycol (0.79g 12.7 mmol) and pyridinium-4- toluenesulphonate (63 mg, 0.25 mmol), in benzene (20 ml) was heated at reflux under Dean-Stark conditions for 16 hr. The mixture was cooled and the solvent evaporated *in vacuo*. Column chromatography (15% ether-petrol) afforded the dioxolane (9) (0.945g, 88%) as a colourless oil, ν_{max} (film) 3070, 2930, 1589, and 1248 cm^{-1}; δ (250 MHz) 7.66 (4H m Ph), 7.39 (6H, m, Ph), 5.26 (6H, m, Ph), 5.26 (1H, m, 9-H), 3.95-3.50 (6H, m), 2.50-2.03 (5H,

m), 1.71 (3H, s, 8-Me), 1.07 (9H, s, ^{t}Bu); m/z 365 (M^{+}-^{t}Bu). (Found: C,74.09; H, 8.04, $C_{26}H_{34}O_3Si$ requires C, 73.87; H, 8.12%).

5. Preparation of (±)(6S,8S,9S)-6-t-Butyldiphenylsilyloxymethyl-9-hydroxy-8-methyl-1,4-dioxaspiro-[4.5]-decane(11) and (±) (6S,8R,9R)-t-Butyl-diphenylsilyloxymethyl-9-hydroxy -8-methyl-1,4-dioxaspiro-[4.5]-decane (10).

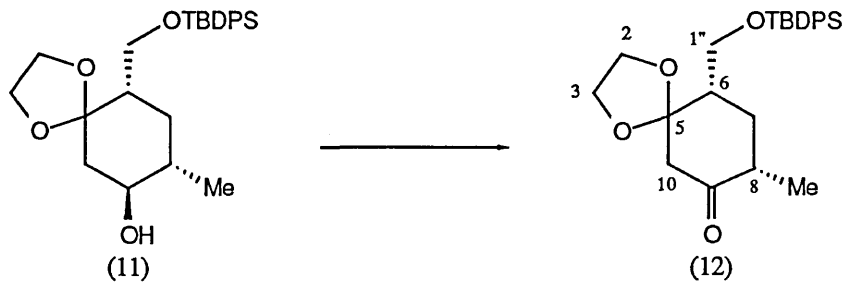


Borane - dimethyl sulphide complex, (0.157 ml of 10 m solution in THF, (1.6 mmol), was added dropwise to a stirred solution of the cyclohexene (9) (1.0 g 2.4 mmol) in THF (20 ml) at O°C, under argon. The mixture was allowed to warm to r.t. over 16h. Water (0.43 ml) was added followed by 3M sodium hydroxide (19.2 ml), and hydrogen peroxide (8.5 ml of 30% solution in water) over 5 min. After 1h, water was added and the solution extracted with ether. Each organic extract was washed with brine, combined and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. Column chromatography (75% ether-petrol) of the residue afforded the *cyclohexanols* - less polar (10) (62 mg, 6%), ν_{max} (film) 3432, 2930, 2885, 1588, 1191, 1111, and 740 cm^{-1}; δ (250 MHz), 7.70-7.60 (4H, m, Ph), 7.45-7.30 (6H, m, Ph), 3.95-3.30

(7H, m, 2-H_2, 3-H_2, 9H and 1'H_2), 2.34 (1H, brs, 9-OH), 2.00-1.88 (2H, m, 6-H and 7-H), 1.79 (1H, dd, J 13.5, 4.0 Hz, 10-H),1.65-1.45 (3H, m, 7-H, 8-H and 10-H), 1.04 (9H, s, ^tBu), 0.97 (3H, d, 6.5 Hz, 8 Me); m/z 423 (MH^+-H_2O), 383 (M^+-^tBu) and 321 (M^+-^tBu-H_2O-C_2H_4O); (Found: C, 70.73; H, 8.20. $C_{26}H_{36}O_4Si$ requires C, 70.87 H; 8.23%).

More polar (11) (885 mg, 85%), ν_{max} (film) 3394, 3049, 2930, 1588, 1360, and 1112 cm^{-1}; δ (250 MHz) 7.70-7.60 (4H, m, Ph), 7.45-7.30 (6H, m, Ph), 3.95-3.60 (5H, m, 2-H_2, 3-H_2, 1'-H), 3.43 (1H, t, J 9.4 Hz, 1'-H), 3.30 (1H, dt, J 4.4 and 10.3 Hz, 9-H), 2.23-1.97 (3H, m, 6-H and 10-H), 1.77 (1H, br s, 9-OH), 1.45-1.20 (3H, m, 7-H_2 and 8-H), 1.08 (12H, m, 8-Me and ^tBu); m/z 423 (MH^+-H_20) 383 (M^+-^tBu) and 321 (M^+-H_2O-^tBu- C_2H_4O); (Found C, 70.78 H; 8.40 $C_{26}H_{36}O_4Si$ requires C, 70.87 H; 8.23%).

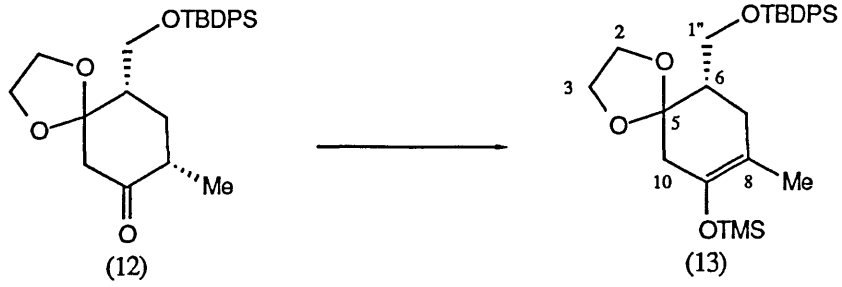
6. Preparation of (±) (6S,8S)-6-t-Butyldiphenylsilyloxymethyl-8-methyl-9-oxo-1,4-dioxaspiro-[4.5]-decane (12).



DMSO (0.388 ml, 5.05 mmol) was added dropwise to a stirred solution of

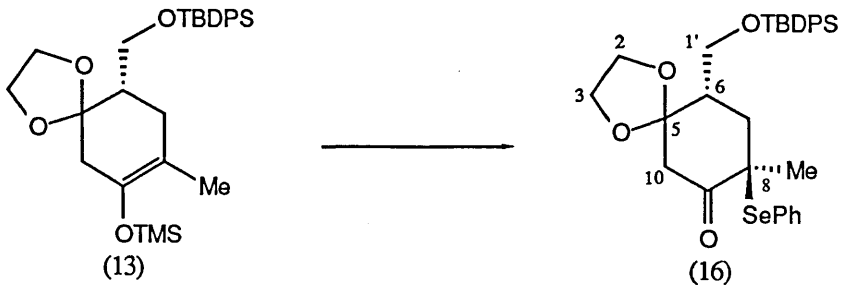
oxalyl chloride (0.237 ml, 2.50 mmol) in DCM (7 ml), under argon at -65°C. After 5 min, the alcohol (11) (370 mg, 0.850 mol) in DCM (3 ml) was added dropwise and after a further 20 min, triethylamine (1.26 ml, 8.50 mol) was added. The mixture was allowed to warm to r.t. poured into water, and extracted with ether. Each extract was washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography of the residue (20% ether-petrol) afforded the *cyclohexanone* (12) (368 mg, 99%) as clear prisms, m.p. 108°C; ν_{max} (film), 3070, 2931, 1713, 1588 and 1111 cm^{-1}; δ (250 MHz), 7.80-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 3.99 (1H, dd, J 10.0 and 4.0 Hz, 1'-H), 3.93-3.60 (4H, m, 2-H_2 and 3-H_2), 3.53 (1H, dd, J 10.0 and 8.5 Hz, 1'-H), 2.59 (1H, d, J 14.0 Hz, 10-H), 2.53 (1H, d, J 14.0 Hz, 10-H), 2.40-2.30 (3H, m, 6-H, 7-H and 8-H), 1.34 (1H, m, 7H), 1.15-1.00 (12H, m, 8-Me and ^tBu); m/z 438 (M^+), 381 (M^+-^tBu) and 337 (M^+-^tBu-C_2H_4O); (Found: C, 71.14; H, 7.87, $C_{26}H_{34}O_4Si$ requires C, 71.12; H, 7.81%).

7. <u>Preparation of (±) (6S)- 6-t-Butyldiphenylsilyloxymethyl-8-methyl-9-trimethylsilyloxy-1,4-dioxaspiro-[4.5]-dec-8-ene (13).</u>



Trimethylsilyl triflate (0.088 ml, 0.456 mmol) was added dropwise to a stirred solution of the ketone (12) (100 mg, 0.228 mmol) and triethylamine (0.064 ml, 0.456 mmol) in ether (2 ml), under argon, at 0°C. After 2h, ether (25 ml) was added and the etheral layer decanted away from the precipitated brown oil. The solvent was evaporated *in vacuo*. Rapid filtration (10% ether-petrol) of the residue through a pad of silica gel afforded the *silyl enolether* (13) (80 mg, 69%) as a colourless oil, ν_{max} (film) 3069, 2956, 2856, 1690, 1588 and 1191 cm^{-1}; δ (250 MHz), 7.75-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 3.95-3.70 (5H, m, 2-H_2, 3-H_2 and 1'-H), 3.51 (1H, t, J 10.0 Hz, 1'-H), 2.50-2.00 (5H, m, 10-H_2, 3-H_2 and 6-H), 1.60 (3H, m, 8-Me), 1.05 (9H, s, ^tBu), 0.15 (9H, s, $SiMe_3$); m/z 510 (M^+), 453 (M^+-^tBu) and 409 (M^+-^tBu-C_2H_4O), Found: M^+, 510.2627 $C_{29}H_{42}O_4Si$ requires M, 510.2622).

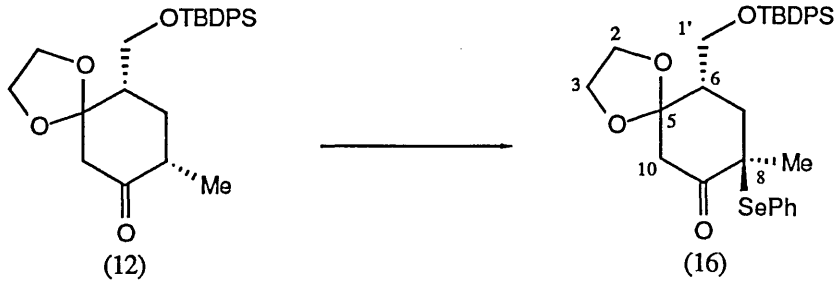
8. Preparation of (±) (6S, 8R)-6-t-Butyldiphenylsilyloxymethyl-9-oxo-8-benzeneselenenyl-8-methyl-1,4-dioxaspiro-[4.5]-decane (16).



Benzeneselenenylchloride (159 mg, 0.833 mmol), in DCM (10 ml) was added dropwise to a stirred solution of the silyl enol ether (13) (386 mg, 0.757 mmol) in

DCM (10 ml) at -78°C, under argon. The resulting pale yellow solution was stirred at this temperature for 5 min, saturated sodium hydrogencarbonate solution was added and the slurry allowed to warm to r.t. The mixture was poured into water, extracted with DCM, dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (25% ether-petrol) of the residue afforded the α *selenenyl ketone* (16) (370 mg, 83%) as a foam. ν_{max} (film), 3069, 2930, 1700, 1588, 1247 and 1112 cm^{-1}; δ (250 MHz), 7.80-7.60 (4H, m, Ph), 7.60-7.20 (11H, m, Ph), 4.06 (1H, dd, J 9.5 and 3.5 Hz, 1'-H), 4.00-3.67 (5H, m, 2-H_2, 3-H_2, 10-H), 3.57 (1H, t, J 9.5 Hz, 1'-H), 2.84 (1H, ddd, J 12.9, 8.5 and 3.5 Hz, 6-H), 2.60 (1H, dd, J 14.5 and 4.0 Hz, 7-H), 2.53 (1H, d, J 14.0 Hz, 10-H), 1.87 (1H, dd, J 14.5 and 12.9 Hz, 7-H), 1.42 (3H, s, 8-Me), 1.15 (9H, s, ^tBu); m/z 537 (M^+-^tBu) 300 (M^+-^tBu-SePh) and 199 (Ph_2SiOH).(Found: M^+-tBu, 537.0991 $C_{28}H_{29}O_4SeSi$ requires M, 537.1000)

9. Preparation of (2S,8R)-2-t-Butyldiphenylsilyloxymethyl-9-oxo-8-benzeneselenenyl-8-methyl-1,4-dioxaspiro-[4,5]-decane (16).

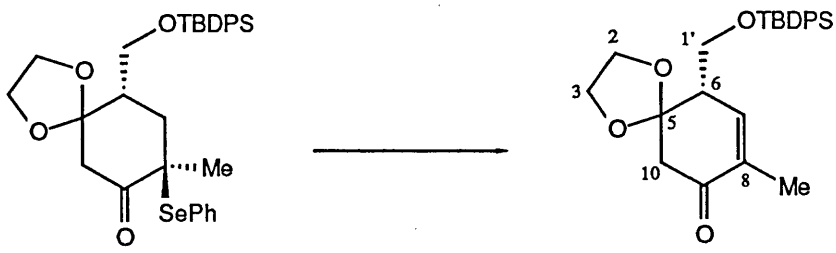


(12) (16)

Trimethylsilyltriflate (0.413 ml, 2.13 mmol) was added dropwise to a stirred solution of the ketone (12) (848 mg, 1.94 mmol) and triethylamine (0.458 ml, 3.29

mmol) in ether (10 ml), under argon, at 0°C. After 2h, t.l.c. indicated complete consumption of ketone, whereupon the two phase mixture was cooled to -78°C, and benzeneselenenyl chloride (740mg, 3.88 mmol in ether (10) was added over 2 min. Saturated sodium hydrogencarbonate solution (10 ml) was added to the resulting yellow solution and the mixture allowed to warm to r.t., poured into water, extracted with DCM and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. Column chromatography (25% ether-petrol) of the residue gave the *selenenyl ketone* (16) (860 mg 75%) identical to previously prepared material.

10. (±) (6S)-6-t-Butyldiphenylsilyloxymethyl-9-oxo-8-methyl-1,4-dioxaspiro-[4.5]-dec-7-ene (15).

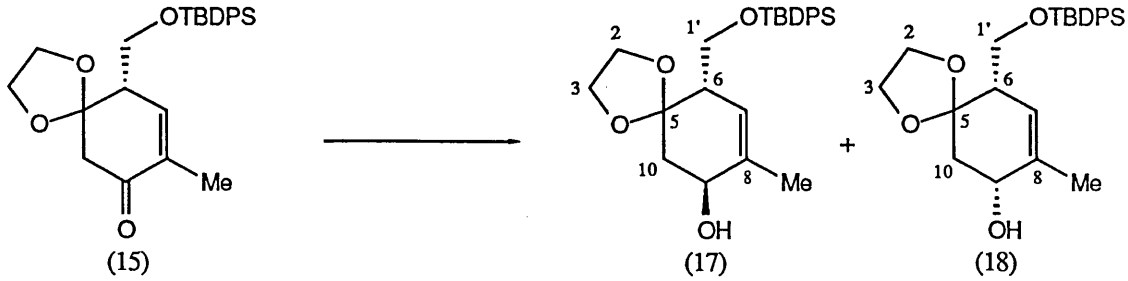


(16) (15)

Hydrogen peroxide (61 µl of a 30% solution in water, 0.541 mmol) was added dropwise to a stirred solution of the selenide (16) (160 mg, 0.270 mmol) and pyridine (44 µl 0.541 mmol) in DCM (10 ml) at r.t. After 45 min, the mixture was poured into water extracted with DCM, dried ($MgSO_4$) and evaporated *in vacuo*. Column

chromatography (20% ether-petrol) the residue afforded the *enone* (15) (98 mg, 83%), as a colourless oil, ν_{max} (film), 2930, 2887, 2857, 1676, 1588, 1309 and 1105 cm^{-1}; δ (250 MHz), 7.70-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 6.73 (1H, dq, J 4.5 and 1.5 Hz, 7-H), 4.00-3.72 (6H, m, 1'-H_2, 2-H_2 and 3-H_2), 2.93 (1H, d, J 15.5 Hz, 10-H), 2.77 (1H, m, 2-H), 2.61 (1H, d, J 15.5 Hz, 10-H), 1.84 (3H, t, J 1.5 Hz, 8 Me), 1.05 (9H, s, t-Bu), m/z 436 (M^+) (Found: C, 71.84; H, 7.66 $C_{26}H_{32}O_4Si$ requires C, 71.53; H, 7.39%) (Found: M^+, 436.2061 $C_{26}H_{32}O_4Si$ requires M, 436.2070)

11. Preparation of (±) (6S,9S)-6-t-Butyldiphenylsilyloxymethyl-9-hydroxy-8-methyl-1,4-dioxaspiro-[4.5]-dec-7-ene(17) and (±) (6S,9R)-6-tButyldiphenyl-silyloxymethyl-9-hydroxy-8-methyl-1,4-dioxaspiro-[4.5]-dec-7-ene (18).



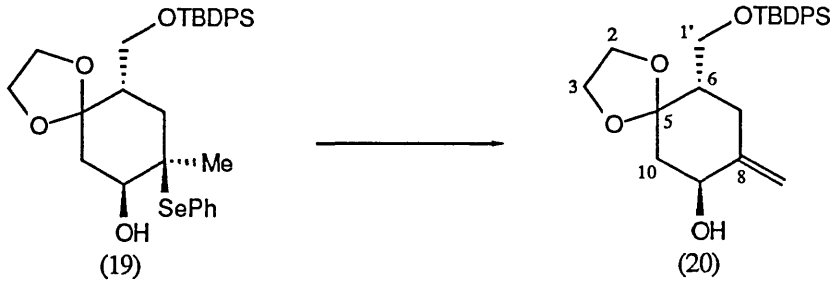
(15) (17) (18)

Sodium borohydride (8 mg, 0.214 mmol) was added portionwise to a stirred solution of the enone (15) (47 mg, 0.107 mmol) and cerium chloride heptahydrate (74 mg, 0.199 mmol) in methanol (1 ml) at -20°C. After 20 min,water (1 ml) was added

and the mixture extracted with ether, each extract was washed with water and brine. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*.

H.P.L.C. (4% IPA-petrol) of the residue afforded the *alcohols* (18) (13 mg, 28%) and (17) (11 mg, 23%) as colourless oils. Less polar:(18), ν_{max} (film), 3400, 2931, 2857, 1410 and 727 , cm^{-1}; δ (250 MHz), 7.67-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 5.69 (1H, br s, 7-H), 4.05-3.65 (6H, m, 2-H_2, 3-H_2, 9-H and 1'H), 3.58 (1H, t, J 9.5 Hz, 1'-H), 2.78 (1H, d, J 11.0 Hz, 9-OH), 2.69 (1H, m, 6-H), 2.08 (1H, dd, J 14.0 and 3.0 Hz,10-H), 1.89 (1H, dd, J 14.0 and 4.5 Hz, 10-H), 1.86 (3H, br t, J 2.0 Hz, 8-Me), 1.05 (9H, s, ^tBu); m/z 438 (M^+), 381 (M^+-^tBu), 333 (M^+-^tBu-CH_20-H_20), 289 (M^+-^tBu-CH_2O-H_20-C_2H_40), 199 (Ph_2SiOH); More polar: (17), ν_{max} (film), 3430, 2930, 2885, 2857, 1425, 727cm^{-1} δ (250 MHz) 7.67-7.30 (10H, m, Ph), 5.51 (1H, br d, J 4.0 Hz, 7-H), 4.00-3.78 (5H, m, 2-H_2, 3-H_2, 9-H), 3.73 (2H, d, J 5.5 Hz, 1'-H_2), 2.88 (1H, d, J 10.5 Hz, 9-OH), 2.35 (1H, m, 6-H), 2.28 (1H, dd, J 13.5 and 4.5 Hz, 10-H), 1.92 (1H, d J 13.5 H2, 10-H), 1.90 (3H, m, 8-Me), 1.01 (9H, s, ^tBu); m/z 438 (M^+), 381 (M^+-^tBu), 333 (M^+-^tBu-CH_2O-H_2O), 289 (M^+-^tBu-CH_2O-H_2O-C_2H_4O), 199 (Ph_2SiOH). (Found: C, 71.42; H, 8.14. $C_{26}H_{34}O_4Si$ requires C, 71.19; H, 7.81%).

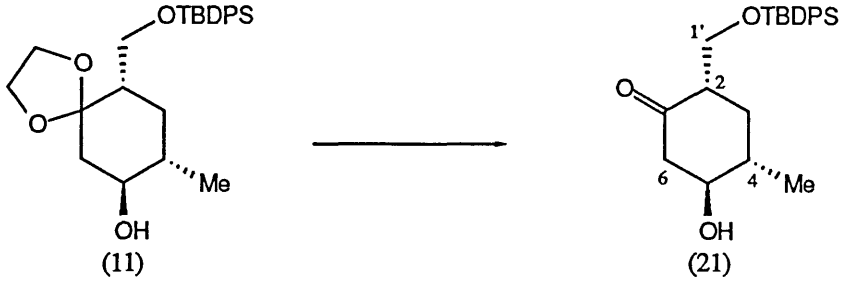
12. Preparation of (±)(6S, 9S)-6-t-Butyldiphenylsilyloxymethyl-9-hydroxy-8-methylene-1,4-dioxaspiro-[4.5]-decane (20).



Hydrogen peroxide (0.100 ml of a 30% solution in water, 0.88 mmol), was added dropwise to a stirred solution of the selenide (19) (23 mg, 0.039 mmol) in DCM (10 ml) at 0°C. After 1h at this temperature, t.l.c. indicated consumption of starting material, whereupon the solution was warmed to 35°C for 10 min. After cooling to r.t. saturated sodium hydrogencarbonate (5 ml) was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$), and evaporated, *in vacuo*. Column chromatography (40% ether-pertol) of the residue afforded the *allylic alcohol* (20) (16 mg, 95%) as a colourless oil, ν_{max} (film) 3424, 3071, 2959, 2884 and 1656 cm^{-1}; δ (250 MHz), 7.66 (4H, m, Ph), 7.40 (6H, m, Ph), 5.00 (1H, brs, 1"-H), 4.88 (1H, br s, 1" H), 4.21 (1H, m, 9-H), 3.93-3.44 (6H, m, 2-H_2, 3-H_2, 1'-H_2), 2.80 (1H, dd, J 13.6 and 4.5 Hz, 7-H), 2.66 (1H, d, J 7.6 Hz, 9-OH), 2.33 (1H, dd, J 13.6 and 8.2 Hz, 7-H), 2.05 (1H, m, 6-H), 1.97 (1H, dd, J 13.5 and 4.3 Hz, 10-H), 1.61 (1H, ddd, J 13.5 , 8.5 and 0.9 Hz, 10-H), 1.05 (9H, s, ^tBu); m/z 438 (M^+);

(Found: C, 71.23, H, 8.02. $C_{26}H_{34}O_4S$: requires C, 71.18; H, 7.83%).

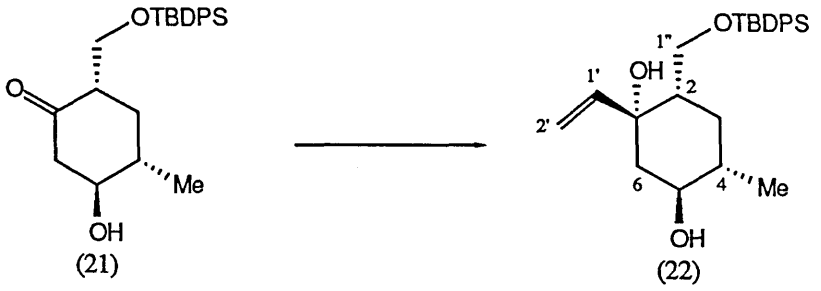
13. Preparation of (±) (2S, 4S, 5S)-2-t-Butyldiphenylsilyloxymethyl-5-hydroxy-4-methylcyclohexanone (21).



Palladium II chloride - acetonitrile complex (50.4 mg, 0.193 mmol) was added to a stirred solution of the ketal (11) (8.40 g,0.002 mol), in acetone (200 ml), in the dark, at r.t. After 7h saturated sodium hydrogencarbonate solution (50 ml) was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) the residue afforded the *hydroxy ketone* (21) (7.41g, 98%), ν_{max} (film), 3422, 3069, 2930, 2857, 1707, 1588, 1388, 1112, and 960 cm^{-1}. δ (250 MHz), 7.71-7.61 (4H, m, Ph), 7.48-7.31 (6H, m, Ph), 3.98 (1H, dd, J 10.4 and 4.9 Hz, 1'-H), 3.63 (1H, dd, J 10.4 and 7.6 Hz, 1'-H), 3.31 (1H, m, 5-H), 2.69 (1H, dd, J 13.2 and 4.9Hz, 6-H), 2.56 (1H, m, 2-H), 2.40 (1H, m, 6-H), 2.23 (1H, ddd, J 13.6, 6.0 and 3.9 Hz, 3-H), 2.00 (1H, br s, 5-OH), 1.80 (1H, m, 4-H), 1.15 (4H, m, 3-H and 4-Me), 1.06 (9H, s, ^tBu), m/z 379 (MH^+-H_20), 363 (M^+-H_20-Me), 339 (M^+-^tBu), 321 (M^+-^tBu-H_20). (Found: C, 72.53, H, 8.21. $C_{24}H_{32}O_3Si$ requires C,

72.68, H, 8.13%).

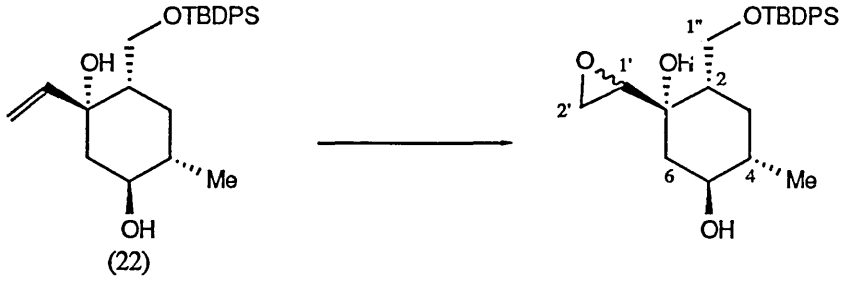
14. Preparation of (±) (1S,2S,4S,5S) -2-t-Butyldiphenylsilyloxymethyl-1-ethenyl-5-hydroxy-4-methylcyclohexan-1-ol (22).



t-Butyl-lithium (7.04 ml of a 1.63 M solution in pentanes, 0.0115 mol) was added dropwise to a stirred solution of vinyl bromide (0.404 ml, 5.74 mmol) in THF (15 ml) at -78°C, under argon. After 5 min, the hydroxyketone (21) (452 mg, 1.147 mmol) in THF (7 ml) was added dropwise to the pale yellow solution. Saturated sodium hydrogencarbonate (9 ml) was added after 2.5h and the mixture allowed to warm to r.t. The mixture was extracted with ether, each extract was washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) of the residue afforded the *diol* (22) (469 mg, 97%) as a colourless oil, ν_{max} (film), 3418, 3070, 2928, 1588, 1427, 1113, and 917cm^{-1}; δ (400 MHz), 7.75-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 5.86 (1H, dd, J 17.0 and 10.5 Hz, 1'-H), 5.55 (1H, dd, J 17.0 and 2.0 Hz 2'-Hb), 5.20 (1H, dd, J 10.5 and 2.0 Hz, 2'-Ha), 4.20 (1H, br s, 1-OH), 4.04 (1H, dd, J 10.0 and 2.5 Hz, 1"-H), 3.71 (1H,

dd, J 10.0 and 2.0 Hz, 1"-H), 2.05-1.85 (2H, m, 3-H and 5-OH), 1.93 (1H, dd, J 13.0 and 4.5 Hz, 6-H), 1.50-1.40 (3H, m, 2-H, 3-H and 4-H), 1.38 (1H, dd, J 13.0 and 11.0 Hz, 6H), 1.13 (3H, d, J 6.0 Hz, 4-Me), 1.10 (9H, s, t-Bu); m/z 367 (M^+-^{t}Bu), 349 (M^+-^{t}Bu-H_2O), 331 (M^+-^{t}Bu-$2H_2O$) 321 (M^+-^{t}Bu-H_2O-C_2H_4). (Found M^+-^{t}Bu, 367.1737, $C_{22}H_{27}O_3Si$ requires M, 367.1729).

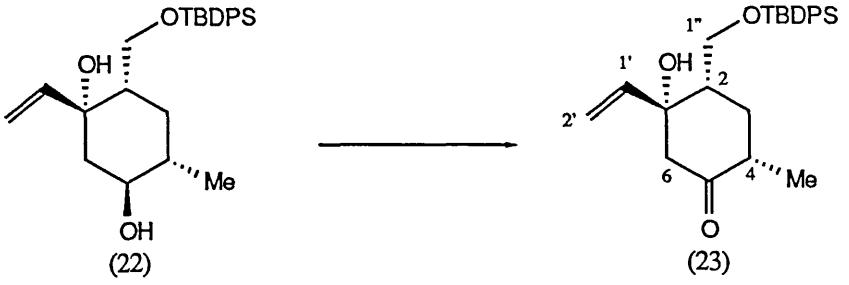
15. Preparation of (±)(1S,2S,4S,5S, 1'S)-2-t-Butyldiphenylsilyloxymethyl-1-(1'-epoxyethyl)-5-hydroxy-4-methylcyclohexan-1-ol and (±)(1S,2S,4S,5S,1'R)-2-t-Butyldiphenylsilyloxymethyl-1-(1'epoxyethyl)-5-hydroxy-4-methylcyclohexan-1-ol.



mCPBA (69 mg, 80%, 0.32 mmol) was added to a stirred solution of the olefin (22) (27 mg, 0.064 mmol) in DCM (1 ml) at 0°C. After 12h, dilute aqueous sodium sulphite solution was added and the mixture extracted with DCM. The combined organic extracts were dried $MgSO_4$ and evaporated *in vacuo*. Column chromatography (40% ether-petrol) of the residue afforded the *epoxides* (21 mg, 75%) as a clear oil; ν_{max} (film) 3422, 2927, 1426, 1260, 1112, and 797 cm^{-1}; δ (90 MHz), 7.80-7.30 (10H, m, Ph), 4.50-3.40 (3H, m), 2.83 (2H, m, 2'-H_2), 2.75-2.50

(1H, m, 1'-H), 2.05 (1H, dd, J 12.5 and 4.0 Hz, 6-H), 1.90-1.20 (7H, m), 1.15-1.00 (12H, m, ^{t}Bu and 4-Me), m/z (397 M^{+} - C_2H_4O), 383 (M^{+}-^{t}Bu), 365 (M^{+}-^{t}Bu-H_2O), (Found: M^{+}-^{t}Bu, 383.1678. $C_{22}H_{27}O_4Si$ requires M, 383.1679).

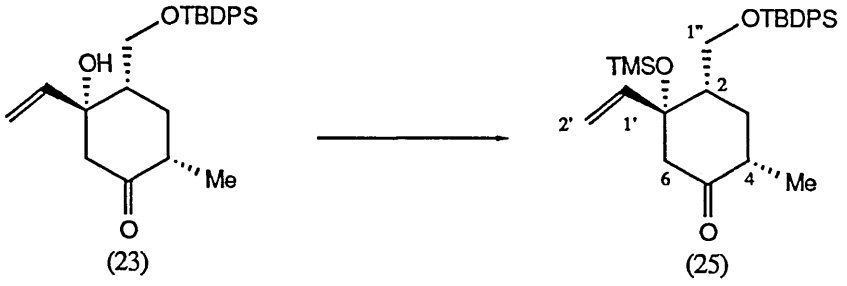
16. Preparation of (±)(2S,4S,5S)-4-t-Butyldiphenylsilyloxymethyl-5-ethenyl-5-hydroxy-2-methylcyclohexanone (23).



DMSO (0.197 ml, 2.78 mmol) in DCM (2.5 ml) was added dropwise to a stirred solution of oxalyl chloride (0.122 ml 1.39 mmol), in DCM (4 ml), under argon at -65°C. After 10 min, the alcohol (22) (469 mg, 1.11 mmol) in DCM (7 ml) was added dropwise. The resulting mixture was stirred for 20 minutes whereupon triethylamine (0.775 ml, 5.55 mmol) was added and the solution allowed to warm to r.t. The mixture was poured into water and extracted with ether, the combined extracts dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (40% ether-petrol) afforded the *ketone* (23) (4.15 mg 89%) as a white foam; ν_{max} (film) 3467, 2929, 1713, 1426, 1107 and 933 cm^{-1}; δ (250 MHz), 7.70-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 5.93 (1H, dd, J 16.9 and 10.6 Hz, 1'-H), 5.56 (1H, dd, J 16.9 and 2.0

Hz, 2'-Hb), 5.23 (1H, dd, J 10.6 and 2.0 Hz, 2'-Ha) 4.08 (1H, dd, J 10.6 and 3.0 Hz, 1"-H), 3.97 (1H, s, 1-OH), 3.60 (1H, dd, J 10.6 and 2.0 Hz, 1"-H), 2.55-2.20 (4H, m), 1.93 (1H, brd J 12.0 Hz), 1.87-1.75 (1H, m), 1.12 (3H, d, J 6.0 Hz, 2-Me), 1.05 (9H, s, ^{t}Bu); m/z 405 (MH^{+}-H_2O), 365 (M^{+}-^{t}Bu), 347 (M^{+}-^{t}Bu-H_2O); (Found: M^{+}, 422.2270. $C_{26}H_{34}O_3Si$ requires M, 422.2277).

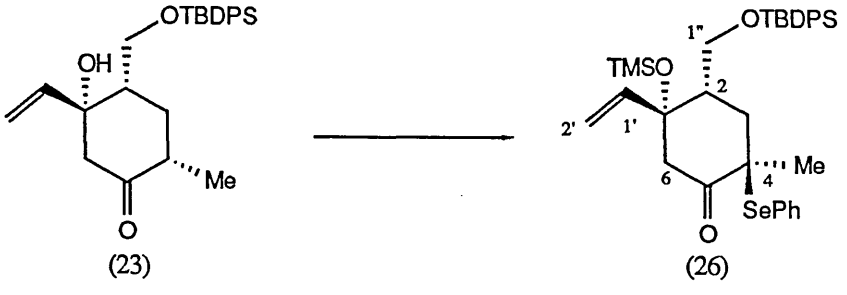
17. Preparation of (±) (2S,4S,5R)-4-t-Butyldiphenylsilyloxymethyl-5-ethenyl-2-methyl-5-trimethylsilyloxycyclohexanone (25).



Trimethylsilyltriflate (0.137 ml, 0.711 mmol) was added dropwise to a stirred solution of the ketone (23) (100mg, 0.237 mmol) and triethylamine (0.109 ml, 0.782 mmol) in ether (4 ml), under argon, at 0°C. The reaction was allowed to warm to r.t. and after 2h saturated sodium hydrogencarbonate solution was added and the mixture extracted with ether. Each extract was washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (35% ether-petrol) afforded the *trimethylsilyl ether* (25) (30mg, 26%) as a colourless oil and the starting

hydroxyketone (23) (70 mg, 70%) identical in all respects to previously prepared material, Less polar: (25), ν_{max} (film), 2930, 1711, 1110 and 730 cm^{-1}; δ (250 MHz), 7.70-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 5.94 (1H, dd, J 16.9 and 10.7 Hz, 1'-H), 4.99 (1H, dd, J 10.7 and 1.0 Hz, 2'-Ha), 4.96 (1H, dd, J 16.9 and 1.0 Hz, 2'-Hb), 3.93 (1H, dd, J 10.3 and 5.0 Hz, 1"-H), 3.44 (1H, dd, J 10.3 and 8.0 Hz, 1"-H), 2.58 (1H, d, J 13.6 Hz, 6-H), 2.45 (1H, d, J 13.6 Hz, 6-H), 2.36 (1H, dq, J 12.4 and 6.0 Hz, 2-H), 2.20 (1H, m, 3-H), 2.00 (1H, m, 4-H), 1.47 (1H, q, J 12.4 Hz, 3-H), 1.06 (9H, s, tBu), 1.02 (3H, d, J 6.0 Hz, 2-Me), 0.01 (9H, s, $SiMe_3$); m/z 479 (M^+-Me) 437 (M^+-^{t}Bu) (Found M^+, 437.1961 $C_{25}H_{33}O_3Si_2$ requires M, 437.1968).

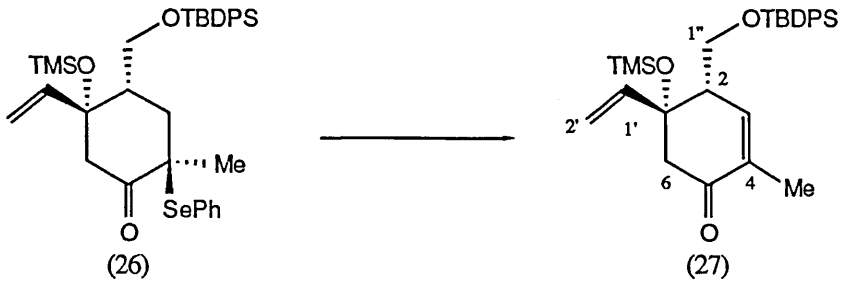
18. Preparation of (±) (2R,4S,5R)-2-Benzeneselenenyl-4-t-butyldiphenyl-silyloxymethyl-5-ethenyl-2-methyl-5-trimethylsilyloxycyclohexanone (26).



Trimethylsilyltriflate (0.322 ml, 1.66 mmol) was added dropwise to a stirred solution of the ketone (23) (160 mg, 0.379 mmol) and triethylamine (0.233 ml, 1.66 mmol) in ether (4 ml), under argon, at 0°C. The reaction was allowed to warm to r.t. After 2h, the reaction was cooled to -78°C and benzeneselenenyl chloride (362 mg,

1.89 mmol) in ether 5 ml was added dropwise over 1 min. Saturated sodium hydrogencarbonate solution (10 ml) was added to the resulting yellow solution, and the mixture allowed to warm to r.t. poured into water, extracted with DCM and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. Column chromatography (5% ether-pertrol) gave the *selenenyl ketone* (26) (205 mg, 83%) ν_{max} (film),2930, 1705, 1110, 720 cm^{-1}; 7.70-7.60 (4H, m, Ph), 7.50-7.25 (11H, m, Ph), 5.87 (1H, dd, J 16.9 and 10.2 Hz 1'-H), 5.08 (1H, d, J 10.2 Hz, 2'-Ha), 5.00 (1H, d, J 16.5 Hz 1'-Hb) 3.95 (1H, dd, J 10.2 and 4.0 Hz, 1"-H), 3.67 (1H, d, J 14.4 Hz, 6-H), 3.46 (1H, dd, J 10.2 and 8.0Hz, 1"-H), 2.40 (1H, d, J 14.4 Hz, 6-H), 2.45-2.25 (2H, m, 4-H and 3-H), 1.98 (1H, br t, J 13.7 Hz, 3-H), 1.38 (3H, s, 2-Me), 1.10 (9H, s, ^tBu), -0.01 (9H, s, $SiMe_3$), m/z 593 (M^+-^tBu), 436 (M^+-^tBu-SePh) (Found: C, 64.44; H, 7.06. $C_{35}H_{46}O_3SeSi_2$ requires C, 64.49; H, 7.13%).

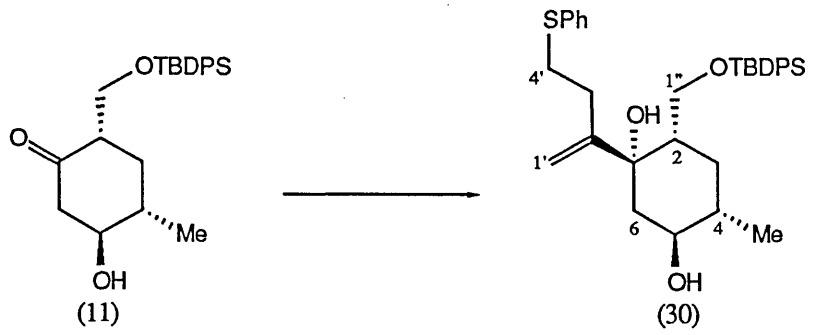
19. Preparation of (±) (4S, 5R)-4-t-Butyldiphenylsilyloxymethyl-5-ethenyl-2-methyl-5-trimethylsilyloxycyclohex-2-enone (27).



Hydrogen peroxide (0.157 ml of a 30% solution in water, 1.38 mmol) was

added dropwise to a stirred solution of the selenide (26) (90 mg, 0.138 mmol) in DCM (5 ml) at r.t. After 2h, the mixture was poured into water, extracted with DCM, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (10% ether-petrol) of the residue afforded the *enone* (27) (48 mg, 70%) as an oil, ν_{max}(film); 2930, 1678, 1587 and 1110 cm^{-1}; δ (250 MHz) 7.75-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 6.67 (1H, dq, J 4.0 and 1.0 Hz, 3-H), 5.81 (1H, dd, J 17.5 and 10.6 Hz, 1'-H), 5.03 (1H, d, J 17.5 Hz, 2"-Hb), 5.03 (1H, d, J 10.6 Hz, 2"-Ha), 3.94 (1H, dd, J 10.0 and 7.0 Hz, 1"-H), 3.87 (1H, dd, J 10.0 and 4.0 Hz, 1"-H), 2.94 (1H, d, J 16.3 Hz, 6-H), 2.70 (1H, J 16.3 Hz, 6-H), 2.52 (1H, m, 4-H), 1.83 (3H, dd, J 1.0 and 1.5 Hz, 2-Me), 1.03 (9H, s, ^tBu), 0.02 (9H, s, $SiMe_3$), m/z 492 (M^+) 477(M^+-CH_3), 435 (M^+-^tBu), (Found: M^+, 492.2500 $C_{29}H_{40}O_3Si_2$ requires M, 492.2516).

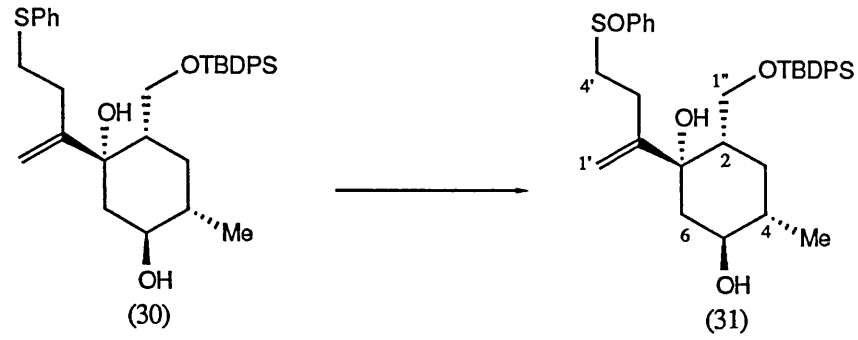
20. <u>Preparation of (±)(1S, 2S, 4S, 5S) 2-t-Butyldiphenylsilyloxymethyl-5-hydroxy-4-methyl-1-(4'-benzenethio-but-1'-ene-2'-yl) cyclohexan-1-ol (30).</u>



^{t}Butyl-lithium (19.6 ml of a 1.7M solution in pentanes, 33.3 mmol) was added

dropwise to a solution of 2-bromo-4-benzenethiobut-1ene (8.1g, 33.3 mmol) in 1:1 ether/THF (150 ml), at -78°C, under argon. After 10 min, the ketone (11) (5.70 g 14.5 mmol), in 1:1 ether/THF (150 ml) was added dropwise over 5 min. Saturated sodium hydrogencarbonate solution (100 ml) was added after 1h and the reaction allowed to warm to r.t. The reaction was poured into water and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromotagraphy (70% ether-pertol) of the residue afforded the *hydroxysulphide* (30) (6.79g, 84%) as a clear oil; ν_{max} (film) 3463, 3070, 2927, 2857, 1585, 1469, 1427 and 703 cm^{-1}; δ (250 MHz), 7.70-7.60 (4H, m, Ph), 7.50-7.34 (6H, m, Ph), 7.30-7.20 (5H, m, SPh), 5.48 (1H, s, 1'-H), 5.07 (1H, s, 1'-H), 4.34 (1H, d, J 2.5 Hz, 1-OH), 3.88 (1H, dd, J 10.0 and 2.4Hz, 1"-H), 3.70 (1H, m, 5-H), 3.43 (1H, dd, J 10.0, 2.0 Hz, 1"-H), 3.07 (2H, t, J. 7.8 Hz, 4'-H), 2.29 (2H, m, 3'-H_2), 1.97-1.67 (2H, m, 3-H and 6-H), 1.43 (4H, m, 2H, 3-H, 4-H and 6-H), 1.10 (3H, d, J 6.8 Hz, 4-Me), 1.03 (9H, s, ^tBu); m/z 503 (M^+-^tBu), 199 (Ph_2SiOH) (Found: M^+-^tBu, 503.2064 $C_{30}H_{35}O_3SSi$ requires M, 503.2076).

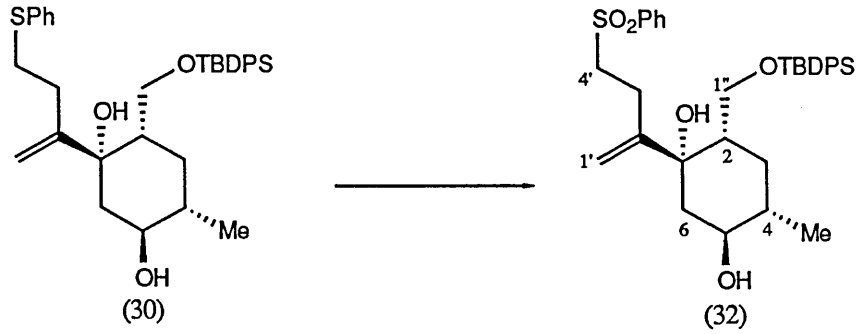
21. Preparation of (±)(1S,2S,4S,5S)-2-t-Butyldiphenylsilyloxymethyl-5-hydroxy-4-methyl-1-(4'phenylsulphinylbut-1'-ene-2'-yl)cyclohexan-1-ol (31).



The sulphide (30) (500 mg, 0.893 mmol) was dissolved in DCM (30 ml) and saturated sodium hydrogencarbonate solution (10 ml) added. mCPBA (195 mg, 80%, 0.893 mmol) was added to the vigorously stirred two-phase mixture. After 20 min, t.l.c indicated consumption of starting material, whereupon, saturated sodium sulphite solution (1 ml) was added and the mixture extracted with DCM. The combined organic extracts were dried and evaporated *in vacuo*. Column chromatography (ethyl acetate) of the residue afforded the *sulphoxides* (31) (508 mg 99%) as a white foam. ν_{max} (film), 3446, 3067, 2929, 2857, 1634, 1442, 1112 and 909 cm^{-1}; δ (250 MHz),7.90-7.20 (15H, m, Ph), 5.47 (2/3 H, s, 1'-Hb), 5.39 (1/3H, s, 1'-Hb), 5.00 (2/3H, s, 1'-Ha), 4.94 (1/3H, s, 1'-Ha), 4.40 (2/3H, s, 1-OH), 4.36 (1/3H, s, 1-OH), 3.85 (2/3H, dd, J 10.0 and 2.0 Hz, 1"-H), 3.78 (1/3H, dd, J 10.0 and 2.0 Hz, 1"-H), 3.74 (1H, m, 5-H), 3.45 (1H, m, 1"-H), 3.10-2.80 (2H, m, $1'H_2$), 2.60-

2.15 (2H, m, 2'H_2), 2.10-1.20 (7H, m), 1.12 (1H, d, J 6.4 Hz, 4-Me), 1.10 (2H, d, J 6.4 Hz, 4-Me), 1.05 (3H, s, ^{t}Bu), 1.02 (6H, s, ^{t}Bu), m/z 519 (M^+-^{t}Bu), 393 (M^+-^{t}Bu-PhSOH), 375 (M^+-^{t}Bu-PhSOH-H_20), 126 (PhSOH); (Found: M^+-^{t}Bu, 519.2030 $C_{30}H_{35}O_4SSi$ requires M, 519.2025).

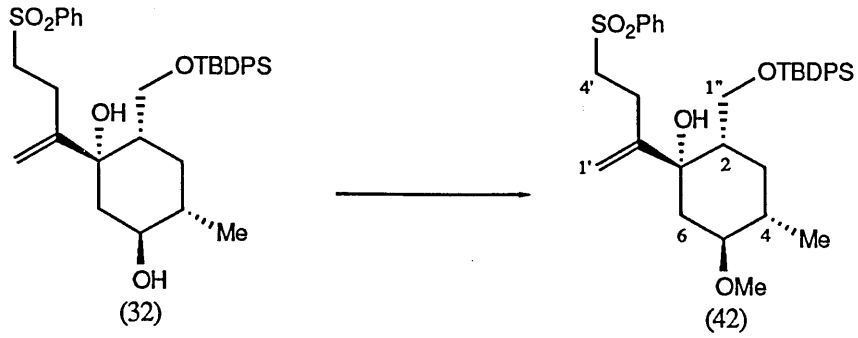
22. Preparation of (±)(1S,2S,4S,5S)-2-t-Butyldiphenylsilyloxymethyl-5-hydroxy-4-methyl-1-(4'-phenylsulphonylbut-1'-ene-2'-yl) cyclohexan-1-ol (32).



The sulphide (30) (6.79g, 12.2 mmol) was dissolved in DCM (400 ml) and saturated sodium hydrogencarbonate solution (200ml) added mCPBA (2.45g, 85%, 12.2 mmol) was added portionwise to the vigorously stirred two phase mixture. After 1h, the mixture was extracted with DCM and the extracts evapourated *in vacuo*, to yield the crude sulphoxides. These were taken up in methanol (500 ml) and an aqueous pH4 buffer solution (320 ml) added with good stirring. Oxone (7.4 g, 12.2 mol) was added portionwise over 10 min. After 5h, water was added and the mixture extracted with ether. The combined organic extracts were washed with saturated sodium hydrogencarbonate solution, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (ether) of the residue afforded the *sulphone* (32) (6.07 g

85%) as a white solid m.p. 131.5-132°C; ν_{max} (film), 3468, 2929, 1446, 1427, 1307, 1150, 1086, 1066 and 741 cm^{-1}; δ (500 MHz), 7.95-7.32 (15H, m, Ph), 5.32 (1H, s, 1'-Hb), 4.90 (1H, s, 1'-Ha), 4.38 (1H, br s, 1-OH), 3.80 (1H, d, J 11.2 Hz, 1"-H), 3.65 (1H, dt, J 4.0 and 10.0 Hz, 5-H), 3.45 (1H, d, J 11.2 Hz, 1"-H), 3.24 (2H, m, $4'H_2$), 2.44 (2H, m, $3'H_2$), 1.94 (1H, q, J 13.0 Hz, 3-H), 1.81 (1H, dd, J 13.0 and 4.0 Hz, 6-H), 1.62 (2H, m, 6-H and 5.0H), 1.39 (3H, m, 2-H, 3-H and 4-H), 1.10 (3H, d, J 7.5 Hz, 4-Me), 1.04 (9H, s, ^tBu); m/z 535 (M^+-^tBu), 517 (M^+-^tBu-H_20). (Found: M^+-^tBu, 535.1972 $C_{30}H_{35}O_5SSi$ requires 535.1974) (Found: C, 69.00; H, 7.55, $C_{30}H_{35}O_5SSi$ requires C, 68.88; H, 7.48%).

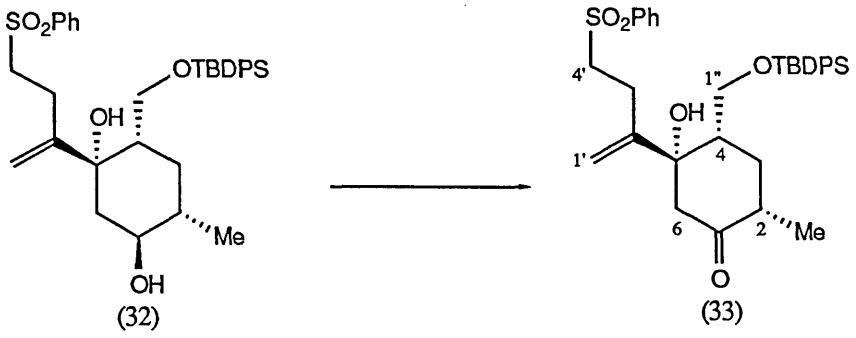
23. Preparation of (±)(1S,2S,4S,5S)-2-t-Butyldiphenylsilyloxymethyl-5-methoxy-4-methyl-1-(4'phenylsulphonyl-but-1'-ene-2'-yl)-cyclohexan-1-ol (42).



Trimethyloxonium tetrafluoroborate (11.8 mg, 0.0798 mmol) was added to a slurry of the alcohol (32) (45 mg, 0.076 mmol) and anhydrous potassium carbonate (106 mg 0.76 mmol) in DCM (5 ml), with stirring, under argon, at 0°C. The reaction

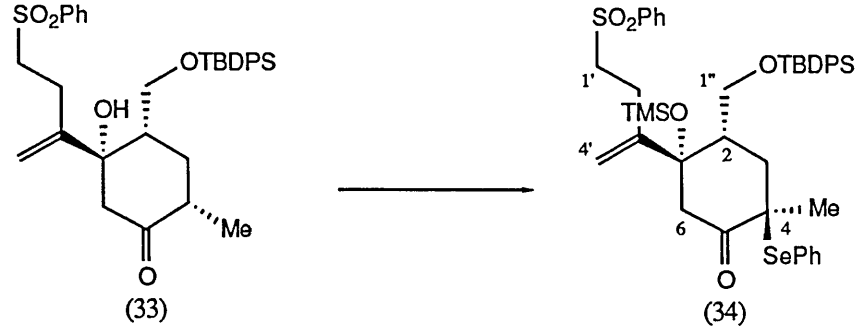
was allowed to warm to r.t. and after 16h was poured into water and extracted with DCM. The combined extracts were washed with saturated sodium hydrogencarbonate solution, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (40% ether-petrol) afforded the *methyl ether* (42) (39 mg, 85%) as a colourless oil; ν_{max} (film), 3471, 3069, 2929, 2858, 1587, 1427, and 798 cm^{-1}; δ (300 MHz), 7.90-7.30 (15H, m, Ph), 5.32 (1H, s, 1'-H), 4.88 (1H, s, 1'-H), 4.37 (1H, d, J 2.5 Hz, 1-OH), 3.79 (1H, dd, J 10.0 and 2.5 Hz, 1"-H), 3.43 (1H, dd, J 10.0 and 2.0 Hz, 1"-H), 3.36 (3H, s, 5-OMe), 3.25 (2H, m, 4'-H_2), 3.15 (1H, dt, J 4.0 and 8.5 Hz, 5-H), 2.42 (2H, m, 3'H_2), 1.95 (2H, m, 3-H and 6-H), 1.60 (1H, m, 2-H), 1.42 (2H, m, 3-H and 4-H), 1.20 (1H, ddd, J 12.0, 9.5 and 2.5 Hz, 6-H), 1.07 (3H, d, J 6.0 Hz, 4-Me) 1.01 (9H, s, ^tBu) m/z 549 M^+-^tBu (Found: M^+-^tBu, 549.2122 $C_{31}H_{37}O_5SSi$ requires M, 549.2131).

24. <u>Preparation of (±)(2S,4S,5S)-4-t-Butyldiphenylsilyloxymethyl-5-hydroxy-2-methyl-5-(4'-phenylsulphonyl-but-1'-ene-2'-yl)-cyclohexanone (33).</u>



DMSO (0.119 ml, 1.68 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.073 ml, 0.84 mmol) in DCM (5 ml), under argron at -65°C. After 5 min, the alcohol (32) (450 mg, 0.760 mmol), in DCM (10 ml) was added dropwise. After a further 20 min, triethylamine (0.410 ml, 2.94 mmol), was added. The mixture was allowed to warm to r.t. poured into water and extracted with ether. The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue afforded the *cyclohexanone* (33) (450 mg, 100%) as a white solid; ν_{max} (film), 3465, 2930, 2858, 1713, 1446, 1150, 1086 and 822 cm^{-1}; δ (250 MHz), 7.86 (2H, m, Ph), 7.70-7.40 (13H, m, Ph), 5.34 (1H, s, 1'-Hb), 4.90 (1H, s, 1'-Ha), 4.20 (1H, d, J 2.0 Hz, 5-OH), 3.85 (1H, dd, J 10.5 and 2.5 Hz, 1"-H), 3.53 (1H, dd, J 10.5 and 1.0 Hz, 1"-H), 3.20 (2H, m, 4'-H_2), 2.45 (3H, m, 3'-H_2 and 6-H), 2.22 (1H, q, J 12.0 Hz, 3-H), 2.21 (1H, d, J 12.0 Hz, 6-H), 2.09 (1H, dq, J 12.0 and 1.0 Hz, 4-H), 1.78 (1H, ddd, J 12.0, 5.5 and 3.0 Hz, 3-H), 1.09 (3H, d, J 6.0 Hz, 2-Me), 0.98 (9H, s, ^{t}Bu), m/z 533 (M^{+}-^{t}Bu), 515 (M^{+}-^{t}Bu-H_20). (Found: M^{+}-^{t}Bu, 533.1827 $C_{30}H_{33}O_5SSi$ requires M, 533.1818). (Found: C, 69.41; H, 7.23 $C_{33}H_{42}O_5SSi$ requires C, 69.12; H, 7.16%).

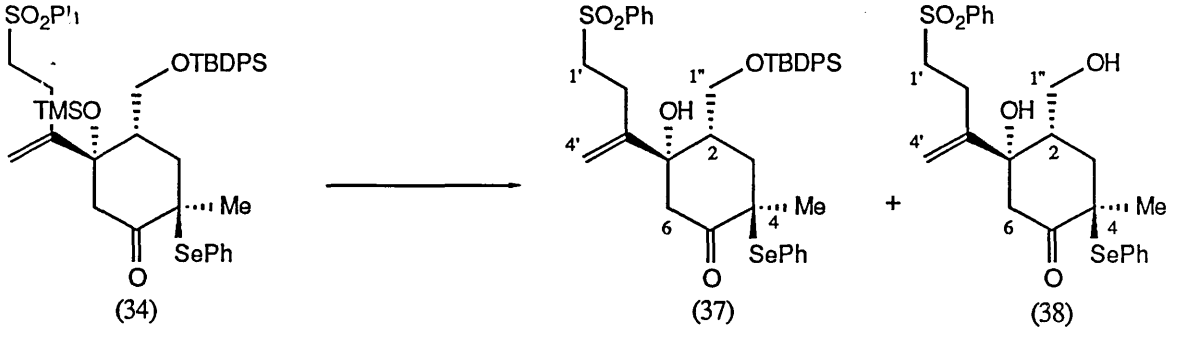
25. Preparation of (±)(2R,4S,5S)-2-Benzeneselenenyl-4-t-Butyldiphenyl-silyloxymethyl-2-methyl-5-(4'-phenylsulphonyl-but-1'-ene-2'-yl)-5-trimethylsilyloxycyclohexanone (34).



Trimethylsilyltriflate (0.052 ml, 0.271 mmol) was added dropwise to a stirred solution of the ketone (33) (32 mg, 0.271 mmol) and triethylamine (0.076 ml 0.542 mmol), in ether (5 ml), under argon, at 0°C. The reaction was allowed to warm to r.t. and after 2h, was cooled to -78°C. Benzeneselenenyl chloride (200 mg, 1.04 mmol) in DCM (5 ml) was added, followed by saturated sodium hydrogencarbonate solution (10 ml) and the mixture allowed to warm to r.t.; whereupon water was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (35% ether-petrol) of the residue afforded the *selenenyl ketone* (34) (43 mg 97%) as a clear oil; ν_{max} (film) 3068, 2955, 2855, 1695, 1426, 1152, 1112 and 843 cm^{-1}; δ (400 MHz), 7.90 (2H, m, Ph), 7.70-7.20 (18H, m, Ph), 5.20 (1H, s, 1'-Hb)4.71 (1H, s, 1'-Ha), 3.60 (1H, d, J 15.0 Hz, 6-H), 3.57 (1H, dd, J 10.0 and 4.0 Hz, 1"-H), 3.33 (1H, t, J 10.0 Hz, 1"-H), 3.15 (2H, m, 4'-H_2), 2.53 (1H, dd, J 14.0 and 3.0 Hz, 3-H), 2.39 (1H, m, 4-

H), 2.31 (2H, m, 3'-H_2), 2.26 (1H, d, J 15.0 Hz, 6-H), 1.93 (1H, dd, J, 14.0 and 12.0 Hz, 3-H), 1.40 (3H, s, 2-Me), 1.10 (9H, s, ^tBu), -0.02 (9H, s, $SiMe_3$), m/z 761 (M^+-^tBu) 605 (M^+-^tBu-PhSe), 515 (M^+-^tBu-PhSe-TMSOH), (Found: M^+-^tBu, 761.1707. $C_{39}H_{45}O_5SSeSi_2$ requires M, 761.1691).

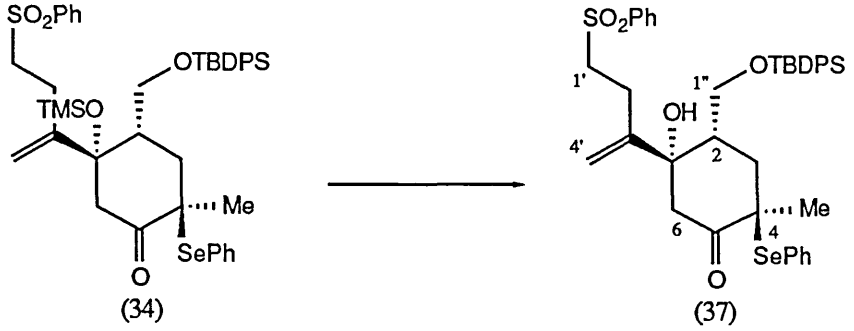
26. Preparation of (±)(2R,4S,5S)-2-Benzeneselenenyl-4-t-Butyldiphenyl-silyloxymethyl-5-hydroxy-2-methyl-5-(4'-phenylsulphonyl-but-1'-ene-2'-yl) cyclohexanone (37) and (2R,4S,5S)-2-Benzeneselenenyl-5-hydroxy-4-hydroxy-methyl-2-methyl-5-(4'-phenylsulphonyl-but-1'-ene-2'-yl) cyclohexanone (38).



Hydrofluoric acid (0.25 ml of a 40% solution in water, 5 mmol) was added dropwise to a stirred solution of the trimethylsilyl ether (34) (55 mg 67.2 mmol) in acetonitrile (5 ml) at 0°C. After 90 min, the solution was poured into water and extracted with ether. The organic extracts were washed with saturated sodium hydrogencarbonate, then brine and dried ($MgSO_4$). The solvent was evaporated *in*

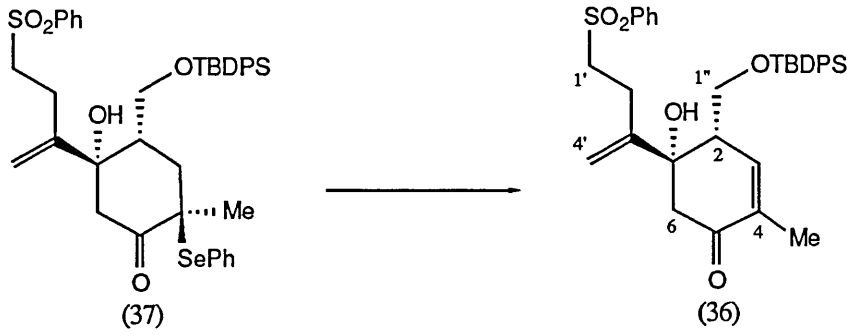
vacuo. Column chromatography (60%-100% ether-petrol) afforded the *alcohols* (37) (15 mg, 30%) and (38) (22 mg, 65 %) both as colourless oils. Less polar (37); ν_{max} (film), 3458, 3068, 2926, 2855, 1697, 1587, 1306, 1112 and 941 cm^{-1}; δ (300 MHz), 7.95-7.80 (2H, m, Ph), 7.70-7.20 (18H, m, Ph), 5.38 (1H, s, 1'-Hb), 4.98 (1H, s, 1'-Ha), 4.18 (1H, d, J 2.0 Hz, 5-OH), 3.89 (1H, dd, J 9.0 and 2.0 Hz, 1'-H), 3.53 (1H, dd, J 9.0 and 1.5 Hz, 1"-H), 3.45 (1H, dd, J 10.5 and 2.0 Hz, 3-H), 3.25 (2H, m, 4'-H_2), 2.72 (1H, dd, J 10.5 and 9.0 Hz, 3-H), 2.51 (2H, m, 3'-H_2), 2.42 (1H, dq, J 9.0 and 2.0 Hz, 4-H), 2.14 (1H, d, J 12.0 Hz, 6-H), 1.88 (1H, dd, J 12.0 and 2.0 Hz), 1.01 (9H, s, ^tBu); m/z 671 (M^+-^tBu-H_20), 515 (M^+-^tBu-H_20-PhSe), (Found: M^+-^tBu-H_20, 671.1166. $C_{36}H_{35}O_4SSeSi$ requires M, 671.1191). More polar (38); ν_{max} 3447, 2922, 1695, 1444, 1149, 1032 and 742 cm^{-1}; δ (300 MHz), 7.95-7.80 (2H, m, Ph), 7.70-7.20 (8H, m, Ph), 5.30 (1H, s, 1'-Hb), 5.04 (1H, s, 1'-Ha), 4.02 (1H, dd, J 10.5 and 2.5 Hz, 1"-H), 3.67 (1H, dd, J 10.5 and 2.0 Hz, 1"-H), 3.63 (1H, s, 5-OH), 3.57 (1H, d, J 15.5 Hz, 3-H), 3.43 (1H, ddd, J 14.0, 10.5 and 6.0 Hz, 4'-H), 3.27 (1H, ddd, J 14.0, 10.0 and 5.5 Hz, 4'-H), 2.73-2.55 (3H, m, 3'-H_2 and 3-H), 2.47 (1H, dq, J 13.5 and 4.0 Hz, 4-H), 2.16 (1H, d, J 14.5 Hz, 6-H), 2.07 (1H, dd, J 14.5 and 3.5 Hz, 6-H), 1.40 (3H, s, 2-Me), m/z 508 (M^+), 490 (M^+-H_20), 472 (M^+-$2H_20$), 368 (MH^+-$PhSO_2$), 333 (M^+-$PhSO_2$-$2H_20$), (Found: M^+, 508.0833 $C_{24}H_{28}O_5SSe$ requires M, 508.0823).

27. Preparation of (±)(2R, 4S, 5S) -2-Benzeneselenenyl-4-t-Butyldiphenyl-silyloxymethyl-5-hydroxy-2-methyl-5-(4'phenylsulphonylbut-1'-ene-2-yl) cyclohexanone (37).



Trifluoroacetic acid (0.75 ml, 9.74 mmol) was added dropwise to a stirred solution of the trimethylsilylether (34) (500 mg, 0.611 mmol) in DCM (50 ml), at 0°C. After 3h, the reaction was poured into saturated sodium hydrogencarbonate solution and extracted with DCM. The organic extracts were combined, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Column chromatography (60%) ether-petrol) of the residue afforded the *alcohol* (37) (407 mg 90%) identical in all respects to previous prepared material.

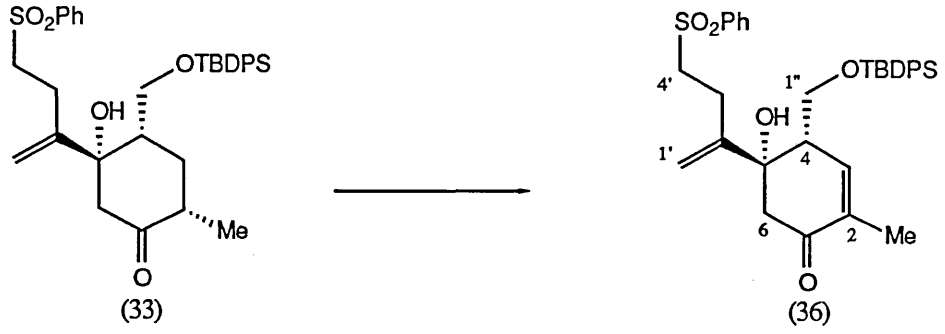
28. Preparation of (±) (4S,5S) 4-t-Butyldiphenylsilyloxymethyl-5-hydroxy-2-methyl-5-(4'-phenylsulphonylbut-1'-ene-2'-yl) cyclohex-2-eneone (36).



Saturated sodium hydrogencarbonate solution (100 ml) was added to a stirred soluiton of the selenide (37) (3.0 g, 4.03 mmol) in DCM (250 ml) at 5°C. mCPBA (1.73 g, 80%, 8.06 mmol) was added portionwise until t.l.c indicated consumption of the starting material. Dilute sodium sulphite solution was added and the mixture extracted with DCM. The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue afforded the *enone* (36) (2.2 g 94%) as a white foam; ν_{max} (film), 3458, 2926, 1675, 1307, 1150, 1113, and 703 cm^{-1}; δ (250 MHz), 7.90 (2H, m, Ph), 7.70-7.30 (13H, m, Ph), 6.27 (1H, m, 3-H), 5.30 (1H, s, 1'-Hb), 4.98 (1H, s, 1'-Ha), 4.02 (1H, dd, J 10.5 and 3.0 Hz, 1"-H), 3.77 (1H, dd, J 10.5 and 3.5 Hz, 1"-H), 3.28 (2H, m, 4'-H_2), 2.73 (1H, m, 4-H), 2.58 (1H, d, J 16.0 Hz, 6-H), 2.50 (2H, m, 3'-H_2), 2.47

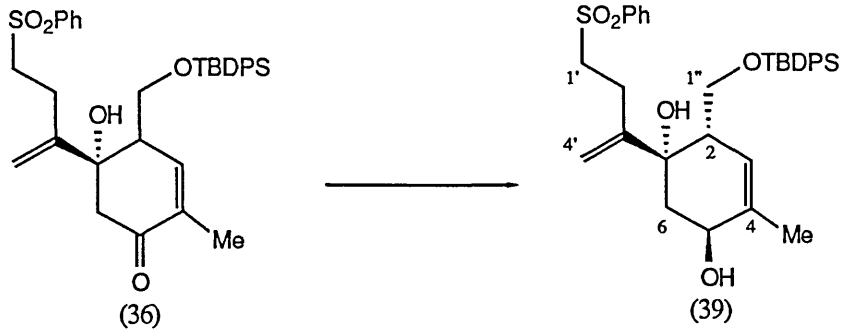
(1H, d, J 16.0 Hz, 6-H), 1.83 (3H, m, 2-Me), 1.05 (9H, s, ^{t}Bu); m/z 531 (M^{+}-^{t}Bu), 513 (M^{+}-^{t}Bu-H_2O). (Found: M^{+}-^{t}Bu, 531.1655 $C_{30}H_{31}O_5SSi$ requires 531.1661). (Found: C, 69.47; H, 6.92, $C_{34}H_{40}O_5SSi$ requires C, 69.35; H, 6.85%).

29. Preparation of (±) (4S,5S)-4-t-Butyldiphenylsilyloxymethyl-5-hydroxy-2-methyl-5-(4'-phenylsulphonylbut-1-ene-2'-yl) cyclohex-2-enone (36).



Benzeneselenenyl chloride (7.85 mg, 0.041 mmol) was added to a solution of the ketone (33) (22 mg, 0.0373 mmol) in ethylacetate (0.5 ml) at r.t. The orange solution paled over a period of 3h and saturated sodium hydrogencarbonate solution (0.5 ml) was added. mCPBA (12.8 mg, 0.0746 mmol) was added portionwise until t.l.c indicated the consumption of the selenide. Dilute sodium sulphite solution was added and the mixture extracted with DCM. The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue, afforded the *enone* (36) (21 mg, 96%), identical in all respects to previously prepared material.

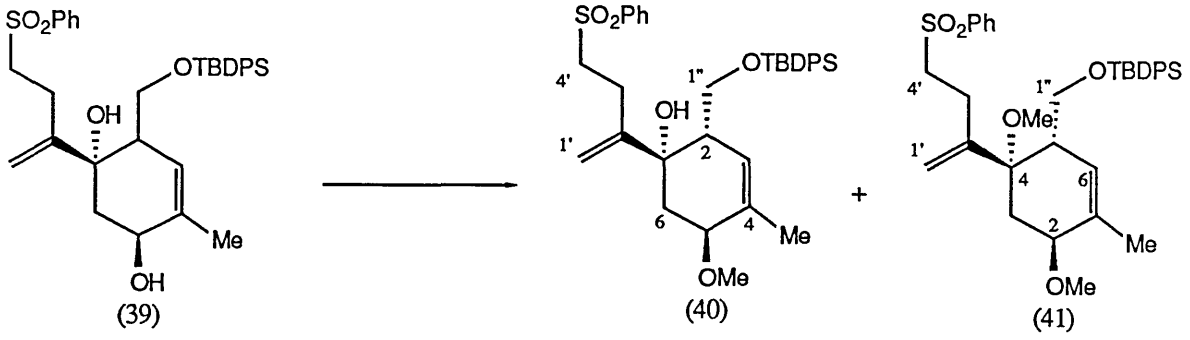
30. Preparation of (±) (1S,2S,5S)-2-t-Butyldiphenylsilyloxymethyl-5-hydroxy-4-methyl-1-(4'-phenylsulphoneylbut-1'-ene-2'-yl) cyclohex-3-en-1-ol (39).



Sodium borohydride (250 mg, 6.60 mmol) was added portionwise to glacial acetic acid (12.5 ml) at 5°C with stirring. After 10 min, evolution of hydrogen ceased whereupon the enone (36) (500 mg, 0.849 mmol) was added. After 10 min, toluene (50 ml) was added and the solvent evaporated *in vacuo* to yield a white solid. The solid was taken up in DCM and washed with saturated sodium hydrogencarbonate solution. The organic exctract was dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (80% ether-petrol) of the residue afforded the *allylic alcohol* (39) (462 mg, 92%); as a white solid; ν_{max} (film), 3456, 2929, 1636, 1306, 1149, 1112, and 910 cm^{-1}; δ (250 MHz), 7.90 (2H, m, Ph), 7.70-7.30 (13H, m, Ph), 5.30 (1H, s, 1'-Hb), 5.15 (1H, m, 3-H), 4.92 (1H, s, 1'-Ha), 4.67 (1H, d, J 1.5 Hz, 1-OH), 4.42 (1H, m, 5-H), 3.87 (1H, dd, J 10.5 and 2.5 Hz, 1"-H), 3.57 (1H, dd, J 10.5 and 3.0 Hz, 1"-H), 3.28 (2H, m, 4'-H_2), 2.46 (2H, m, 3'-H_2), 2.35 (1H, m, 2-H), 2.05 (1H, dd, J 12.5 and 6.0 Hz, 6-H), 1.83 (3H, s, 4-Me), 1.56 (1H, ddd, J 12.5 , 9.0 and 1.5 Hz, 6-H), 1.37 (1H, d, J 7.0 Hz, 5-OH), 1.03 (9H, s, ^tBu). m/z

572 (M^+-H_2O), 533 (M^+-^tBu), 515 (M^+-^tBu-H_2O), 497 (M^+-^tBu-$2H_2O$), 373 (M^+-^tBu-H_2O-$PhSO_2H$), (Found: C, 69.27; H, 7.28, $C_{34}H_{42}O_5SSi$ requires, C, 69.10; H, 7.16%).

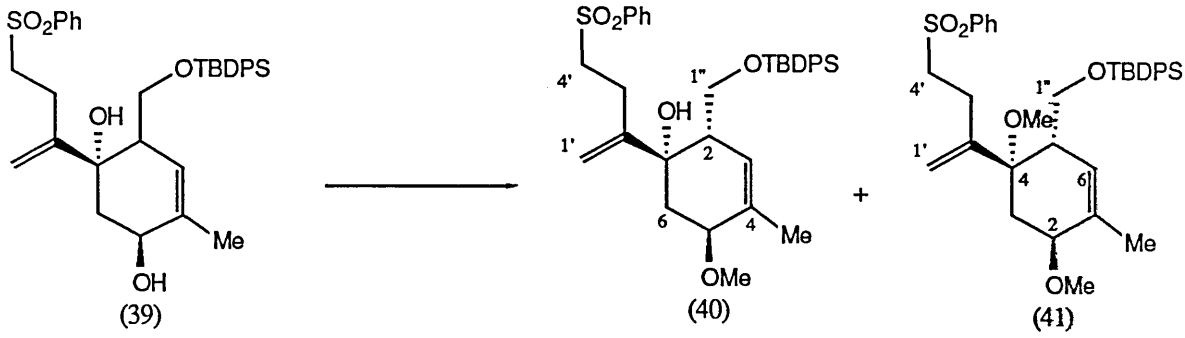
31. Preparation of (±)(2S,4S,5S)-5-t-Butyldiphenylsilyloxymethyl-1-methyl-2,5-methoxy-5-(4'-phenylsulphonylbut-1'-ene-2'-yl) cyclohexene (41) and (±)(1S,2S,5S)-2-t-Butyldiphenylsilyloxymethyl-4-methyl-5-methoxy-1-(4'-phenylsulphonylbut-1'-ene-2'-yl) cyclohex-3-ene-1-ol (40).



The alcohol (39) (700 mg, 1.18 mmol) in DCM (5 ml) was added to a stirred solution of diazomethane (1.61 g, 38.2 mmol) in DCM (10 ml) at -78°C. After 5 min, hydrogen tetrafluoroborate - diethyl ether complex (5.0 mg, 0.030 mmol) was added and the yellow solution allowed to warm to r.t. After the solution had decolourised, saturated sodium hydrogencarbonate (5 ml) was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (50% ether-petrol) afforded the *methyl ethers* (41) (8 mg, 1%) and (40) (660 mg, 94%) both as white foams. less polar: (41) ν_{max} (film), 3069,

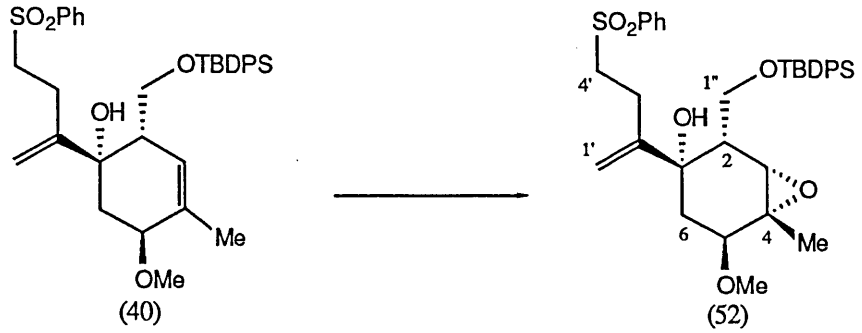
2934, 2891, 1637, 1588, 1447, 1152 and 704 cm^{-1}; δ (250 MHz), 7.90 (2H, m, Ph), 7.70-7.30 (13H, m, Ph), 5.76 (1H, m, 6-H), 4.85 (1H, s, 1'-H), 4.78 (1H, s, 1'-H), 3.70 (1H, dd, J 9.5 and 4.0 Hz, 1"-H), 3.58 (1H, m, 2-H), 3.53 (1H, t, J 9.5 Hz, 1"-H), 3.23 (3H, s, OMe), 3.14 (2H, m, 4'-H_2), 2.88 (3H, s, OMe), 2.40 (1H, m, 5-H), 2.27 (2H, m, 2'-H_2), 2.08 (1H, dd, J 13.5 and 5.5 Hz, 3-H), 1.83 (1H, dd, J 13.5 and 6.0 Hz, 3-H),1.74 (3H, s, 1-Me), 1.00 (9H, s, ^tBu), m/z 587 (MH^+-MeOH), 561 (M^+-^tBu), 529 (M^+-^tBu-MeOH); More polar: (40), ν_{max} (film), 3466, 3070, 2931, 2858, 1636, 1588, 1308, 1151, 1030 and 741 cm^{-1}; δ (250 MHz), 7.90 (2H, m, Ph), 7.70-7.30 (13H, m, Ph), 5.30 (1H, s, 1'-Hb), 5.16 (1H, m, 3-H), 4.91 (1H, s, 1'-Ha), 4.72 (1H, d, J 1.5 Hz, 1-OH), 4.02 (1H, m, 5-H), 3.87 (1H, dd, J 10.0 and 2.5 Hz, 1"-H), 3.55 (1H, dd, J 10.0 and 3.0 Hz, 1"-H), 3.34 (3H, s, 5-OMe), 3.27 (2H, m, 4'-H_2), 2.44 (2H, m, 3'-H_2), 2.30 (1H, m, 2-H), 2.08 (1H, dd J 12.5 and 6.0 Hz, 6-H), 1.78 (3H, s, 4-Me), 1.57 (1H, ddd, J 12.5, 9.5 and 1.5 Hz, 6-H), 0.98 (9H, s, ^tBu); m/z 589 (M^+-H_20), 547 (M^+-^tBu), 529 (M^+-^tBu-H_20), 497 (M^+-^tBu-H_20-MeOH), (Found. C 69.62; H, 7.58, $C_{35}H_{44}O_5SSi$ requires C, 69.50; H, 7.33%).

32. Preparation of (±) (2S,4S,5S)-5-t-Butyldiphenylsilyloxymethyl-1-methyl-2,5-methoxy-5-(4'-phenylsulphonylbut-1'-ene-2'-yl)cyclohexene (41), and (±) (1S,2S,5S)-2-t-Butyldiphenylsilyloxymethyl-4-methyl-5-methoxy-1-(4'phenylsulphonylbut-1'-ene-2'-yl)cyclohex-3-ene-1-ol (40).



The allylic alcohol (39), (100 mg, 0.169 mmol) in THF (1 ml) was added dropwise ot a stirred slurry of sodium hydride (8.2 mg, 0.339 mmol) in THF (2 ml), under argon, at 0°C. After 15 min, DMPU (0.050 ml, 0.406 mmol) was added and after a further 15 min, methyliodide (0.063 ml, 1.02 mmol), was added. The reaction was allowed to warm to r.t. and stirring continued. After 16h, saturated ammonium chloride (1 ml) was added and the mixture extracted with ether. Each extract was washed with water, brine, combined and evaporated *in vacuo*. Column chromatography (50-75% ether-petrol) of the residue afforded the *methyl ethers* (41) (16 mg 15%), (40) , (46 mg, 45%), and the starting alcohol (39), (7 mg, 7%) all identical in all respects to previously prepared material.

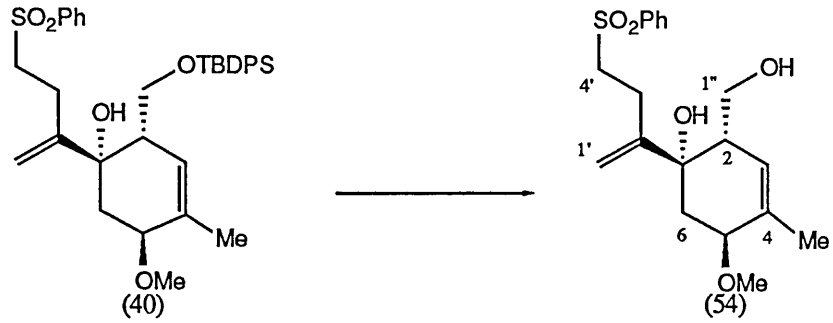
33. Preparation of (±)(1S, 2S,3S,4R,5S) 2-t-Butyldiphenylsilyloxymethyl-3,4-epoxy-4-methyl-5-methoxy-1-(4'-phenylsulphonylbut-1'-ene-2'-yl) cyclohexan-1-ol (52).



Vanadyl acetylacetonate (1.0 mg, 7.5 μmol) was added to a solution of the diene (40) (56 mg, 0.093 mmol), in toluene (2 ml) under argon, at 0°C. After 15 min, ^{t}Butylhydrogen- peroxide (0.052 ml of a 3.5M solution in toluene, 0.185 mmol), was added dropwise. The reaction was allowed to warm to r.t. and after 4h, was poured into diluted sodium sulphite solution and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (40% ether-petrol) afforded the *epoxide* (52) (38 mg 66%), as a clear oil; ν_{max} (film) 3461, 3069, 2931, 1639, 1588, 1151, 1041 and 823 cm^{-1}; δ (270 MHz), 7.94 (2H, m, Ph), 7.75-7.30 (13H, m, Ph), 4.82 (1H, s, 1'-H), 4.66 (1H, s, 1'-H), 3.79 (1H, t, J 10.0 Hz, 1"-H), 3.68 (1H, dd, J 10.0 and 4.0 Hz, 1"-H), 3.65-3.58 (2H, m, 3-H and 5-H), 3.41 (1H, s, 1-OH), 3.38 (3H, s, 5-OMe), 3.10 (2H, m, 4'-H_2), 2.34 (2H, m, 3'-H_2), 2.23 (1H, br dd, J 9.6 and 4.0 Hz, 2-H), 2.09 (1H, dd, J 14.0 and 7.2 Hz, 6-H), 1.45 (3H, s, 4-Me), 1.32 (1H, dd, J 14.0

and 10.0 Hz, 6-H), 1.01 (9H, s, ^{t}Bu); m/z 602 (M^{+}-H_2O), 563 (M^{+}-^{t}Bu), 545 (M^{+}-^{t}Bu-H_2O),. (Found: M^{+}-^{t}Bu, 563.1921 $C_{31}H_{35}O_6SSi$ requires 563.1924). (Found: C, 67.50 ; H, 7.24, $C_{35}H_{44}O_6SSi$ requires C, 67.71; H, 7.14%).

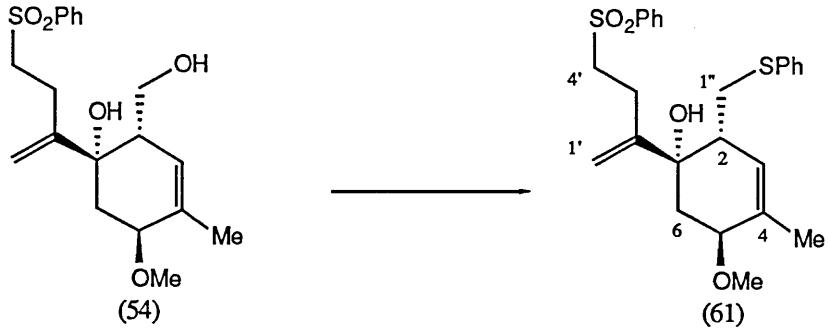
34. Preparation of (±)(1S,2S,5S) -2-Hydroxymethyl-4-methyl-5-methoxy-1-(4'-phenylsulphonylbut-1'-ene-2-yl) cyclohex-3-ene-1-ol (54).



Tetrabutylammonium fluoride (0.182 ml of a 1M solution in THF, 0.182 mmol) was added dropwise to a solution of the silyl ether (40) (100 mg 0.165 mmol), in THF (3 ml), under argon at 0°C. After 30 min, the solvent was evaporated *in vacuo*. Column chromatography (ether) of the residue afforded the *diol* (54) (49 mg, 81%) as a white solid, m.p. 128-130°C; ν_{max} (film), 3390, 2927, 1447, 1307, 1149 and 861 cm^{-1}; δ (500 MHz), 7.92 (2H, dd, J 6.3 and 0.8 Hz, Ph), 7.67 (1H, t, J 7.4 Hz, Ph), 7.58 (2H, t, J 8.1 Hz, Ph), 5.34 (1H, q, J 1.5 Hz, 3-H), 5.27 (1H, s, 1'-H), 4.93 (1H, s, 1'-H), 3.97 (1H, m, 5-H), 3.84 (1H, dd, J 11.05 and 2.7 Hz, 1"-H), 3.71 (1H, dd, J 11.05 and 4.9 Hz, 1"-H), 3.69 (1H, d, J 1.0 Hz, 1-OH), 3.34

(3H, s, 5-OMe), 3.31 (2H, m, 4'-H_2), 2.50 (2H, m, 3'-H_2), 2.42 (1H,m, 2-H), 2.07 (1H, dd, J 9.8 and 5.9 Hz, 6-H), 2.06 (1H, m, 1"-OH), 1.81 (3H, t, J 1.1 Hz, 4-Me), 1.66 (1H, ddd, J 12.8, 9.5 and 1.0 Hz, 6-H), m/z; 366 (M^+), 348 (M^+-H_20), 335 (M^+-OMe), 330 (M^+-$2H_20$), 142 ($PhSO_2H$), (Found: C, 62.24; H, 7.15, $C_{19}H_{26}O_5SSi$, requires C, 62.27 ; H, 7.15%).

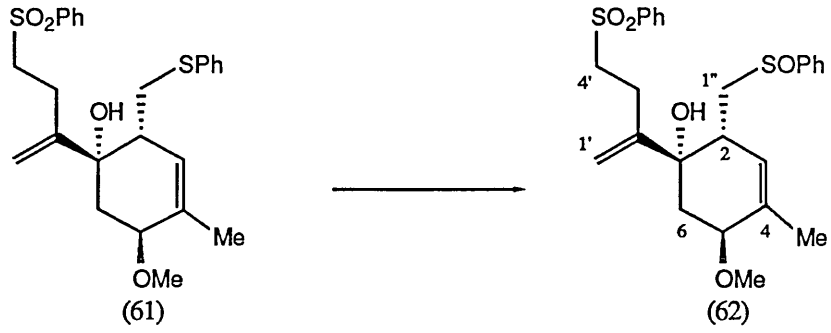
35. Preparation of (±) (1S, 2R, 5S)-4-methyl-5-methoxy-1-(4'-phenylsulphonylbut-1'-ene-2'-yl)-2-phenylthiomethylcyclohex-3-ene-1-ol (61).



The alcohol (54) (92 mg, 0.251 mmol), in THF (4 ml) was added dropwise to a solution of diphenyldisulphide (275 mg, 1.255 mmol), and tri-n-butyl-phosphine (0.315 ml, 1.255 mmol) in THF (1 ml), under argon, at r.t. After 16h, water (5 ml) was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) of the residue afforded the sulphide (61) (113 mg, 98%) as a clear oil; ν_{max} (film),

3502, 1642, 1583, 1446, 1307, 1150, 1057 and 742 cm^{-1}; δ (250 MHz), 7.90 (2H, m, Ph), 7.75-7.50 (3H, m, Ph), 7.35-7.15 (5H, m, SPh), 5.62 (1H, d, J 1.5 Hz, 3-H), 5.08 (1H, s, 1'-H), 4.85 (1H, s, 1'-H), 3.87 (1H, br t, J 12.1 Hz, 1"-H), 3.32 (3H, s, 5-OMe), 3.25 (2H, m, 4'-H_2), 3.06 (1H, dd, J 12.1 and 1.3 Hz, 1"-H), 2.65-2.30 (5H, m), 2.13 (1H, dd, J 13.4 and 6.3 Hz, 6-H), 1.79 (3H, s, 4-Me), 1.64 (1H, dd, J 13.4 and 9.7 Hz, 6-H), m/z 458 (M^+), 440 (M^+-H_20), 349 (M^+-SPh), 317 (M^+-SPh-MeOH), (Found: M^+, 458.1590 $C_{25}H_{30}0_4S_2$ requires M, 458.1586). (Found: C 65.18; H, 6.70 $C_{25}H_{30}0_4S_2$ requires C, 65.47; H, 6.59%).

36. Preparation of (±) (1S, 2R, 5S)-4-methyl-5-methoxy-(4'-phenylsulphonylbut-1'-ene-2'-yl)-2-phenylsulphinylmethylcyclohex-3-ene-1-ol (62).

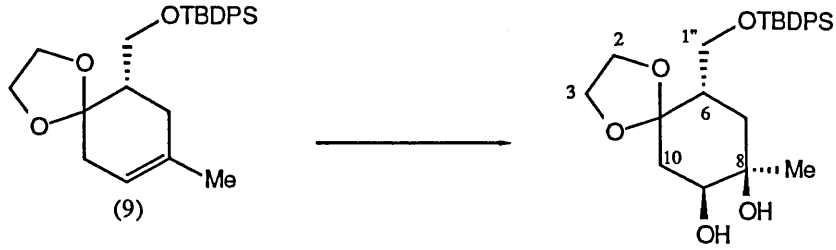


(61) (62)

The sulphide (86 mg, 0.188 mmol) was dissolved in DCM (5 ml) and saturated sodium hydrogencarbonate solution (2 ml) added. mCPBA (32 mg, 90%, 0.188 mol) was added portionwise to the vigorously stirred two-phase mixture. After 20 min, saturated sodium sulphite 0.5 ml was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column

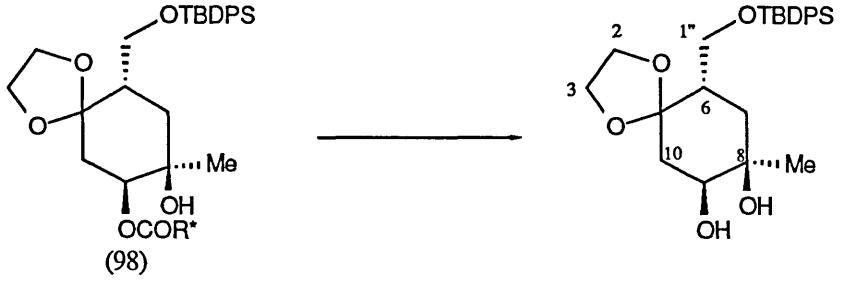
chromatography (50% DCM- ethylacetate) of the residue afforded the sulphoxides (62) (85 mg, 96%), ν_{max} (film) 3338, 2923, 1639, 1584, 1307, 1150, 1087, and 1020 cm^{-1}; less polar: δ (250 MHz), 8.0-7.9 (2H, m, Ph), 7.70-7.40 (8H, m, Ph), 5.53 (1H, br s, 3-H), 5.28 (1H, s, 1'-H), 4.92 (1H, s, 1'-H), 3.86 (1H, br t, J 8.0 Hz, 5-H), 3.45-3.20 (2H, m, 4'-H_2), 3.35 (3H, s, 5- OMe), 3.05 (1H, br d, J 8.9 Hz, 2-H), 2.82 (1H, dd, J 13.7 and 3.5 Hz 1"-H), 2.60 (1H, dd, J 13.7 and 10.0 Hz, 1"-H), 2.43 (2H, m, 3'H_2), 2.23 (1H, s, 1-OH), 2.10 (1H, dd, J 13.8 and 6.0 Hz, 6-H), 1.80 (3H, s, 4-Me), 1.75 (1H, dd, J 13.8 and 9.0 Hz, 6-H), more polar: δ (250 MHz), 8.00-7.90 (2H, m, Ph), 7.75-7.40 (8H, m, Ph), 5.34 (2H, d, J 1.0 Hz, 3-H), 5.19 (1H, s, 1'-H), 4.93 (1H, s, 1'-H), 4.00 (1H, s, 0H), 3.95 (1H, m, 5-H), 3.35 (3H, s, 5-OMe), 3.29 (2H, m, 4'-H_2), 3.00 (1H, m, 2-H), 2.87 (1H, s, 1"-H), 2.85 (1H, d, J 2.0 Hz, 1"-H), 2.65 (2H, m, 3'-H_2), 2.12 (1H, dd, J 12.8 and 5.8 Hz, 6-H), 1.80 (3H, s, 4-Me), 1.69 (1H, ddd, J 12.8, 9.1 and 0.8 Hz, 6-H), m/z 348 (M^+-PhSOH), 33O (M^+-PhSOH-H_20), (Found: M^+-PhSOH-H_20, 330.1281 $C_{19}H_{22}O_3S$ requires M, 330.1290), (Found: C, 63.39; H, 6.46 $C_{25}H_{30}O_5S_2$ requires C, 63.27; H, 6.37%).

37. Preparation of (±)(6S,8R,9S)-6-t-Butyldiphenylsilyloxymethyl-8,9-hydroxy-8-methyl-1,4-dioxaspiro-[4.5]-decane .



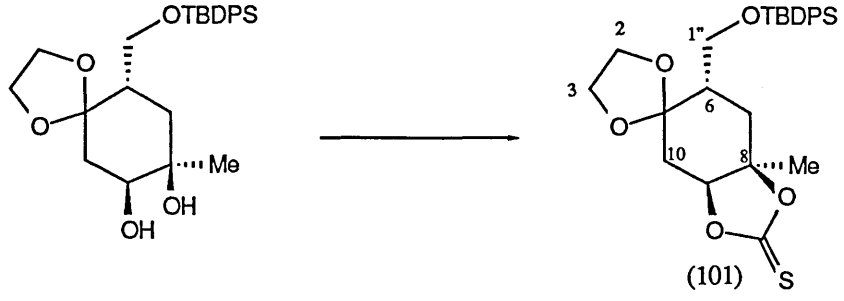
Osmium tetroxide (5 mg, 0.02 mmol) was added to a solution on N-methylmorpholine-N-oxide (80 mg, 0.68 mmol) and the alkene (9) (250 mg, 0.592 mmol) in 10:3:1 t-butanol-THF-water (5 ml), under argon, at r.t. After 1h, a slurry of dilute aqueous sodium sulphite solution and talc was added and after 15 min, the fixture filtered. The filtrate was extracted with ether and each extract washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (ether) of the residue afforded the diol (184 mg, 68%), as a foam, ν_{max} (film) 3431, 3071, and 2933 cm^{-1}; δ (250 MHz), 7.64 (4H, m, Ph), 7.37 (6H, m, Ph), 3.94-3.40 (7H, m, 1'-H_2, 2-H_2, 3-H_2 and 9-H), 2.33 (1H, m, 6-H), 2.16 (1H, m, 10-H), 1.94-1.60 (4H, m), 1.42 (1H, m, 7-H), 1.30 (3H, s, 8-Me), 1.04 (9H, s, ^tBu), m/z 441 (M^+-Me), and 399 (M^+-^tBu), (Found: C, 68.14; H, 8.22. $C_{26}H_{36}O_5Si$ requires C, 68.37; H, 7.96%).

38. Prepartion of (+) (6S, 8R, 9S)-6-t-Butyldiphenylsilyloxymethyl-8,9-hydroxy-8-methyl-1,4-dioxaspiro-[4.5]-decane .



The ester (98) (300 mg, 0.471 mmol) in methanol (2 ml), was added to a slurry of anhydrous potassium carbonate (340 mg, 2.36 mmol) in methanol (15 ml), at r.t. After 2h, the mixture was filtered and the filtrate diluted with ether and acetic acid (0.5 ml) added. The mixture was extracted with ether, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (70% ether-petrol) of the residue afforded the *diol* (214 mg, 100%) as an oil $[\alpha]^{25}_D$ + 13.3 (c 2.2, $CHCl_3$); spectral data identical to previously prepared racemic material.

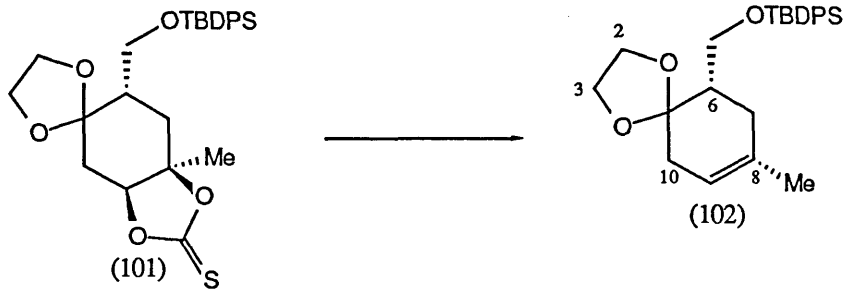
39. <u>Preparation of (+) (6S, 8R, 9S) -6-t-Butyldiphenylsilyloxymethyl-8-methyl-8,9-O-(thiocarbonyl)-1,4-dioxaspiro-[4.5]-decane (101).</u>



Thiocarbonyl diimidazole (110 mg, 0.605 mmol), was added to a solution of

the diol (100 mg, 0.220 mmol), in acetone (10 ml), under argon and the mixture heated to reflux. After 24h the mixture was evaporated *in vacuo*. Column chromatography (50% ether-petrol) of the residue afforded the *thiocarbonate* (101) (104 mg, 97%) as a colourless oil, $[\alpha]^{25}_D$ = + 7.1° (c 2.1 $CHCl_3$): ν_{max} (film), 3134, 3070, 3049, 2958, 2857, 1307, and 712 cm^{-1}; δ (250 MHz), 7.62-7.38 (10H, m, Ph), 4.58 (1H, dd, J 8.8 and 7.0 Hz, 9-H), 3.91-3.65 (5H, m, 2-H_2, 3-H_2 and 1'-H), 3.44 (1H, dd, J 10.0 and 8.8 Hz, 1'-H), 2.67 (1H, dd, J 16.5 and 4.5 Hz, 10-H), 2.22 (2H, m), 1.70 (2H, m), 1.50 (3H, s, 8-Me), 1.01 (9H, s, ^tBu), m/z 499 (MH^+), 441 (M^+-^tBu), 397 (M^+-^tBu-C_2H_4O), 199 (Ph_2SiOH). (Found: M^+-^tBu, 441.1184 $C_{22}H_{25}O_5SSi$ requires M, 441.1191).

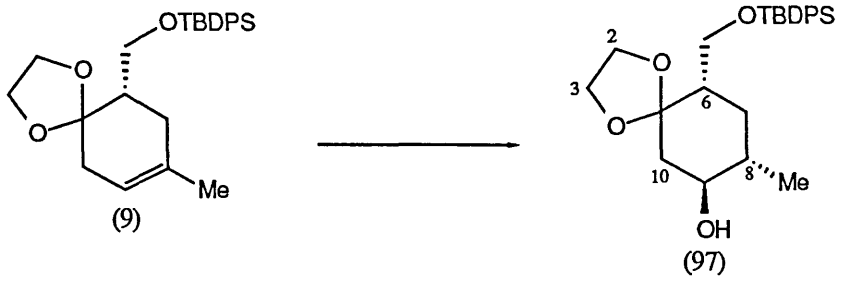
40. Preparation of (+) 6(S)-6-t-Butyldiphenylsilyloxymethyl-8-methyl-1,4-dioxaspiro-[4.5]-dec-8-ene (102).



The thiocarbonate (101) (105 mg, 0.21 mmol), in THF (2.0 ml), was added to a slurry of activated Raney nickel (250 mg, 4.35 mmol) in THF (20 ml) under argon. The mixture was heated to reflux. After 16h, the solution was decanted away from the residual solids. The solids were washed with ether and the combined organic extracts

were evaporated *in vacuo*. Column chromatography (6% ether-petrol) afforded the *alkene* (102) (35 mg, 40%) as a colourless oil $[\alpha]^{25}_D = +7.4°$ (c 1.7 $CHCl_3$) spectral data identical to previously prepared racemic material.

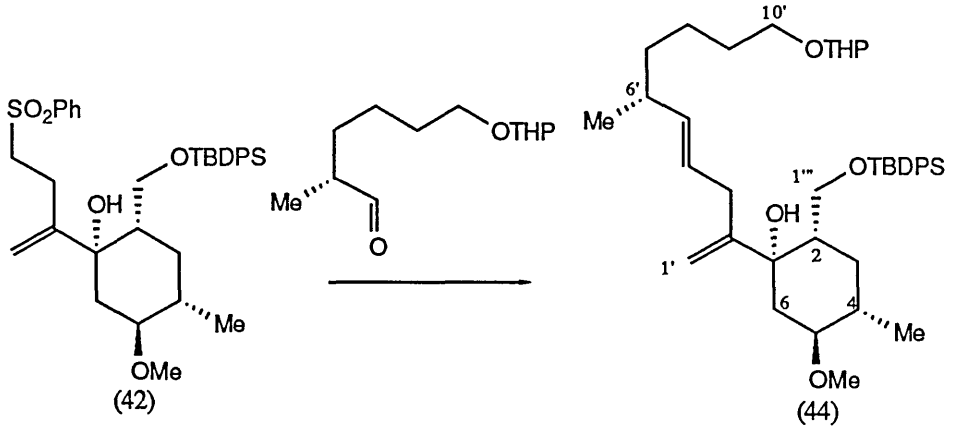
41. Preparation of (-)(6R, 9R)-6-t-Butyldiphenylsilyloxymethyl-9-hydroxy-8-methyl-1,4-dioxaspiro-[4.5]-undercane (97).



(+) $IPCBH_2$ (0.74 ml of a 0.8 M solution in THF, 0.592 mmol) was added dropwise to a stirred solution of the alkene (9) (500 mg; 1.18 mmol) in THF (0.18 ml), under argon, at -25°C. After 168h methanol (0.060 ml), sodium hydroxide (0.225 ml, of a 3M aqueous solution) and hydrogen peroxide (0.176 ml, of a 30% solution in water) were added sequentially to the opaque solution. The reaction was warmed to 40°C for 30 min and then to 50°C for 1h. The mixture was allowed to cool to r.t. and water (20 ml) was added and extracted with ether. Each organic extract was washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) of the residue afforded the *alcohol* (97) (77 mg, 30%) $[\alpha]^{25}_D$ - 2.8° ± 0.8 (c 0.96 $CHCl_3$) spectral data identical to previously

prepared racemic material.

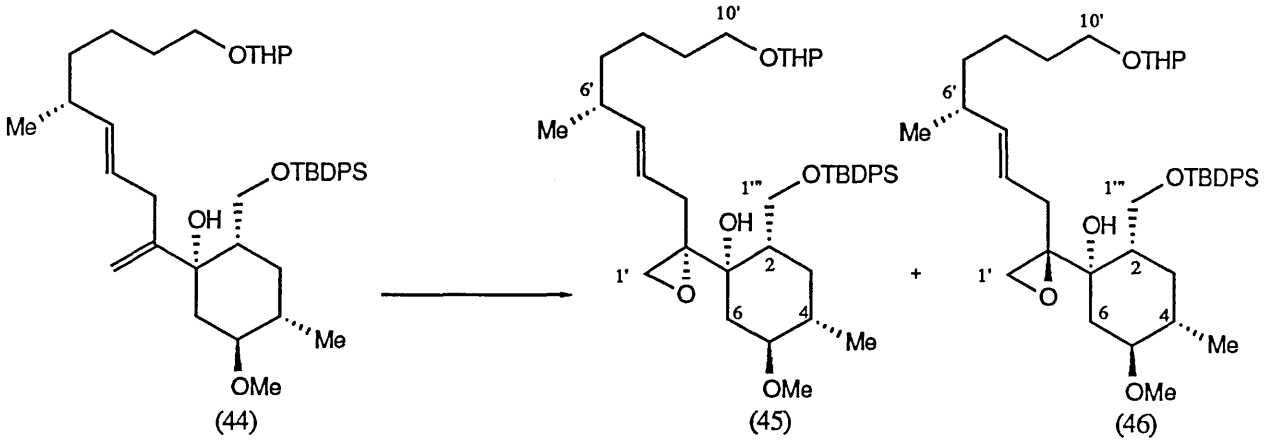
42. Preparation of (±)E (1S, 2S, 4S,5S, 6'R)-2-t-Butyldiphenylsilyloxymethyl-5-methoxy-4-methyl-1-{6'-methyl-10'-tetrahydro-2"H-pyran-2"-yloxydeca-1',4'-diene-2'yl}cyclohexan-1-ol (44) and its diastereomer .



n-Butyl-lithium (0.607 ml of a 1.45 M soluton in hexane, 0.88) mmol) was added dropwise to a stirred solution of the sulphone (42) (243 mg, 0.400 mmol) in THF:HMPA, 4:1 (2.5 ml), under argon at -78°C, over 3 min. After 20 min, the aldehyde (43) (188 mg, 0.990 mmol) in THF (1.6 ml) was added. After 3h benzoyl chloride (0.102 mml, 0.880 mmol) was added dropwise and the mixture allowed to warm to r.t. over 1h. N-dimethylaminopropylamine (0.111 ml, 0.880 mmol) was added, before the mixturewas poured into saturated sodium hydrogencarbonate solution. After extraction with ether, the extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Rapid column chromatography (50% ether-petrol) of the residue afforded the crude benzoxysulphones. These were dissolved in

THF/methanol 3:1 (40 ml) under argon and powdered disodium hydrogenphosphate (1.10 g 7.75 mmol) added, and the mixture cooled to -20°C. Powdered 6% sodium amalgam (745 mg, 5.42 mmol) was added to the vigorously stirred mixture. After 2h the mixture was decanted into water and the solids washed with ether. The ether extracts were washed with water then brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (25% ether-petrol) of the residue afforded the *dienes* (44) (173 mg, 65%) as a clear oil, ν_{max} (film), 3487, 3069, 2931, 2858, 1628, 1589, 1457, 1360, and 869 cm^{-1}; δ (300 MHz), 7.70-7.61 (4H, m, Ph), 7.50-7.35 (6H, m, Ph), 5.49 (1H, s, 1'-H), 5.29 (2H, m, 4'-H and 5'-H), 5.02 (1H, s, 1'-H), 4.59 (1H, m, 2"-H), 4.30 (1H, brs, 1-0H), 3.90 (2H, m, 6"-H and 1"-H), 3.73 (1H, m, 10'-H), 3.55-3.30 (3H, m), 3.38 (3H, s, 5-OMe), 3.25 (1H, dt, J 4.0 and 10.5 Hz, 5-H), 2.69 (1H, dd, J 10.0 and 3.3 Hz, 3'-H), 2.57 (1H, brd, J 10.0 Hz, 3'-H), 2.15-1.95 (2H, m, 6-H and 6'-H), 1.90-1.20 (17H, m), 1.10 (3H, d, J 8.0 Hz, 4-Me), 1.07 (9H, s, tBu), 0.97 (3/2H, J 8.0 Hz, 6'-Me), 0.95 (3/2H, J 8.0 Hz, 6'-Me), m/z 587 (M^+-^{t}Bu-H_20), 573 (M^+-^{t}Bu-MeoH), 560 (M^+-THPOH), 503 (M^+-^{t}Bu-THPOH), 471 (M^+-^{t}Bu-THPOH-MeOH), (Found C, 74.02; H, 9.71 $C_{41}H_{62}O_5Si$ requires C, 74.27; H, 8.43%).

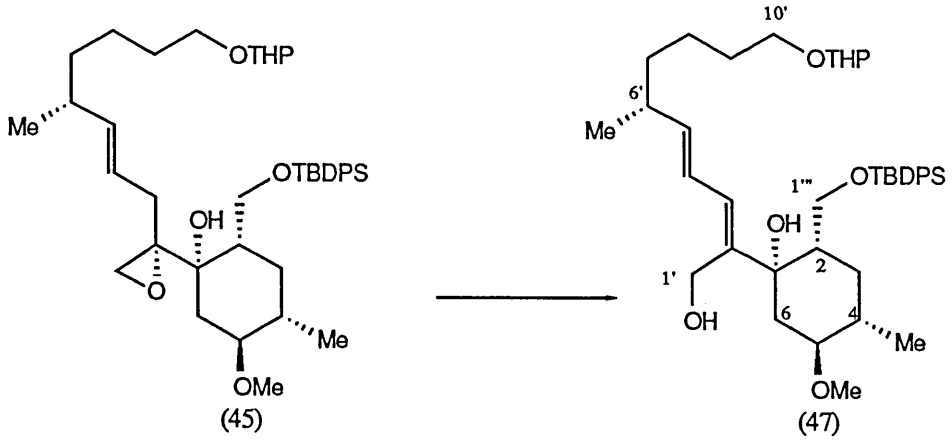
43. Preparation of (±) E (1S, 2S, 2'S, 4S, 5S, 6'R)-2-t-Butyldiphenyl silyloxymethyl-1-{1',2'-epoxy-6'-methyl-10'-tetrahydro-2"H-pyran-2"-yloxydec-4'-ene-2'-yl}-5-methoxy-4-methylcyclohexan-1-ol (45) and (±)E (1S, 2S, 2'R, 4S, 5S, 6'R)-2-t-Butyldiphenylsilyloxymethyl-1-{1',-2'-epoxy-6'-methyl-10'-tetrahydro-2"H-pyran-2"-yloxydec-4'-ene-2'-yl}-5-methoxy-4-methyl-cyclohexan-1-ol (46).



Vanadyl acetylacetonate (3 mg, 11.2 μmol), was added to a solution of the allylic alcohol (148 mg, 0.223 mmol) in toluene (5 ml), under argon, at 0°C. After 15 min, t-butylhydrogenperoxide (0.30 ml of a 3M solution in toluene, 0.90 mmol) was added dropwise. The reaction was allowed to warm to r.t. and after 4h, poured into dilute aqueous sodium sulphite solution and extracted with ether. The ether extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (30% ether-petrol) of the residue afforded the *epoxides* (46) (15 mg, 10%) and (45) (112 mg, 74%) both as colourless oils. Less polar: (46) ν_{max}

(film), 3488, 2930, 2858, 1617, 1426, 1112 and 967 cm^{-1}; δ (250 MHz), 7.80 (2H, m, Ph), 7.67 (2H, m, Ph), 7.50-7.30 (6H, m, Ph), 5.23 (1H, dd, J 15.3 and 7.2 Hz, 5'-H), 5.20-5.05 (1H, m, 4'-H), 4.50 (1H, s, 2'-H), 4.05 (1H, dd, J 10.0 and 3.0 Hz, 1'''-H),3.95-3.40 (4H, m, 6'H_2, 1'''-H and 1-OH), 3.13 (1H, dt, J 4.3 and 10.5 Hz, 5-H), 2.91 (1H, d, J 5.6 Hz, 1'-H), 2.50 (1H, d, J 5.6 Hz, 1'-H), 2.35 (1H, dd, J 14.8 and 7.4 Hz, 3'-H), 2.24 (1H, m, 3'-H), 2.15-1.15 (24H, m), 1.10-1.00 (12H, m, ^tBu and 4-Me), 0.94 (3/2 H, d, J 7.0 Hz, 6'-Me), 0.92 (3/2H, d, J 7.0 Hz, 6'-Me), m/z 648 (M^+-CH_20), 621(M^+-^tBu), 603 (M^+-^tBu-H_20), 591 (M^+-^tBu-CH_20), 559 (M^+-^tBu-CH_20-MeOH), 519 (M^+-^tBu-THPOH), (Found: M^+-^tBu-H_20, 603.3493 $C_{37}H_{51}O_5Si$ requires M, 603.3506); More polar: (45), ν_{max} (film), 3465, 3067,3048, 2859, 1587, 1457, 1322, 1200, 1112 and 867 cm^{-1}; δ (250 MHz), 7.70-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 5.25-4.95 (2H, m, 4'-H and 5'-H), 4.55 (1H, m, 2'-H), 3.95-3.25 (6H, m, 1'''-H_2, 6'-H_2, and 10'-H_2), 3.35 (3H, s, 5-OMe), 3.13 (1H, dt, J 3.9 and 10.0 Hz, 5-H), 2.87 (1H, dd, J 5.0 and 1.5 Hz, 1'-H), 2.83 (1H, s, 1-OH), 2.48 (1H, d, J 5.0 Hz, 1'-H), 2.36 (1H, dd, J 14.8 and 4.4 Hz, 3'-H), 2.22 (1H, dd, J 14.8 and 7.4 Hz, 3'-H), 2.12 (1H, dd, J 12.7 and 4.0 Hz), 2.00 (1H, m), 1.90-1.15 (17H, m), 1.14-1.00 (12H, m, ^tBu and 4-Me), 0.93 (3/2H, d, J 7.0 Hz, 6'-Me), 0.91 (3/2H, d, J 7.0 Hz, 6'-Me), m/z 621 (M^+-^tBu), 603 (M^+-^tBu-H_20), 591 (M^+-^tBu-CH_2O), 559 (M^+-^tBu-CH_2O-MeOH), 519 (M^+-^tBu-THPOH), (Found: C, 72.34; H, 9.17, $C_{41}H_{62}O_6Si$ requires C, 72.52; H, 9.20%).

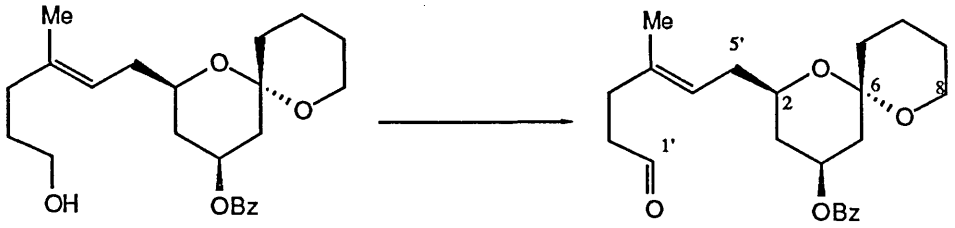
44. Preparation of (±) EE (1S,2S,4S,5S,6'R)-2-t-Butyldiphenylsilyloxymethyl-1-{6'-Methyl-10'-tetrahydro-2"H-pyran-2"-yl oxydec-2',4'-ene-1-ol-2'-yl}-5-methoxy-4-methylcyclohexan-1-ol (47).



n-Butyl-lithium (0.147 ml of a 2.4M solution in pentanes, 0.35 mmol) was added dropwise to a stirred soluton of tetramethylpiperidine (0.059 ml 0.35 mmol) in toluene (0.5 ml), under argon at -10°C. The mixture was warmed to 0°C over 10 min and diethylaluminium chloride (0.170 ml of a 2M solution in hexane, 0.35 mmol) was added. The reaction was allowed to warm to r.t. after 30 min. The epoxide (24 mg, 0.035 mmol) in toluene (0.90 ml) was added dropwise over 5 min. After 30 min, saturated ammonium chloride (2 ml) was added and the mixture extracted with ether. The ether extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue afforded the *1,3-diene* (47) (9 mg, 38%) and the starting epoxide (45) (7 mg, 29%) both as colourless oils, ν_{max} (film), 3458, 2930, 1462, 1428, 1378, 1113 and 805 cm^{-1}; δ

(500 MHz), 7.70-7.55 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 6.50-6.30 (2H, m, 3'-H and 4'-H), 5.69 (1H, m, 5'-H), 4.58 (2H, s, 2"-H and 1-OH), 4.33 (1H, dd, J 12.0 and 6.5 Hz, 1'-H), 4.26 (1H, dd, J 12.0 and 6.5 Hz, 1'-H), 3.95 (1H, br d J 10.0 Hz), 3.87 (1H, t, J 9.0 Hz), 3.74 (1H, q, J 8.0 Hz), 3.49 (2H, m), 3.36 (3H, s, 5-OMe), 3.21 (1H, tt, J 10.5 and 3.0 Hz), 2.27 (1H, m, 6'-H), 2.13 (1H, m), 2.10-1.2 (19H, m), 1.15-1.00 (15H, m, ^{t}Bu, 6'-Me and 4-Me); m/z 660 (M^{+}-H_2O), 642 (M^{+}-$2H_2O$), 603 (M^{+}-^{t}Bu-H_2O), 576 (M^{+}-H_2O-DHP), 558 (M^{+}-$2H_2O$-DHP), 526 (M^{+}-DHP-CH_2O-MeOH), 469 (M^{+}-^{t}Bu-DHP-$2H_2O$-MeOH), 199 (Ph_2SiOH) (Found:M^{+}-H_2O, 660.4211 $C_{41}H_{60}O_5Si$ requires M, 660.4210

45. Preparation of E(2S,4S,6S)-4-Benzoyloxy-2-{4'-Methylhex-4'-enal-6'-yl}-6-{1,7-dioxaspiro-[5,5]-undecane} (48).

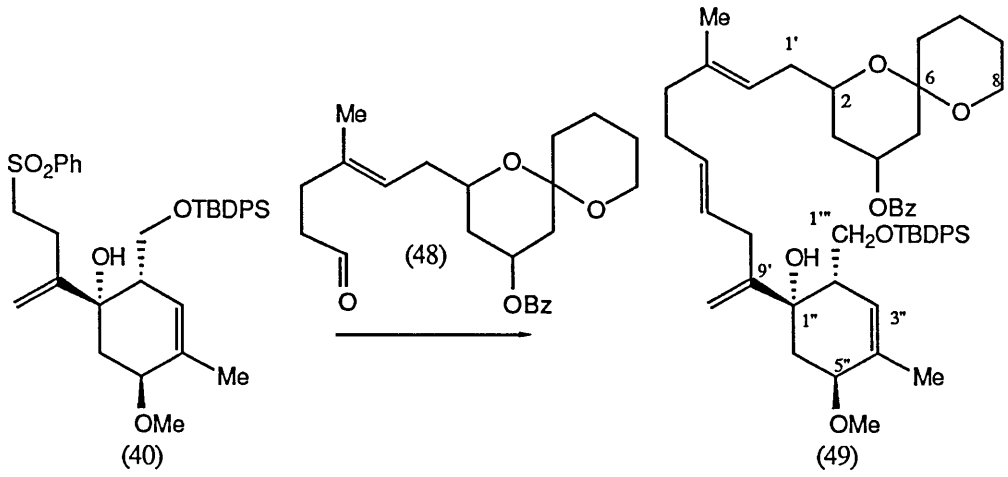


(48)

DMSO (0.333 mol, 4.69 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.207 ml, 2.37 mmol), in DCM (25 ml), under argon, at -65°C. After 5 min, the alcohol (460 mg, 1.18 mmol) in DCM (18 ml) was added dropwise. After a further 20 min, triethylamine (1.61 ml, 11.5 mmol) was added. The mixture was allowed to warm to r.t., poured into water and extracted with ether. The organic

extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (30% ether-petrol) afforded the *aldehyde* (48) (146 mg, 91%) as a clear oil; ν_{max} (film), 2942, 2721, 1716, 1603, 1450, 1314, 1199, 1111, and 991; δ (500 MHz), 9.77 (1H, t, J 2.0 Hz, 1'-H), 8.02 (2H, m, Ph), 7.56 (1H, m, Ph), 7.42 (2H, m, Ph), 5.42 (1H, tt, J 11.5 and 5.0 Hz, 4-H), 5.30 (1H, br t, J 7.0 Hz, 5'-H), 3.73 (1H, m, 2-H), 3.62-3.55 (2H, m, 8-H_2) , 2.54 (2H, dt, J 2.0 and 7.6 Hz, 2'-H_2), 2.36 (2H, t, J 7.6 Hz, 3'-H_2), 2.29 (1H, dt, J 14.0 and 6.5 Hz, 6'-H), 2.23 (1H, dt, J 14.0 and 6.5 Hz, 6'-H), 2.17-2.12 (2H, m), 1.86 (1H, tq, J 4.0 and 14.0 Hz, 10-H), 1.73-148 (6H, m), 1.65 (3H, s, 4'-Me), 1.33 (1H, q, J 11.5 Hz, 3-H), m/z: 386 (M^+), 275 ($C_{16}H_{19}O_4$) 153 ($C_{16}H_{19}O_4$ -$PhCO_2H$), (Found: C, 71.39; H, 8.03. $C_{23}H_{30}O_5$ requires C, 71.48; H, 7.82%).

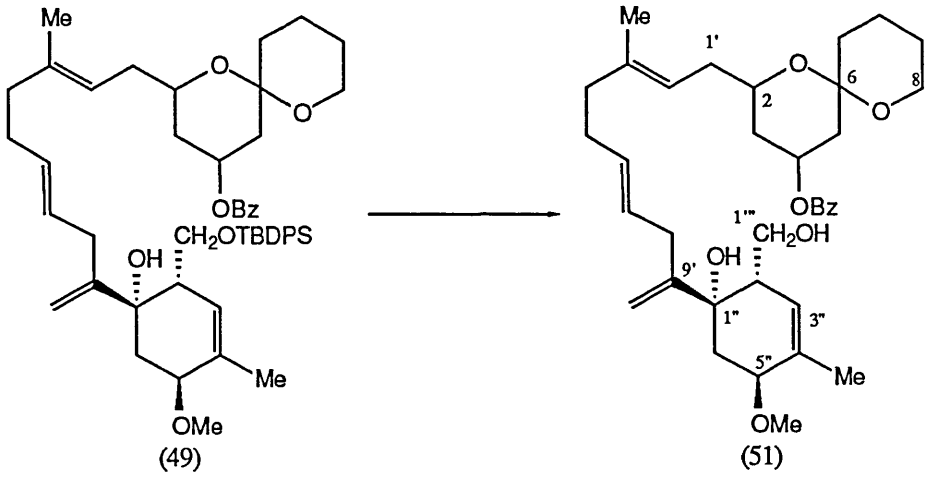
46. Preparation of (±) EE (1"S,2S, 2"S, 4S,4"S,5"S,6S) 4-Benzoyloxy-2-{9'-t-butyldiphenylsilyloxymethyl-1"-Hydroxy-4"-methyl-5"-methoxycyclohex-3"-eneyl)-3'-methyldeca-2',6',9'-trienyl}-6-{1,7-dioxaspiro-[5.5]-undecane} (49).



n-Butyl-lithium (0.498 ml of a 2.5 M solution in pentanes, 1.24 mmol) was added dropwise to a stirred solution of the sulphone (40) (350 mg, 0.579 mmol) in THF:toluene, 1:1 (5 ml), under argon, at -78°C, under 3 min. After 40 min, the aldehyde (162 mg, 0.419 mmol) in THF:toluene, 1:1 (1.8 ml) was added and after a further 4h, benzoyl chloride (0.134 ml, 1.16 mmol) was added and the reaction allowed to warm to r.t. over 1h. 3- Dimethylaminopropylamine (0.074 ml, 0.59 mmol) was added, before the mixture was poured into saturated sodium hydrogencarbonate solution. The mixture was extracted with ether. The extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (35% ether-petrol) afforded the benzoxysulphones. These were

dissolved in THF: methanol 3:1 (9.5 ml) under argon, powdered disodium hydrogenphosphate (2.0g 14.1 mmol) was added, and the mixture cooled to -25°C. Powdered 6% sodium amalgam (828 mg, 6.02 mmol) was added to the vigorously stirred slurry. After 2h, ethylacetate (50 ml) was added and the solution filtered rapidly through a pad of solid ammonium chloride and silica gel. The filtrate was evaporated *in vacuo*. Column chromatography (35% ether-petrol) afforded the *diene* (49) (158 mg, 45%) as a clear oil and a 6:1 mixture of E:Z isomers; ν_{max} (film), 3475, 2933, 1717, 1603, 1588, 1385, 1111 and 821 cm^{-1}; δ (400 MHz), 8.02 (2H, m, Ph), 7.70-7.35 (13H, m, Ph), 5.48-5.36 (4H, m, 6'-H, 7'-H, 4-H and 3"-H), 5.24 (1H, m, 2'-H), 5.03 (1H, s, 10'-H), 4.57 (1H, s, 10'-H), 4.11 (1H, br t, J 8.0 Hz, 5"-H), 3.97 (1H, dd, J 10.5 and 3.0 Hz, 1"'-H), 3.74 (1H, m, 2-H), 3.70-3.50 (3H, m, 1"'H and 8-H_2) 3.39 (3H, s, 5"-OMe), 2.72 (1H, br d, J 16.0 Hz, 8'-H), 2.62 (1H, br d J 16.0 Hz, 8'-H), 2.42 (1H, s), 2.38-2.00 (8H, m), 1.80 (3H, s, 4"-Me), 1.75-1.50 (9H, m), 1.62 (3H, s, 3'-Me), 1.40-1.15 (2H, m), 1.04 (9H, s, ^{t}Bu), m/z 832 (M^+), 814 (M^+-H_2O), 775 (M^+-^{t}Bu), 653 (M^+-^{t}Bu-$PhCO_2H$), 153 $C_9H_{13}O_2$.

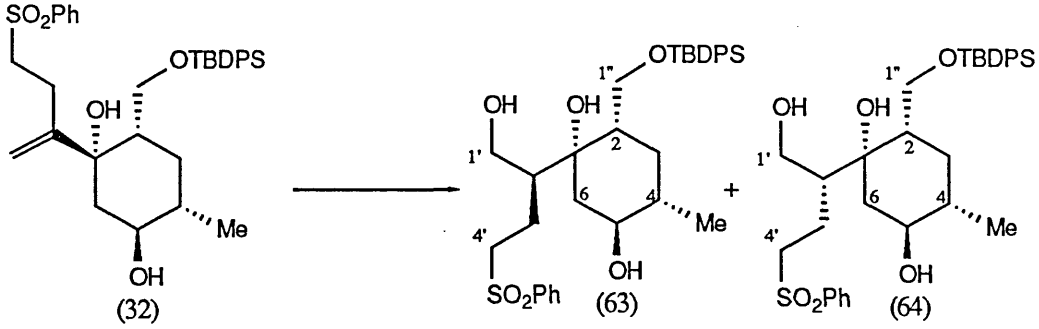
47. Preparation of (±) EE (1"S,2S, 2"S, 4S,4"S,5R,5"S,6S) -4-Benzoyloxy-2-{9'-(1"-Hydroxy-2"-hydroxymethyl-4"-methyl-5"-methoxycyclohex-3"-eneyl)-3'-methyldeca-2',6',9'-trienyl}6-{1,7-dioxaspiro-[5.5]-undecane} (51).



Tetrabutylammonium fluoride (0.064 mol of a 1M solution in THF, 0.064 mmol) was added dropwise to a stirred solution of the silyl ether (49) (45 mg, 0.054 mmol), in THF (8 ml), under argon, at 0°C. After 40 min, the solvent was evaporated *in vacuo*. Column chromatography (50% ether-petrol) of the residue afforded the *diol* (51) (27 mg, 84%) as a clear oil and a 6:1 mixture of E:Z isomers; ν_{max} (film), 3420, 2928, 1716, 1390 and 710 cm^{-1}; δ (300 MHz), 8.03 (2H, d, J 7.8 Hz, Ph), 7.55 (1H, t, J 7.7 Hz, Ph), 7.43 (2H, t, J 7.6 Hz, Ph), 5.55-5.34 (4H, m, 4-H, 6'-H, 7'-H and 3"H), 5.26 (1H, t, J 7.0 Hz, 2'-H), 5.02 (1H, s, 10'-H), 4.04 (1H, br s, 5"-H), 3.88 (1H, br d , J 7.5 Hz, 1'''-H), 3.77-3.56 (4H, m, 2-H, 8-H_2 and 1'''-H), 3.38 (3/2H, s, 5"-OMe), 3.36 (3/2H, s, 5"-OMe), 3.20 (1H, d, J 3.0 Hz), 2.77

(1H, br dd, J 16.5 and 3.7 Hz, 9'-H), 2.68 (1H, br dt, J 16.5 and 2.5 Hz, 9'-H),2.49 (1H, s), 2.40-2.00 (8H, m), 1.82 (3H, s, 4"-Me), 1.65 (3H, s, 3'-Me), 1.90-1.20 (12H, m); m/z 576 (M^+-H_2O), 544 (M^+-H_2O-MeOH), 472 (M^+-$PhCO_2H$), 454 (M^+-$PhCO_2H$-H_2O), 275 ($C_{16}H_{19}O_4$), 153 ($C_{16}H_{19}O_4$-$PhCO_2H$) (Found: M^+-H_2O, 576.3439 $C_{36}H_{48}O_6$ requires M, 576.3451).

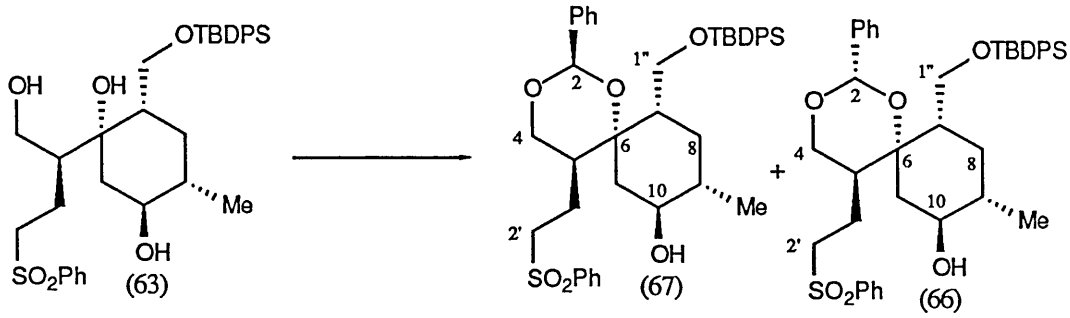
48. Preparation of (-)(1S,2S, 2'S, 4S,5S) -2-t-Butyldiphenylsilyloxymethyl-5-hydroxy-4-methyl-1-(4'phenylsulphonyl-butan-1'-ol-2'-yl)-cyclohexan-1-ol (63) and (1S,2S, 2'R, 4S,5S) -2-t-Butyldiphenylsilyloxymethyl-5-hydroxy-4-methyl-1-(4'phenylsulphonyl-butan-1'-ol-2'-yl)-cyclohexan-1-ol (64).



Borane-dimethylsulphide complex (0.306 ml of a 10M solution in THF 3.06 mmol) was added dropwise to a stirred solution of the alkene (32) (590 mg 1.0 mmol) in THF (50 ml), under argon, at 0°C. The solution was allowed to warm to r.t. over 16h, whereupon water (0.27), sodium hydroxide (12 ml of a 3M aqueous solution) and hydrogen peroxide (5.3 ml of a 30% aqueous solution) were added sequentially. After 30 min, water was added and the mixture extracted with ethylacetate. Each

organic extract was washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ethylacetate-petrol) of the residue afforded the *triols* (63) (413 mg, 68%) and (64) (103 mg, 17% both as clear oils. Less polar : (63) $[\alpha]^{25}_D$ -19.23 (c 2.2, $CHCl_3$), ν_{max} (film), 3466, 2930, 1446, 1427, 1113, 1086 and 793 cm^{-1}; δ (500 MHz), 7.90 (2H, m, Ph), 7.80-7.30 (13H, m, Ph), 4.08 (1H, dd, J 10.8 and 2.9 Hz, 1"-H), 3.83 (1H, br s 1-OH), 3.60-3.50 (3H, m, 1'-H, 1"-H, and 5-H), 3.40 (1H, dd, J 11.1 and 6.5 Hz, 4'-H), 3.32 (1H, m, 3'-H), 2.90-1.50 (9H, m), 1.40-1.20 (2H, m), 1.15-0.90 (13H, m, 3-H, 4-Me and ^tBu), m/z 553 (M^+-^tBu), 517 (M^+-^tBu-$2H_20$), 410 (M^+-^tBu-$PhSO_2$), 199 (Ph_2SiOH), (Found: C, 67.06; H, 7.70, $C_{34}H_{46}O_6SSi$ requires C, 66.85; H, 7.59%); More polar: (64); ν_{max} (film), 3414, 2930, 1447, 1428, 1147, 1086 and 735 cm^{-1}; δ (500 MHz), 7.80 (2H, m, Ph), 7.75-7.35 (13H, m, Ph), 4.40-4.32 (2H, m, 1"-H and 1'-H), 3.66 (1H, dt, J 5.0 and 12.5 Hz, 5-H), 3.56 (1H, br d, J 13.0 Hz, 1'-H), 3.50 (1H, dd, J 12.5 and 5.0 Hz, 1"-H), 3.09 (1H, ddd, J 12.5, 11.5 and 6.0 Hz, 4'-H), 2.61 (1H, ddd, J 12.5, 12.0 and 7.0 Hz, 4'-H), 2.38 (1H, s, 1-OH), 2.06 (1H, dd, J 15.0 and 6.1 Hz, 6-H), 1.95 (1H, q, J 15.0 Hz, 3-H), 1.84 (1H, m, 2-H), 1.65-1.50 (2H, m), 1.48-1.15 (5H, m), 1.09 (3H, d, J 8.0 Hz, 4-Me), 1.07 (9H, s, ^tBu), 1.04 (1H, dd J 16.0 and 15.0 Hz, 3-H).

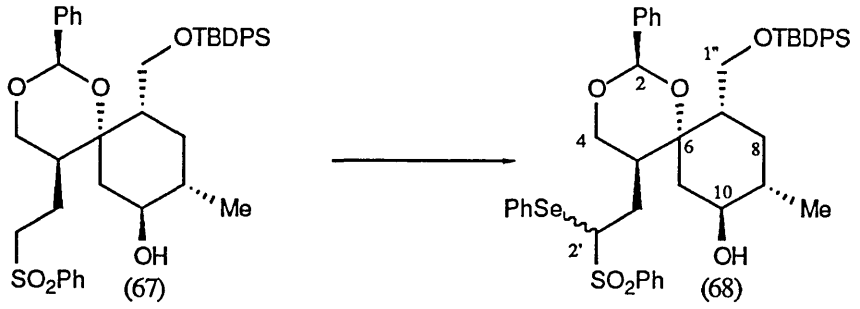
49. Preparation of (+) (2S,5S,6S,7S,9S,10S)-7-t-Butyldiphenylsilyloxymethyl-10-hydroxy-9-methyl-2-phenyl-5-(2'-phenylsulphonylethan-1'-yl)-1,3-dioxaspiro-[5.5]-undecane (67) and (-) (2R,5S,6S,7S,9S,10S)-7-t-Butyldiphenylsilyloxy-methyl-10-hydroxy-9-methyl-2-phenyl-5-(2'-phenylsulphonylethan-1'-yl)-1,3-dioxaspiro-[5.5]-undecane (66).



A solution of the triol (63) (335 mg, 0.480 mmol), benzaldehyde (2 ml, 19.7 mmol) and pyridinium-p-toluene sulphonate (188 mg, 0.75 mmol) in benzene (60 ml) was heated at reflux under Dean-Stark conditions, under argon, for 1h. Saturated sodium hydrogencarbonate solution (20 ml) was added to the vigorously stirred hot solution. The mixture was allowed to cool to r.t. and extracted with ether. The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (90% ether-petrol) of the residue afforded the *acetals* (66), (198 mg 52%), and (67), (171 mg, 45%), both as white foams. Less polar: (66), $[\alpha]^{25}_D$ + 0.40 (c 1.24, $CHCl_3$); ν_{max} (film), 3508, 3068, 2930, 1587, 1307, 1151, 1029 and 798 cm^{-1}; δ (500 MHz), 7.91 (2H, m, Ph), 7.80-7.20 (18H, m, Ph), 5.35 (1H, s, 2-H), 3.94 (1H, dd, J 9.7 and 3.6 Hz, 1"-H), 3.80 (1H, dd, J

11.7 and 5.6 Hz, 4-H), 3.65-3.55 (2H, m, 1"-H and 10-H), 3.38 (1H, t, J 11.7 Hz, 4-H), 2.97 (2H, m, 2'-H_2), 2.05-1.75 (5H, m), 1.54 (1H, dd, J 12.4 and 11.1 Hz), 1.50-1.20 (3H, m), 1.15-0.9 (13H, m, 9-Me, ^tBu, and 8-H), m/z: 641 (M^+-^tBu), 623 (M^+-^tBu-H_20), 517 (M^+-^tBu-H_20-PhCHO), 199 (Ph_2SiOH); More polar: (67) ; $[\alpha]^{25}_D$ -3.30 (c 0.91, $CHCl_3$); ν_{max} (film), 3508, 3068, 2930, 1587, 1307, 1151, 1086 and 937 cm^{-1}; δ (500 MHz), 7.90 (2H, m, Ph), 7.70-7.20 (18H, m, Ph), 5.84 (1H, s, 2-H), 4.00 (1H, dd, J 10.4 and 5.0 Hz, 4-H), 3.83 (1H, dd, J 10.4 and 6.0 Hz, 1"-H), 3.65 (1H, dd, J 10.5 and 10.4 Hz, 4-H), 3.61 (1H, dd, J 10.4 and 7.8 Hz, 1"-H), 3.38 (1H, m, 10-H), 2.97 (2H, m, 2'-H_2), 2.25 (1H, dd, J 13.2 and 4.6 Hz, 11-H), 2.20 (1H, m, 5-H), 1.97 (1H, m), 1.42 (1H, dd, J 13.1 and 10.7 Hz), 1.40 (1H, d, J 5.2 Hz), 1.31 (1H, m), 1.23 (1H, t, J 13.2 Hz, 11-H), 1.05 (9H, s, ^tBu); 1.00 (3H, d, J 7.4 Hz, 9-Me), m/z 641 (M^+-^tBu), 517 (M^+-^tBu-H_20-PhCHO), 199 (Ph_2SiOH), (Found: C, 70.60; H, 7.32 $C_{41}H_{50}O_6SSi$ requires C, 70.45; H, 7.21%).

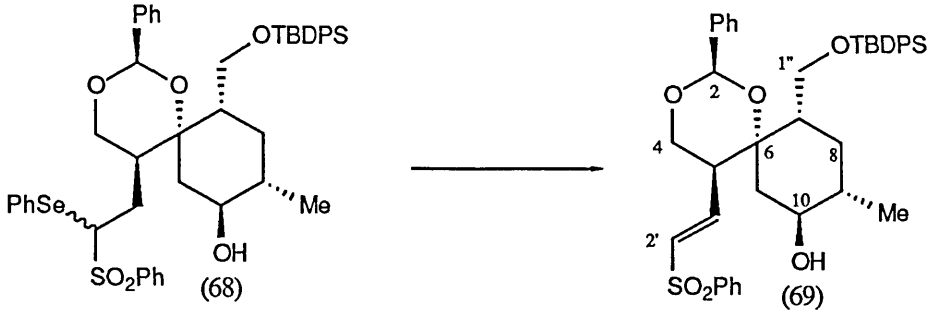
50. Preparation of (2R,2'(R,S),5S,6S,7S,9S,10S)-5'-(2'-Benzeneselenenyl-2'-phenylsulphenylethan-1'-yl)-7-t-butyldiphenylsilyloxymethyl-10-hydroxy-9-methyl-2-phenyl-1,3-dioxaspiro-[5.5]-undecane (68).



n-Butyl-lithium (0.462 ml of a 2.46M solution in hexane, 1.14 mmol) was added dropwise to a stirred solution of the sulphone (67) (360 mg, 0.516 mmol) in THF (10 ml), under argon, at -78°C. After 30 min, benzeneselenenyl chloride (130 mg, 0.679 mmol) in THF (3 ml) was added rapidly, to yield a dark green solution. After 10 min, saturated sodium hydrogencarbonate (10 ml) was added and the mixture allowed to warm to r.t. The pale yellow two-phase mixture was poured into water and extracted with DCM. The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75-100% ether-petrol) of the residue afforded the *selenides* (68), (156 mg, 35%), (68) (159 mg, 35%) and *starting sulphone* (67) (38 mg, 11%) all as white foams. Less polar: $[\alpha]^{25}_D$ +13.8 (c 1.4, $CHCl_3$); ν_{max} (film), 3509, 3067, 2930, 1587, 1307, 1112 and 823 cm^{-1}; δ (500 MHz), 7.95-7.10 (25H, m, Ph), 5.85 (1H, s, 2-H), 3.98 (1H, dd, J 10.3 and 4.6 Hz, 4-H), 3.95 (1H, dd, J 7.4 and 5.2 Hz, 2'-H), 3.87 (1H, dd, J 10.3 and 5.7 Hz, 1"-

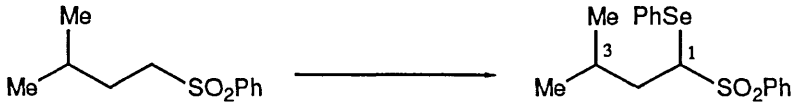
H), 3.66 (1H, t, J 10.3 Hz, 4-H), 3.62 (1H, dd, J 10.3 and 8.3 Hz, 1"-H), 3.31 (1H, m, 10-H), 2.49 (1H, dt, J 15.4 and 4.7 Hz, 8-H), 2.39 (1H,m, 5-H), 2.15 (1H, dd, J 13.4 and 4.2 Hz, 11-H), 1.91 (1H, dd, J 9.7 and 4.0 Hz), 1.80-1.65 (2H, m), 1.30-1.10 (4H, m), 1.07 (9H, s, ^{t}Bu), 0.99 (3H, d, J 5.7 Hz 9-Me); More polar: $[\alpha]^{25}_{D}$ - 0.41 (c 1.7, $CHCl_3$), 7.90-7.15 (25H, m, Ph), 5.85 (1H, s, 2-H), 3.98 (1H, dd, J 10.2 and 4.3 Hz, 2-H), 3.87 (1H, dd J 12.0 and 2.5 Hz), 3.70-3.60 (2H, m), 3.49 (1H, t, J 10.8 Hz), 3.36 (1H, m, 10-H), 2.58 (1H, ddd, J 10.0, 5.4 and 2.0 Hz), 2.57-2.22 (2H, m), 2.03-1.90 (2H, m), 1.76 (1H, m), 1.40-1.10 (4H, m), 1.08 (9H, s, ^{t}Bu), 0.99 (3H, d, J 6.2 Hz, 9-Me); m/z 797 (M^{+}-^{t}Bu), 691 (M^{+}-^{t}Bu-PhCHO), 673 (M^{+}-^{t}Bu-PhCHO-H_20), 515 (M^{+}-^{t}Bu-PhCHO-H_20-PhSeH), (Found: C, 66.20; H, 6.57 $C_{47}H_{54}O_6SSeSi$ requires C, 66.10; H, 6.37%).

51. Preparation of (-)E(2R,5S,6S,7S,9S,10S)7-t-Butyldiphenylsilyloxymethyl-10-hydroxy-9-methyl-2-phenyl-5-(2'-phenylsulphonyleth-1'-ene-1'-yl)-1,3-dioxaspiro-[5.5]-undecane (69).



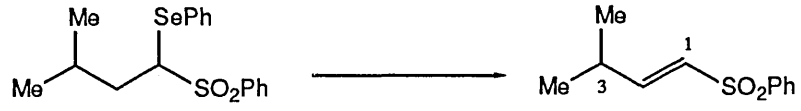
mCPBA (150 mg, 85%, 0.74 mmol) was added portionwise to a vigorously stirred mixture of the selenides (68) (316 mg 0.370 mmol) in DCM (10 ml) and saturated sodium hydrogencarbonate solution (4 ml), at 10°C. After 20 min, the mixture was poured into dilute aqueous sodium sulphite solution and extracted with DCM. The organic extracts were combined, dried and evaporated *in vacuo*. Column chromatography (ether) of the residue afforded the *vinyl sulphone* (69) (242 mg 94%), as a white foam; $[\alpha]^{25}_{D}$ -15.3 (c 1.0, $CHCl_3$), ν_{max}(film), 3507, 2929, 1619, 1591, 1446, 1390, 1147, 910, and 823 cm^{-1}; δ (500 MHz), 7.84 (2H, m, Ph), 7.75-7.20 (19H, m, Ph and 1'-H), 6.41 (1H, d, J 15.0 Hz, 2'-H), 5.87 (1H, s, 2-H), 4.12 (1H, dd, J 10.4 and 4.9 Hz, 1"-H), 4.08 (1H, dd, J 10.9 and 4.9 Hz, 4-H),3.95 (1H, dd, J 10.9 and 8.2 Hz, 4-H), 3.58 (1H, dd, J 10.4 and 7.6 Hz, 1"-H), 3.35 (1H, dt, J 3.7 and 10.4 Hz 10-H), 2.71 (1H, m, 5-H), 2.51 (1H, dd, J 13.6 and 4.1 Hz, 11-H), 1.86 (1H, dt, J 3.9 and 13.6 Hz, 11-H), 1.81 (1H, m, 7-H), 1.47 (1H, br s, 10-OH), 1.37 (1H, dd, J 13.6 and 10.9 Hz, 8-H), 1.29 (1H, m, 9-H), 1.13 (1H, q, J 13.6 Hz, 8-H), 1.09 (9H, s, ^{t}Bu), 0.96 (3H, d, J 6.4 Hz, 9-Me), m/z: 639 (M^{+}-^{t}Bu), 533 (M^{+}-^{t}Bu-PhCHO), 391 (M^{+}-^{t}Bu-PhCHO-$PhSO_2H$), 373 (M^{+}-^{t}Bu-PhCHO-$PhSO_2H$-H_2O), 199 (Ph_2SiOH) (Found: C, 70.97; H, 7.04, $C_{41}H_{48}O_6SiS$ requires, C, 70.66; H, 6.94%).

52. Preparation of (±) 1-Benzeneselenenlyl-3-methyl-1-phenylsulphonylbutane.



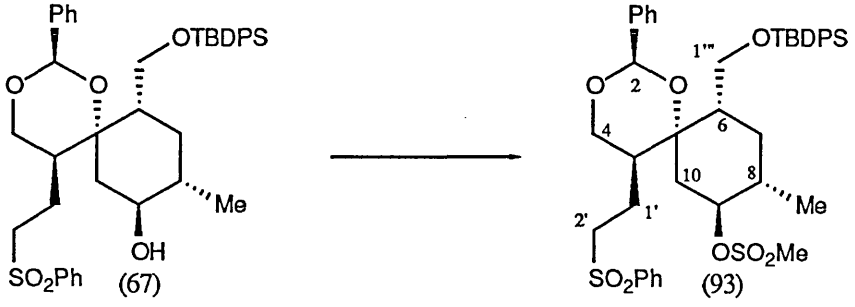
t-Butyl-lithium (0.382 mml of a 1.7M solution in pentanes, 0.649 mmol) was added dropwise to a stirred solution of the sulphone (115 mg, 0.542 mmol) in THF (5.5 ml) under argon, at -78°C. After 30 min, benzeneselenenyl chloride (135 mg, 0.7 mmol) in THF (1 ml) was added dropwise. After a further 10 min saturated sodium hydrogencarbonate solution (1 ml) was added and the mixture allowed to warm to r.t. The two phase mixture was poured into water and extracted with DCM.The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (10% ether-petrol) afforeded the *selenide* (75 mg, 38%) as a clear oil, ν_{max} (film),3059, 2957, 2869, 1576, 1446, 1307, 1083 920 and 773 cm^{-1}; δ (90 MHz), 7.95 (2H, m, Ph), 7.75-7.10 (8H, m, Ph), 4.20-3.95 (1H, m, 1-H), 2.30-1.30 (3H, m, 2-Hz and 3-H), 0.90 (3H, d, J 6.5 Hz), 0.75 (3H, d, J 6.5 Hz), m/z; 368 (M^+), 227 (M^+-$PhSO_2$), Found: C, 55.55; H, 5.46 $C_{17}H_{20}O_2SSe$ C, 55.58; H, 5.49%).

53. Preparation of E-3-methyl-1-phenylsulphonyl-but-1-ene.



mCPBA (55 mg, 85%, 0.272 mmol) was added portionwise to a vigorously stirred mixture of the selenide (50 mg, 0.136 mmol) in DCM (10 ml) and saturated sodium hydrogencarbonate solution (7 ml) at 10°C. After 10 min, the mixture was poured into dilute aqueous sodium sulphite solution and extracted with DCM. The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography of the residue afforded the *vinyl sulphone* (26 mg, 94%) as a clear oil; ν_{max} (film), 2978, 2930, 1625, 1198 and 752 cm^{-1}; δ(250MHz),7.88(2H, m, Ph),7.70-7.50(3H,m,Ph), 6.98(1H, dd, J 15.3 and 6.4Hz, 2-H), 6.25(1H, dd, J 15.3 and 1.5 Hz, 1-H), 2.51(1H, doct, J 1.5 and 6.6 Hz, 3-H), 1.07 (6H, d, J 6.6Hz, Me), m/z 210 (M^+) 141 ($PhSO_2$), 69 (C_5H_9), 43 (C_3H_7).

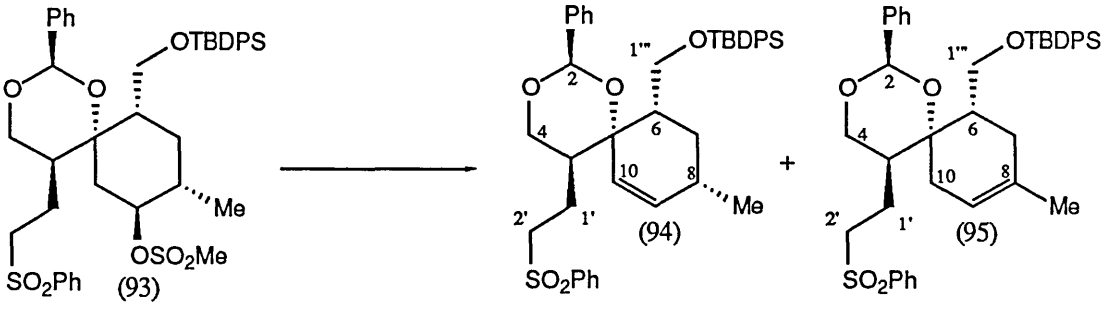
54. Preparation of (±) (2R,5S,6S,7S,9S,10S)7-t-Butyldiphenylsilyloxymethyl-10-methansulphonate-9-methyl-2-phenyl-5-(2'-phenylsulphonyl-ethan-1'-yl)-1,3-dioxaspiro-[5.5]-undecane (93).



Methanesulphonyl chloride (0.006 ml, 0.076 mmol) was added dropwise to a strirred solution of the alcohol (67) (38 mg, 0.057 mol) and triethylamine (0.031 ml, 0.218 mmol) in DCM (5 ml), under argon, at -10°C. After 5 min, water (5 ml) was

added and the mixture allowed to warm to r.t. The two phase mixture was extracted with DCM, the extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) of the residue afforded the *mesylate* (93) (38 mg, 90%) as cubes m.p. 130-131°C. ν_{max} (film) 2934, 1447, 1353, 1173, 1087 and 925 cm^{-1}; δ (500 MHz), 7.90 (2H, m Ph), 7.75-7.50 (8H, m, Ph), 7.45-7.20 (10H, m, Ph), 5.83 (1H, s, 2-H), 4.36 (1H, dt, J 4.3 and 11.0 Hz, 10-H), 3.98 (1H, dd, J 10.5 and 4.0 Hz), 3.83 (1H, dd, J 10.5 and 3.0 Hz), 3.70-3.50 (2H, m), 3.10-2.85 (2H, m, 2'-H_2), 2.99 (3H, s, 10-SO_3Me), 2.58 (1H, dd, J 13.8 and 4.5 Hz, 11-H), 2.16 (1H, m), 2.10-1.45 (6H, m), 1.25 (1H, m), 1.05 (9H, s, ^tBu), 1.00 (3H, d, J 7.0 Hz, 9-Me); m/z 623 (M^+-^tBu-$MeSO_3H$), 517 (M^+-^tBu-$MeSO_3H$-PhCHO), 199 (Ph_2SiOH). (Found: C, 64.87; H, 6.84, $C_{42}H_{52}O_8S_2Si$ requires C, 64.92; H, 6.75%).

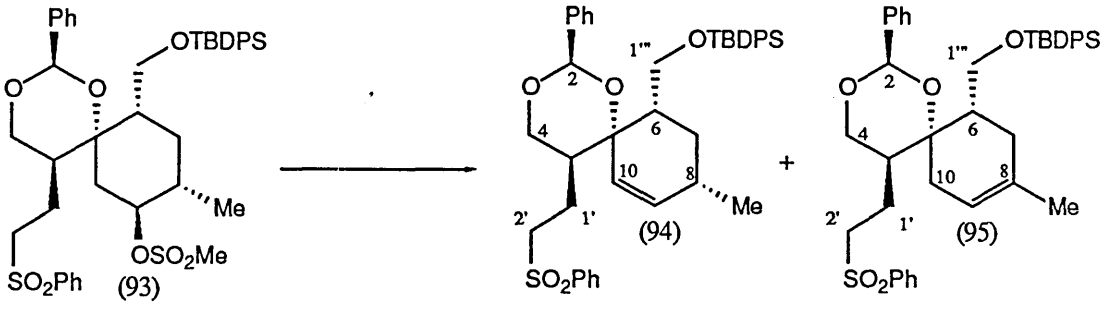
55. Preparation (±) (2R, 5S,6S,7S,9S)-7-t-Butyldiphenylsilyloxymethyl-9-methyl-2-phenyl-5-(2'-phenylsulphonyl ethan-1'-yl)-1,3-dioxaspiro-[5.5]-undec-10-ene (94), and (±) (2R, 5S,6S,7S)-7-t-Butyldiphenylsilyloxymethyl-9-methyl-2-phenyl-5-(2'-phenylsulphonylethan-1'-yl)-1,3-dioxaspiro-[5.5]-undec-9-ene (95).



DBU (0.023 ml, 0.154 mmol) was added to a solution of the mesylate (93) (10 mg, 0.013 mmol) in toluene (2 ml) under argon, at reflux. After 16h, the solvent was evaporated in vacuo. Column chromatography (40% ether-petrol) of the residue afforded the alkenes (94) and (95), (7.5 mg 86%) as a clear oil and a 1:1 mixture of regioisomers; ν_{max} (film), 2933, 1447, 1307, 1110, and 702 cm-1; δ (500 MHz), 8.00-7.85 (2H, m, Ph), 7.75-7.10 (18H, m, Ph), 6.21 (1/2H, dd, J 10.4 and 2.1 Hz, 11-H), 5.85 (1/2H, s, 2-H), 5.70 (1/2H, dd, J 10.4 and 2.5 Hz, 10-H), 5.63 (1/2H, s, 2-H), 5.19 (1/2H, br s, 10-H), 4.28 (1/2H, dd, J 12.6 and 2.0 Hz), 4.15 (1/2H, dd, J 12.1 and 2.8 Hz), 3.90-3.82 (1H, m), 3.62-3.50 (1H, m), 3.45-3.40 (1/2H, m), 3.35-3.20 (1H, m), 3.19-3.10 (1/2H, m), 2.88 (1/2H, dd, J 17.6 and 4.9 Hz, 11-H), 2.43 (1/2H, dd, J 18.3 Hz), 2.40-1.70 (7H, m), 1.60 (1/2H, m), 1.57

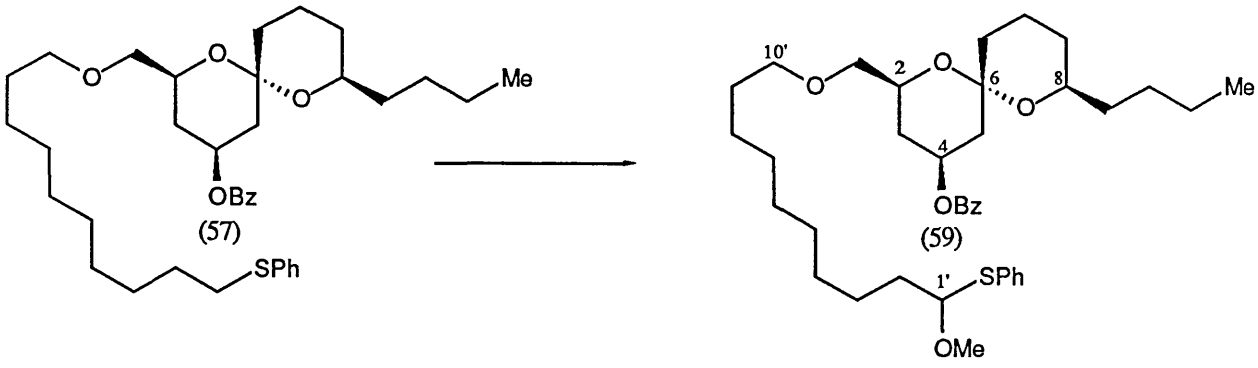
(3/2H, s, 9-Me), 1.14 (3/2H, d, J 5.5 Hz, 9-Me), 1.07 (9/2H, s, ^{t}Bu), 1.05 (9/2H, s, ^{t}Bu), m/z 623 (M^{+}-^{t}Bu), 517 (M^{+}-PhCHO), 487 (M^{+}-PhCHO-CH_2O), 199 (Ph_2SiOH).(Found: M^{+}-^{t}Bu, 623.2273 $C_{37}H_{39}O_5SSi$ requires M, 623.2288)

56. Preparation of (±)(2R,5S,6S,7S,9S)-7-t-Butyldiphenylsilyloxymethyl-9-methyl-2-phenyl-5-(2'-phenyslulphonylethan-1'-yl)-1,3-dioxaspiro-[5.5]-undec-10-ene (94), and (2R,5S,6S,7S)-7-t-Butyldiphenylsilyloxymethyl-9-methyl-2-phenyl-5-(2'-phenyslulphonylethan-1'-yl)-1,3-dioxaspiro-[5.5]-undec-9-ene (95).



Basic Woelm alumina (1.0g) was added to a solution of the mesylate (93) (10 mg, 0.013 mmol) in carbon tetrachloride (2 ml) under argon at r.t. After 16h ether was added and the solids removed by filtration. The filtrate was evaporated *in vacuo*. Column chromatography (40% ether-petrol) afforded the *alkenes* (94) and (95) (4.5 mg, 52%) as a clear oil and a 3:1 mixture of regioisomers. Spectral data identical to previously prepared material.

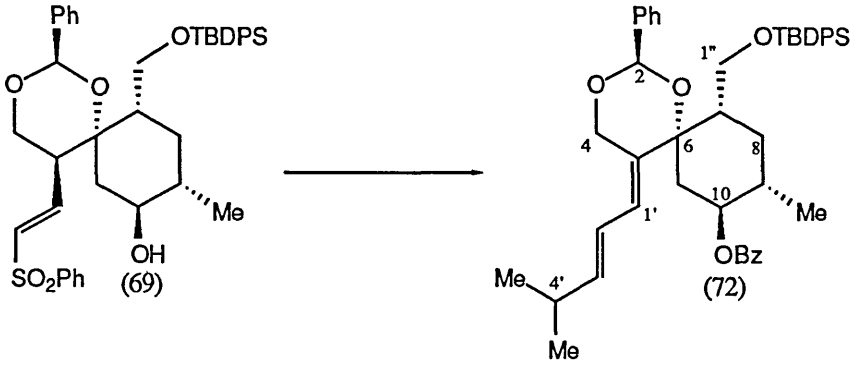
57. Preparation of (±) (2S,4S,6S,8R,1'(SR)) 8-Butyl-4-hydroxy-2-methyloxy-(1'-methoxy-1'-phenylthiodecan-10'-yl)-{1,7-dioxaspiro-[5.5]-undecane}(59).



N-Chloro-succinimide (5.5 mg, 0.041 mmol) was added to a solution of the sulphide (57) (20 mg, 0.039 mmol), in carbon tetrachloride (5 ml) , in the dark, under argon, at 0°C. The reaction was allowed to warm to r.t. After 4h anhydrous potassium carbonate (45 mg, 0.326 mmol) and sodium iodide (20 mg, 0.134 mmol) were added. After a further 2h, methanol (0.3 ml) was added, and the mixture poured into water and extracted with DCM. The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (50% ether-petrol) afforded the *mixed acetal* (59) (7 mg, 33%) as a clear oil; ν_{max} (film), 3388, 2929, 2855, 1538, 1437, 1366, 1097 and 986 cm^{-1}; δ (500 MHz), 7.48 (2H, m, Ph), 7.35-7.20 (3H, m, Ph), 4.63 (1H, t, J 6.5 Hz, 1'-H), 4.16 (1H, m, 4-H), 3.75 (1H, ddt, J 11.3, 2.0 and 5.5 Hz, 2-H), 3.60-3.40 (5H, m), 3.46 (3H, s, 1'-OMe), 2.0 (2H, br t, J 17.0 Hz), 1.86 (1H, qt, J 13.7 and 4.2 Hz, 10-H), 1.80-1.1 (22H, m), 0.88 (3H, d, J 7.4 Hz, Me),mz 504(M^+-MeOH), 426(M^+-PhSH), 395(M^+-PhSH-OMe)

(Found: M^+-MeOH, 504.3281 $C_{30}H_{48}O_4S$ requires M, 504.3273)

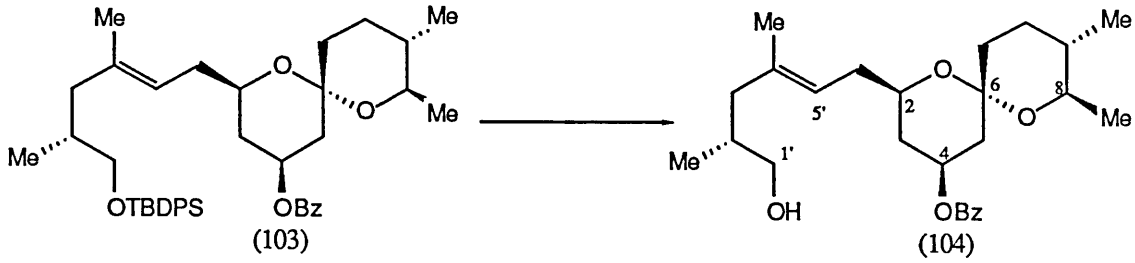
58. Preparation of (±) EE (2R,6S,7S,9S,10S) -10-Benzoyloxy-7-t-Butyldiphenyl-silyloxymethyl-9-methyl-5-(4'-methyl-2-pentenediylidene)-1,3-dioxaspiro[5.5]-undecane (72).



t-Butyl-lithium (0.077 ml, of a 1.7 M solution in pentanes, 0.131 mmol) was added dropwise to a stirred solution of the sulphone (69) (38 mg, 0.0545 mmol) in THF (0.75 ml), under argon, at -78°C. After 15 min, isobutyraldehyde (0.100 ml, 1.10 mmol) was added. After a further 2h, benzoyl chloride (0.127 ml, 1.10 mmol) was added and the mixture allowed to warm to r.t. 3-Dimethylaminopropylamine (0.10 ml, 0.8 mmol) was added before the mixture was poured into saturated sodium hydrogencarbonate solution. The mixture was extraced with ether, the extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (25% ether-petrol) of the residue afforded the benzoxysulphones. These were dissolved in THF: methanol 3:1 (4 ml), under argon, powdered disodium hydrogenphosphate (300 mg, 2.1 mmol) added, and the mixture cooled to -30°C.

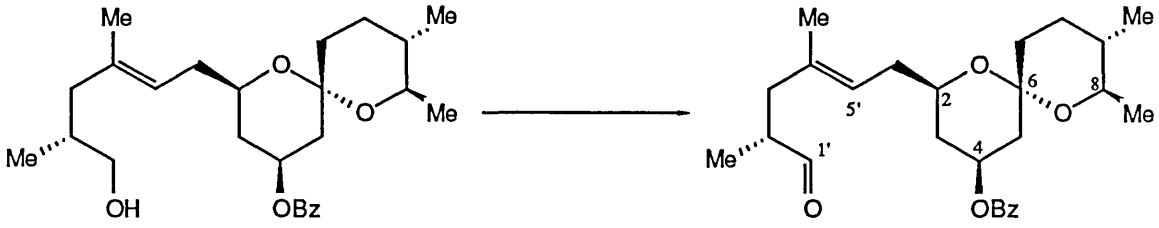
Powdered 6% sodium amalgam (240 mg, 1.74 mmol) was added to the vigorously stirred slurry. After 2h,ethylacetate (40 ml) was added and the solution filtered through a pad of solid ammonium chloride and silica gel and the filtrate evaporated *in vacuo*. Column chromatography (10% ether-petrol) of the residue afforded the *E,E diene* (72) (9 mg, 23%) as a clear oil, ν_{max} (film),3068, 2929, 2931, 2858, 1713, 1601, 1272, 1112, and 703 cm^{-1}; δ (500 MHz), 8.1-8.0 (2H, m, Ph), 7.75-7.60 (4H, m, Ph), 7.55-7.30 (14H, m, Ph), 5.95 (1H, ddd, J 15.0, 11.0 and 1.5 Hz, 2'-H), 5.96 (1H, s, 2-H), 5.87 (1H, d, J 11.0 Hz, 1'-H), 5.58 (1H, dd, J 15.0 and 7.0 Hz, 3'-H), 4.82 (1H, dt, J 3.5 and 10.8 Hz, 10-H), 4.65 (1H, d, J 13.5 Hz, 4-He), 4.52 (1H, d, J 13.5 Hz, 4-Ha), 4.09 (1H, dd, J 10.0 and 3.5 Hz, 1"-H), 3.63 (1H, t, J 10.0 Hz, 1"-H), 3.08 (1H, dd, J 13.6 and 4.0 Hz, 11-H), 2.35 (1H, m, 4'-H), 2.25 (2H, m, 7-H and 8-H), 1.93 (1H, m, 9-H), 1.51 (1H, q, J 13.0 Hz, 8-H), 1.39 (1H, dd, J 13.6 and 10.8 Hz, 11-H), 1.15-0.8 (18H, m, ^{t}Bu 9'-Me and 4'-Me_2); mz 675 (M^{+}-^{t}Bu), 608 (M^{+}-PhCHO), 593 (M^{+}-$PhCO_2$), 551 ((M^{+}-^{t}Bu-PhCHO), 199 (Ph_2SiOH), 43 (C_3H_7), (Found: M^{+}-^{t}Bu, 657.3029 $C_{42}H_{45}O_5Si$ requires M, 657.3005).

59. Preparation of (+)E-(2S,2'R,4S,6S,8R,9S) 4-Benzoyloxy-8-9-dimethyl-2-{2',4'-dimethylhex-4'-ene-1'-ol-6'-yl}-1,7-dioxaspiro-[5.5]-undecane (104).



Tetrabutylammonium fluoride (0.825 ml, of a 1M solution in THF, 0.825 mmol) was added dropwise to a stirred solution of the silylether (103) (368 mg, 0.550 mmol), in THF (5 ml), under argon, at 0°C. The solution was allowed to warm to r.t. over 10h, and the solvent evaporated *in vacuo*. Column chromatography (30% ether-petrol) of the residue afforded the *alcohol* (104) $[\alpha]^{25}_{D}$ + 67.7 (c 1.1 $CHCl_3$) (218 mg, 92%) as a clear oil; ν_{max} (film), 3426, 1716, 1273 and 713 cm^{-1}; δ (250 MHz), 8.05-7.34 (5H, m, Ph), 5.44 (1H, tt, J 10.0 and 4.8 Hz, 4-H), 5.26 (1H, t, J 6.9 Hz, 5'-H), 3.69 (1H, m, 2-H), 3.51 (1H, dd, J 10.0 and 4.5 Hz, 1'-H), 3.41 (1H, dd, J 10.0 and 4.5 Hz, 1'-H), 3.27 (1H, dq, J 9.4 and 6.5 Hz, 8-H), 2.32-1.20 (17H, m), 1.13 (3H, d, J 6.5 Hz, 8-Me), 0.88 (3H, d, J 6.5 Hz, 12-Me), 0.84 (3H, d, J 6.5 Hz, 9-Me), m/z 430 (M^+), 308 (M^+-$PhCO_2H$), 181 ($C_{18}H_{23}O_4$-$PhCO_2H$). (Found: C, 72.27; H, 9.07. $C_{26}H_{38}O_5$ requires C, 72.53; H, 8.90%).

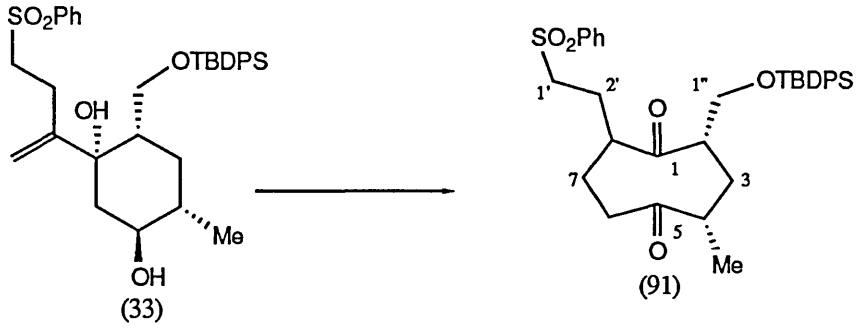
60. Preparation of (+) E, (2S, 2'R, 4S, 6S, 8R, 9S) 4-Benzoyloxy-8,9-dimethyl-2-{2'-4'-dimethylhex-4'-enal-6'-yl} -6- {1,7-dioxaspiro- [5.5]-undecane} (105).



DMSO (0.116 ml, 1.63 mol) was added dropwise to a stirred solution of oxalyl chloride (71µl, 0.814 mmol) in DCM (7.6 ml), under argon, at -65°C. After 5 min, the alcohol (104) (167 mg, 0.388 mmol) in DCM (9 ml), was added dropwise. After a further 20 min, triethylamine (0.272 ml, 1.95 mmol) was added and the reaction allowed to warm to r.t.. Water was added and the mixture extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (15% ether-petrol) of the residue afforded the aldehyde (105) (165mg, 99%) as a clear oil, $[\alpha]^{25}_D$ + 48.4 (c.1.8, $CHCl_3$), ν_{max} (film), 2929, 1717, 1449 and 713 cm^{-1}; δ (500MHz), 9.63 (1H, d, J 2.0 Hz, 1'-H), 8.00 (2H, m, Ph), 7.54 (1H, m, Ph), 7.42 (2H, m, Ph), 5.45 (1H, tt, J 10.5 and 4.0 Hz,4'-H), 5.28 (1H, t, J 6.5 Hz, 5'-H), 3.68 (1H, m, 2-H), 3.25 (1H, dq, J 9.4 and 6.3 Hz, 8-H), 2.52 (1H, m, 2'-H), 2.45 (1H, dd, J 13.8 and 6.4 Hz, 3'-H), 2.26 (2H, m, 6'-Hz), 2.17 (1H, m, 3'-H), 2.11 (1H, ddd, J 12.2, 4.9 and 1.7Hz), 2.01 (1H, dd, J 13.6 and 7.9 Hz), 1.70 (1H, dd, J 9.1 and 2.4 Hz), 1.66-

1.47 (7H, m), 1.32 (1H, q, J 11.6 Hz, 3-H), 1.26 (1H, m, 9-H), 1.13 (3H, d, J 6.3 Hz, 2' -Me), 1.05 (3H, d, J 6.8Hz, 2'-Me), 0.82 (3H, d, J 6.6 Hz, 9-Me); m/z 428 (M^+), 384 ($M^+ - C_2H_4O$), 327 ($M^+ - C_2H_4-C_3H_5O$), 303 ($C_{18}H_{23}O_4$), 181 ($C_{18}H_{23}O_4 - PhCO_2H$), (Found: $M^+ - C_2H_4O$, 384.2303 $C_{24}H_{32}O_4$ requires M, 384.2301).

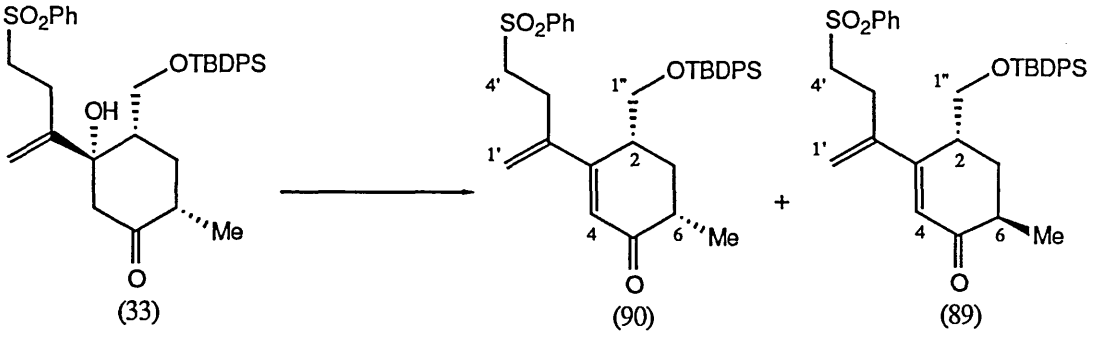
61. Preparation of (±) (2S,4S, 8R) -2-t-Butyldiphenylsilyloxymethyl-4-methyl-5-oxo-8-(1'-phenylsulphonylethan-2'-yl) cyclooctan-1-one (91).



Diisopropylamine (0.050ml, 0.357mmol) was added dropwise to a stirred solution of potassium t-butoxide (40mg, 0.357mmol) in THF (1ml), under argon, at -40°C. After 5min, the solution was cooled to -78°C and n-butyl-lithium (0.148 ml of a 2.4M solution in hexane, 0.355 mmol) was added over 3 min. After a further 1h, the ketone (33) (100mg, 0.169 mmol) was added in THF (1.5ml). T.L.C. analysis, (75% ether-petrol) after 1h, showed that the ketone had been almost consumed and a slightly more polar product had been formed. MoOPH (78 mg, 0.179 mmol) was added to the briefly opened flask and the resulting mixture allowed to warm to r.t. After 30 min

saturated ammonium chloride solution was added to the syrupy yellow solution and the mixture extracted with ether. The ether extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) afforded the *starting ketone* (33) (20 mg 20%) and the cyclooctanone (91) (60mg, 60%) both as white foams. More polar: (91), ν_{max} (film), 3070, 2933, 2858, 1709, 1588, 1448, 1373, 1307, 1112, 1087 and 802 cm^{-1}. δ (400MHz), 8.00-7.30 (15H, m, Ph), 3.81 (1H, t, J 9.5Hz, 1"-H), 3.45 (1H, dd, J 9.5 and 5.0 Hz, 1"-H), 3.28 (2H, m, 2-H and 1'-H), 2.95-2.83 (2H, m, 1'-H and 4-H), 2.81 (1H, m, 8-H), 2.68 (1H, m, 6-H), 2.49 (1H, ddd, J 15.0, 7.0 and 3.0 Hz, 7-H), 2.34 (1H, ddd, J 15.0, 12.0 and 3.0Hz, 7-H), 2.20 (1H, m, 2'-H), 1.98 (1H, dtd, J 16.0, 7.0 and 3.0 Hz, 6-H), 1.73 (1H, ddd, J 19.0, 10.0 and 4.0Hz, 2'-H), 1.53 (1H, dt, J 13.0 and 3.0Hz, 3-H), 1.40 (1H, q, J 13.0Hz, 3-H), 0.98 (9H, s, ^tBu), 0.96 (3H, d, J 7.0Hz, 4-Me), m/z 533 (M^+-^tBu), 455 (M^+-^tBu-Ph), 391 (M^+-^tBu-$PhSO_2H$), 334 (M^+- ^tBu Ph_2SiOH).(Found: M^+-^tBu, 533.1827 $C_{30}H_{33}O_5SSi$ requires M, 533.1818)

62. Preparation of (±)(4S, 6S) 4-t-Butyldiphenylsilyloxymethyl-6-methyl-3-(4'-phenylsulphonylbut-1'-ene-2'-yl) cyclohexeneone (89) and (±) (4S, 6R) 4-t-Butyldiphenylsilyloxymethyl-6-methyl-3-(4'-phenyl-sulphonylbut-1'-ene-2'-yl) cyclohexeneone (90).



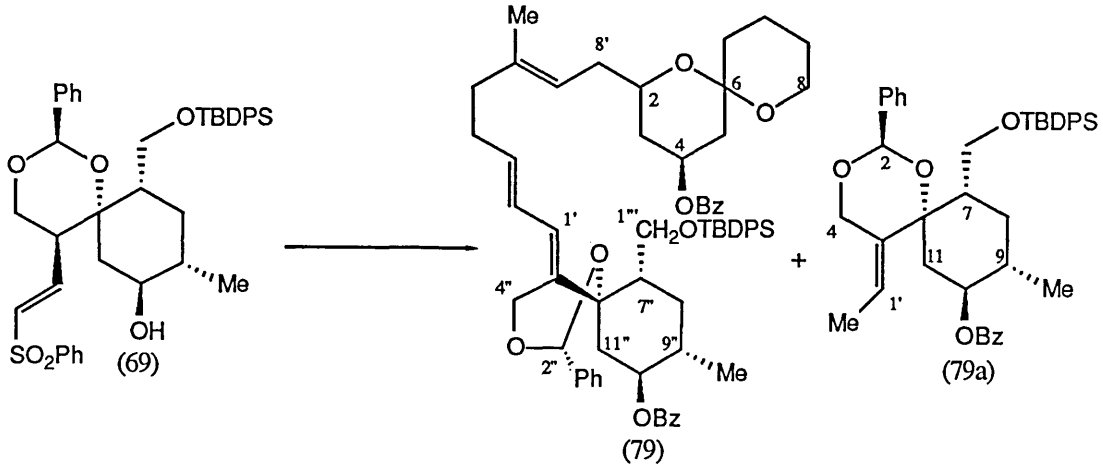
N-methyl N-trimethylsilyl O-trimethylsilylhydroxylamine (32.4 mg, 0.169 mmol), acetyl chloride (0.013 ml, 0.186 mmol and the ketone (33) (100 mg, 0.169 mmol) in toluene (1ml) under argon, were heated at reflux. After 5 min, the reaction was cooled to r.t. and the solvent evaporated *in vacuo*. Column chromatography (50% ether-petrol) afforded the *enones* (89) and (90), (75mg, 77%) as a clear oil and a 10:1 mixture of diastereoisomers: ν_{max}(film) 2930, 2857, 1673, 1666 and 703cm^{-1};

Major: (90), δ (300 MHz), 7.90-7.30 (15H, m, Ph), 5.69 (1H, s, 2-H), 5.16 (1H, s, 1'-H), 5.14 (1H, s, 1'-H), 3.60 (2H, m, 1"-H_2), 3.00 (2H, m, 4'-H_2), 2.76 (1H, m, 6-H), 2.55 (2H,m, 3'-H_2), 2.42-2.28 (2H, m, 4-H and 5-H), 1.67 (1H, dt, J 14.4 and 5.0 Hz, 5-H), 1.05 (3H, d, J 7.0Hz, 6-Me), 0.98 (9H, s, ^{t}Bu).

Minor: (89), δ (250MHz), 7.90-7.35 (15H, m, Ph), 5.81 (1H, d, J 1.0Hz, 2-H), 4.97, (1H, s, 1'-H), 4.91 (1H, s, 1'-H), 3.68 (1H, dd, J 10.0 and 4.0 Hz, 1"-H),

3.56 (1H, dd, J 10.0 and 6.5Hz, 1"-H), 3.01 (2H, m, 4'-H_2), 2.78 (1H, m, 6-H), 2.53 (2H, m, 3'-H_2), 2.36 (1H, m, 4-H), 2.19 (1H, m, 5-H), 1.78 (1H, m, 5-H), 1.16 (3H, d, J 7.5Hz, 6-Me), 1.00 (9H, s, ^{t}Bu); m/z 515 (M^+-^{t}Bu), 316 (M^+-^{t}Bu Ph_2SiOH), 199 (Ph_2SiOH) (Found: M^+-^{t}Bu, 515.1702 $C_{30}H_{31}O_4SSi$ requires M, 515.1712).

63. Preparation of (±) EEE (2S,2"R, 4S, 6S, 6"S, 7"S, 9"S, 10"S) 4-Benzoyloxy-2-10"-benzoyloxy-7"-t-butyldiphenylsilyloxymethyl-9"-methyl-5"-(6'-methylocta-2',6'- enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-1,7-dioxaspiro-[5.5]-undecane (79) and (±) E (2R, 6S, 7S, 9S, 10S)-10-Benzoyloxy-7-t-butyldiphenylsilyloxymethyl-5-ethylidene-9-methyl-1,3-dioxaspiro-[5.5]-undecane (79a).

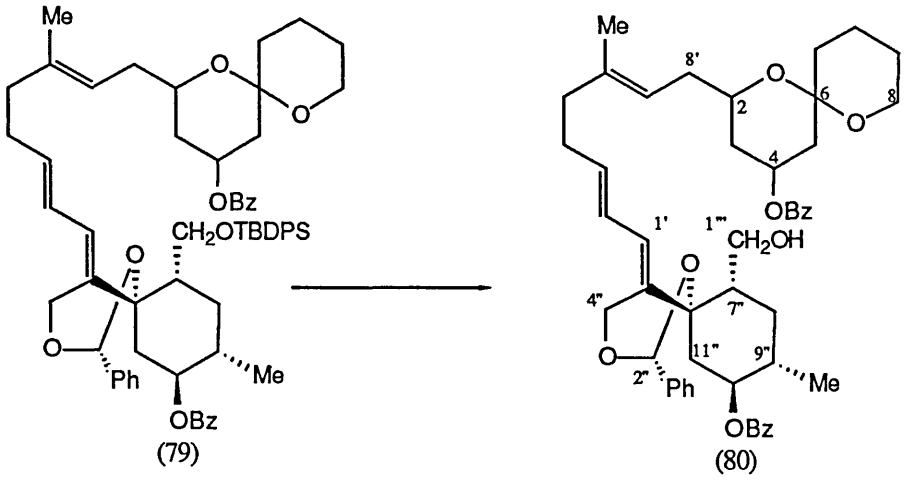


t-Butyl-lithium (0.425 ml of a 1.7m solution in pentanes, 0.723 mmol) was added dropwise to a stirred solution of the sulphone (69) (240mg, 0.344mmol) in THF (3.25

ml), under argon, at -78°C. After 20 min, the aldehyde (78) (102 mg, 0.264 mmol) in THF (2 ml) was added. After a further 1.5h benzoyl chloride (0.12 ml, 1.03 mmol) was added and the mixture allowed to warm to r.t. 3 dimethylaminopropylamine (0.10 ml, 0.8 mmol) was added before the mixture was poured into saturated sodium hydrogencarbonate solution. The mixture was extracted with ether, the extracts washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (50% ether-petrol) afforded the *benzoxy sulphones*. These were dissolved in THF: ethanol 3:1 (7.3 ml), under argon and powdered disodium hydrogenphosphate (660 mg, 4.6 mmol) added, and the mixture cooled to -30°C. Powdered 6% sodium amalgam (543 mg, 1.42 mmol) was added to the vigorously stirred slurry. After 35 min, the reaction was cooled to -78°C, ethylacetate (100 ml) and powdered ammonium chloride were added and the mixture rapidly filtered through a pad of solid ammonium chloride and silica gel. The filtrate was evaporated *in vacuo*. Column chromatography (20% ether-petrol) afforded the *alkene* (79a) (258mg, 13%) and the *EE diene* (79) (68 mg, 25%) both as clear oils.Less Polar: (79a), ν_{max} (film), 3068, 2931, 2857, 1710, 1602, 1450, 1112, and 737 cm^{-1}; δ (500MHz), 8.15-8.05 (2H, m, Ph), 7.75-7.65 (4H, m, Ph), 7.58 (1H, m, Ph), 7.50-7.30 (14H, m, Ph), 5.98 (1H, s, 2-H), 5.22 (1H, br q, J 6.0 Hz, 1'-H), 4.88 (1H, dt, J 10.5 and 3.0 Hz, 10-H), 4.56 (1H, d, J 14.0 Hz, 4-H), 4.43(1H, d, J 14.0Hz, 4-H), 4.30 (1H, dd, J 10.5 and 3.0 Hz, 1"-H), 3.70 (1H, d, J 10.5 Hz, 1"-H), 3.12 (1H, dd, J 13.5 and 4.5 Hz, 11-H), 2.29 (1H, dt, J 14.0 and 3.0Hz, 8-H),

2.17 (1H, m, 7-H), 1.90 (1H, m, 9-H), 1.53 (1H, q, J 14.OHz, 8-H), 1.44 (3H, d, J 13.5 and 11.5Hz, 11-H), 1.33 (1H, ddd, J 13.5 and11.5 Hz, 11-H), 1.08 (9H, s, ^{t}Bu), 1.06 (3H, d, J 7.0 Hz, 9-Me), m/z 660 (M^{+}), 603 (M^{+}-^{t}Bu), 573 (M^{+}-^{t}Bu-CH_2O), 497 (M^{+}-^{t}Bu-PhCHO), 481 (M^{+}-^{t}Bu-$PhCO_2H$), 375 (M^{+}-^{t}Bu-PhCHO-$PhCO_2H$), 199 (Ph_2SiOH); More Polar: (79) ν_{max} (film), 3067, 3932, 1712, 1602, 1585, 1273, 1111 and 710 cm^{-1}; δ (500MHz). 8.02 (4H, m, Ph), 7.75-7.30 (21H, m, Ph), 6.04 (1H, dd, J 14.5 and 11.0Hz, 2'-H), 5.96 (1H, s, 2"-H), 5.87 (1H, d, J 10.9 Hz, 1'-H), 5.62 (1H, ddt, J 14.5, 2.9 and 7.5Hz, 3'-H), 5.43 (1H, tt, J 11.4 and 4.9Hz, 4-H), 5.29 (1H, t, J 7.2Hz, 7'-H), 4.85 (1H, dt, J 4.0 and 10.9 Hz, 10"-H), 4.66 (1H, d, J 14.5Hz, 4"-H), 4.53 (1H, d, J 14.5Hz, 4"-H), 4.10 (1H, dd, J 10.2 and 3.2 Hz, 1'"-H), 3.73 (1H, m, 2-H), 3.70-3.55 (3 H, m, 1'"-H and 8-H_2), 3.09 (1H, dd, J 13.6 and 4.0Hz, 11"-H), 2.40-2.05 (6H, m), 2.00-1.80 (1H, m), 1.68 (1H,m), 1.64 (3H, s, 6'-Me), 1.62-1.20 (13H, m,) 1.08-1.01 (12H, m, ^{t}Bu and 9"-Me); m/z 800 (M^{+}-PhCHO-$PhCO_2H$) 678 (M^{+}-PhCHO-2$PhCO_2H$), 660 (M^{+}-PhCHO-2$PhCO_2H$-H_2O), 153 ($C_9H_{13}O_2$).

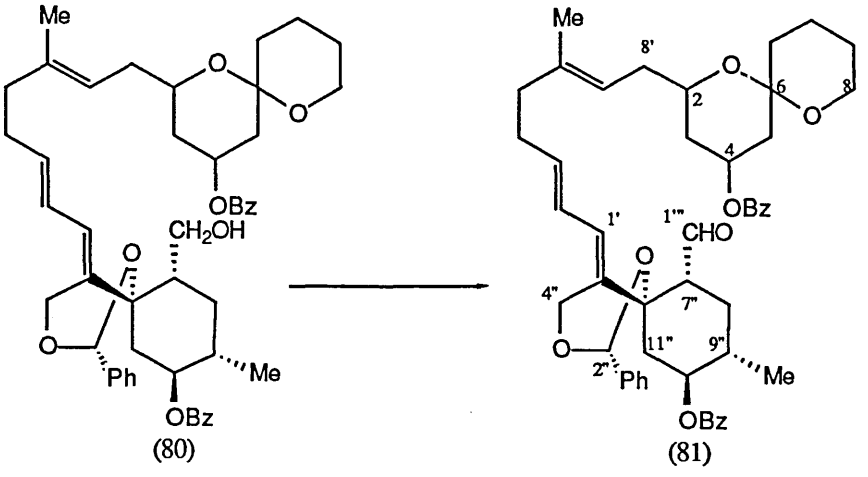
64. Preparation of (±) EEE (2S, 2"R, 4S, 6S, 6"S, 7"S, 9"S, 10"S) 4-Benzoyloxy-2-{10"-Benzoyloxy-7"-hydroxymethyl-9"-methyl-5"-(6'-methylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-1,7-dioxaspiro-[5.5]undecane (80).



Tetrabutylammonium fluoride (0.055 ml, of a 1 M solution in THF, 0.055 mmol) was added dropwise to a stirred solution of the silylether (79) (37 mg 0.036 mmol) in THF (3 ml) under argon, at r.t. The solution was heated to reflux and after 50 min, cooled to r.t., and the solvent evaporated *in vacuo*. Column chromatography (50% ether-petrol) of the residue afforded the *alcohol* (80) (22 mg, 77%) as a clear oil. ν_{max} (film), 3498, 2937, 1711, 1449, 1273, 1111 and 713 cm^{-1}; δ (500MHz), 8.05-7.90 (4H, m, Ph), 7.60-7.30 (11H, m, Ph), 6.10 (1H, dd, J 14.5 and 10.9Hz, 2'-H), 6.00 (1H, s, 2"-H), 5.87 (1/2 H, d, J 10.9 Hz, 1'-H), 5.85 (1/2 H. d. J 10.9 Hz, 1'-H), 5.68 (1H, dt, J 14.5 and 7.4Hz, 3'-H), 5.37 (1H, tt, J 11.4 and 4.9Hz, 4-H), 5.21 (1H, t, J 7.3Hz, 6'-H), 4.90-4.80 (2H, m, 4"-H and 10"-H), 4.63 (1H, d, J 14.0Hz, 4"-H), 3.91 (1H, br d, J 10.6Hz, 2-H0, 3.75-3.45 (4H, m, 1"'-Hz and 8-Hz), 3.10

(1H, dd, J 14.0 and 3.0Hz, 11"-H), 2.35-1.20 (25H, m), 1.02(3H,d,J 6.1 Hz, 9"-Me), mz639 (MH^+-$PhCO_2H$-H_2O), 562 (M^+-$PhCO_2H$-PhCHO), 544 (M^+-$PhCO_2H$-PhCHO-H_2O), 440 (M^+-2$PhCO_2H$-PhCHO), 422(M^+-2PhCO2H-PhCHO-H_2O), 153 ($C_9H_{13}O_2$), (Found: M^+-$PhCO_2H$-PhCHO-H_2O, 544.3184 $C_{35}H_{44}O_5$ requires M, 544.3189).

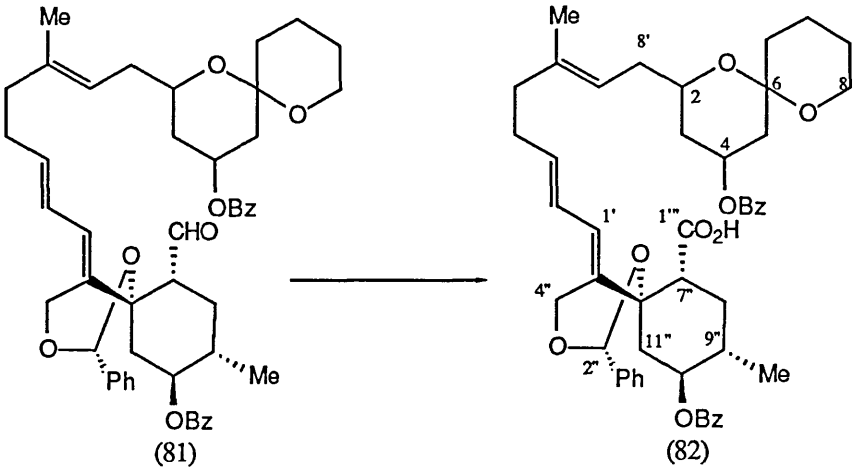
65. Preparation of (±)EEE(2S, 2"R, 4S, 6S, 6"S, 7"S, 9"S, 10"S) 4-Benzoyloxy-2-{10"-benzoyloxy-7"-formyl-9"-methyl-5"-(6'-methylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-1,7-dioxaspiro-[5.5]-undecane (81).



DMSO (0.0156 ml, 0.22 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.0096 ml, 0.11 mmol) in DCM (1 ml) under argon at -78°C. After 5 min, the alcohol (81) (29 mg, 0.037 mmol) in DCM (3 ml) was added dropwise.

After a further 20 min triethylamine (0.052 ml, 0.37 mmol) was added and the reaction allowed to warm to r.t. Water was added and the mixture extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (25% ether-petrol) afforded the *aldehyde* (81) (29 mg, 100%) as a clear oil. ν_{max} (film) 2930, 1713, 1601, 1449, 1272, 1110 and 713 cm^{-1}; δ (500MHz), 9.89 (1/2H, d, J 2.2 Hz, 1'''-H), 9.88 (1/2H, d, J 2.2 Hz, 1'''-H), 8.10-8.00 (4H, m, Ph), 7.60-7.35 (11H, m, Ph), 6.17 (1H, dd, J 14.9 and 10.7Hz, 2'-H), 6.14 (1H, s, 2"-H), 5.98 (1H, d, J 10.7 Hz, 1'-H), 5.79 (1H, dt, J 14.0 and 6.9Hz, 3'-H), 5.41 (1H, tt, J 11.4 and 4.9Hz, 4-H), 5.27 (1H, t, J 7.0Hz, 7-H), 4.93 (1H, d, J 14.2Hz, 4"-H), 4.91 (1H, m, 10"-H), 3.75-3.70 (1H, m, 2-H), 3.65-3.50 (2H, m, 8-H_2), 3.30 (1H, dd, J 13.8 and 3.9Hz, 11"-H), 2.83 (1H, m, 7"-H), 2.35-2.00 (8H, m), 2.00-1.25 (12H,m) 1.57 (3H, s, 6'-Me), 1.06 (3/2H, d, J 6.1Hz, 9"-Me), 1.05 (3/2H, d, J 6.1Hz, 9"-Me), m/z 666 (M^+-$PhCO_2H$) 542 (M^+-$PhCO_2H$-PhCHO-H_2O), 420 (M^+-2$PhCO_2H$-PhCHO-H_2O), 153, ($C_9H_{13}O_2$). (Found: M^+-$PhCO_2H$-PhCHO-H_2O, 542.3026 $C_{34}H_{42}O_5$ requires M, 542.3032).

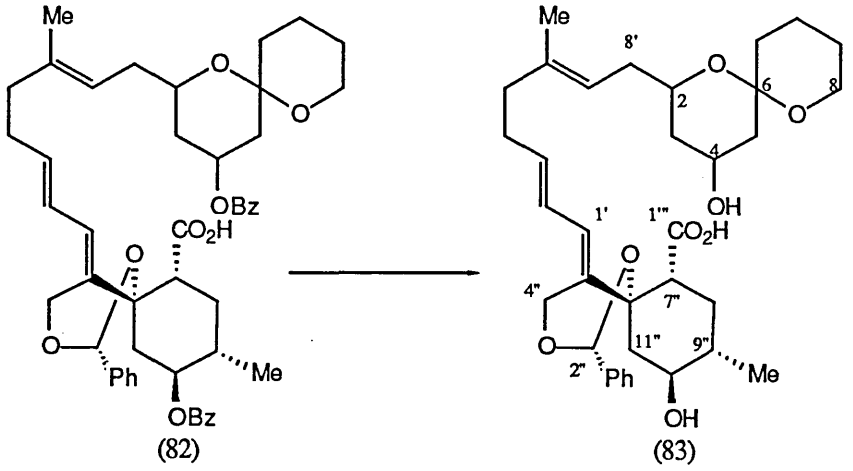
66. Preparation of (±) EEE (2S, 2"R 4S, 6S, 6"S, 7"S, 9"S, 10"S) 4-Benzoxyloxy-2 {10"-benzoyloxy-7"carboxyl-9"-methyl-5"-(6'-methylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl)-1,7-dioxaspiro-[5.5]-undecane (82).



2-Methyl-2-butene (0.5 ml), was added to a stirred solution of the aldehyde (81) (28 mg, 0.035 mmol) in t-butanol (0.8 ml) and water (0.8 ml) at r.t. Potassium dihydrogen phosphate (96 mg, 0.69 mmol) and sodium chlorite (32 mg, 0.35 mmol) were added. After 2.5h the mixture was diluted with DCM and dilute aqueous sodium sulphite solution added. The mixture was extracted with DCM, the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the *acid* (82) (28 mg, 100%) as a clear oil. ν_{max} (film), 3500-2600, 2934, 1711, 1449, 1272, 1177, 1111 and 713 cm^{-1}; δ (500MHz), 9.95 (1H, br, s, 1'''-H), 8.10-7.95 (4H, m, Ph), 7.70-7.35 (11H, m, Ph), 6.26 (1H, s, 2"-H), 6.20-6.10 (2H, m, 1'H and 2'-H), 5.93-5.82 (1H, m, 3'-H), 5.42 (1H, m, 4-H), 5.26 (1H, t, 6.7 Hz, 7'-H), 5.00 (1/2H, d, J 14.3 Hz, 4"-H), 4.97 (1/2H, d, J 14.3 Hz, 4"-H), 4.93 (1H, dt, J 2.8 and 10.9 Hz, 10"-

H), 4.62 (1H, d, J 14.3 Hz, 4"-H), 3.73 (1H, m, 2-H), 3.68-3.55 (2H, m, 8-H_2), 3.35 (1H, dd, J 3.8 and 14.1 Hz, 11"-H), 3.14 (1H, dt, J 4.5 and 13.2 Hz, 7"-H), 2.40-1.15 (20H, m), 1.65 (3H, s, 6'-Me), 1.07 (3H, d, J 6.1 Hz, 9"-Me).

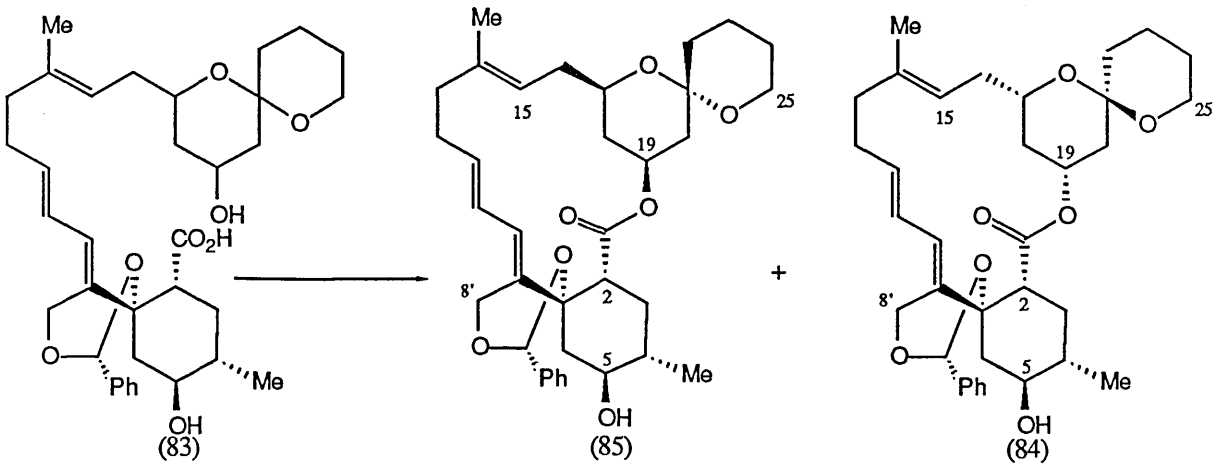
67. Preparation of (±) EEE (2S, 2"R, 4S, 6S, 6"S, 7"S, 9"S, 10"S) 2{7"-carboxy-10"-hydroxy-9"-methyl-5"-(6'-methylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-4-hydroxy-1,7-dioxaspiro-[5.5]-undecane (83).



Sodium methoxide (0.15 ml of a 1.81 M solution in methanol, 0.272 mmol) was added dropwise to a stirred solution of the acid (82) (4.7 mg, 5.85 mmol) in methanol (0.5 ml), under argon at r.t. After 6h, powdered ammonium chloride and toluene 20 ml were added and the mixture filtered. The solids were washed exhaustively with ethyl acetate. The filtrate was evaporated *in vacuo* to afford the *hydroxy acid* (83) (3.3 mg, 100%) as a clear oil. ν_{max} (film), 3385-2500, 2926, 1717, 1449, 1380 and

1043 cm^{-1}; δ (500MHz), 7.50-7.30 (5H, m, Ph), 6.20-6.05 (2H, m, 1'-H and 2'-H), 6.03 (1/2H, s, 2"-H), 6.00 (1/2H, s, 2"-H), 5.84 (1/2H, dt, J 13.6 and 6.9 Hz, 3'-H), 5.76 (1/2H, ddd, J 14.6, 8.3 and 5.3 Hz, 3'-H), 5.20 (1/2H, t, J 6.8 Hz, 7'-H), 5.16 (1/2H, t, J 7.5 Hz, 7'-H), 4.97 (1/2H, d, J 14.1 Hz, 4"-H), 4.94 (1/2H, d, J 14.1 Hz, 4"-H), 4.62 (1/2H, d, J 14.1 Hz, 4"-H), 4.58 (1/2H, d, J 14.1 Hz, 4"-H), 4.10 (1/2H, tt, J 11.0 and 4.8 Hz, 4-H), 4.03 (1/2H, tt, J 11.2 and 6.4 Hz, 4-H), 3.75-3.45 (4H, m, 2-H, 8-H_2 and 10"-H), 3.10-3.00 (2H, m, 7"-H and 11"-H), 2.40-2.10 (6H, m), 2.10-1.70 (6H, m), 1.67 (3/2H, s, 6'-Me), 1.65 (3/2H, s, 6'-Me), 1.70-1.20 (10H, m), 1.08 (3/2H, d, J 6.1Hz, 9'-Me), 1.07 (3/2H, d, J 6.1Hz, 9'-Me), m/z; 560 (M^+-$2H_2O$), 542 (M^+-$3H_20$), 454 (M^+-PhCHO-$2H_2O$), 436 (M^+-PhCHO-$3H_2O$), 418 (M^+-PhCHO-$4H_2O$), 153 ($C_9H_{13}O_2$). (Found: M^+-PhCHO-$3H_2O$, 436.2622 $C_{28}H_{36}O_4$ requires 436.2614).

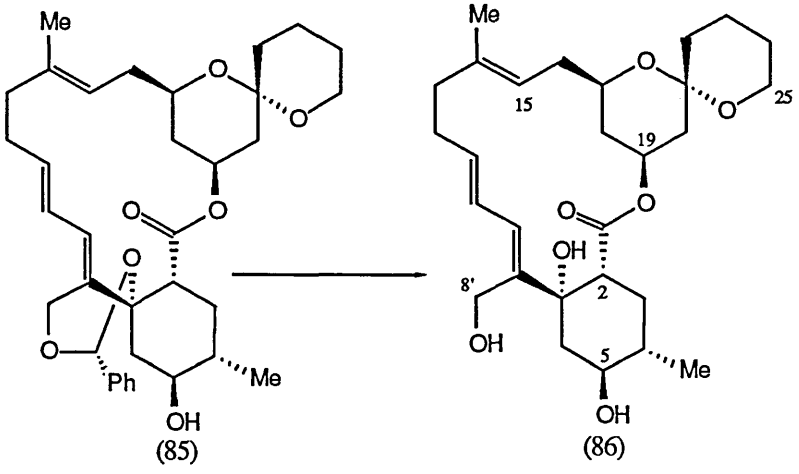
68. Preparation of (±) 5-O-demethyl-12,24,25-demethyl-3,4-dihydro-7,8'-O-phenylmethylatropomilbemycin β1 (85) and its diastereoisomer (84)



A solution of the seco-acid (83) (12.5 mg, 0.021 mmol) and triethylamine (0.023 ml in 0.165 mmol), in acetonitrile (1.65 ml) was added (below the liquid surface) over 8h to a solution of 2-chloro-1-methyl pyridinium iodide (21.2 mg, 0.083 mmol) in acetonitrite (2 ml) at reflux under argon. After a further 1h the reaction was cooled to r.t. and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue afforded the *macrolactones* (84) (1.8 mg, 15%) and (85) (1.6 mg, 13%) both as clear colourless oils. Less polar: (84), ν_{max} (film) 3482, 2926, 1742, 1449, 1377, 1259, 1220, 1101, 1041 and 907 cm^{-1}. δ (500MHz), 7.64 (2H, m, Ph), 7.40-7.30 (3H, m, Ph), 6.08-6.00 (2H, m, 9-H and 10-H), 5.93 (1H, s, PhCH), 5.59 (1H, m, 11-H), 5.24 (1H, tt, J 11.3 and 5.2 Hz, 19-H) 5.14 (1H, m, 15-H), 4.78 (1H, d, J 13.9 Hz, 8'-H), 4.49 (1H, d, J 13.9 Hz, 8'-H), 3.76 (1H, m, 17-H), 3.60-3.45 (3H, m, 5-H and 25-H_2), 2.99 (1H, dd, J 13.9 and 4.3 Hz, 6-H), 2.91 (1H, dd, J 12.6 and 3.5 Hz, 2-H), 2.40-2.15 (4H, m), 2.05-1.82 (3H, m), 1.80-1.63 (3H, m,), 1.60-1.40 (8H, m), 1.48 (3H, s, 14-Me), 1.36(1H, t, J 11.9 Hz), 1.25-1.05 (2H, m), 1.03 (3H, d, J 6.4 Hz, 4-Me), m/z 578 (M^+), 560 (M^+-H_2O), 472 (M^+-PhCHO), 454 (M^+-PhCHO-H_2O), 436 (M^+-PhCHO-$2H_2O$), 153 ($C_9H_{13}O_2$). (Found: M^+, 578.3244 $C_{35}H_{46}O_7$ requires M, 578.3244). More polar: (85); ν_{max} (film), 3482, 2930, 1704, 1448, 1253, 1218 and 1035 cm^{-1}; δ (500 MHz). 7.55-7.50 (2H, m, Ph), 7.38-7.30 (3H, m, Ph), 5.99(1H, dd, J 14.1 and 10.8 Hz, 10-H), 5.94 (1H, s, PhCH), 5.93 (1H, d, J 10.8 Hz, 9-H), 5.55 (1H, ddd, J 14.1, 10.3 and 4.6 Hz, 11-H), 5.27 (1H, tt, J 11.5 and 4.6 Hz, 19-H), 4.88 (1H, d, J 9.7 Hz, 15-H),

4.74 (1H, d, J 13.7 Hz, 8'-H), 4.50 (1H, d, J 13.7 Hz, 8'-H), 3.70 (1H, dt, J 11.6 and 6.4 Hz, 17-H), 3.60 (1H, dt, J 11.1 and 2.7 Hz, 25-H), 3.53 (1H, br d, J 11.1 Hz, 25-H), 3.48 (1H, tt, J 10.5 and 4.5 Hz, 5-H), 3.02 (1H, dd, J 13.9 and 4.4 Hz, 6-H), 2.97 (1H, m, 2-H), 2.40-1.80 (10H, m), 1.70-1.20 (9H, m), 1.51 (3H, s, 14-Me), 1.02 (3H, d, J 6.4 Hz, 4-Me), 0.74 (1H, q, J 11.8 Hz, 18-H); m/z 578 (M^+), 560 (M^+-H_2O), 472 (M^+-PhCHO), 454 (M^+-PhCHO-H_2O), 153 ($C_9H_{13}O_2$).(Found: M^+, 578.3244 $C_{35}H_{46}O_7$ requires M, 578.3244).

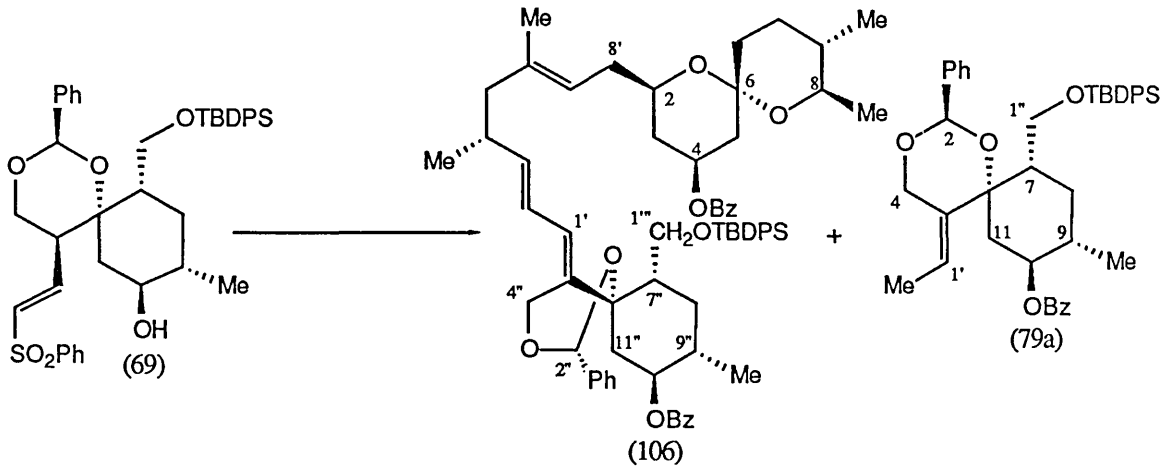
69. Preparation of (±) 5-O-demethyl-12,24,25-demethyl-3,4-dihydroatropomilbemycin β_1 (86).



Trifluoroacetic acid (0.005 ml, 0.065 mmol) was added to a stirred solution of the macrolide (85) (1.0 mg, 1.73 mmol) in DCM (0.5 ml) at r.t. After 30 min, benzene (5 ml) was added and the solvent evaporated *in vacuo*. Column chromatography (ether) of the residue afforded the *triol* (86) (1.0 mg, 100%) as a clear oil. ν_{max} (film) 3390, 2934, 1724, 1436, 1250, 1219, 1040, 1013 and 731cm^{-1}; δ (500 MHz), 6.28-

6.21 (2H, m, 9H and 10-H), 5.61 (1H, m, 11-H), 5.17 (1H, tt, J 11.6 and 4.7 Hz, 19-H), 5.04 (1H, brt, J 6.6 Hz, 15-H), 4.26 (2H, m, 8'-Hz), 3.74 (1H, m, 17-H), 3.66 (1H, m, 25-H), 3.57 (1H, dt, J 2.5 and 11.3 Hz, 5-H), 3.52 (1H, m, 25-H), 3.28 (1H, d, J 2.7 Hz, 7-OH), 2.87 (1H, dd, J 12.8 and 3.6Hz, 2-H), 2.40-2.30 (2H, m, 16-H_2), 2.06 (1H, dd, J 13.2 and 4.6 Hz), 1.93 (1H, ddd, J 12.1, 4.8 and 1.9 Hz), 1.90-1.80 (2H, m), 1.77 (1H, m), 1.72-1.24 (15H, m), 1.51 (3H, s, 14-Me), 1.07 (3H, d, J 6.4 Hz, 4-Me), 0.88 (1H, q, J 11.8 Hz, 18-H); m/z 490 (M^+), 472 (M^+-H_2O), 454 (M^+-$2H_2O$), 436 (M^+-$3H_2O$), 171 ($C_9H_{15}O3$), 153 ($C_9H_{13}O_2$), 125 ($C_9H_{13}O_2$-C_2H_4). (Found: M^+, 490.2926, $C_{28}H_{42}O_7$ requires M, 490.2931)

70. Preparation of (-) EEE (2S, 2"R, 4S, 4'R, 6S, 6"S, 7"S, 8R, 9S, 9"S, 10"S) 4-Benzoyloxy-2-{10"-benzoyloxy-7"-t-butyldiphenylsilyloxymethyl-9"-methyl-5"- (4',6'- dimethylocta-2'6'- enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane- 8'-yl}-8,9-dimethyl-1,7-dioxaspiro-[5.5]-undecane (106) and E (2R, 6S, 7S, 9S, 10S) 10-Benzoxyloxy-7-t-butyldiphenylsilyloxymethyl-5-ethylidene-9-methyl-1,3-dioxaspiro-[5.5]-undecane (79a).

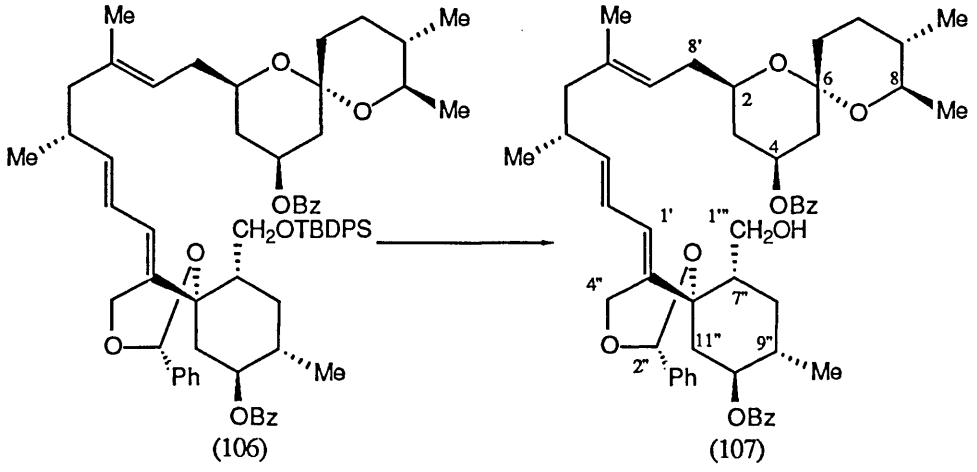


t-Butyl-lithium (0.190 ml of a 1.7M solution in pentanes, 0.323 mmol) was added dropwise to a stirred solution of the sulphone (69) (103 mg, 0.148 mmol) in THF (1.5 ml), under argon, at -78°C. After 15 min, the aldehyde (105) (60 mg, 0.140 mmol) in THF (2.5 ml) was added. After a further 1h, saturated ammonium chloride solution (1 ml) was added and the mixture allowed to warm to r.t. Water was added and the mixture extracted with ether. The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) of the residue gave the *hydroxy sulphones* (120 mg, 77%) as a white foam.

Benzoyl chloride (0.247 ml, 0.543 mmol) was added to a stirred solution of the hydroxysulphones (120 mg, 0.083 mmol) and 4-N,Ndimethylaminopyridine (13 mg, 0.106 mmol) in pyridine (5 ml) under argon at O°C. After 48h, the reaction was poured into saturated copper II sulphate solution and extracted with DCM. The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (25-60% ether - petrol) afforded the benzoxysulphones (146 mg, 95%) as an oil. Powdered 6% sodium amalgam (410 mg, 1.07 mmol) was added to a vigourously stirred slurry of disodiumhydrogen phosphate (665 mg, 4.6 mmol) and the benzoxy sulphones (146 mg, 0.104 mmol) in THF: methanol, 3:1, (6 ml) under argon, at -40°C. After 40 min, the reaction was cooled to -78°C, ethyl acetate (50 ml) and powdered ammonium chloride were added and the mixture filtered rapidly through a pad of ammonium chloride and silica gel. The filtrate was evaporated *in vacuo*. Column chromatography (10% ether-petrol) of the residue afforded the *alkene* (79a) (12 mg, 12%) and the *EE diene* (106) (44 mg, 29%) both as clear oils. (Less polar (79a); spectral data identical to previously prepared material. More polar (106) $[\alpha]^{25}_D$ - 1.2° (C, 0.1); ν_{max}(film), 2929, 1713, 1605, 1581, 1449,1271, 1111, 1025 and 757 cm^{-1}; δ (500 MHz), 8.06-8.00 (4H, m, Ph), 7.70-7.28 (21H, m, Ph), 6.02 (1H, dd, J 14.8 and 10.8 Hz, 2'-H), 5.99 (1H, s, 2"-H), 5.88 (1H, d, J 10.8 Hz, 1'-H), 5.59 (1H, dd, J 14.8 and 7.1 Hz, 3'-H), 5.47 (1H, tt, J 11.4 and 4.9 Hz, 4-H), 5.25 (1H, t, J 7.0 Hz, 7'-H), 4.86 (1H, dt, J 3.9 and 10.9 Hz, 10"-H), 4.68 (1H, d, J 14.4 Hz, 4"-H), 4.54 (1H, d, J 14.4 Hz, 4"-H), 4.12 (1H, dd, J 10.2 and

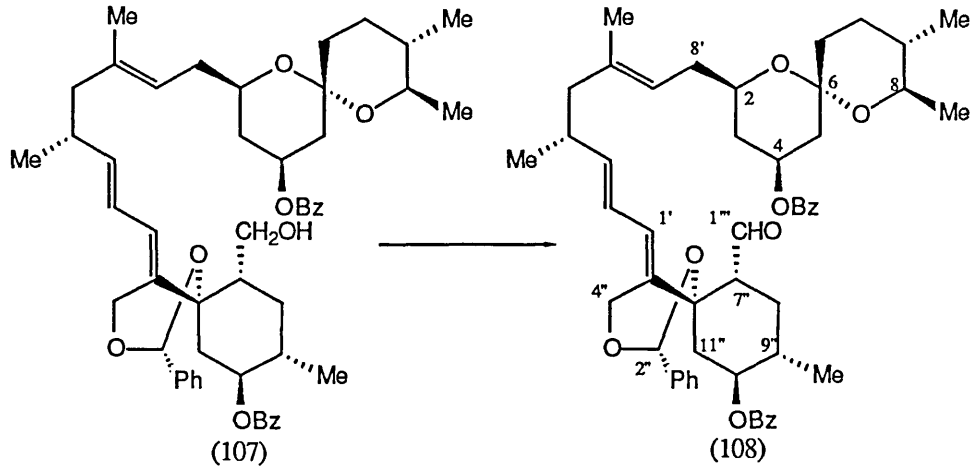
3.0 Hz, 1'''-H), 3.71-3.60 (2H, m, 1'''-H and 2-H), 3.30 (1H, dq, J 9.7 and 6.3 Hz, 8-H), 3.11 (1H, dd J 13.5 and 3.9 Hz, 11"-H), 2.38 (1H, m, 4'-H), 2.35-2.05 (8H, m,), 1.90 (1H, m), 1.88 (1H, dd, J 13.5 and 9.1 Hz), 1.72 (1H, m), 1.62 (3H, s, 6'-Me), 1.60-1.20 (7H, m), 1.14 (3H, d, J 6.3 Hz, 8-Me), 1.06 (9H, s, ^{t}Bu), 1.05 (3H, d, J 6.6 Hz, Me), 0.95 (3H, d, J 6.7 Hz, Me), 0.83 (3H, d, J 6.6 Hz, Me); m/z 842 (M^{+}-$PhCO_2H$-PhCHO), 824 (M^{+}-2$PhCO_2H$), 785 (M^{+}-^{t}Bu-$PhCO_2H$-PhCHO), 720 (M^{+}-2$PhCO_2H$-PhCHO), 702 (M^{+}-2$PhCO_2H$-PhCHO-H_2O), 663 (M^{+}-2$PhCO_2H$-PhCHO-^{t}Bu), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4), (Found: M^{+}-2$PhCO_2H$-PhCHO, 720.4556 $C_{47}H_{64}O_4Si$ requires M, 720.4574).

71. Preparation of (-)EEE (2S,2"R,4S,4'R,6S,6"S,7"S,8R,9S,9"S,10"S) 4-Benzoyloxy-2-{10"-Benzoyloxy-7"-hydroxymethyl-9"methyl-5"-(4',6'-dimethylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-8,9-dimethyl-1,7-dioxaspiro-[5.5]-undecane (107).



Tetrabutylammonium fluoride (0.300 ml) of a 1M solution in THF, 0.30 mmol) was added dropwise to a stirred solution of the silylether (106) (157 mg, 0.147 mmol) in THF (3 ml), under argon, at r.t. The solution was heated to reflux and after 1h cooled to r.t. and the solvent evaporated *in vacuo*. Column chromatography (40% ether-petrol) of the residue afforded the *alcohol* (107) (110 mg, 90%) as a clear oil. $[\alpha]^{25}_{D} = -23°$ (c. 1.5, $CHCl_3$); ν_{max} (film), 3501, 2940, 1712, 1440, 1275, 1112, 710 cm^{-1}; δ (500MHz), 8.10 (15H, m, Ph), 6.01 (1H, dd, J 15.3 and 10.6 Hz, 2'-H), 5.97 (1H, s, 2"-H), 5.86 (1H, d, J 10.6 Hz, 1'-H), 5.58 (1H, dd, J 15.3 and7.0 Hz, 3'-H), 5.46 (1H, m, 4-H), 5.23(1H, m, 7'-H), 4.85 (1H, dt, J 4.7 and10.8 Hz, 10"-H), 4.67 (1H, d, J 14.7 Hz, 4"-H), 4.54 (1H, d, J 14.7 Hz, 4"-H), 4.11 (1H, m, 1'"-H), 3.66 (1H, m, 1'"-H), 3.61 (1H, m, 2-H), 3.25 (1H, dq, J 12.1 and 6.2 Hz, 8-H), 3.10 (1H, dd, J 12.0 and 6.3 Hz, 11"-H), 2.45-1.83 (10H, m), 1.70-1.15 (10H, m), 1.61 (3H, s, 6'-Me), 1.10 (3H, d, J 6.6 Hz, Me), 1.05 (3H, d, J 6.6 Hz, Me), 0.94 (3H, d, J 6.6 Hz, Me), 0.80 (3H, d, J 6.6 Hz, Me), m/z; 586 (M^+-PhCO2H-PhCHO-H2O, 482 (M^+-2$PhCO_2H$-PhCHO), 464 (M^+-2$PHCO_2H$, PhCHO-H_20), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4), (Found: M^+-$PhCO_2H$-PhCHO-H_2O), 586.3651, $C_{38}H_{50}O_5$ requires M, 586.3659).

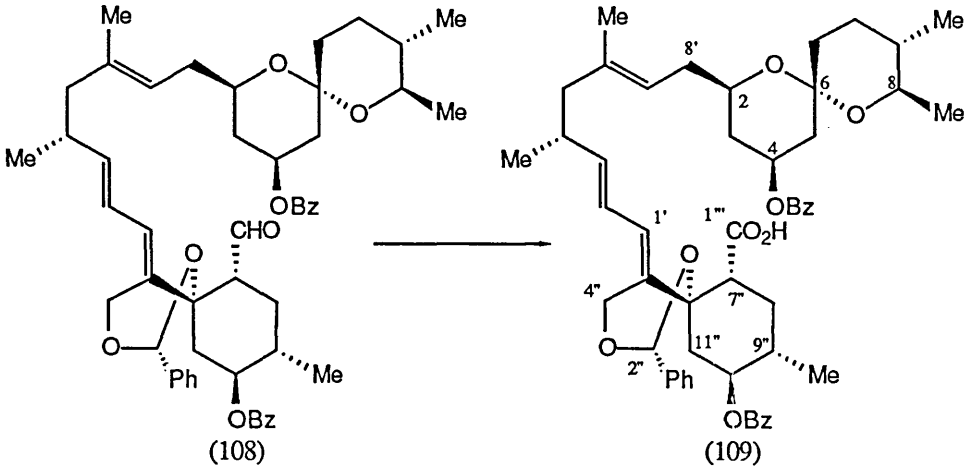
72. Preparation of (-)EEE (2S,2"R,4S,4'R,6S,6"S,7"S,8R,9S,9"S,10"S) -4-Benzoyloxy-2-{10"-Benzoyloxy-7"-formyl-9"methyl-5"-(4',6'-dimethylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-8,9-dimethyl-1,7-dioxaspiro-[5.5]-undecane (108).



DMSO (0.075 ml, 1.06 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.046 ml, 0.527 mmol) in DCM (6 ml), under argon, at -65°C. After 5 min the alcohol (107) (110 mg, 0.132 mmol) in DCM (12 ml) was added dropwise. After a further 20 min triethylamine (0.185 ml 1.32 mmol), was added and the reaction allowed to warm to r.t. Water was added, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (25% ether-petrol) of the residue afforded the *aldehyde* (108) (102 mg, 93% as a clear oil. [a]25D -27.4° (C 2.1, $CHCl_3$); ν_{max} (film) 3065, 2962, 2928, 1714, 1602, 1584, 1450, 1314, 1272, 1112, and 713 cm^{-1}; δ (500 MHz), 9.88 (1H, d, J 2.3 Hz, 1'''-H), 8.10-7.90 (4H, m, Ph),

7.60-7.30 (11H, m, Ph), 6.14 (1H, s, 2"-H), 6.11 (1H, ddd, J 14.9, 10.7 and 0.9 Hz, 2'-H), 5.97 (1H, d, J 10.7 Hz, 1'-H), 5.74 (1H, dd, J 14.9 and 7.1 Hz, 3'-H), 5.45 (1H, tt, J 11.4 and 4.9 Hz, 4-H), 5.22 (1H, t, J 6.5 Hz, 7'-H), 4.91 (1H, d, J 14.2 Hz, 4"-H), 4.90 (1H, m, 10"-H), 4.66 (1H, dd, J 14.2 and 1.0 Hz, 4"-H), 3.68 (1H, m, 2-H), 3.35-3.25 (2H, m, 8-H and 11"-H), 2.82 (1H, ddd, J 12.2, 4.3 and 2.3 Hz, 7"-H), 2.41 (1H, m, 4'-H), 2.35-2.25 (1H, m), 2.25-2.15 (2H, m), 2.15-2.00 (2H, m), 1.95-1.70 (3H, m), 1.60 (3H, s, 6'-Me), 1.60-1.45 (6H, m), 1.41 (1H, dd, J 13.8 and 11.3 Hz), 1.32 (1H, q, J 11.6 Hz), 1.13 (3H, d, J 6.2 Hz, 8-Me), 1.05 (3H, d, J 6.1 Hz, Me), 0.96 (3H, d, J 6.7 Hz, Me), 0.83 (3H, d, J 6.6 Hz, Me), m/z 602 (M^+-PhCHO-$PhCO_2H$), 584 (M^+-PhCHO-$PhCO_2H$-H_20), 480 (M^+-PhCHO-2$PhCO_2H$), 462 (M^+-PhCHO-2$PhCO_2H$-H_20), 181 ($C_{11}H_{17}O_2$). (Found: M^+-PhCHO-2$PhCO_2H$-H_2O, 462.3134 $C_{31}H_{42}O_3$ requires M, 462.3134).

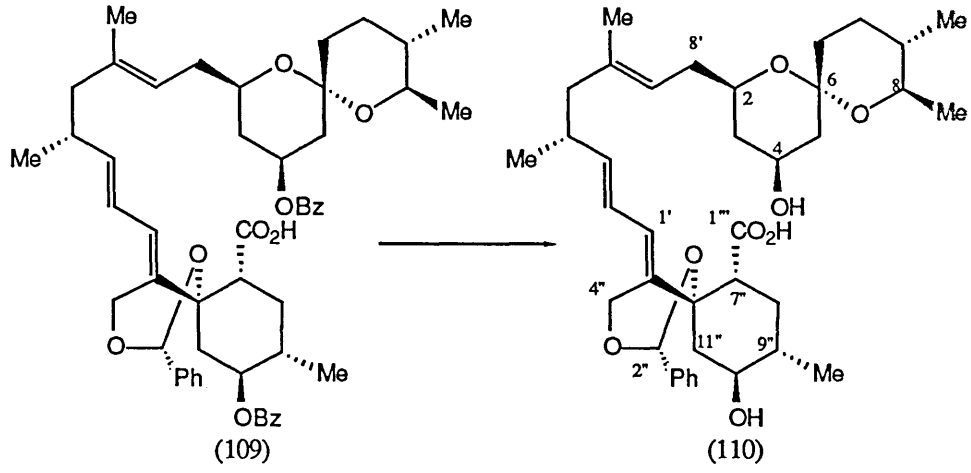
73. Preparation of (-) EEE (2S,2"R,4S,4'R,6S,6"S,7"S,8R,9R,9"S,10"S)-4-Benzoyloxy-2{10"-benzoyloxy -7"-carboxyl-9"-methyl-5"-(4',6-dimethylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-8,9-dimethyl-1,7-dioxaspiro-[5.5]-undecane (109).



2-Methyl-2-butene (2 ml) was added to a stirred solution of the aldehyde (108) (102 mg, 0.144 mmol) in t-butanol (2.5 ml) and water (2.5 ml), at r.t. Potassium dihydrogen phosphate (335 mg, 2.41 mmol) and sodium chlorite (111 mg, 1.21 mmol) were added. After 2.5 h, the mixture was diluted with DCM and dilute aqueous sodium sulphite solution added. The mixture was extracted with DCM, the combined extracts were dried ($MgSO_4$), and evaporated *in vacuo* to afford the *acid* (109) (102 mg, 99%), as a clear oil $[\alpha]^{25}_D$ - 34.3° (c 2.3, $CHCl_3$), ν_{max} (film), 3600-2800, 3063, 2966, 2929,1713,1601,1584, 1272, 1113 and 713 cm^{-1}; δ (500 MHz), 9.95 (1H, br s, 1"-H), 8.10-7.90 (4H, m, Ph) 7.60-7.35 (11H, m, Ph), 6.26 (1H, s, 2"-H), 6.15-6.05 (2H, m, 1'-H and 2'-H), 5.84 (1H, dd, J 13.7 and 7.0 Hz, 3'-H),

5.45 (1H, tt, J 11.4 and 4.9 Hz, 4-H), 5.23 (1H, t, J 7.5 Hz, 7'-H), 4.99 (1H, d, J 14.2 Hz, 4"-H), 4.94 (1H, dt, J 3.8 and 11.0 Hz, 10"-H), 4.63 (1H, d, J 14.2 Hz, 4"-H), 3.68 (1H, m, 2-H), 3.35 (1H, dd, J 14.0 and 3.8 Hz, 11"-H), 3.28 (1H, dq, J 9.8 and 6.3 Hz, 8-H), 3.14 (1H, dd, J 12.8 and 4.0 Hz, 7"-H), 2.41 (1H, m, 4'-H), 2.35-2.00 (7H, m), 2.00-1.60 (4H, m), 1.60 (3H, s, 6'-Me), 1.58-1.16 (6H, m), 1.13 (3H, d, J 6.3 Hz, 8-Me), 1.06 (3H, d, J 6.4 Hz, Me), 0.95 (3H, d, J 6.7 Hz, Me), 0.83 (3H, d, J 6.6 Hz, Me); m/z 696 (M^+-PhCHO-CO_2), 574 (M^+-PhCHO-$PhCO_2H$-CO_2), 556 (M^+-PhCHO-$PhCO_2H$-CO_2-H_2O),452 (M^+-PhCHO-2$PhCO_2H$-CO_2), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4), (Found: M^+-PhCHO-2$PhCO_2H$-CO_2 452.3281 $C_{30}H_{44}O_3$ requires M, 452.3290).

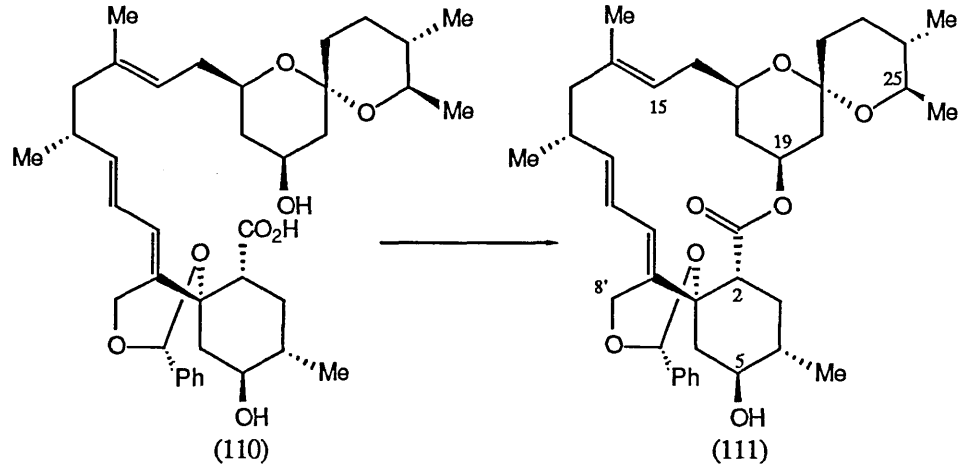
74. Preparation of EEE (2S,2"R,4S,4'R,6S,6"S,7"S,8R,9R,9"S,10"S)-2-{ 7"-carboxyl-10"-hydroxy-9"-methyl-(4',6'-dimethylocta-2',6'-enediylidene)-2"-phenyl-1",3"-dioxaspiro-[5.5]-undecane-8'-yl}-4-hydroxy-8,9-dimethyl-1,7-dioxaspiro-[5.5]-undecane (110).



Sodium methoxide (5.0 ml of a 2.8 M solution in methanol, 14.0 mmol) was added dropwise to a stirred solution of the acid (109) (102 mg, 0.120 mmol) in methanol (5 ml), under argon, at r.t. After 2h, powdered ammonium chloride and toluene were added and the mixture filtered. The solids were washed exhaustively with ethyl acetate and the combined filtrate evaporated *in vacuo*; to yield the *hydroxy acid* (110), (76 mg, 99%) as a clear oil. ν_{max} (film), 3386, 2927, 1716, 1570, 1449, 1381, 1096, 1030 and 733 cm^{-1}; δ (500 MHz), 10.10 (1H, br s, 1'''-H), 7.50-7.30 (5H, m, Ph), 6.15-5.85 (2H, m, 1'-H and 2'-H), 5.92 (1H, s, 2"-H), 5.56 (1H, dd, J 14.2 and 8.5 Hz, 3'-H), 5.06 (1H, t, J 7.3 Hz, 7'-H), 4.75 (1H, br d, J 14.5 Hz, 4"-H), 4.56 (1H, d, J 14.5 Hz, 4"-H), 4.01 (1H, tt, J 11.2 and 4.8 Hz, 4-H),

3.48 (1H, dt, J 4.0 and 11.0 Hz, 10"-H), 3.46 (1H, m, 2-H), 3.29 (1H, dq, J 9.8 and 6.2 Hz, 8-H), 2.89 (2H, m, 7"-H and 11-H), 2.40 (1H, m, 4'-H), 2.25-2.10 (2H, m), 2.10-1.85 (5H, m), 1.76 (1H, q, J 12.7 Hz), 1.59 (3H, s, 6'-Me), 1.70-1.10 (11H, m), 1.14 (3H, d, J 6.2 Hz, 8-Me), 1.07 (3H, d, J 6.3 Hz, Me), 1.00 (3H, d, J 6.7 Hz, Me), 0.81 (3H, d, J 6.5 Hz, Me), m/z 620 (M^+-H_2O), 532 (M^+-PhCHO), 514 (M^+-PhCHO-H_2O), 496 (M^+-PhCHO-$2H_2O$), 470 (M^+-PhCHO-H_2O-CO_2), 181 ($C_{11}H_{17}O_2$). (Found: M^+-PhCHO-H_2O-CO_2, 470.3388 $C_{30}H_{46}O_4$ requires M, 470.3396).

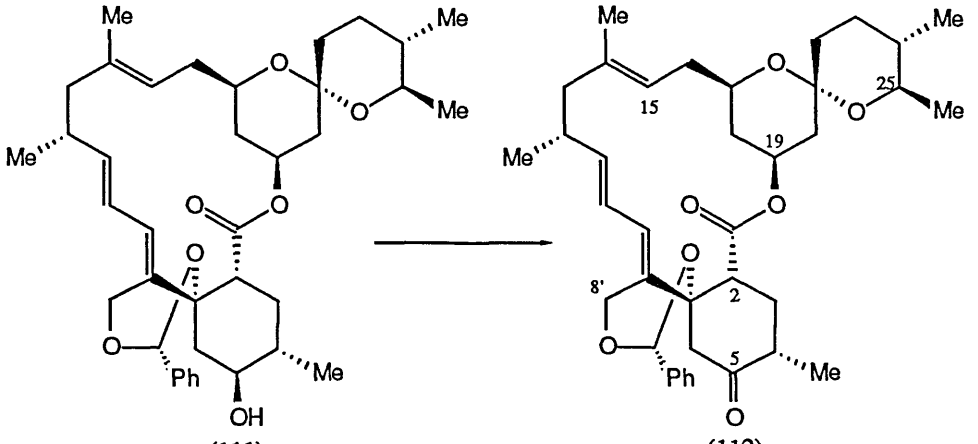
75. Preparation of (+) 5-O-Demethyl-3,4-dihydro-7,8'-O-phenylmethylatropomilbemycin β1 (111).



A solution of the seco acid (110) (76 mg, 0.119 mmol) and triethylamine (0.152 ml, 1.09 mmol), in acetonitrile (5 ml) was added (below the liquid surface) over 8h, to a solution of 2-chloro-1-methylpyridinium iodide (139 mg, 0.544 mmol) in

acetonitrile (18 ml), at reflux, under argon. After a further 2h, the reaction was cooled to r.t. and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue afforded the *macrolactone* (111) (50 mg, 68%) as a clear oil. $[\alpha]^{25}_{D}$ + 142° (c 1.0, $CHCl_3$), ν_{max} (film), 3482, 2954, 2926, 1704, 1449, 1308, 1097 and 995 cm^{-1}; δ (500 MHz), 7.56-7.50 (2H, m, Ph), 7.36-7.28 (3H, m, Ph), 6.05-5.95 (2H, m, 9-H and 10-H), 5.94 (1H, s, PhCH), 5.36 (1H, dd, J 13.5 and 10.2 Hz, 11-H), 5.30 (1H, tt, J 11.5 and 4.4 Hz, 19-H), 4.85 (1H, d, J 11.1 Hz, 15-H), 4.73 (1H, d, J 13.6 Hz, 8'-H), 4.51 (1H, d, J 13.6 Hz, 8'-H), 3.64 (1H, ddt, J 5.2, 2.0 and 10.6 Hz, 17-H), 3.47 (1H, tt, J 10.6 and 5.0 Hz, 5-H), 3.26 (1H, dq, J 9.7 and 6.2 Hz, 25-H), 3.02 (1H, dd, J 13.8 and 4.4 Hz, 6-H), 2.97 (1H, m, 2-H), 2.43 (1H, m, 12-H), 2.24 (1H, br d, J 13.5 Hz), 2.17 (1H, br d, J 13.1 Hz), 2.11 (1H, dt, J 13.5 and 11.0 Hz), 2.00 and 1.80 (5H, m), 1.65-1.40 (7H, m), 1.52 (3H, s, 14-Me), 1.25 (1H, m), 1.16 (1H, dd, J 13.8 and 11.2 Hz), 1.12 (3H, d, J 6.2 Hz, 25-Me), 1.02 (3H, d, J 6.0 Hz, Me), 1.01 (3H, d, J 6.2 Hz, Me), 0.81 (3H, d, J 6.6 Hz, Me), 0.70 (1H, q, J 11.8 Hz, 18-H), m/z 620 (M^+), 602 (M^+-H_2O), 576 (M^+-CO_2), 514 (M^+-PhCHO), 496 (M^+-PhCHO-H_2O), 478 (M^+-PhCHO-$2H_2O$), 470 (M^+-PhCHO-CO_2), 452 (M^+-PhCHO-CO_2-H_2O), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^+, 620,3726 $C_{38}H_{52}O_7$ requires M, 620.3713)

76. Preparation of (+) 3,4-Dihydro-5-oxo-7,8'-O-phenylmethylatropomilbemycin β1 (112).

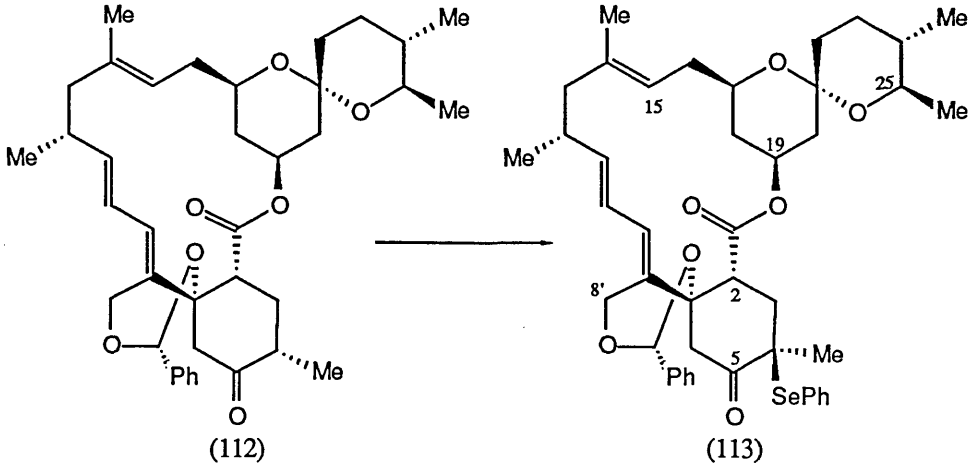


(111) (112)

DMSO (0.046 ml, 0.648 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.028 ml, 0.321 mmol) in DCM (3 ml), under argon, at -65°C. After 5 min, the alcohol (111) (50mg, 0.081 mmol) in DCM (5 ml) was added dropwise. After a further 20 min, triethylamine (0.112 ml, 0.804 mmol) was added and the reaction allowed to warm to r.t. Water was added and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (30% ether-petrol) afforded the *ketone* (112) (45 mg, 90%) as a clear oil, $[\alpha]^{25}_D$ + 207° (c 1.15, $CHCl_3$), ν_{max} (film), 2966, 1712, 1450, 1307, 1257, 1095, 997 and 733 cm^{-1}; δ (500 MHz), 7.50-7.40 (2H, m, Ph), 7.35-7.28 (3H, m, Ph), 6.05 (1H, d, J 10.7 Hz, 9-H), 5.97 (1H, dd, J 14.5 and 10.7 Hz, 10-H), 5.88 (1H, s, PhCH), 5.41 (1H, dd, J 14.5 and 10.1 Hz, 11-H), 5.31 (1H, tt, J 11.5 and 4.9 Hz, 19-H), 4.86 (1H, d, J 11.2 Hz, 15-H), 4.73 (1H, d, J 13.8 Hz, 8'-H), 4.45 (1H, d, J 13.8 and 1.0 Hz, 8'-H), 3.65 (1H,

ddt, J 2.0, 5.3 and 12.6 Hz, 17-H), 3.47 (1H, d, J 14.3 Hz, 6-H), 3.43 (1H, dd, J 12.7 and 3.8 Hz, 2-H), 3.27 (1H, dq, J 9.7 and 6.2 Hz, 25-H), 2.50-2.30 (2H, m), 2.35-2.05 (6H, m), 1.92 (1H, br t, J 12.1 Hz), 1.86 (1H, t, J 12.4 Hz), 1.65-1.40 (6H, m), 1.54 (3H, s, 14-Me), 1.26 (1H, m), 1.12 (3H, d, J 6.2 Hz, 25 -Me), 1.02 (3H, d, J 6.6 Hz, Me), 1.01 (3H, d, J 6.4 Hz, Me), 0.82 (3H, d, J 6.6 Hz, Me), 0.70 (1H, q, J 11.8 Hz, 18-H); m/z: 618 (M^+), 600 (M^+-H_2O), 512 (M^+-PhCHO), 494 (M^+-PhCHO-H_2O), 476 (M^+-PhCHO-$2H_2O$), 188 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^+, 618.3564 $C_{38}H_{50}O_7$ requires 618.3557)

77. Preparation of (+) 4β-Benzeneselenenyl-5-oxo-7,8'-O-phenylmethylatropomilbemycin β1 (113).

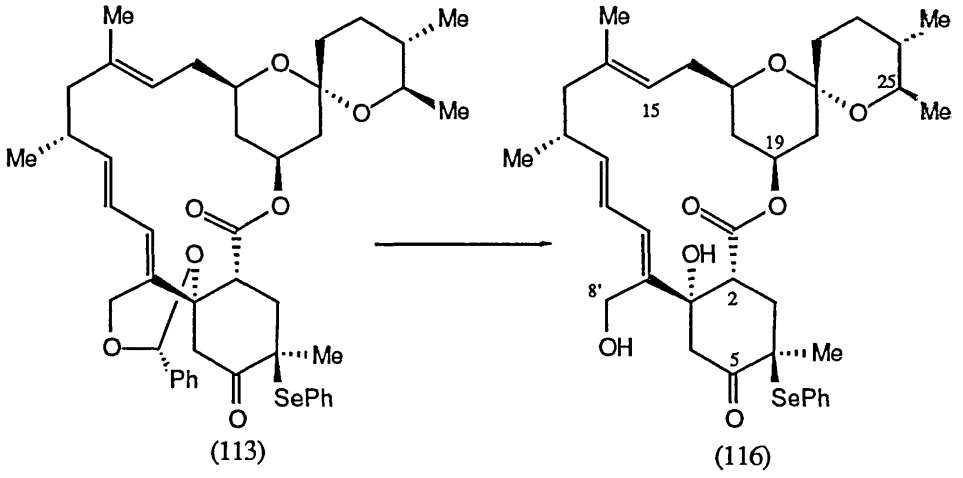


t-Butyldimethylsilyltriflate (37.2 µl, 0.162 mmol), was added dropwise to a stirred solution of the ketone (112) (10 mg; 0.0016 mmol) and triethylamine (0.073 ml, 0.524 mmol) in DCM (1 ml), under argon, at r.t. After 3h, the reaction was

cooled to -78°C and benzeneselenenyl chloride (155 mg, 0.809 mmol) in DCM (1 ml) was added dropwise. The reaction was stirred at - 20°C for 10 min, whereupon saturated sodium hydrogencarbonate solution (1 ml) was added and the mixture allowed to warm to r.t. Water was added and the mixture extracted wtih DCM. The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue afforded the *selenide* (113) (11.5 mg, 92%) as a clear oil, $[\alpha]^{25}_D$ + 194° (c 0.6, $CHCl_3$), ν_{max} (film), 2963, 1702, 1450, 1307, 1265, 1195, 993 and 741 cm^{-1}; δ (500 MHz), 7.49 (2H, dd, J 7.5 and 1.1 Hz, Ph), 7.40 (2H, m, Ph), 7.35-7.20 (6H, m, Ph), 6.12 (1H, d, J 10.6 Hz, 9-H), 6.10 (1H, dd, J 14.5 and 10.6 Hz, 10-H), 5.84 (1H, s, PhCH), 5.43 (1H, dd, J 14.5 and 9.5 Hz, 11-H), 5.32 (1H, tt, J 11.6 and 4.3 Hz, 19-H), 4.88 (1H, d, J 10.85 Hz, 15-H), 4.77 (1H, d, J 12.5 Hz, 8'-H), 4.46 (1H, d, J 12.5 Hz, 8'-H), 3.82 (1H, dd, J 13.2 and 4.3 Hz, 2-H), 3.66 (1H, dt, J 10.6 and 4.4 Hz, 17-H), 3.37 (1H, d, J 13.0 Hz, 6-H), 3.31 (1H, d, J 13.0 Hz, 6-H), 3.28 (1H, dq, J 9.7 and 6.2 Hz, 25-H), 2.55 (1H, t, J 13.2 Hz), 2.47 (1H, m), 2.35-2.05 (4H, m), 1.96 (1H, br d, J 11.5 Hz), 1.92-1.85 (2H, m), 1.62 (1H, d, J 9.3 Hz), 1.56 (3H, s, 14-Me), 1.55-1.40 (3H, m), 1.36 (3H, s, 4-Me), 1.30-1.20 (2H, m), 1.13 (3H, d, J 6.2 Hz, 25-Me), 1.04 (3H, d, J 6.6 Hz, Me), 0.83 (3H, d, J 6.7 Hz, Me), 0.71 (1H, q, J 11.6 Hz, 18-H); m/z: 668 (M^+-PhCHO), 618 (MH^+-PhSeH), 600 (MH^+-PhSeH-H_2O), 512 (MH^+-PhCHO-PhSeH), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^+-PhCHO, 668.2606 $C_{37}H_{48}O_6Se$ requires M,

668.2616).

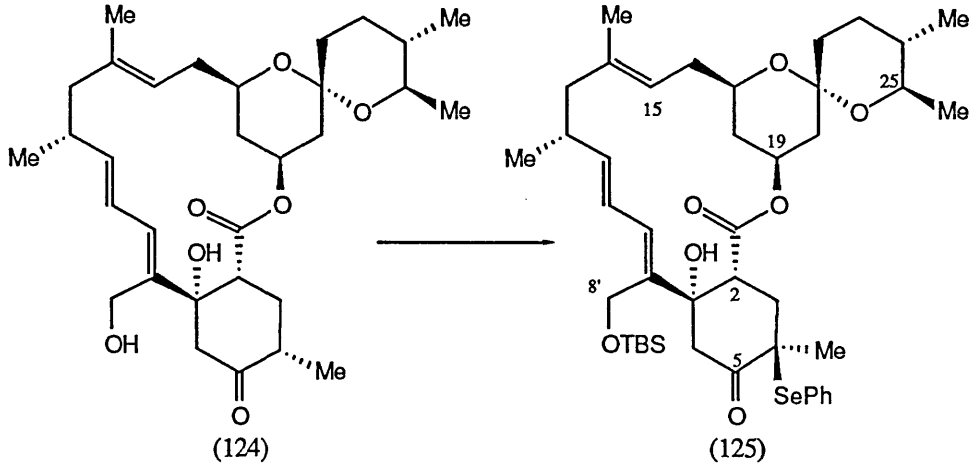
78. Preparation of (+) 4β-Benzeneselenenyl-5-oxoatropomilbemycin β1 (116)



Trifluoroacetic acid (0.125 ml 1.62 mmol) was added to a stirred solution of the macrolide (113) (24 mg, 0.031 mmol) in DCM (4 ml), at r.t. After 30 min, saturated sodium hydrogencarbonate solution was added and the mixture extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (60% ether-petrol) of the residue afforded the *diol* (116) (16.5 mg, 78%) as a clear oil, $[\alpha]^{25}_D$ +139° (c 0.57, $CHCl_3$), ν_{max} (film), 3590, 2925, 1700, 1194 and 994 cm^{-1}; δ (500 MHz), 7.46 (2H, dd, J 7.6 and 1.2 Hz, Ph), 7.39 (1H, t, J 7.4 Hz, Ph), 7.30 (2H, t, J 7.6 Hz, Ph), 6.24 (1H, dd, J 14.7 and 10.7 Hz, 10-H), 6.14 (1H, d, J 10.7 Hz, 9-H), 5.51 (1H, dd, J 14.7 and 9.4 Hz, 11-H), 5.33 (1H, tt, J 11.6 and 4.6 Hz, 19-H), 4.85 (1H, d, J 10.8 Hz, 15-H), 4.39 (1H, dd, J 12.0 and 4.2 Hz, 8'-H), 4.33 (1H, dd, J 12.0 and 3.8 Hz, 8'-

H), 3.75 (1H, dd, J 13.1 and 3.8 Hz, 2-H), 3.64 (1H, dt, J 9.8 and 4.4 Hz, 17-H), 3.29 (1H, dd, J 14.8 and 2.9 Hz, 6H), 3.26 (1H, dq, J 9.8 and 6.2 Hz, 25-H), 3.18 (1H, d, J 2.9 Hz, 7-OH), 2.63 (1H, d, J 14.8 Hz, 6-H), 2.52 (1H, m), 2.43 (1H, t, J 13.7 Hz), 2.35-2.20 (3H, m), 2.18-2.10 (1H, m), 1.95-1.80 (2H, m), 1.64 (1H, m), 1.57 (3H, s, 14-Me), 1.56-1.41 (7H, m), 1.44 (3H, s, 4-Me), 1.11 (3H, d, J 6.2 Hz, 25-Me), 1.06 (3H, d, J 6.6 Hz,Me), 0.82 (3H, d, J 6.6 Hz,Me), 0.67 (1H, q, J 11.7 Hz, 18-H), mz, 668 (M^+-H_2O), 650 (M^+-$2H_2O$), 642 (M^+-CO_2-H_2O), 530 (MH^+-PhSe), 512 (MH^+-PhSe-H_2O), 494 (MH^+-PhSe-$2H_2O$), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_2) (Found: M^+-H_2O, 668.2606 $C_{37}H_{48}O_6Se$ requires M, 668.2616).

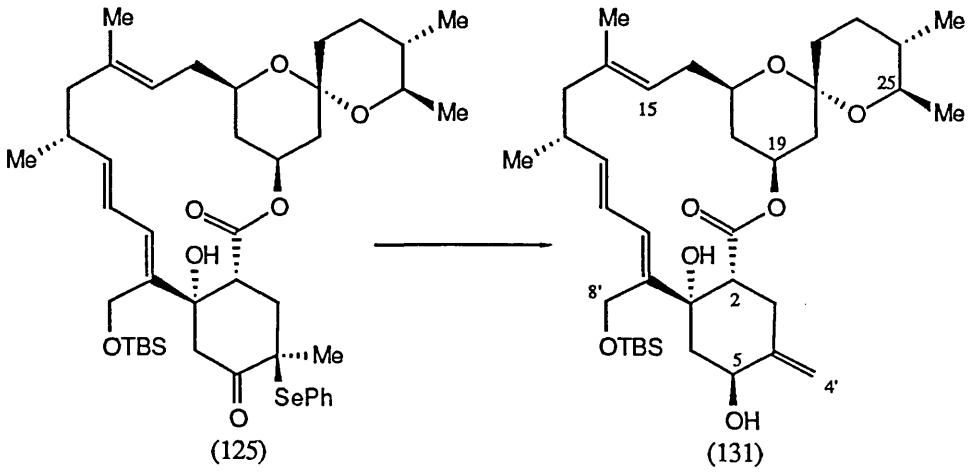
79. Preparation of 4-β-Benzeneselenenyl-8'-t-Butyl-dimethylsilyloxy-5-oxo atropomilbemycin β1 (125).



t-Butyldimethylsilyltriflate (0.015 ml, 0.065 mmol) was added dropwise to a stirred solution of the hydroxy ketone (124) (4.5 mg, 0.00 85 mmol) and triethylamine

(0.118 ml, 0.847 mmol) in DCM (1 ml), under argon, at r.t. After 1.5h, the reaction was cooled to -78°C and benzeneselenenyl chloride (75 mg, 0.392 mmol) in DCM (0.5 ml) was added dropwise. The reaction was stirred at -20°C for 10 min, whereupon saturated sodium hydrogencarbonate solution was added and the mixture allowed to warm to r.t. Water was added and the mixture extracted wtih DCM. The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (15% ether-petrol) of the residue afforded the selenide (125) (4.5 mg, 66%), as a clear oil, δ (500 MHz), 7.47 (2H, dd, J. 7.5 and 0.5 Hz, Ph), 7.42-7.27 (3H, m, Ph), 6.18 (1H, dd, J 14.5 and 10.5 Hz, 10-H), 6.16 (1H, d, J 10.5 Hz, 9-H), 5.46 (1H, dd, J 14.5 and 9.5 Hz, 11-H), 5.31 (1H, tt, J 11.6 and 4.6 Hz, 19-H), 4.86 (1H, br d, J 9.7 Hz, 15-H), 4.38 (1H, d, 12.1 Hz, 8'-H), 4.21 (1H, d, J 12.1 Hz, 8'-H) 3.74 (1H, dd, J 13.5 and 4.1 Hz, 2-H), 3.65 (1H, m, 17-H), 3.25 (1H, dq, J 10.5 and 6.2 Hz, 25-H), 3.20 (1H, dd, J 13.5 and 2.5 Hz, 6-H), 3.14 (1H, d, J 2.5 Hz, 7-OH), 2.55 (1H, d, J 13.5 Hz, 6-H), 2.50 (1H, m), 2.46 (1H, t, J 12.5 Hz), 2.30 (1H, m), 2.24 (2H, m), 2.14 (1H, m), 1.92-1.80 (3H, m), 1.70-1.15 (6H, m), 1.57 (3H, s, 14-Me), 1.45 (3H, s, 4-Me), 1.12 (3H, d, J 6.2 Hz, 25-Me), 1.06 (3H, d J 6.6 Hz, Me), 0.93 (9H, s, ^tBu), 0.82 (3H, d, J 6.5 Hz, Me), 0.76 (1H, q, J 11.6 Hz, 18-H), 0.14 (6H, s, $SiMe_2$), m/z 743 (M^+-^tBu), 725 (M^+-^tBu-H_2O), 643 (M^+-PhSe), 625 (M^+-PhSe-H_2O), 550 (M^+-PhSe-^tBu-$2H_2O$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4). (Found: M^+-^tBu, 743.2880 $C_{39}H_{55}O_7SeSi$ requires M, 743.2882).

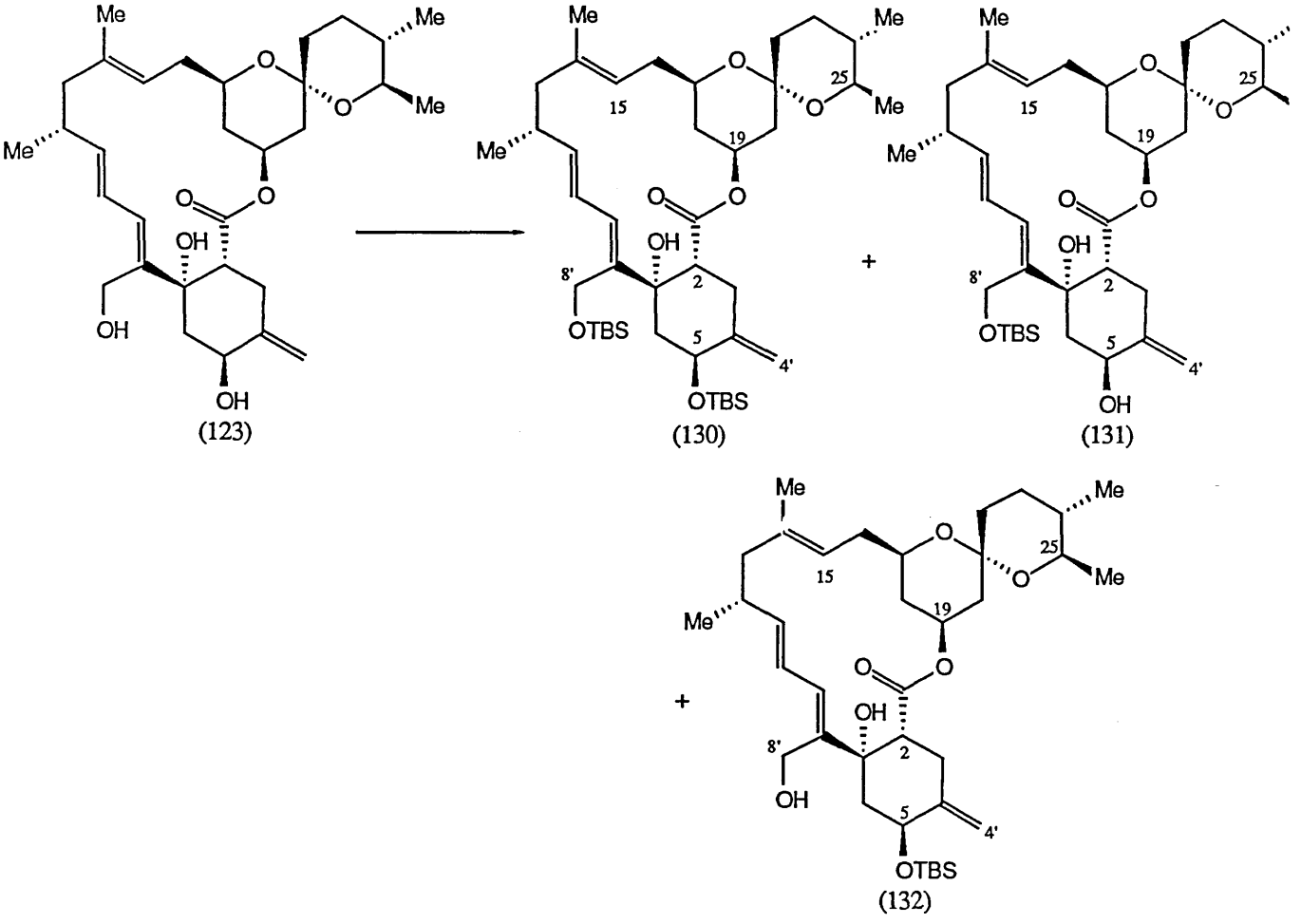
80. Preparation of 8'-t-Butyldimethylsilyloxy-4-methylene-5-O-demethylatropomilbemycin β1 (131).



The oxaziridine (115) (1.5 mg, 5.00 μmol) was added to a stirred solution of the selenide (125) (2 mg, 2.50 μmol), in methanol (0.5 ml) at r.t. After 1h, the rection was cooled to 0°C and cerium III chloride heptahydrate (37 mg, 0.10 mmol) added. After 5 min, sodium borohydride was added portionwise until t.l.c indicated consumption of the enone. After a further 5 min, saturated ammonium chloride solution was added and the mixture extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (20% ether-petrol) of the residue afforded the *allylic alcohol* (131) (0.5 mg, 31%) as a clear oil: δ (500 MHz), 6.16 (1H, dd, J 14.9 and 10.7 Hz, 10-H), 5.94 (1H, d, J 10.7 Hz, 9-H), 5.34 (1H, dd, J 14.9 and 9.6 Hz, 11-H), 5.30 (1H, m, 19-H), 5.01 (1H, s, 4'-H), 4.91 (1H, s, 4'-H), 4.83 (1H, br d, J 10.8 Hz, 15-H), 4.52 (1H, m, 5-H), 4.36 (1H, d, J 10.5 Hz, 8'-H), 4.24 (1H, d, J 10.5 Hz, 8'-

H), 3.62 (1H, m, 17-H), 3.30-3.20 (2H, m, 7-H and 25-H), 2.89 (1H, dd, J 13.2 and 3.8 Hz, 2-H), 2.71 (1H, t, J 13.2 Hz, 3-H), 2.53 (1H, dd, J 13.2 and 3.8 Hz, 3H), 2.46 (1H, m), 2.40-2.00 (4H, m), 1.92-1.80 (3H, m), 1.65-1.15 (8H, m), 1.56 (3H, s, 14-Me), 1.11 (3H, d, J 6.3 Hz, 25-Me), 1.02 (3H, d, J 6.6 Hz, Me), 0.93 (9H, s, ^{t}Bu), 0.82 (3H, d, J 6.6 Hz, Me), 0.76 (1H, q, J 11.9 Hz, 18-H), 0.13 (6H, s, $SiMe_2$); m/z 644 (M^+), 626 (M^+-H_2O), 608 (M^+-$2H_20$), 587 (M^+-^{t}Bu) , 569 (M^+-$^{t}BuH_2O$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4); (Found: M^+-H_2O, 626.3993 $C_{37}H_{58}O_6Si$ requires 626.4003).

81. Preparation of 5,8'-t-Butyldimethylsilyloxy-4-methyleneatropomibemycin β1 (130), 8'-t-Butyldimethylsilyloxy-4-methylene-5-O-demethylatropomilbemycin β1 (131) and 5-t-Butyldimethylsilyloxy-4-methyleneatropomilbemycin β1 (132).

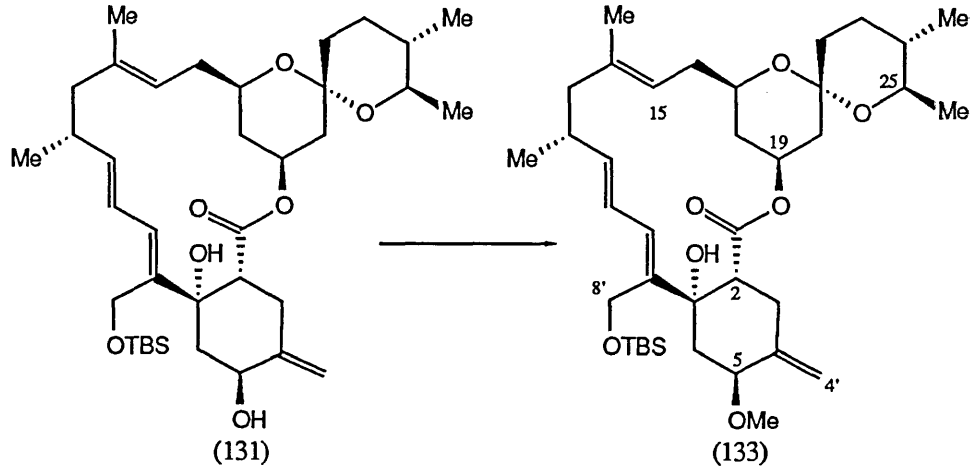


t-Butyldimethylsilylchloride (5 mg, 0.033 mmol) in DCM (0.1 ml) was added dropwise to a solution of the triol (123) (0.7 mg, 1.32 μmol), 4-N,N-dimethylaminopyridine (0.5 mg, 4.09 μmol) and triethylamine (0.02 ml, 0.143 mmol) in DCM (0.2 ml), under argon, at 0°C. After 1h, the reaction was diluted with DCM and saturted sodium hydrogencarbonate solution was added. The mixture was

extracted with DCM, the organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (25% ether-petrol) of the residue afforded the *allylic alcohols* (130) (0.3 mg, 30%), (132) 0.1 mg, 12%) and (131) (0.3 mg, 35%), less polar: (130), δ (500 MHz), 6.16 (1H, dd, J 14.8 and 10.6 Hz, 10-H), 5.93 (1H, d, J 10.6 Hz, 9-H), 5.34 (1H, dd, J 14.8 and 9.6 Hz, 11-H), 5.30 (1H, m, 19-H), 5.03 (1H, s, 4'-H), 4.85 (1H, s, 4'-H), 4.83 (1H, d, J 10.1 Hz, 15-H), 4.51 (1H, m, 5-H), 4.36 (1H, d, J 10.6 Hz, 8'-H), 4.19 (1H, d, J 10.6 Hz, 8'-H), 3.61 (1H, m, 17-H), 3.25 (1H, m, 25-H), 3.24 (1H, d, J 2.4 Hz, 7-OH), 2.85 (1H, dd, J 13.0 and 3.8 Hz, 2-H), 2.67 (1H, t, J 13.0 Hz, 3-H), 2.51 (1H, dd, J 13.0 and 3.8 Hz, 3-H), 2.42 (1H, m), 2.35-1.75 (10H, m), 1.70-1.15 (16H, m), 1.56 (3H, s, 14-Me), 1.10 (3H, d, J 6.2 Hz, 25-Me), 1.02 (3H, d, J 6.6 Hz, Me), 0.93 (9H, s, ^{t}Bu), 0.91 (9H, s, ^{t}Bu), 0.81 (3H, d, J 6.6 Hz, Me), 0.73 (1H, q, J 11.7 Hz, 18-H); m/z 758 (M^+), 740 (M^+-H_2O), 701 (M^+-^{t}Bu), 626 (M^+-$^{t}BuMe_2SiOH$), 608 (M^+-$^{t}BuMe_2SiOH0H_2O$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4), (Found: M^+-H_2O, 740.4852 $C_{42}H_{72}O_6Si_2$ requires M, 740.4867). More polar: (132), δ (500 MHz), 6.22 (1H, dd, J 14.6 and 10.9 Hz, 10-H), 5.98 (1H, d, J 10.9 Hz, 9-H), 5.43 (1H, dd, J 14.6 and 10.2 Hz, 11-H), 5.33 (1H, m, 19-H), 5.07 (1H, s, 4'-H), 4.88 (1H, s, 4'-H), 4.84 (1H, d, J 10.6 Hz, 15-H), 4.50 (1H, m, 5-H), 4.35 (2H, m, 8'-H_2), 3.64 (1H, m, 17-H), 3.43 (1H, d, J 2.5 Hz, 7-OH), 3.27 (1H, m, 25-H), 2.90 (1H, dd, J 13.0 and 3.6 Hz, 2-H), 2.65 (1H, t, J 13.0 Hz, 3-H) 2.52 (1H, dd, J 13.0 and 3.6 Hz, 3-H), 2.50 (1H, m), 2.35-1.20 (18H, m), 1.60 (3H, s, 14-

Me), 1.12 (3H, s, J 6.2 Hz, 25-Me), 1.03 (3H, d, J 6.6 Hz, Me), 0.90 (9H, s, ^{t}Bu), 0.81 (3H, d, J 6.6 Hz, Me), 0.74 (1H, q, J 11.8 Hz, 18-H), 0.09 (3H, s, SiMe), 0.08 (3H, s, SiMe),mz, 644(M+), 608 (M^{+}-$2H_2O$), 551 (M^{+}-^{t}Bu-$2H_2O$), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^{+}, 644.4093 $C_{37}H_{60}O_7Si$ requires M, 644.4108), most polar : (131) spectral data identical to previously prepared material.

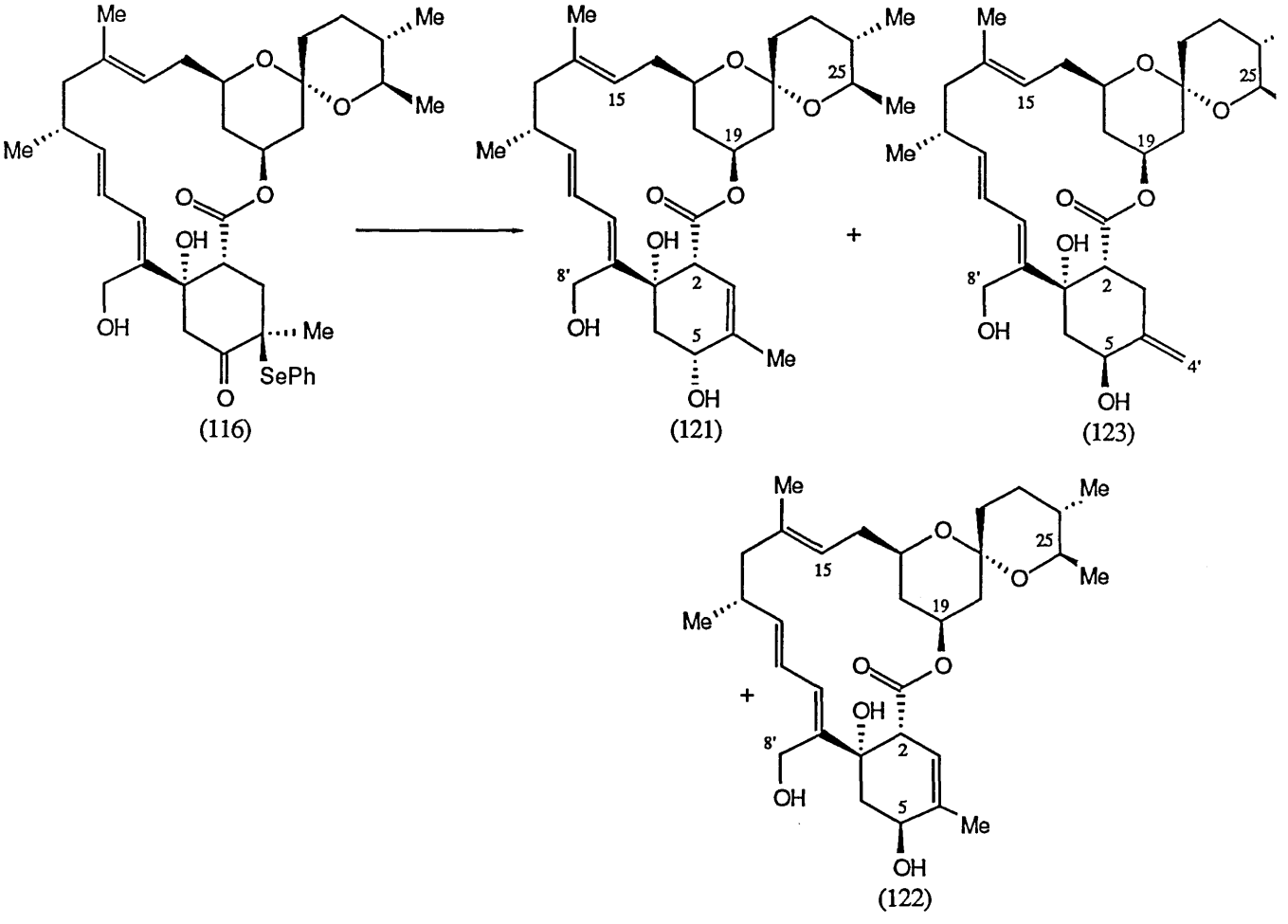
82. Preparation of 8'-t-Butyldimethylsilyloxy-4-methyleneatropomilbemycin β1 (133).



Trimethyloxoniumtetrafluoroborate (10 mg, 0.068 mmol) was added to a stirred slurry of the alcohol (131) (0.3 mg, 0.466 μmol) and anhydrous potassium carbonate (24 mg, 0.174 mmol) in DCM (0.20 ml), under argon, at r.t. After 5 h, saturated ammonium chloride solution was added and the mixture extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*.

Column chromatography (20% ether-petrol) of the residue afforded the *methyl ether* (133) (0.12 mg, 40%) as a clear oil, δ (500 MHz), 6.16 (1H, dd, J 14.6 and 10.9 Hz, 10-H), 5.93 (1H, d, J 10.9 Hz, 9-H), 5.34 (1H, dd, J 14.6 and 9.2 Hz, 11-H), 5.30 (1H, m, 19-H), 4.98 (1H, s, 4'-H), 4.89 (1H, s, 4'-H), 4.83 (1H, br d, J 10.8 Hz, 15-H), 4.36 (1H, d, J 10.4 Hz, 8'-H), 4.28 (1H, m, 5-H), 4.23 (1H, d, J 10.4 Hz, 8'-H), 3.60 (1H, m, 17-H), 3.43 (3H, s, 5-OMe), 3.28 (1H, m, 25-H), 3.25 (1H, d, J 12.5 Hz, 7-OH), 2.89 (1H, dd, J 12.6 and 3.6 Hz, 2-H), 2.66 (1H, t, J 13.0 Hz, 3-H), 2.59 (1H, dd, J 12.9 and 3.6 Hz, 3-H), 2.40-1.15 (18H, m), 1.11 (3H, d, J 6.3 Hz, 25-Me), 1.02 (3H, d, J 6.6 Hz, Me), 0.94 (9H, s, ^{t}Bu), 0.81 (3H, d, J 6.6 Hz, Me), 0.76 (1H, q, J 11.7 Hz, 18-H), 0.05 (6H, s, $SiMe_2$), m/z 658 (M^+), 640 (M^+-H_2O), 626 (M^+-MeOH), 608 (M^+-MeOH-H_2O), 601 (M^+-^{t}Bu), 583 (M^+-^{t}Bu-H_2O), 526 (M^+-^{t}BuSiMe$_2$OH), 508 (M^+-^{t}BuSiMe$_2$OH-H_2O), 494 (M^+-^{t}BuSiMe$_2$OH-MeOH), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^+-H_2O, 640.4163 $C_{34}H_{60}O_6Si$ requires M, 640.4159).

83. Preparation of 5α-O-Demethylatropomilbemycin β_1 (121), 5-O-Demethyl-4-methylene atropomilbemycin β_1 (123), and 5-O-Demethylatropomilbemycin β_1 (122).

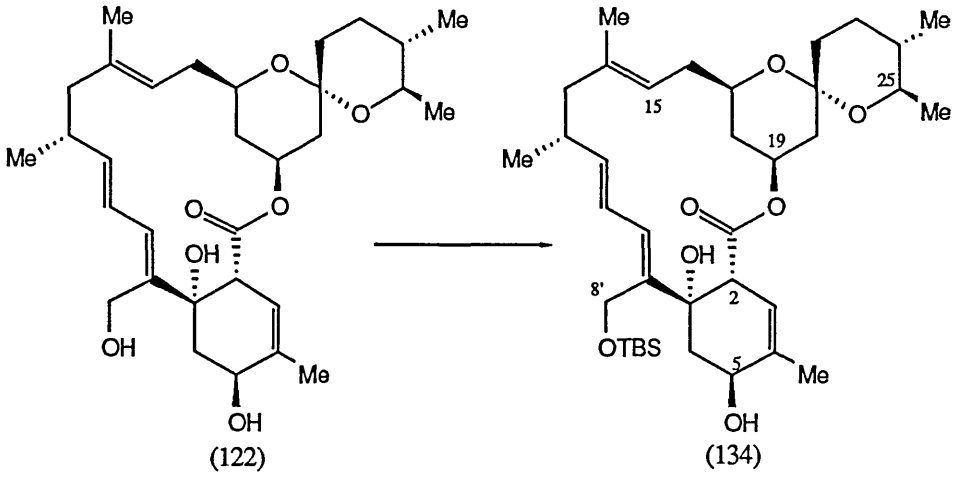


The oxaziridine (115) (4 mg, 0.013 mmol) was added to a stirred solution of the selenide (116) (8 mg, 0.012 mmol) in deuterochloroform (1 ml) at r.t. After 1h, the reaction was cooled to 0°C, methanol (1 ml) and cerium III chloride heptahydrate (37 mg, 0.1 mmol) were added. After a further 5 min, sodium borohydride was added portionwise until t.l.c. indicated consumption of the enone. After 5 min, saturated ammonium chloride solution was added and the mixture extracted with ethyl

acetate. The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (90% ether-petrol) of the residue afforded the *triols* (121) (0.77 mg, 13%) (123) (1.44 mg, 23%) and (122) (1.3 mg, 21%) all as clear oils.Less polar: (121) ν_{max} (film) 3382, 2926, 1721, 1610, 1225, 1162 cm^{-1}; δ (500 MHz), 6.16 (1H, dd, J 14.7 and 10.7 Hz, 10-H), 5.86 (1H, d, J 10.7 Hz, 9-H), 5.42-5.35 (2H, m, 3-H and 11-H), 5.23 (1H, tt, J 11.7 and 5.1 Hz, 19-H), 4.83 (2H, m, 15-H and 5-H), 4.42-4.35 (2H, m, 8'-H_2), 4.24 (1H, m, 2-H), 3.65 (1H, m), 3.56 (1H, m, 17-H), 3.44 (1H, d, J 5.0 Hz), 3.30-3.20 (2H, m), 2.78 (1H, m), 2.55-1.20 (14H, m), 1.92 (3H, s, 4-Me), 1.61 (3H, s, 14-Me), 1.08 (3H, d, J 6.6 Hz, Me), 1.02 (3H, d, J 6.6 Hz, Me), 0.81 (3H, d, J 6.6 Hz, Me), 0.62 (1H, q, J 11.6 Hz, 18-H); More polar: (123) ν_{max}(film), 3363, 2926, 2858, 1715, 1676 cm^{-1}; 6.21 (1H, dd, J 14.9 and 10.7 Hz, 10-H), 5.99 (1H, d, J 10.7 Hz, 9-H), 5.42 (1H, dd, J 14.9 and 9.4 Hz, 11-H), 5.33 (1H, tt, J 11.6 and 4.4 Hz, 19-H), 5.04 (1H, s, 4'-H), 4.92 (1H, s, 4'-H), 4.84 (1H, br d, J 10.6 Hz, 15-H), 4.36 (2H, m, 8'-Hz), 3.63 (1H, m, 17-H), 3.41 (1H, d, J 2.5 Mz, 7-OH), 3.26 (1H, dq, J 9.7 and 6.2 Hz, 25-H), 2.92 (1H, dd, J 13.2 and 3.9 Hz, 2-H), 2.68 (1H, br t, J 13.2 Hz, 3-H), 2.53 (1H, dd, J 13.2 and 3.9 Hz, 3-H), 2.48 (1H, m), 2.43 (1H, dd, J 12.8 and 5.3 Hz, 6-H), 2.32-2.20 (2H, m), 2.13 (1H, dt, J 13.5 and 10.7 Hz) 2.10-1.88 (2H, m), 1.82 (1H, t, J 12.3 Hz), 1.71-1.65 (1H, m), 1.56 (3H, s, 14-Me), 1.59-1.40 (7H, m), 1.20 (1H, br dt, J 2.5 and 12.2 Hz, 6H), 1.11 (3H, d, J 6.3 Hz, 25-Me), 1.02 (3H, d, J, 6.6 Hz, Me), 0.82 (3H, d, J 6.6 Hz, Me), 0.67

(1H, q, J 11.8 Hz, 18-H); m/z 530 (M^+), 512 (M^+-H_20), 494 (M^+-$2H_20$), 476 (M^+-$3H_20$), 468 (M^+-CO_2-H_20), 450 (M^+-CO_2-$2H_20$), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4), (Found: M^+, 530.3237 $C_{31}H_{46}O_7$ requires M, 530.3185). Most polar: (122), ν_{max} (film), 3369, 1734, 1449, 1379, 1116, 1054 and 993 cm^{-1}; δ(500MHz) 6.18 (1H, dd, J 14.9 and 10.2 Hz, 10-H), 5.87 (1H, d, J 10.2 Hz, 9-H), 5.62 (1H, m, 3-H), 5.37 (1H, dd, J 14.9 and 8.5 Hz, 11-H), 5.36 (1H, m, 19-H), 4.84 (1H, br d, J 10.0 Hz, 15-H), 4.36 (2H, m, 8'-H_2), 4.22 (1H, m, 5-H), 3.59 (1H, t dd, J 10.5, 5.0 and 2.8 Hz, 17-H), 3.32 (1H, br s), 3.28-3.22 (2H, m), 2.57-1.20 (17H, m), 1.88 (3H, s, 4-Me), 1.58 (3H, s, 14-Me), 1.10 (3H, d, 7.0 Hz, Me), 1.02 (3H, d, 7.0 Hz, Me), 0.82 (3H, d, 6.8 Hz, Me), 0.59 (1H, q, 11.7 Hz, 18-H), m/z 530 (M^+), 512 (M^+-H_2O), 494 (M^+-$2H_2O$), 486 (M^+-CO_2), 476 (M^+-$3H_2O$), 450 (M^+-CO_2-$2H_2O$), 432 (M^+-CO_2-$3H_2O$), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), (Found: M^+, 530.3237 $C_{31}H_{46}O_7$ requires M, 530.3185).

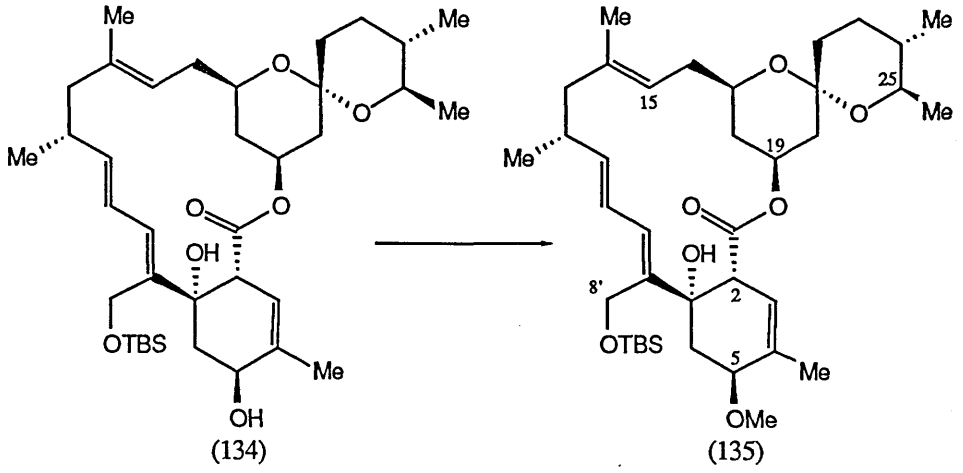
84. Preparation of 8'-t-Butyldimethylsilyloxy-5-O-demethylatropomilbemycin β_1 (134)



t-Butyldimethylsilylchoride (10 mg, 0.066 mmol) in DCM (0.5 ml) was added dropwise to a solution of the triol (122) (2.9 mg, 1.89 μmol) 4-N,N-dimethylaminopyridine (1 mg, 8.2 μmol) and triethylamine (0.02 ml, 0.143 μmol) in DCM (0.1 ml) under argon, at 0°C. After 1h, the reaction was diluted with DCM and saturated sodium hydrogencarbonate solution was added. The mixture was extracted with DCM, the organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (35% ether-petrol) of the residue afforded the *silyl ether* (134) (1.4 mg, 40%) as a clear oil, δ (500 MHz), 6.02 (1H, dd, J 14.8 and 11.0 Hz, 10-H), 5.86 (1H, d, J 11.0 Hz, 9-H), 5.50 (1H, m, 3-H), 5.36 (1H, dd, J 14.8 and 10.3 Hz, 11-H), 5.30 (1H, tt, J 11.6 and 4.6 Hz, 19-H), 4.86 (1H, d, J 10.5 Hz, 15-H), 4.46 (1H, d,J 11.0 Hz, 8'-H), 4.43 (1H, d, J 11.0 Hz, 8'-H), 4.31 (1H, s, 7-OH), 4.28 (1H, br q, J 6.0 Hz, 5-H), 3.59 (1H, ddt, J 1.1, 4.6 and 11.1 Hz, 17-H),

3.32 (1H, s, 2-H), 3.25 (1H, dq, J 9.5 and 6.2 Hz, 25-H), 2.42 (1H, dd, J 12.8 and 7.0 Hz, 6-H), 2.28 (1H, m), 2.25-2.15 (2H, m), 2.11 (1H, dd, J 12.8 and 5.5 Hz, 6-H), 1.87 (3H, s, 4-Me), 1.94-1.60 (2H, m), 1.56 (3H, s, 14-Me), 1.54-1.15 (9H, m), 1.10 (3H, d, J 6.2 Hz, 25-Me), 1.03 (3H, d, J 6.4 Hz, Me), 0.92 (9H, s, ^{t}Bu), 0.82 (3H, d, J 6.4 Hz, Me), 0.59 (1H, q, J 11.6 Hz, 18-H), 0.15 (3H, s, SiMe), 0.13 (3H, s, SiMe), m/z 644 (M^+), 626 (M^+-H_2O), 608 (M^+-$2H_2O$), 600 (M^+-CO_2), 587 (M^+-^{t}Bu), 569 (M^+-^{t}Bu-H_2O), 551 (M^+-^{t}Bu-$2H_2O$), 512 (M^+-^{t}BuSiMe$_2$OH), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^+, 644.4000 $C_{37}H_{60}O_7Si$ requires M, 644.4108)

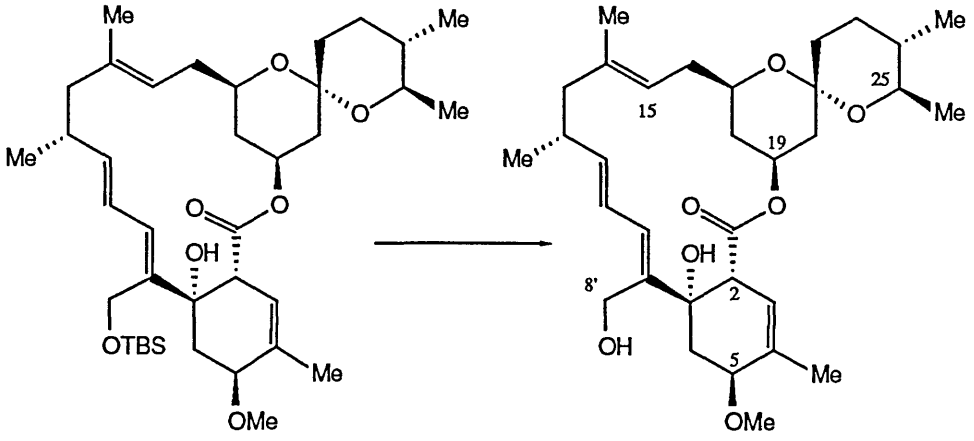
85. Preparation of 8'-t-Butyldimethylsilyloxyatropomilbemycin β_1 (135).



The alcohol (134) (0.7 mg, 0.011 mmol) in DCM (1 ml) was added to a stirred solution of diazomethane (160 mg, 3.8 mmol) in DCM (1 Ml) at -78°C. After 5 min, hydrogen tetrafluoroborate -diethylether complex (0.5 mg, 0.003 mmol), was added,

and the yellow solution allowed to warm to r.t. After the solution had decolourised, saturated sodium hydrogencarbonate solution (1 ml) was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (25-100% ether-petrol) afforded the methyl ether (135) (0.5 mg, 70%) and starting alcohol (134) (0.2 mg, 30%) both as clear oils. Less polar: δ (500 MHz), 5.98 (1H, dd, J 14.4 and 10.9 Hz, 10-H), 5.91 (1H, d, J 10.9 Hz, 9-H), 5.40 (1H, m, 11-H), 5.28 (1H, m, 19-H), 4.86 (1H, br d, J 9.3 Hz, 15-H), 4.55 (1H, d, J 0.8 Hz, 7-OH), 4.51 (2H, s, 8'-H_2), 4.19 (1H, m, 5-H), 3.57 (1H, dt, J 9.8 and 5.7 Hz, 17-H), 3.37 (3H, s, 5-OMe), 3.32 (1H, s, 2-H), 3.24 (1H, dq, J 10.7 and 6.2 Hz, 25-H), 2.61 (1H, t, J 11.5 Hz, 6-H), 2.43 (1H, m), 2.27 (1H, d, J 11.4 Hz, 6-H), 2.24-2.10 (2H, m), 2.00 (1H, dd, J 8.7 and 5.5 Hz), 1.82 (3H, s, 4-Me), 1.88-1.75 (2H, m), 1.60 (3H, s, 14-Me), 1.70-1.10 (8H, m), 1.08 (3H, d, J 6.2 Hz, 25-Me), 1.04 (3H, d, J 6.6 Hz, Me), 0.95 (9H, s, ^tBu), 0.82 (3H, d, J 6.6 Hz, Me), 0.62 (1H, q, J 11.6 Hz, 18-H), 0.15 (3H, s, SiMe) 0.13 (3H, s, SiMe); m/z 658 (M^+), 640 (M^+-H_2O), 626 (M^+-MeOH) 601 (M^+-^tBu), 683 (M^+-^tBu-H_2O), 569 (M^+-^tBu-MeOH), 551 (M^+-^tBu-MeOH-H_2O), 526 (M^+-$^tBuMe_2SiOH$), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^+, 658.4274 $C_{38}H_{62}O_7Si$ requires M, 658.4265). More polar: (134) spectral data identical to previously prepared material.

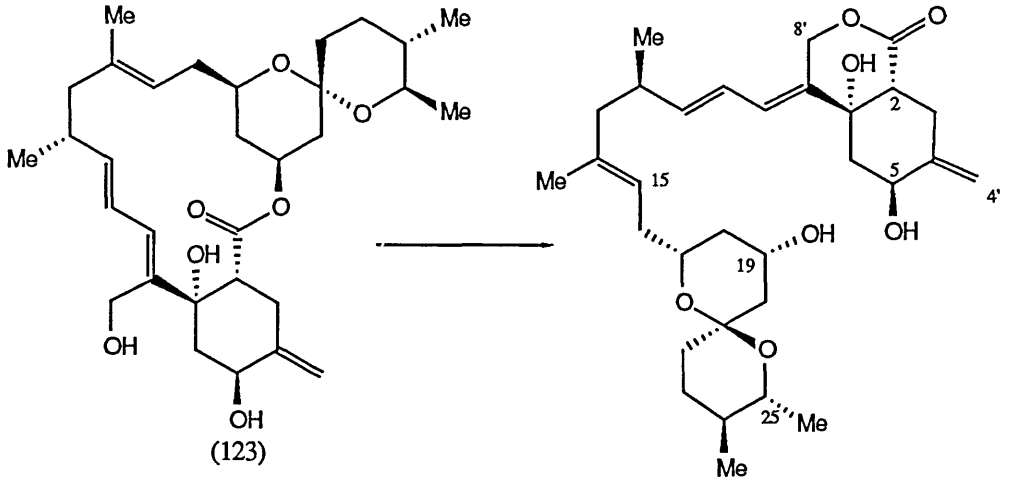
86. Preparation of Atropomilbemycin β_1 (136).



A solution of hydrofluoric acid (5% of a 40% aqueous solution in acetonitrile) was added periodically to a stirred solution of the silyl ether (135) (0.4 mg, 0.608 μmol) and pyridine (0.010 ml) in acetonitrile (0.1 ml), at r.t. After 3h, t.l.c. indicated consumption of the starting material, whereupon saturated sodium hydrogencarbonate solution was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (75% ether-petrol) afforded the *alcohol* (136) (0.2 mg, 60%) as a clear oil, ν_{max} (film), δ (500 MHz), 6.17 (1H, dd, J 14.9 and 10.8 Hz, 10-H), 5.91 (1H, d, J 10.8 Hz, 9-H), 5.51 (1H, m, 3-H), 5.39 (1H, dd, J 14.9 and 9.9 Hz, 11-H), 5.30 (1H, tt, J 11.7 and 4.7 Hz, 19-H), 4.83 (1H, d, J 8.3 Hz, 15-H), 4.35 (2H, d, J 5.6 Hz, 8'-H_2), 4.03 (1H, t, J 6.4 Hz, 5-H), 3.58 (1H, br t, J 10.9 Hz, 17-H), 3.38 (3H, s, 5-OMe), 3.28 (1H, m, 2-H), 3.23 (1H, dq, J 9.7 and 6.1 Hz, 25-H), 3.11 (1H, s, 7-OH), 2.64 (1H, dd, J 13.0 and 8.2 Hz, 6-H), 2.45 (1H, m), 2.36-2.30 (2H, m), 2.20-2.10 (2H, m), 2.04 (2H, m), 2.00-1.70 (2H, m), 1.83 (3H, s, 4-Me), 1.69-1.40

(9H, m), 1.08 (3H, d, J 6.1 Hz, 25-Me), 1.03 (3H, d, J 6.6 Hz, Me), 0.81 (3H, d, J 6.5 Hz, Me), 0.61 (1H, q, J 11.6 Hz, 18-Me), m/z 544 (M^+), 526 (M^+-H_2O), 512 (M^+-MeOH), 494 (M^+-H_2O-MeOH), 476 (M^+-$2H_2O$-MeOH), 458 (M^+-$3H_2O$-MeOH), 402 ($C_{25}H_{38}O_4$), 384 ($C_{25}H_{38}O_4$-H_2O), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4), (Found: M^+, 544.3390 $C_{32}H_{48}O_7$ requires 544.3400)

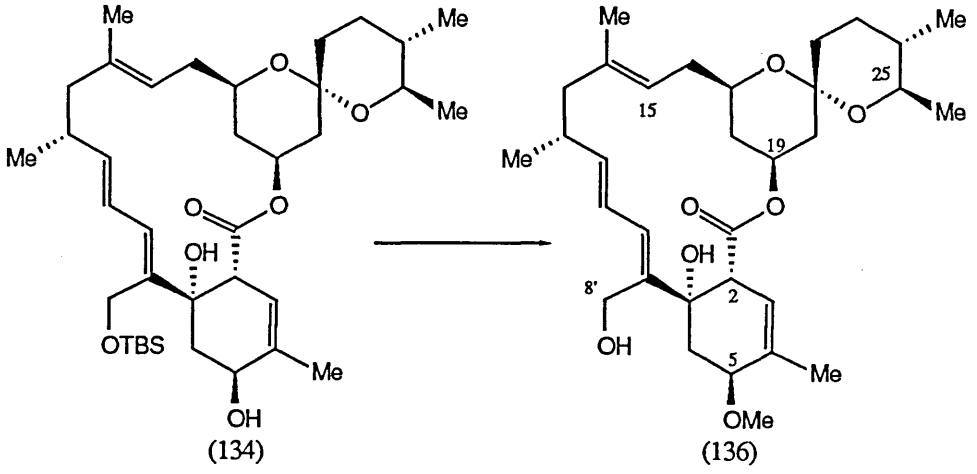
87. Preparation of 4- Methylenemilbemycin ß$_1$ δ lactone (137).



A solution of the triol (123) (1.0 mg, 1.89 μmol), in 1 methylnaphalene was heated at 180°C for 9h. The reaction was cooled and the solvent evaporated *in vacuo*. Column chromatography (ether) of the residue afforded the *starting macrolactone* (123) (0.4 mg, 40%), and the *δ lactone* (137) (0.4 mg, 40%) both as clear oils Less polar: (123) spectral properties identical to previously prepared material. More polar: (137) ν_{max} (film),3403, 2926, 2853, 1734 cm^{-1}; δ (500 MHz), 6.33 (1H, d, J 10.0

Hz, 9-H), 6.04 (1H, dd, J 15.2 and 10.0 Hz, 10-H), 5.84 (1H, dd, J 15.2 and 7.0 Hz, 11-H), 5.19 (1H, dd, J 14.7 and 1.2 Hz, 8'-H), 5.10 (1H, dd, J 12.7 and 6.0 Hz, 15-H), 5.04 (1H, s, 4'-H), 4.94 (1H, s, 4'-H), 4.84 (1H, d, J 14.7 Hz, 8'-H), 4.51 (1H, m, 5-H), 4.09 (1H, m, 19-H), 3.54 (1H, m, 17-H), 3.24 (1H, dq, J 9.8 and 6.2 Hz, 25-H), 2.90-1.20 (22H, m), 1.63 (3H, s, 14-Me), 1.10 (3H, d, J 6.2 Hz, 25-Me), 1.03 (3H, d, J 6.7 Hz, Me), 0.82 (3H, d, J 6.6 Hz, Me), m/z 530 (M^+), 512 (M^+-H_2O), 494 (M^+-$2H_2O$), 476 (M^+-$3H_2O$), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$)

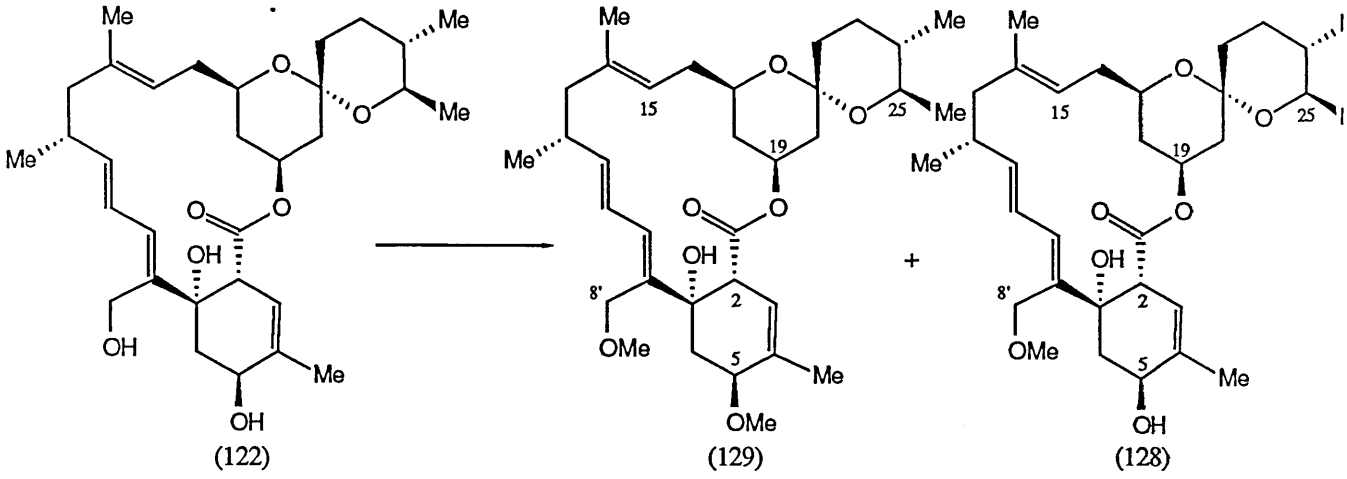
88. Preparation of Atropomilbemycin β_1 (136).



Trimethyloxoniumtetrafluoroborate (10 mg, 0.068 mmol) was added to a stirred slurry of the alcohol (134) (0.2 mg, 0.31 μmol) and anhydrous potassium carbonate (20 mg, 0.145 mmol) in DCM (0.5 ml), under argon, at r.t. After 1.2h, saturated ammonium chloride solution was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column

chromatography (ether) of the residue afforded the *methyl ether* (0.1 mg, 50%), spectral data identical to previously prepared material.

89. Preparation of 8'-O-Methylatropomilbemycin β_1 (129) and 5-O-Demethyl-8'-O-methylatropomilbemycin β_1 (128).



Trimethyloxoniumtetrafluoroborate (10 mg, 0.068 mmol) was added to a stirred slurry of the alcohol (122) (0.4 mg, 0.75m μmol) and anhydrous potassium carbonate (20 mg, 0.145 mmol) in DCM (0.2 ml), under argon, at 0°C. After 2h, saturated ammonium chloride solution was added and the mixture extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*.

Column chromatography (75-100% ether-petrol) afforded the *methyl ethers* (129) (1 mg, 25%) (128) (2 mg, 50%) and starting alcohol (122) (0.8 mg, 15%) all as clear oils. Less polar: (129), δ (500 MHz), 6.10-6.03 (2H, m, 9-H and 10-H), 5.43 (1H

dt, J 10.2 and 3.8 Hz, 11-H), 5.38 (1H, m, 3-H), 5.25 (1H, m, 19-H), 4.83 (1H, d, J 12.3 Hz, 15-H), 4.22 (1H, d, J 11.1 Hz, 8'-H), 4.19 (1H, m, 5-H), 4.14 (1H, d, J 11.1 Hz, 8'-H), 4.07 (1H, s, 7-OH), 3.57 (1H, br t, J 11.4 Hz, 17-H), 3.39 (1H, s, OMe), 3.37 (1H, s, OMe), 3.27 (1H, m, 2-H), 3.22 (1H, dq, J 9.9 and 6.3 Hz, 25-H), 2.62 (1H, dd, J 12.4 and 9.6 Hz, 6H), 2.45 (1H, m), 2.35-2.25 (1H, m), 2.24-2.10 (2H, m), 1.98 (1H, dd, J 12.4 and 6.2 Hz), 1.87-1.80 (3H, m), 1.82 (3H, s, 4-Me), 1.74-1.65 (2H, m), 1.60 (3H, s, 14-Me), 1.55-1.35 (8H, m), 1.07 (3H, d, J 6.3 Hz, 25-Me), 1.04 (3H, d, J 6.6 Hz, Me), 0.81 (3H, d, J 6.6 Hz, Me), 0.59 (1H, q, J 11.7 Hz, 18-H), m/z; 558 (M^+), 540 (M^+-H_2O), 526 (M^+-MeOH), 508 (M^+-H_2O-MeOH), 494 (M^+-2MeOH), 476 (M^+-H_2O-2MeOH), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4) (Found: M^+, 558.3545 $C_{33}H_{50}O_7$ requires M, 558.3557). More polar : (128), δ (500 MHz), 6.05 (1H, dd, J 14.6 and 10.8 Hz, 10-H), 5.96 (1H, d, J 10.8 Hz, 9-H), 5.50 (1H, m, 3-H), 5.38 (1H, dd, J 14.6 and 9.9 Hz, 11-H), 5.30 (1H, m, 19-H), 4.84 (1H, d, J 11.2 Hz, 15-H), 4.25 (1H, m, 5-H), 4.16 (1H, d, J 10.7 Hz, 8'-H), 4.05 (1H, d, J 10.7 Hz, 8'-H), 3.96 (1H, s, 7-OH), 3.58 (1H, br t, J 12.4 Hz, 17-H), 3.39 (3H, s, 8'-OMe), 3.36 (1H, m, 2-H), 3.24 (1H, dq, J 9.7 and 6.3 Hz, 25-H), 2.44 (1H, m), 2.42 (1H, dd, J 12.9 and 7.0 Hz, 6-H), 2.35-2.25 (2H, m), 2.20-1.90 (5H, m), 1.87 (3H, s, 4-Me), 1.86-1.70 (2H, m), 1.70-1.20 (8H, m), 1.09 (3H, d, J 6.3 Hz, 25-Me), 1.03 (3H, d, J 6.6 Hz, Me), 0.82 (3H, d, J 6.6 Hz, Me), 0.58 (1H, q, J 11.6 Hz, 18-H), m/z; 544 (M^+), 526 (M^+-H_2O), 512 (M^+-MeOH), 494 (M^+-H_2O-

MeOH), 199 ($C_{11}H_{19}O_3$), 181 ($C_{11}H_{17}O_2$), 153 ($C_{11}H_{17}O_2$-C_2H_4), (Found: M^+, 544.3401 $C_{32}H_{48}O_7$ requires M, 544.3341). Most polar: (122) identical spectral properties to material prepared previously.

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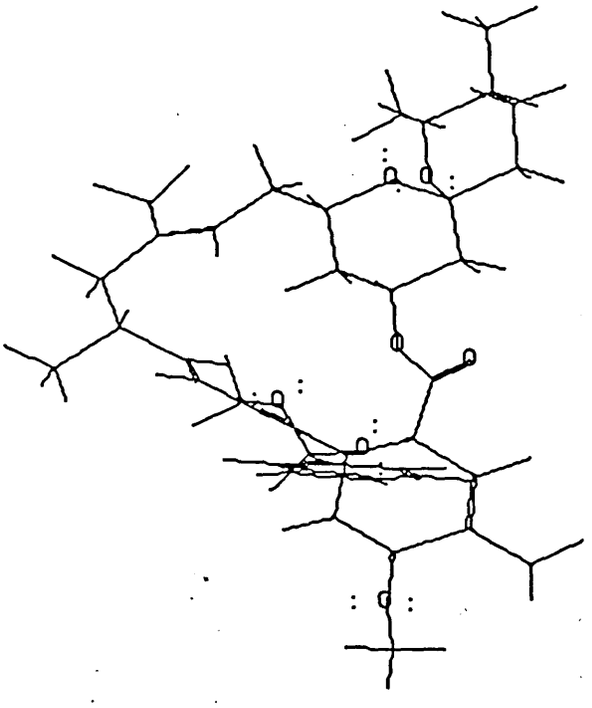
124. This 2-Sulphonyloxaziridine was initially prepared in our laboratory and subsequently reported by F.A. Davies, M.S. Haque, T.G. Ulatowski and J.C. Towson *J. Org. Chem.*, 1986, *51*, 2402.

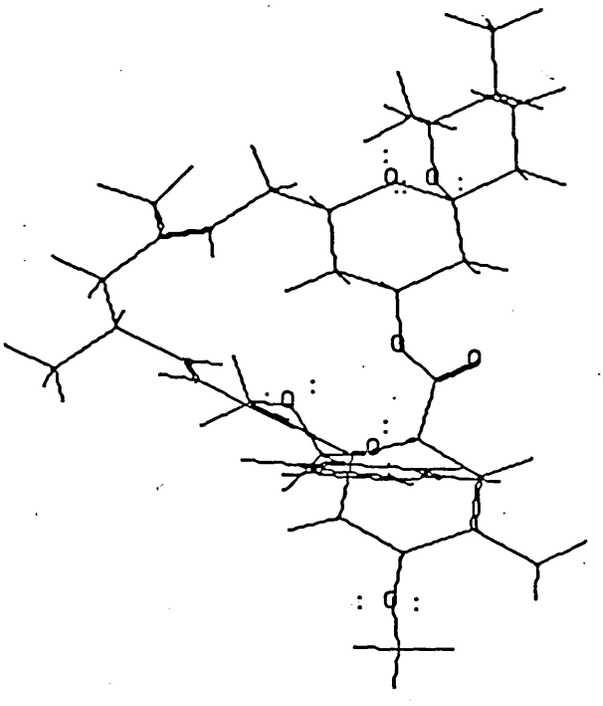
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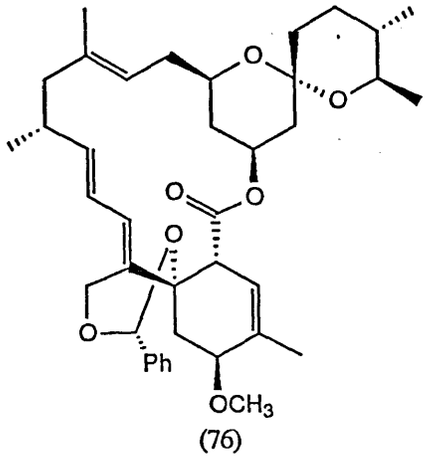
126. Thanks to Pfizer for a 300 MHz NMR spectrum of milbemycin β_1.

Appendix

Stereo View of Benzylidene Acetal (76)
Energy = 115.89 Kjoul

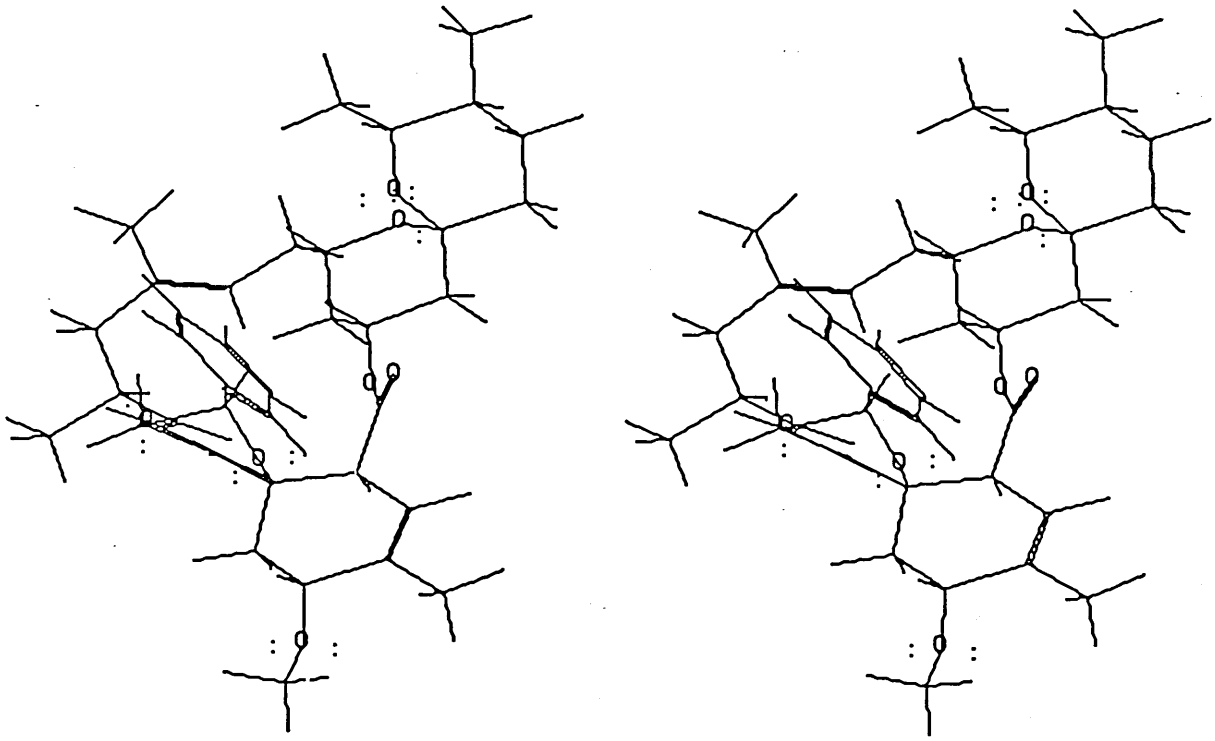


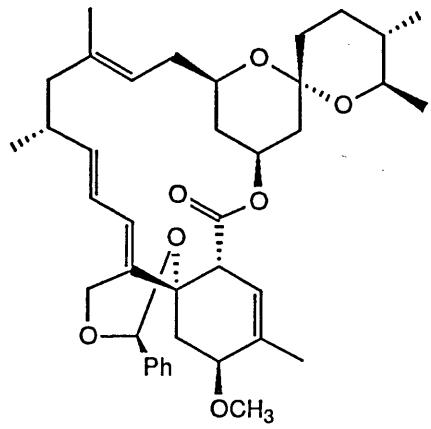




(76)

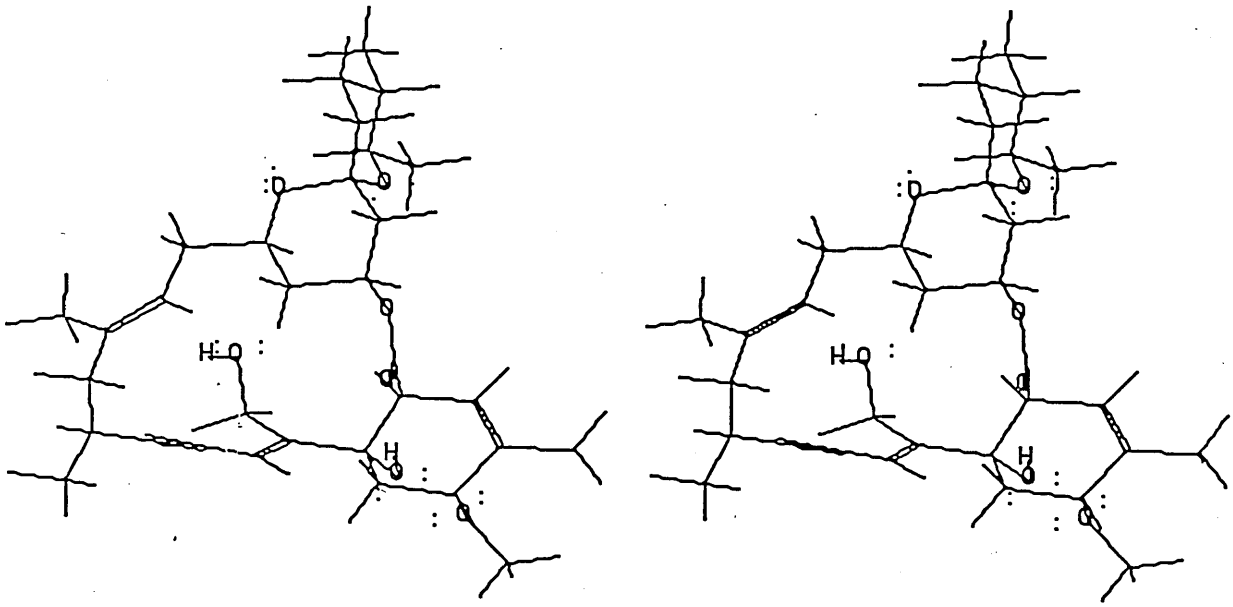
Stereo View of Benzylidene Acetal (77)
Energy = 119.68 Kjoul

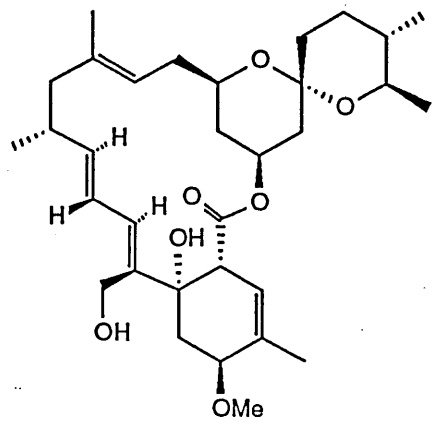




(77)

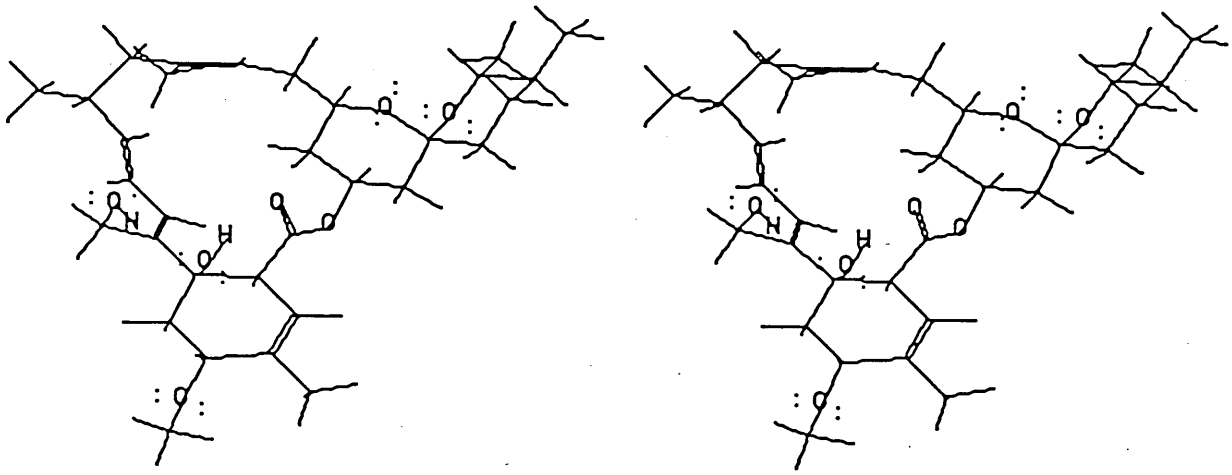
Stereo View of Milbemycin β_1 Conformer A
Energy = 100.46 Kjoul

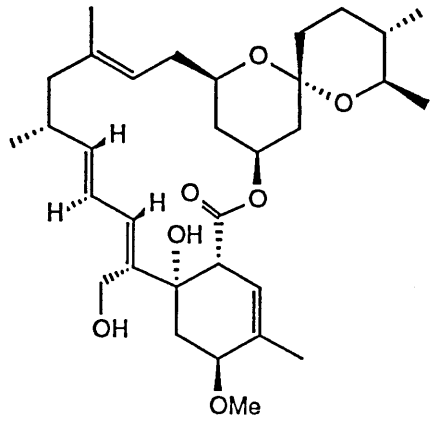




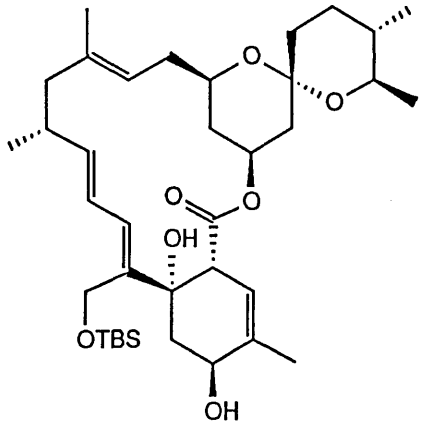
A

Stereo View of Milbemycin β_1 Conformer B
Energy = 102.53 Kjoul



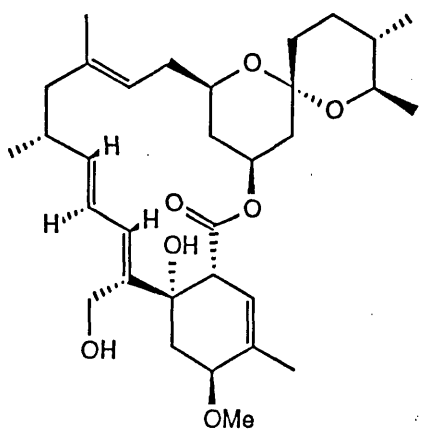


B

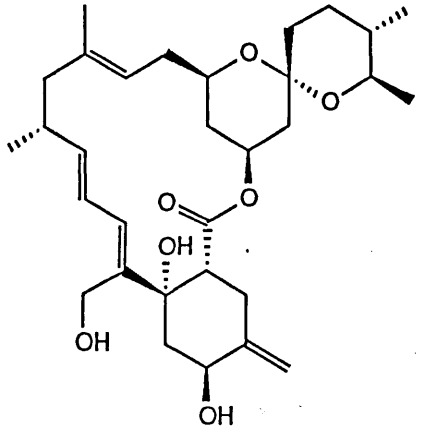


(134)

ATROPOMILBEMYCIN B1



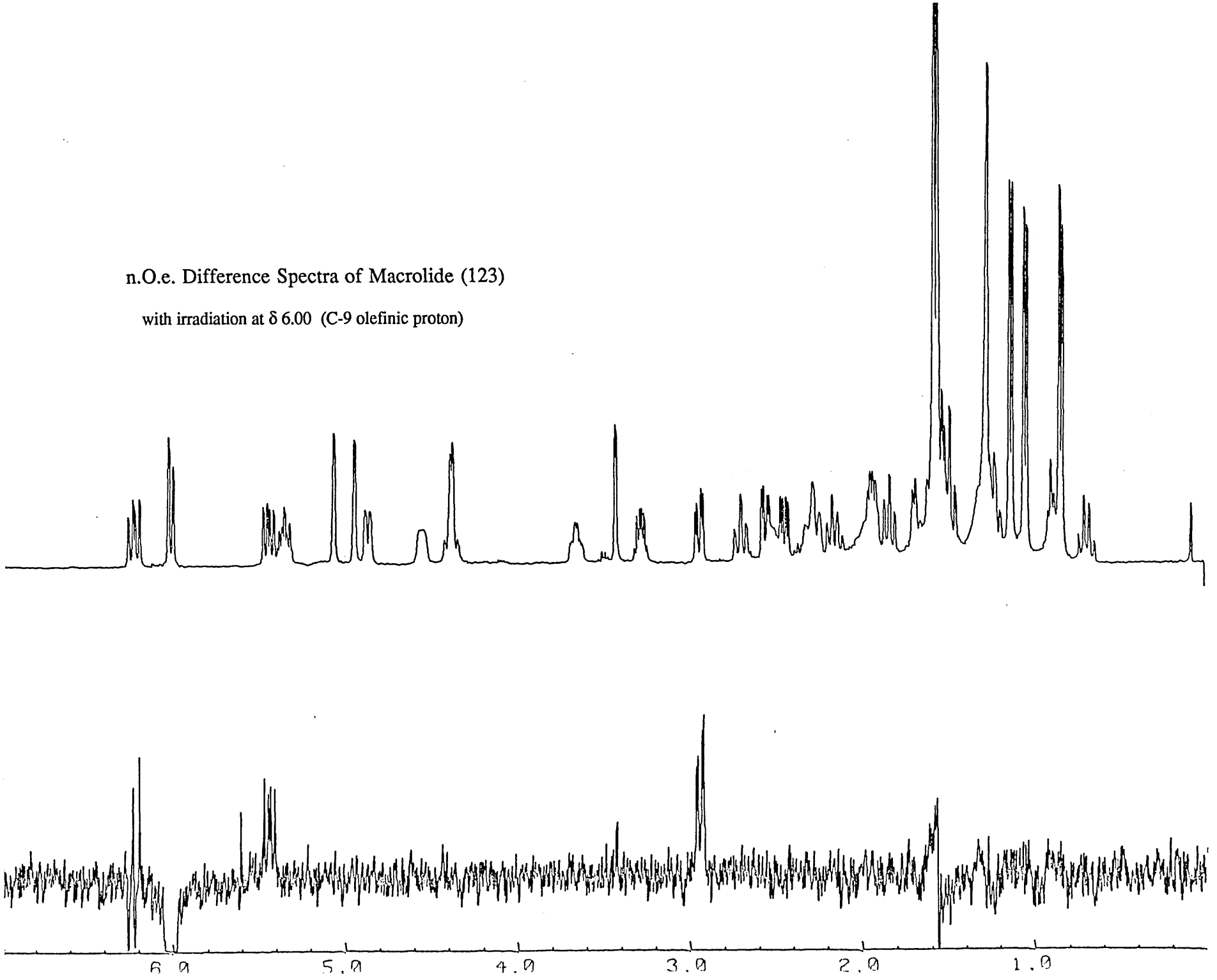
(136)



(123)

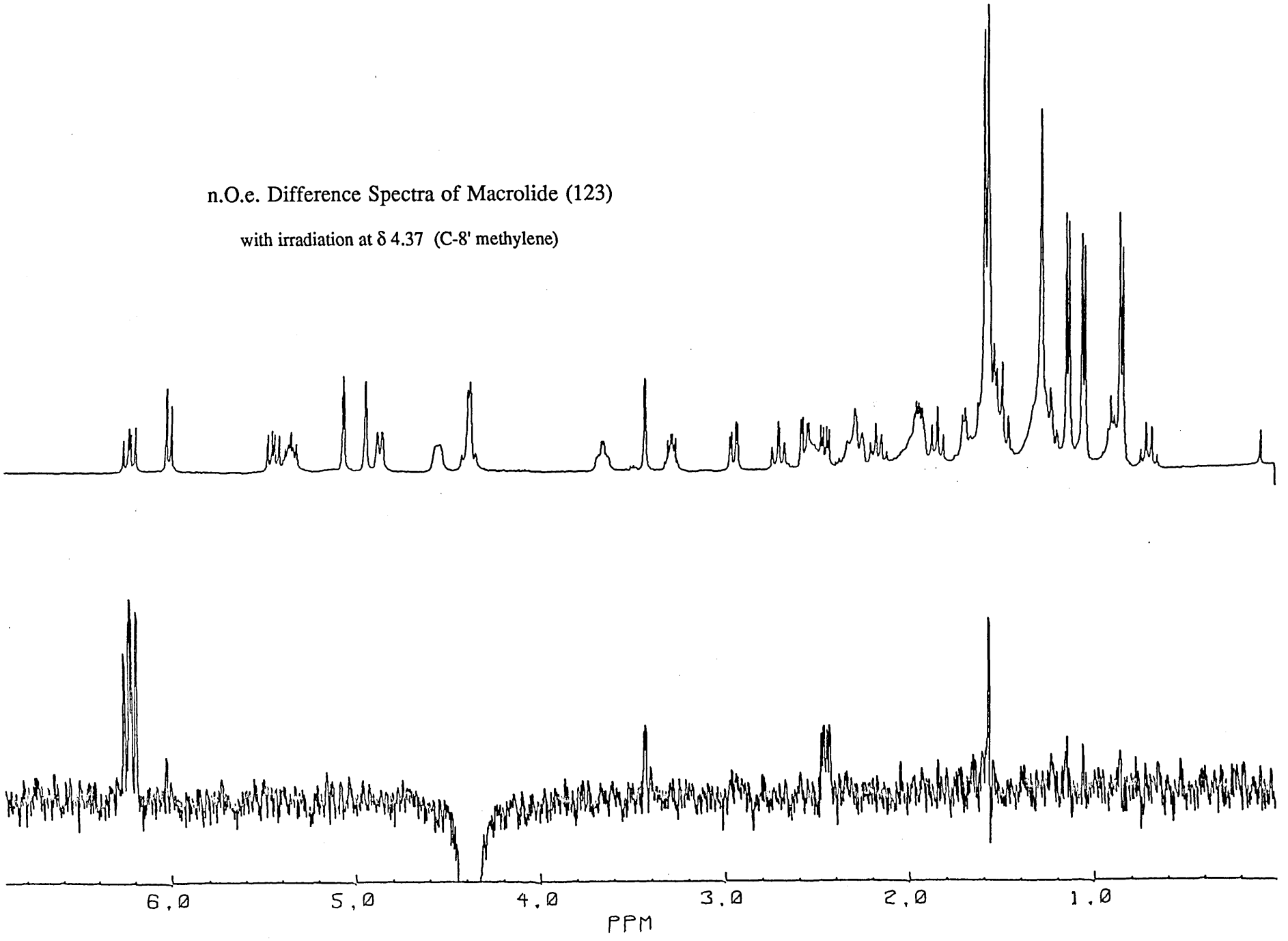
n.O.e. Difference Spectra of Macrolide (123)

with irradiation at δ 6.00 (C-9 olefinic proton)



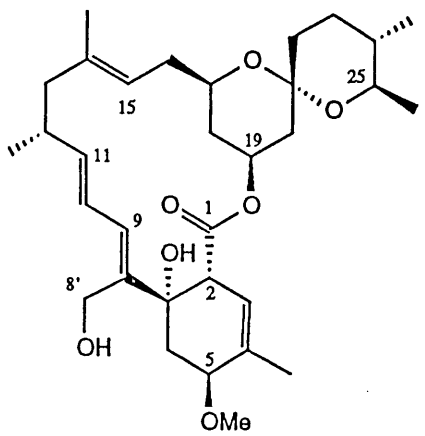
n.O.e. Difference Spectra of Macrolide (123)

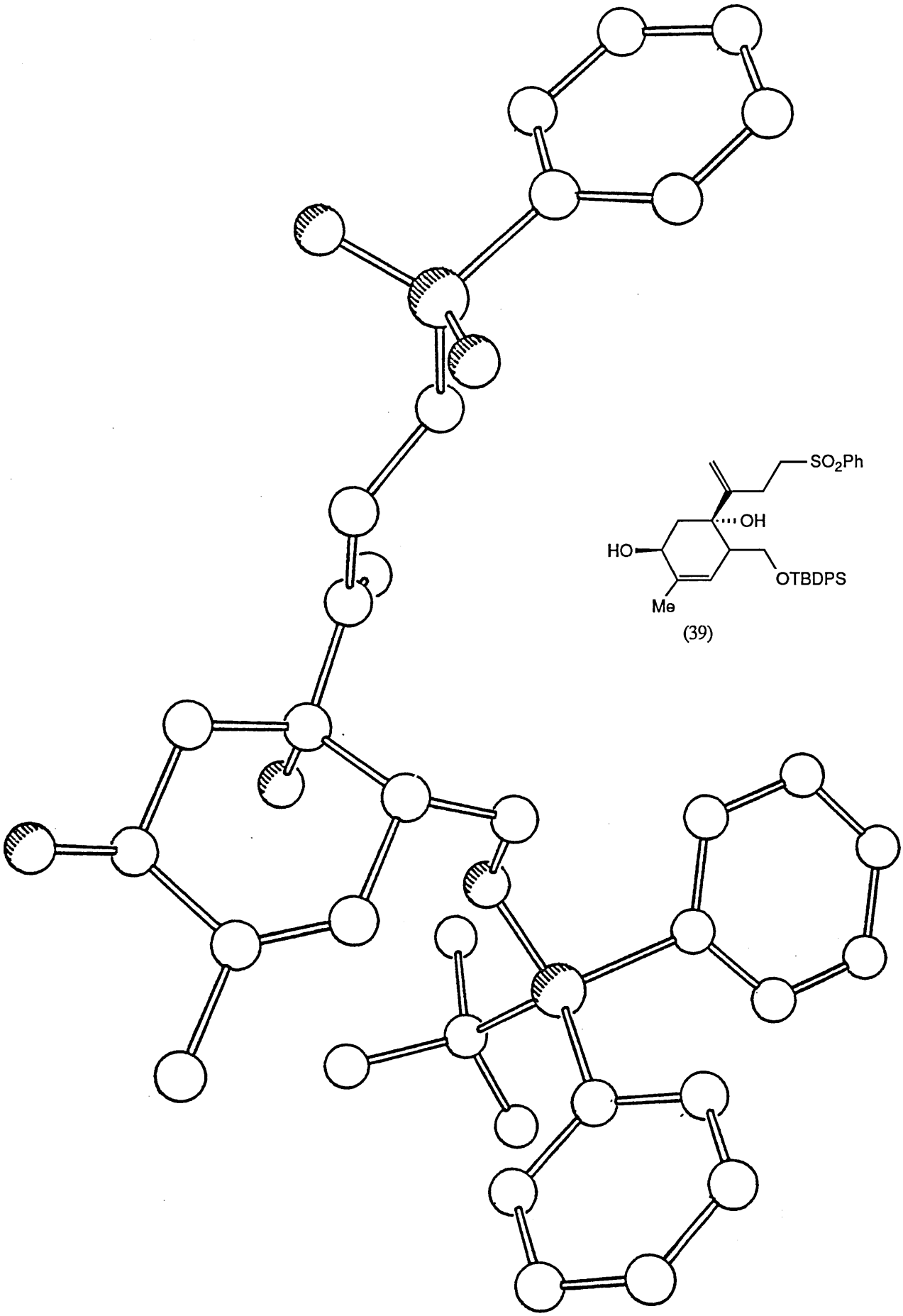
with irradiation at δ 4.37 (C-8' methylene)



300MHz 1H NMR Spectrum of

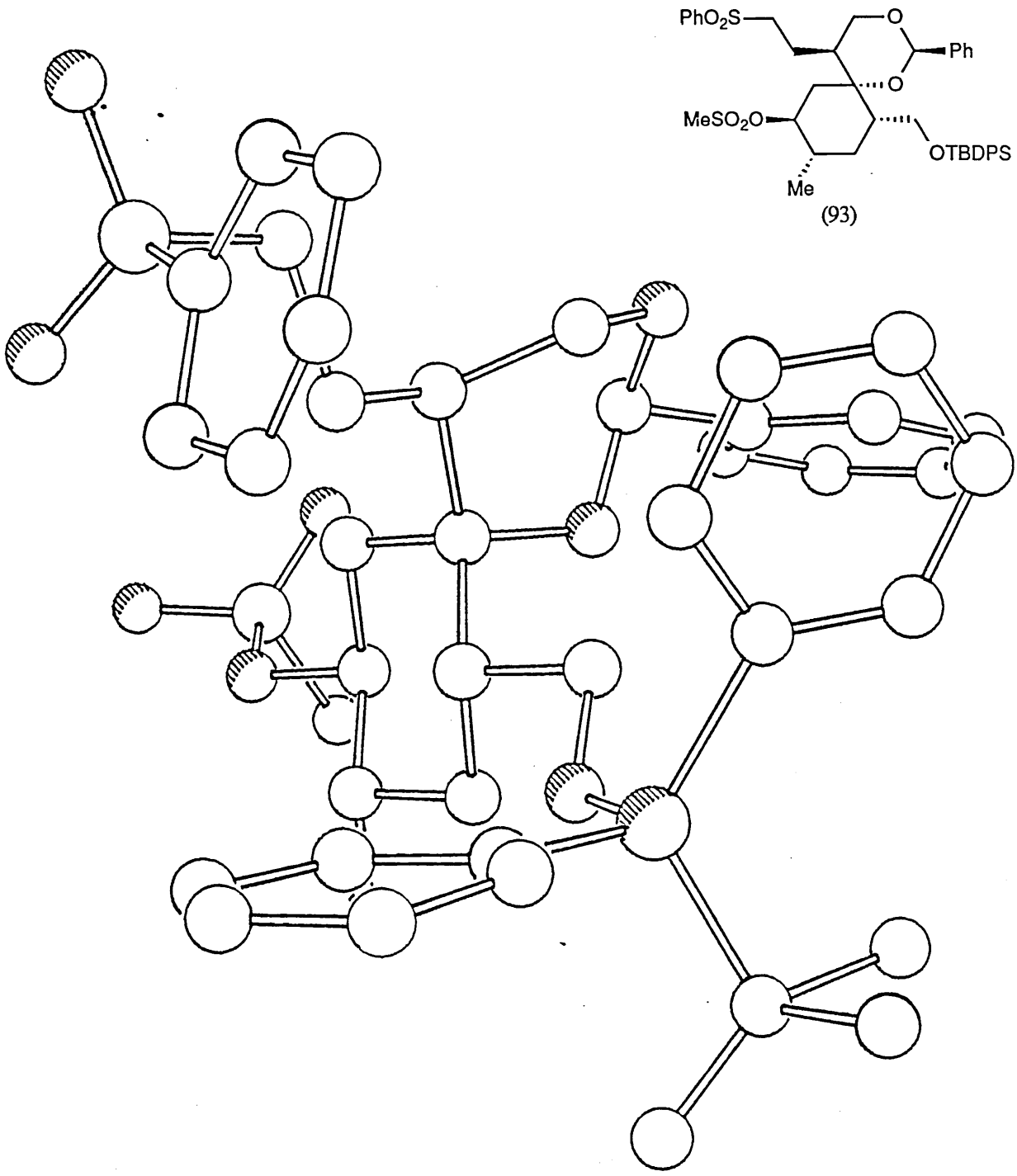
Milbemycin β1





(39)

Crystal data: $C_{34}H_{42}O_6Si$, M = 591.9, monoclinic, a = 12.100(3), b = 8.179(2), c = 33.536(8)Å, β = 90.39(2)°, U = 3319Å^3, space group $P2_1/n$, Z = 4, D_c = 1.18gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 15cm^{-1}, F(000) = 1268. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 3397 Independent reflections were measured ($2\theta \leq 100°$), of which 3178 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. A ΔF map revealed that C(34) had two orientations for the methyl groups, which were fixed at 50% occupancies and refined as rigid bodies. The hydroxy protons on O(5) and O(7) were located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to R = 0.048, R_w = 0.056 [$w^{-1} = \sigma^2(F) + 0.00236F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.23 and -0.31eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.087 and 0.752 respectively.



(93)

Crystal data: $C_{32}H_{52}O_8S_2Si$, M = 657.0, monoclinic, a = 40.573(41), b = 11.249(13), c = 20.051(13)Å, β = 95.20(8)°, U = 9114Å3, space group C2/c, Z = 8, D_C = .96gcm-3, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 16cm-1, F(000) = 2032. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 4684 Independent reflections were measured ($2\theta \leq 100°$), of which 3474 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The structure possessed a large degree of disorder and consequently it was only possible to refine the structure isotropically. Refinement was by block-cascade, full-matrix least-squares to R = 0.240, R_w = 0.240 [w-1 = σ2(F) + 0.00000F2]. The maximum and minimum residual electron densities in the final ΔF map were 1.30 and -1.01eÅ-3 respectively. The mean and maximum shift/error in the final refinement were 0.190 and 0.936 respectively.