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SYNTHESIS TOWARDS THE AVERMECTINS AND MILBEMYCINS

a thesis presented by

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TO MY PARENTS

WITH GRATITUDE AND AFFECTION.

ABSTRACT

The review section of this thesis is in two parts, outlining firstly the isolation, structure determination, and biological activity of the highly potent, broad-spectrum antiparasitic agents the avermectins and milbemycins, and secondly the successful approaches towards these natural products.

The thesis then describes our initial synthetic efforts towards the preparation of model compounds related to the southern hemisphere of the avermectins.

Firstly, γ-alkylation of ^{t}butyl acetothioacetate with various aldehydes followed by transesterification with (2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-ol gave seco-model derivatives such as (2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 3',5'-dihydroxy-6'-methylhept-6'-enoate. These compounds were submitted for biological screening but were found to be inactive.

In a second model study, preparation and treatment of a suitable alkenyl epoxide with nonacarbonyldiiron followed by oxidation of the resulting π-allyltricarbonyliron lactone complex with ceric ammonium nitrate did not provide access to a potentially reactive bicyclic α-alkenyl-β-lactone model.

The last part of this thesis describes attempts to prepare a cyclohexenone sub-unit required for the synthesis of milbemycin β_1. This has been achieved by a novel trimethylaluminium catalysed Prins reaction between the electron rich methyl enol ether of 2,5-dihydro-*p*-methylanisole and formaldehyde to give a homoallylic alcohol. Elaboration of the resulting ene-adduct gave the endocyclic isomer 2-^{t}butyldiphenylsilyloxymethyl-5-methoxy-4-methylenecyclohexanone in eight steps and 13.9% overall yield from *p*-methylanisole. Nucleophilic

addition of vinylmagnesium bromide into the ketone carbonyl group of this compound was shown to proceed regioselectively with a 12:1 ratio in favour of attack from the β-face. Further elaboration of this adduct demonstrated the viability of the synthetic strategy for milbemycin synthesis.

LIST OF CONTENTS

ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to Prof. Steven Ley for his guidance and inspiration throughout the past three years.

Thanks are also due to the technical staff of the Chemistry Department for their skilful assistance and friendly cooperation.

Special thanks to all my colleagues in the Whiffen Laboratory, both past and present, for their enthusiasm and friendship. In particular, I wish to record my gratitude to Dr. Brian Palmer for valuable advice and encouragement.

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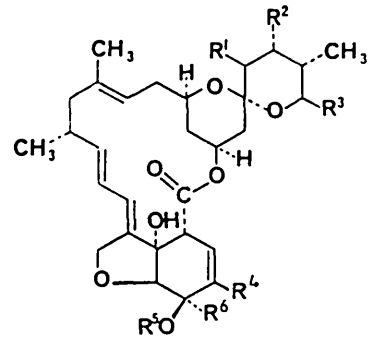
INTRODUCTION

Since the days of the early antibiotics, it has become increasingly evident that microorganisms are a rich source of novel chemical structures. The milbemycins[1], found and structurally elucidated in 1975, are a group of fermentation products of *Streptomyces hygroscopicus* subsp. *aureolacrimosus* which show potent, broad-spectrum anthelmintic, insecticidal and acaricidal activity.[2] All the twenty milbemycins so far isolated are tetra- or pentacyclic 16-membered macrocyclic lactones containing a fused [5,5] spiroacetal ring. They can be divided structurally into two groups known as an α- and β-series: the α-series incorporates a tetrahydrofuran ring *cis*-fused to the cyclohexene ring whereas the β-series has no tetrahydrofuran ring. Single crystal X-ray crystallography unambiguously defined the absolute stereochemistry and conformation of the milbemycins as shown in Figures 1 and 2.

In 1979, the Merck group reported on the related avermectins, a family of new and very potent anthelmintic agents[3], produced as fermentation products of *Streptomyces avermitilis* MA 460 (NRRL 8165).[4] They are glycoside derivatives containing a α-L-oleandrosyl-α-L-oleandrosyl moiety at the C-13 of the milbemycin series.

The avermectins were first separated chromatographically[4b] into four major components, collectively designated as the a-series. Mass spectroscopic analysis revealed the presence, in each of them, of 5 → 10% of a minor homologue, collectively designated as the b-series, which was subsequently separated from the major component by reverse phase high performance liquid chromatography. The structures of the various components were largely determined by high resolution mass spectrometry and ^{13}C nuclear magnetic resonance spectroscopy.[4c] These techniques suggested a number of structural units which, when compared with the milbemycins[1b], showed many common features.

Figure 1



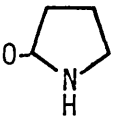
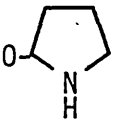
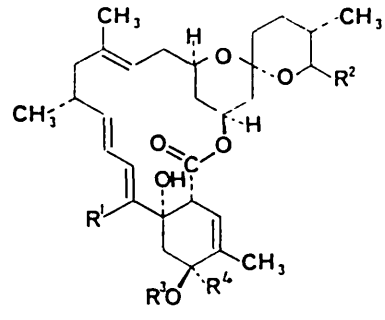
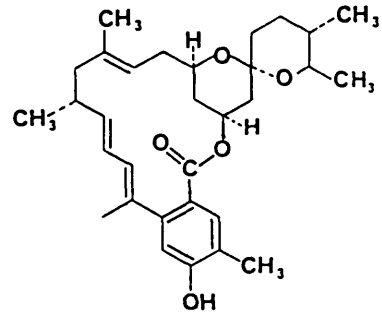
	Milbemycin	R_1	R_2	R_3	R_4	R_5	R_6
(1)	α_1	H	H	CH_3	CH_3	H	H
(2)	α_2	H	H	CH_3	CH_3	CH_3	H
(3)	α_3	H	H	CH_2CH_3	CH_3	H	H
(4)	α_4	H	H	CH_2CH_3	CH_3	CH_3	H
(5)	α_5	OH	$OCOCH(CH_3)C_4H_9$	CH_3	CH_3	H	H
(6)	α_6	OH	"	CH_3	CH_3	CH_3	H
(7)	α_7	OH	"	CH_2CH_3	CH_3	H	H
(8)	α_8	OH	"	CH_2CH_3	CH_3	CH_3	H
(9)	α_9	H	H	CH_3	CH_2OCO- 	H	H
(10)	α_{10}	H	H	CH_2CH_3	"	H	H
(11)	D	H	H	$CH(CH_3)_2$	CH_3	H	H
(12)	F	H	H	$CH(CH_3)_2$	CH_2OCO- 	H	H
(13)	G	H	H	$CH(CH_3)_2$	CH_3	CH_3	H
(14)	J	H	H	CH_3	CH_3	=O	
(15)	K	H	H	CH_2CH_3	CH_3	=O	

Figure 2



	Milbemycin	R_1	R_2	R_3	R_4
(16)	β_1	CH_2OH	CH_3	CH_3	H
(17)	β_2	CH_2OH	CH_2CH_3	CH_3	H
(18)	E	CH_2OH	$CH(CH_3)_2$	CH_3	H
(19)	H	CH_3	$CH(CH_3)_2$	=O	



β_3

(20)

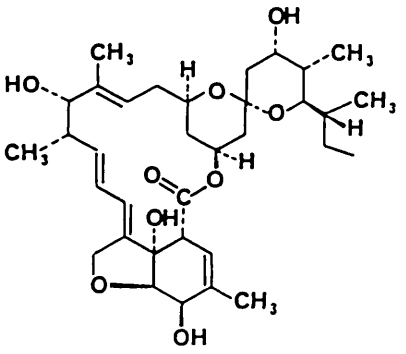
It was possible to interpret the complex avermectin spectral data convincingly by considering three structural changes when compared to the milbemycins:

(1) a disaccharide substituent is attached *via* a new hydroxyl function at C-13;

(2) a C-22, 23 - double bond or a C-23 hydroxyl group; and

(3) sec-butyl or iso-propyl substituents at the C-25 position instead of usual methyl or ethyl substituents.

Single crystal X-ray diffraction experiments on the avermectin B_{2a} aglycone (21) and avermectin B_{1a} (26) confirmed the eight avermectins to possess the gross structure shown in Figure 3.[4d]

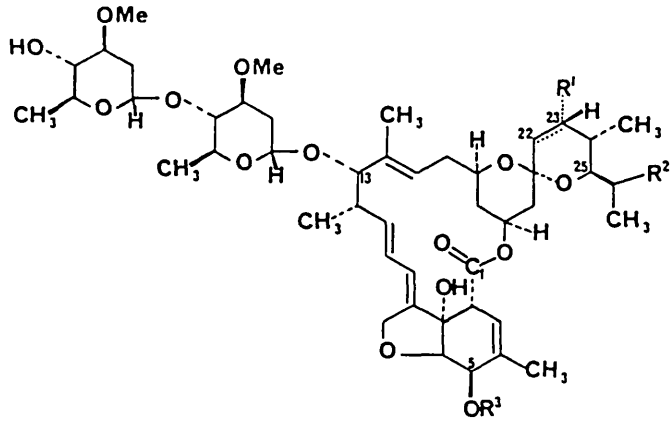


(21)

In addition, circular dichroism (CD) measurements have established the avermectins and milbemycins (*vide infra*) to have identical absolute configurations.

The avermectins were found to be extraordinarily active against a wide range of parasitic helminths[3,5], arachnids and ectoparasites[4e,6] in doses as low as 10μg kg^{-1}, yet they are devoid of antibacterial or antifungal activity.[7] Despite their macrocyclic lactone structure,

Figure 3



	Avermectin	R_1*	R_2	R_3
(22)	A_{1a}	-	CH_2CH_3	CH_3
(23)	A_{1b}	-	CH_3	CH_3
(24)	A_{2a}	OH	CH_2CH_3	CH_3
(25)	A_{2b}	OH	CH_3	CH_3
(26)	B_{1a}	-	CH_2CH_3	H
(27)	B_{1b}	-	CH_3	H
(28)	B_{2a}	OH	CH_2CH_3	H
(29)	B_{2b}	OH	CH_3	H

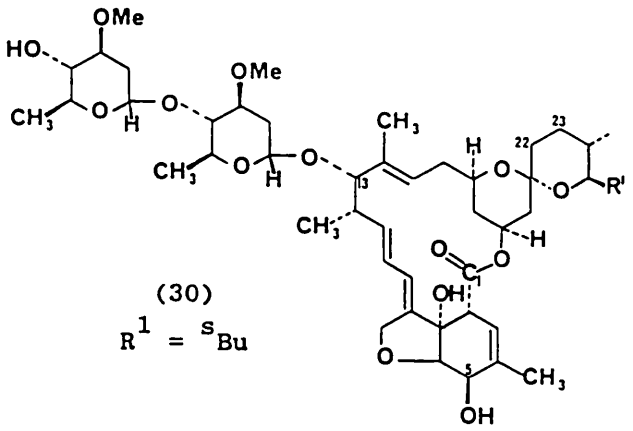
*Where R is absent, the double bond (⎓) is present.

they neither inhibit protein synthesis nor act as ionophores but appear to interfere with the neurotransmission of many invertebrates.[8]

Biological testing showed all the avermectins to have a broad spectrum of activity but with considerable variation in potency depending upon the parasite investigated. The antiparasitic activities of the a- and b-series are virtually identical and consequently, the need for difficult separations does not exist. Compounds of the B-series (those containing a C-5 hydroxyl group) were generally more potent than those of the A-series. Protection of the C-5 hydroxyl group as the 5-O-^{t}butyldimethylsilyl derivative resulted in complete loss of biological activity indicating the possible importance of the C-5 hydroxyl group for activity. Removal of one of the α-L-oleandrose units decreased activity to between 25 and 50% compared to that of the natural disaccharide. Removal of both sugar units cut activity to approximately 3%. However, selective acylation of the 4"-O-hydroxyl group resulted in little loss of activity.[9]

Differences in potency between the 1- and 2-series were found to be more subtle. The presence of the double bond at C-22, 23 as opposed to the hydroxyl group has a profound effect on the conformation of the ring bearing these functionalities and consequently causes subtle changes in bioactivity.[10] For example, while avermectin B_1 was more active than B_2 upon oral administration, the converse was true when each was administered parenterally. Preparation of compounds with the conformation of the 2-series but lacking the C-23 hydroxyl group, with the hope that such compounds would retain the desirable features of both series, became an important objective for the scientists at Merck.

Selective hydrogenation of the *cis*-substituted target olefin in avermectin B_1, using Wilkinson's homogeneous hydrogenation catalyst $RhCl(PPh_3)_3$ which is known to be highly sensitive to the steric environment of the olefin, gave the desired 22, 23-dihydroavermectin B_1 (30) in 85% yield together with 3, 4, 22, 23-tetrahydroavermectin B_1 (3%).[10] Reduction of the 3,4-double bond on the other hand caused considerable lowering of anthelmintic activity with respect to the original avermectin. On the basis of its overall efficacy *via* oral and parenteral routes in sheep[11] and cattle and for its better safety profile, (30) is now marketed under the non-proprietary name "ivermectin".[10]



(30)
$R^1 = {}^{s}Bu$

Ivermectin has an extremely broad spectrum of antinematodal activity in a variety of domestic animals, being active against genera of the superfamilies *Trichostrongyloidea, Strongyloidea, Metastrongyloidea, Rhabditoidea, Ascaridoidea, Oxyuroidea, Spiruroidea, Filarsidea* and *Trichuroidea*.[12] Indeed, all nematode genera against which ivermectin has been tested proved to be affected during at least one stage

of the life-cycle. The minimum dosage used is also very much less than that of any other anthelmintic agent.[10]

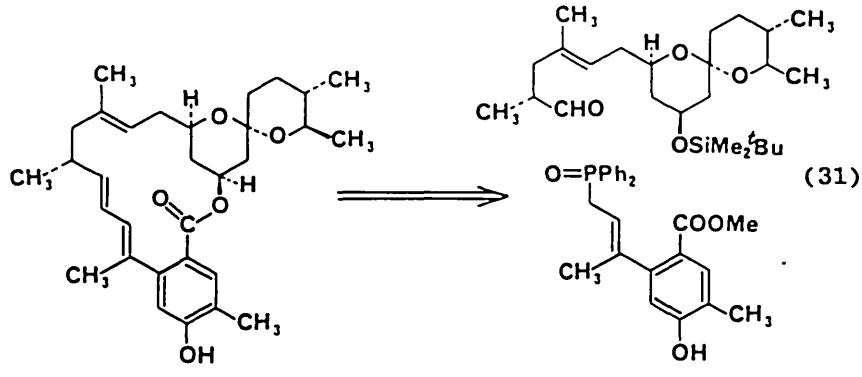
Studies on the mode of action have been carried out with avermectin B_1, but it is presumed that all avermectins share a common mechanism.[8,13] The avermectins paralyse worms, as do many other anthelmintics, though they appear to do so in a unique way. It is believed that they behave as agonists for γ-aminobutyric acid (GABA), the neurotransmitter involved in sending inhibitory signals from the interneurons to the motorneurons.[8,13,14] Stimulation of pre-synaptic release of GABA and enhanced binding to the post-synaptic receptor induce an irreversible "resting" condition on the parasite which usually results in death. This is consistent with the apparent lack of efficacy of the avermectins against trematodes and cestodes which are thought not to use GABA as a neurotransmitter.

REVIEW

The current high level of interest in the avermectins and milbemycins is demonstrated by the large number of publications and the increased synthetic effort in this area. These synthetic studies resulted in 1982 with the publication of two routes to milbemycin β_3, the simplest member of the series.

The first published total synthesis of milbemycin β_3 (20) by Smith[15] involved the coupling of two major fragments, a northern spiroacetal unit (31) with an aromatic southern zone (32) (Scheme 1).

Scheme 1



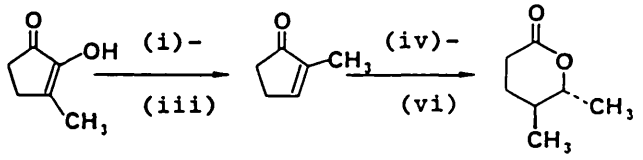
(20) (32) (31)

The spiroacetal moiety (33) was synthesised and elaborated to (31) by the highly stereoselective Ireland-Claisen rearrangement.[16] This unit was coupled by Horner-Wittig reaction[17] with the southern hemisphere (32). Deprotection and macrocyclic lactonisation[18] completed the synthesis.

Stereocontrolled construction of the aldehyde (33) was achieved by Michael addition to an appropriately designed α,β-unsaturated aldehyde (39), under thermodynamic and stereoelectronic control[19], to produce a spiroacetal with the ether oxygens in axial dispositions and the side chain adopting an equatorial position.

Lactone (34) was prepared in racemic form, on 50g scale, from cyclotene in 55% overall yield (Scheme 2).

Scheme 2

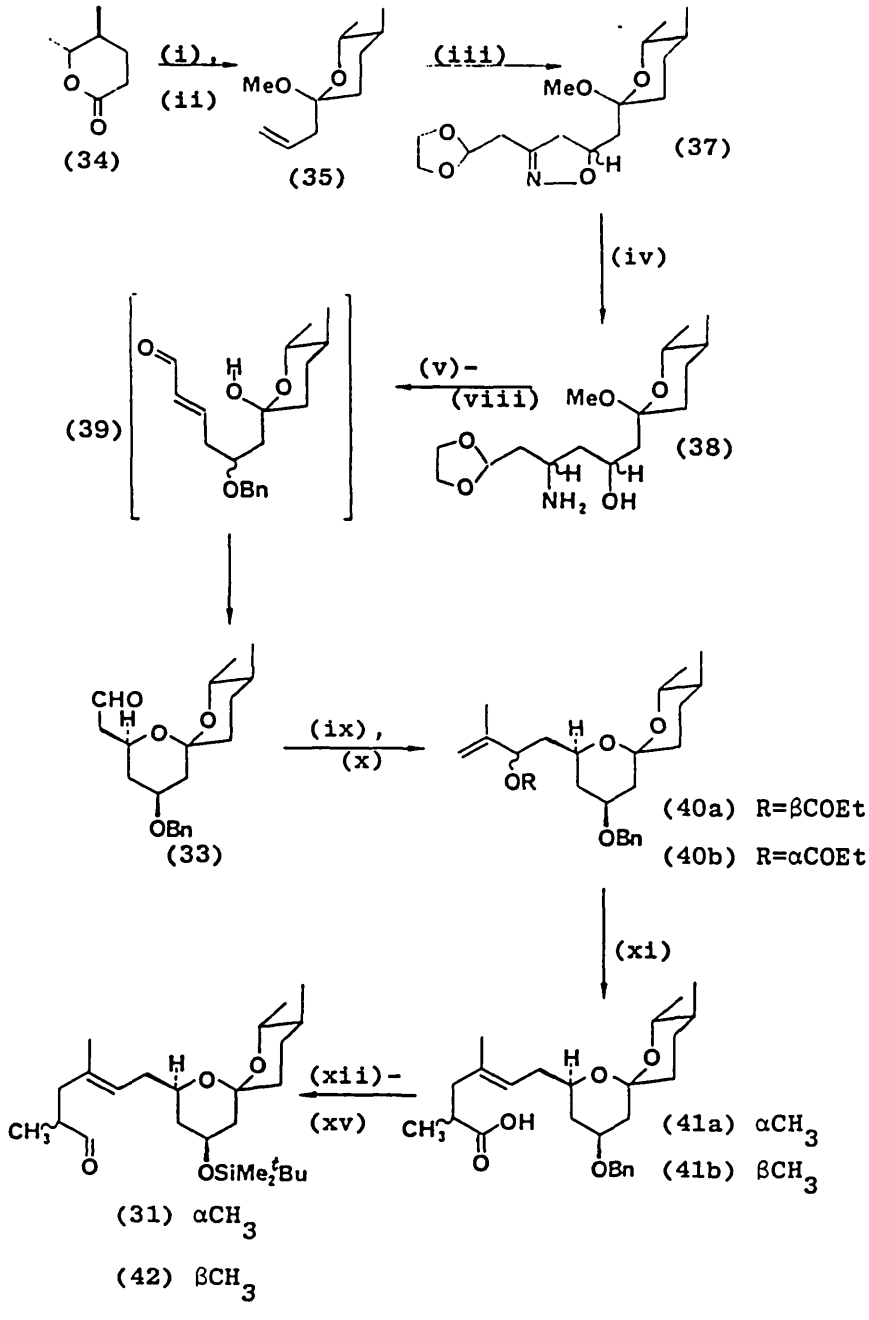


(34)

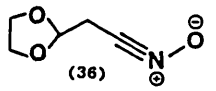
Reagents: (i) MeOH, HCl; (ii) $LiAlH_4$, Et_2O; (iii) H_3O^+;
(iv) Me_2CuLi, THF; (v) HCl, Et_2O; (vi) mCPBA.

This was converted in two steps to the mixed methyl ketal (35) (Scheme 3) which after dipolar cycloaddition of the nitrile oxide (36) produced a 2:1 mixture of the isoxazolines (37), only one diastereoisomer of which would ultimately have the correct geometry to undergo the spiroacetal cyclisation reaction. However, without separation, reduction of the diastereoisomeric isoxazolines (37) afforded the aminol (38) as a mixture of four diastereoisomers. This mixture was converted in four steps to an α,β-unsaturated aldehyde (39) which under the reaction conditions cyclised to give the desired crystalline aldehyde (33) in 20-25% overall yield.

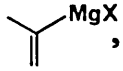
Scheme 3


(i),
(ii)
(iii)
(iv)
(v)-
(viii)
(ix),
(x)
(xi)
(xii)-
(xv)
(34)
(35)
(37)
(38)
(39)
(33)
(40a) R=βCOEt
(40b) R=αCOEt
(41a) αCH3
(41b) βCH3
(31) αCH3
(42) βCH3

Reagents: (i)  , -78°C, THF; (ii) $CH(OCH_3)_3$, $CeCl_3.7H_2O$;

(iii)  ; (iv) $LiAlH_4$; (v) KH (15 eq.),

0°C; (vi) $C_6H_5CH_2I$, 0°C; (vii) MeI; (viii) TsOH, H_2O;

(ix)  , -78°C, Et_2O; (x) CH_3CH_2COCl; (xi) $KN(TMS)_2$,

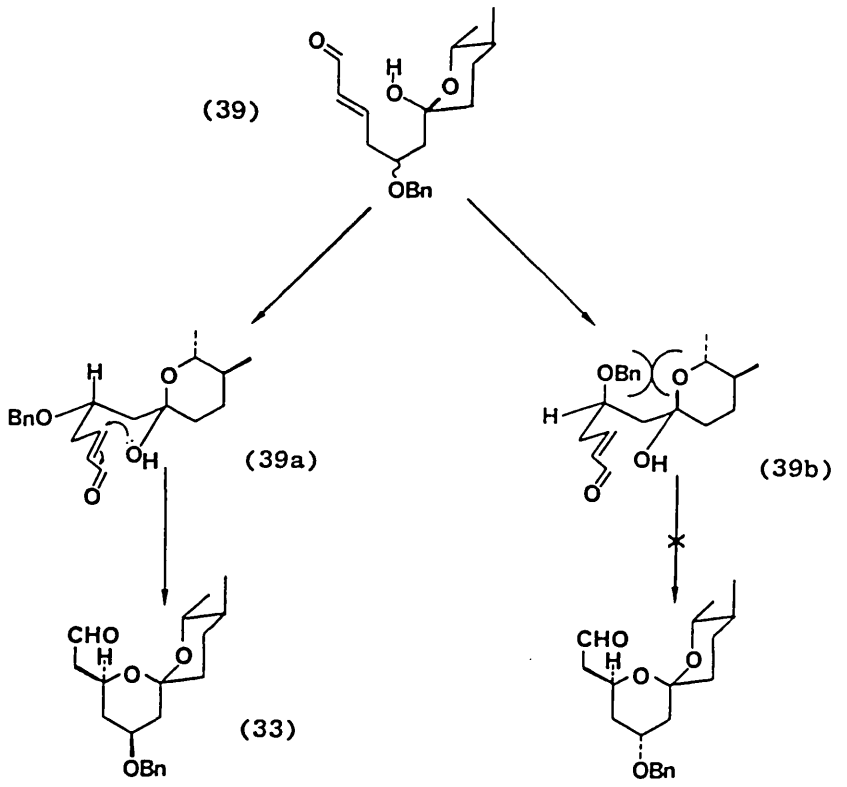
TMSCl, -78 → 25°C; (xii) Li/NH_3; (xiii) TBDMSCl, DMF,

imidazole; (xiv) $LiAlH_4$; (xv) Collins' oxidation.

This favourable result can be explained by two facts: (1) the Michael addition of oxygen nucleophiles to α,β-unsaturated aldehydes is a reversible process[20] and proceeds therefore to afford the isomer possessing the most thermodynamically favourable conformation; and (2), facile cyclisation of the α,β-unsaturated aldehyde (39) would require the molecule to attain a specific transition state conformation. In the case of unsaturated aldehyde (39a), wherein the benzyl ether occupies an equatorial position, ring closure to afford the aldehyde (33) proceeds smoothly. However, in the other diastereoisomer (39b), a considerable 1,3-diaxial interaction may prevent this isomer from attaining the required transition state conformation and consequently, cyclisation is disfavoured (Scheme 4).

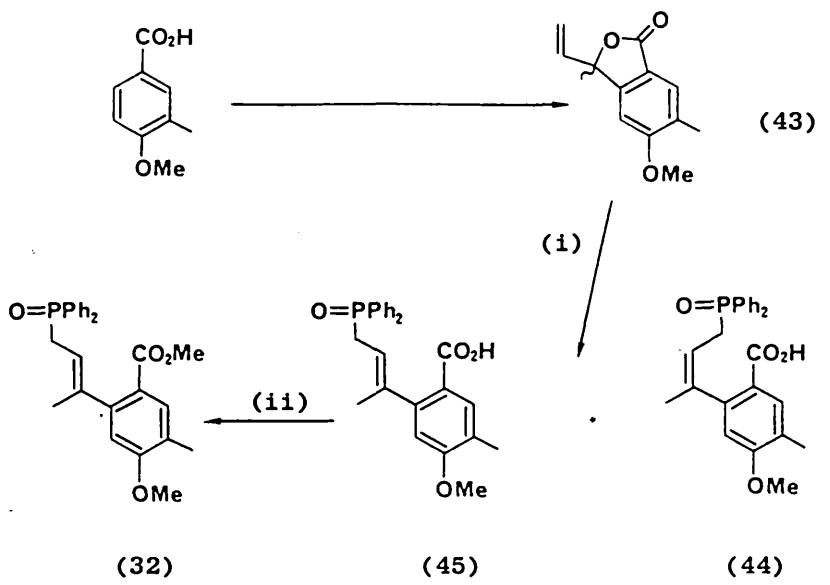
Extension of the side chain was achieved by isopropenyl Grignard addition into the aldehyde (33) followed by alkoxide acylation with propionyl chloride. This afforded a 2:1 mixture of the propionates (40a) and (40b) which were separable by flash chromatography. Application of the highly stereoselective Ireland-Claisen rearrangement[16] to each propionate gave the epimerically distinct acids (41a) and (41b). Both acids were converted to the corresponding aldehydes (31) and (42) in an overall yield of 59%.

Scheme 4



Construction of the southern hemisphere involved a straightforward seven step sequence to convert the readily available 3-methyl-p-anisic acid into the lactone (43) in 33% overall yield. A novel S_N2' displacement employing lithium diphenylphosphide[21] on lactone (43) gave a 3:1 mixture of isomeric phosphine oxides. Treatment with strong base gave a more favourable 1:1 mixture of the Z and E isomers (44) and (45). The E isomer (45) was separated by flash chromatography and esterified to afford the desired aromatic southern hemisphere (32) (Scheme 5).

Scheme 5

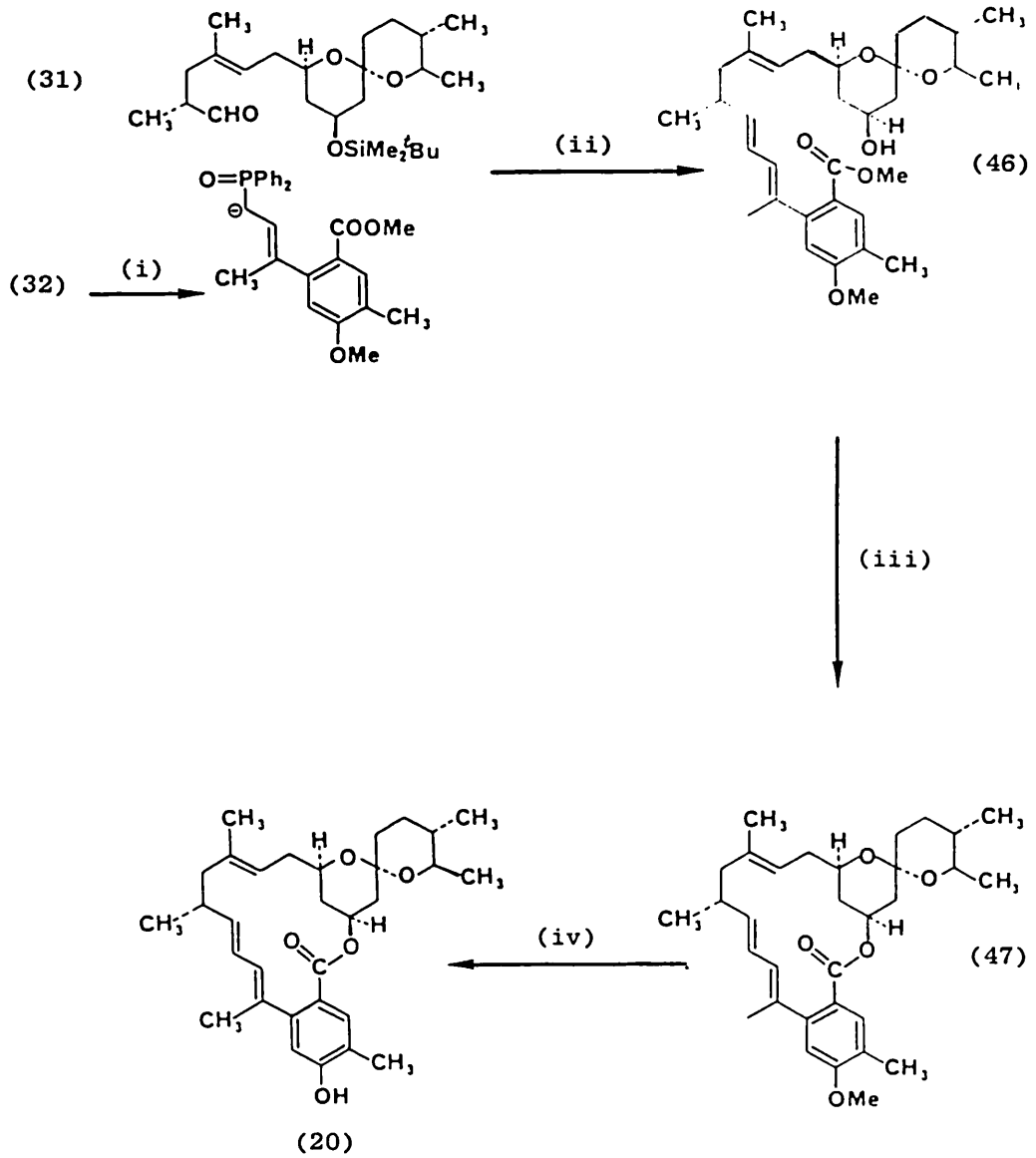


Reagents: (i) $Ph_2P^-Li^+$, THF, -22 → 25°C; (ii) O_2; (iii) CH_2N_2, Et_2O.

Horner-Wittig coupling[17] of the aldehyde (31) to the anion of (32) gave the diene (46) in 85 → 95% yield and as a mixture (7:1) of *trans* and *cis* isomers, with no epimerisation at the C-12 methyl group (Scheme 6). Deprotection of the alcohol and cyclisation yielded milbemycin β_3 methyl ether (47) in 76% based on (45). This upon demethylation of the aryl methyl ether gave (±) milbemycin β_3 (20) directly.

The second and more elegant synthesis of milbemycin β_3 was achieved by Williams[22] and provided material in its optically pure form. The synthetic approach was quite similar in overall concept to that of Smith, *ie.* a convergent process from two or three major components but quite different in the construction of these components.

Scheme 6

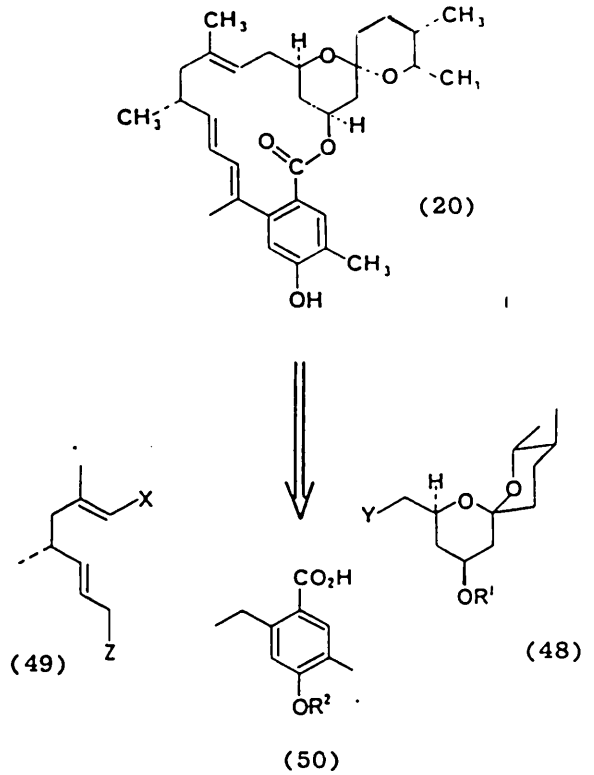


Reagents: (i) $NaN(TMS)_2$, -78^oC, THF; (ii) $(^nBu)_4NF$, THF;
(iii) KH, THF, 4h; (iv) NaSEt, DMF, 1h.

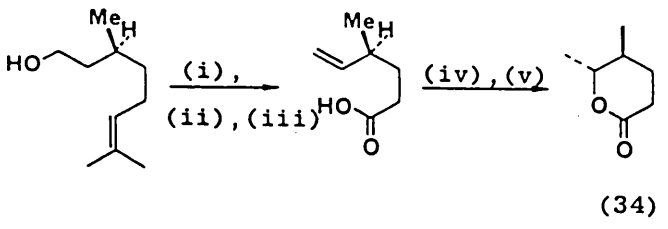
Williams' synthesis of milbemycin β_3 (20) relied on the preparation of three units: (1) a spiroacetal moiety (48); (2) a linking carbon chain (49) bearing a remote chiral centre at C-12; and (3) a substituted benzoic acid fragment (50) (Scheme 7).

trans-4,5-Dimethylvalerolactone (34) was prepared in its optically pure form in five steps and approximately 40% overall yield from (-)-(S)-citronellol (Scheme 8). The synthesis of the spiroacetal moiety was achieved by condensation of (34) with the α-lithiosulphinyl carbanion (51) to afford the adduct (52) as a mixture of two diastereoisomers (Scheme 9). Internal ketalisation of (52) gave the spiroacetal (53). As in the Smith synthesis, the stereochemistry of the resulting asymmetric centre is thermodynamically and stereoelectronically controlled[19], thereby placing the oxygens of the spiroacetal in axial dispositions. Additionally, equilibration occurs at C-20 to provide the equatorial sulphoxide. A small residual amount (10%) of the axial sulphoxide was carried through the synthetic scheme. Protection followed by pyrolysis gave the expected olefin (54). *Syn*-elimination of the axial sulphoxide on the other hand required more forcing conditions (xylene, ↯ , 49h, 72%) than the equatorial sulphoxide showing a significant rate difference between the two isomers. Chlorohydrin formation from (54) gave the separable crystalline products (55) and (56) in a 5:1 ratio, the major isomer having the undesired configuration resulting from diaxial addition to the double bond. Reduction of (55) and (56) gave the axial (57) and equatorial (58) alcohols. Inversion of the undesired axial alcohol was achieved by oxidation to the ketone and subsequent reduction to give (58) in 70% overall. Protection of (58) followed by saponification gave the primary alcohol (59) in 96% yield. This product was transformed into the bromide (60) and the aldehyde (48), two key intermediates for the attachment of the side chain.

Scheme 7

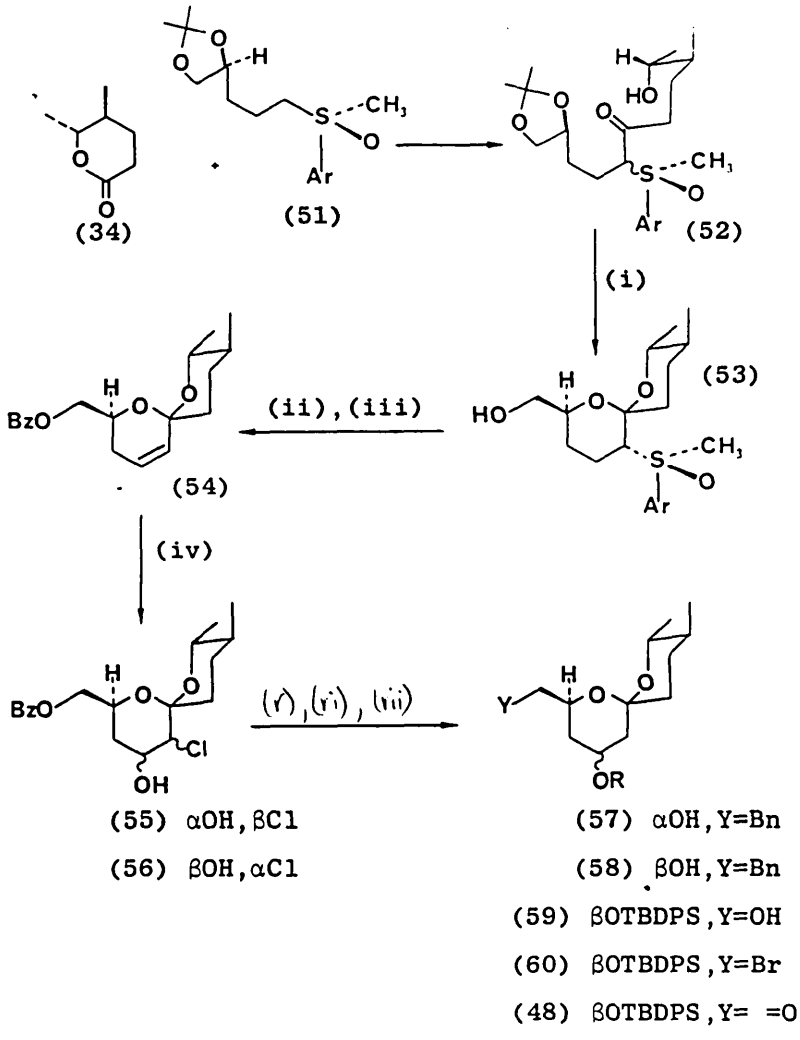


Scheme 8



Reagents: (i) NaH,CS_2; MeI; 240°C; (ii) mCPBA; H_3O^+; $Pb(OAc)_4$; (iii) Jones' oxidation; (iv) I_2, CH_3CN; (v) $^nBu_3SnH$.

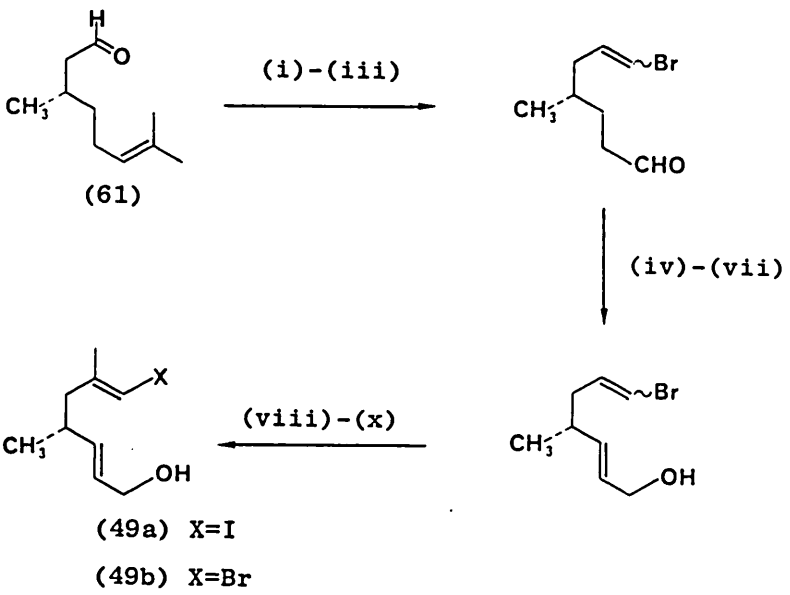
Scheme 9



Reagents: (i) cat. MsOH, H_2O, benzene; (ii) BzCl; (iii) toluene, Δ, $P(OMe)_3$; (iv) ^tBuOCl, H_2O, acetone; (v) $^nBu_3SnH$, toluene ; (vi) $Ph_2{}^tBuSiCl$, DMAP, CH_2Cl_2; (vii) LiOH, THF.

Williams elegantly utilised the same chiral starting material for the construction of the side-chain as for the production of the spiro-acetal moiety. The *trans* disubstituted olefin (49) was prepared in seven steps and 46% overall yield from (-)-(S)-citronellal (61), with no epimerisation of the chiral methyl substituent (Scheme 10). Elimination to the terminal acetylene and stereospecific formation of the tri-substituted olefin (49), using Negishi methodology[23], afforded either vinyl iodide (49a) or vinyl bromide (49b).

Scheme 10



(49a) X=I

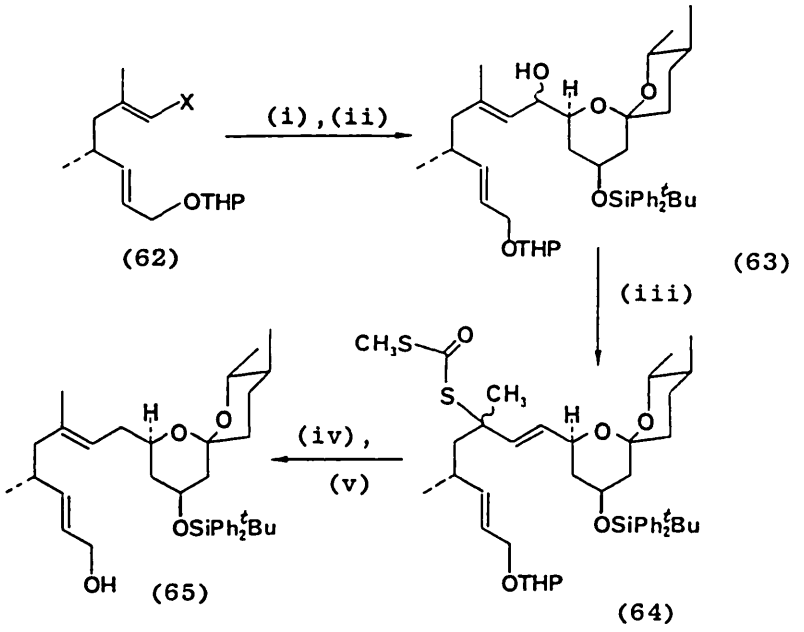
(49b) X=Br

Reagents: (i) $LiCHBr_2$, -78°C; (ii) O_3; (iii) Zn, AcOH; (iv)  ;
(v) C_6H_5SeCl, -110°C; (vi) $LiAl(O^tBu)_3H$; (vii) mCPBA;
(viii) MeLi, 0°C; (ix) $AlMe_3$, Cp_2ZrCl_2; (x) I_2, THF, -30°C.

Coupling to the spiroacetal was achieved by metalation of the tetrahydropyranyl ether (62) and addition to the aldehyde (48) giving efficient formation of the allylic alcohols (63) (Scheme 11). No alkylation was observed between the vinyl lithium reagent (62) and the

bromide (60). Formation of the dithiocarbonates (64) bearing exclusively the *trans*-olefin geometry was achieved by xanthate formation with concomitant [3,3] sigmatropic rearrangement.

Scheme 11



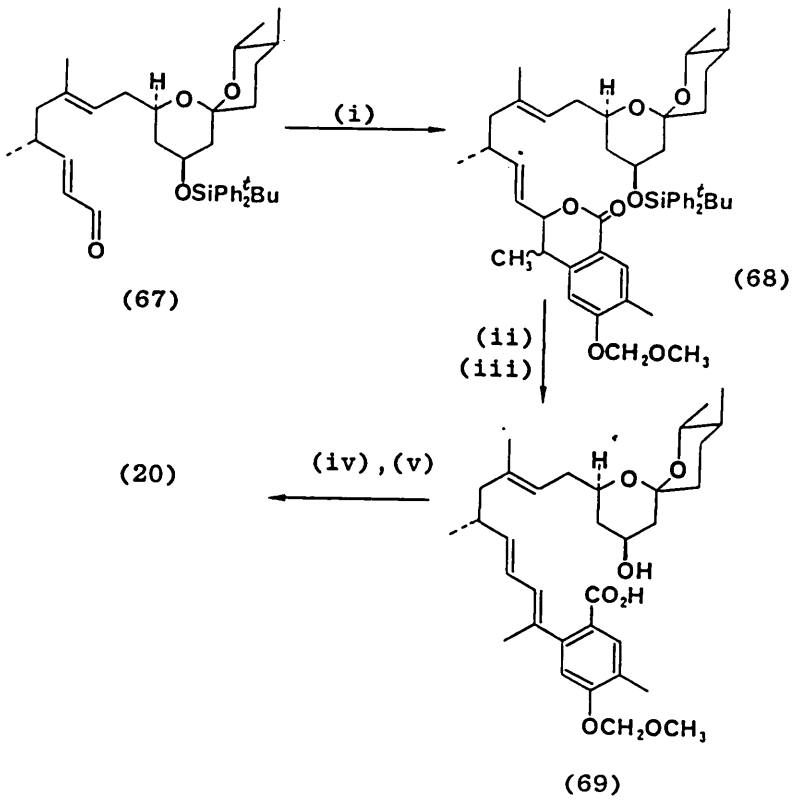
Reagents: (i) ^{t}BuLi, THF, -100^{o}C; (ii) (48); (iii) CS_2, THF, NaH, MeI, 55^{o}C; (iv) ^{n}Bu$_3$SnH, 80^{o}C; (v) PPTS, MeOH.

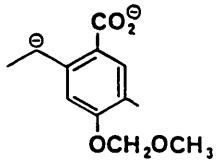
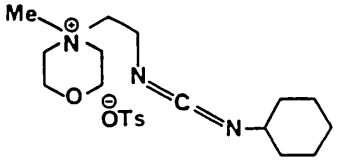
Reduction and mild acid hydrolysis gave the desired alcohol (65).

Addition of dianion (66) to the aldehyde (67), derived from Swern oxidation of the alcohol (65), afforded the desired 6-membered lactone (68) as a mixture of two diastereoisomers (Scheme 12). Desilylation and elimination resulted in a single dienecarboxylic acid (69) which upon macrocyclic lactonisation, using 1-cyclohexyl-3-(2-morpholino-ethyl) carbodiimide metho-*p*-toluenesulphonate as coupling agent,

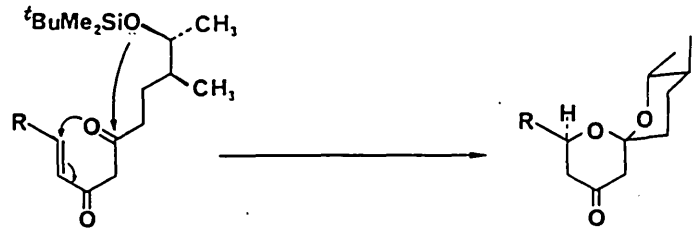
followed by deprotection of the methoxy methyl ether gave (+)-milbemycin β_3 (20).

Scheme 12



Reagents: (i)  (66); (ii) (^{n}Bu)$_4$NF, 40°C; (iii) KH, THF, 40°C; (iv)  ; (v) NaI, acetone cat HCl, 50°C.

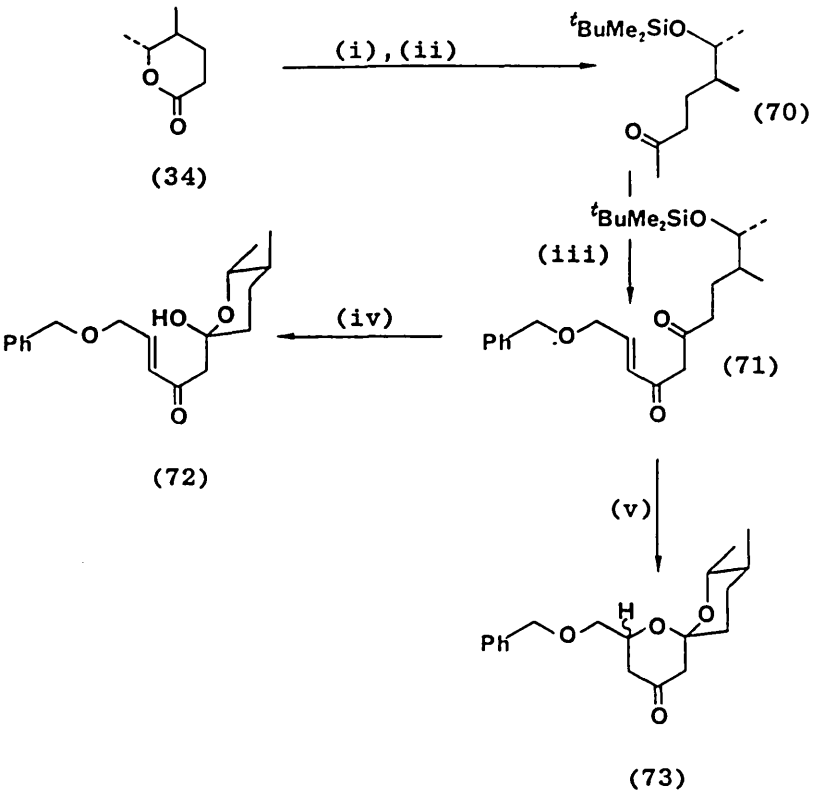
Williams has since developed a second, shorter synthesis of 1,7-dioxaspiro[5,5]undecan-4-anes, the spiroacetal moiety of milbemycin β_1 (16) and β_3 (20).[24] The new strategy involves an internal "cascade cyclisation" onto a 1,3-diketone intermediate as shown below.

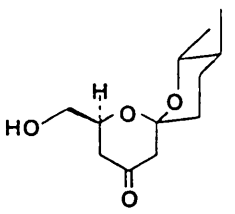


Addition of methyllithium to *trans*-4,5-dimethylvalerolactone (34) and subsequent silyl ether protection gave the methyl ketone (70) in 65% overall yield (Scheme 13). Kinetic deprotonation and reaction with *trans*-4-benzyloxycrotonyl chloride afforded the β-diketone adduct (71) in only 30-35% yield. ^{1}H N.m.r. shows (71) to exist primarily in the enolised form (>90%). Partial cyclisation of (71) was achieved under acid conditions to afford (72). However, a two-phase acid-cyclisation procedure provided the desired spiroacetal (73) in 40% yield as a mixture of isomers (3:2). The corresponding alcohols (75) and (76) were separated by flash chromatography. Once again, the stereochemistry at the spirocentre C-6 was anticipated by thermodynamic and stereoelectronic control.[19]

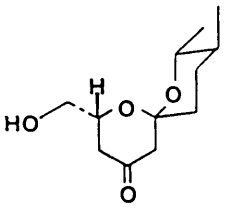
Baker[25] has also prepared the spiroacetal moiety of milbemycin β_1 (16) and β_3 (20) in the correct enantiomeric form. The synthesis employs a key lactone intermediate (78), derived from the chiral starting material laevoglucosan. This intermediate was coupled to an appropriately designed acetylide to provide access to the spiroacetal fragments common to the avermectin and milbemycin series.

Scheme 13

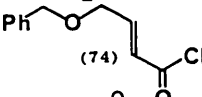




(75)



(76)

Reagents: (i) CH_3Li, THF, -78°C; (ii) $^{t}BuMe_2SiCl$, DMAP; (iii) LDA (2 eq.), THF, HMPA, -78°C,  (74); (iv) H^+, Bio-rad AG W-X4 exchange resin, toluene, 100°C; (v) 20% HBF_4 in Et_2O, 1½, 24h.

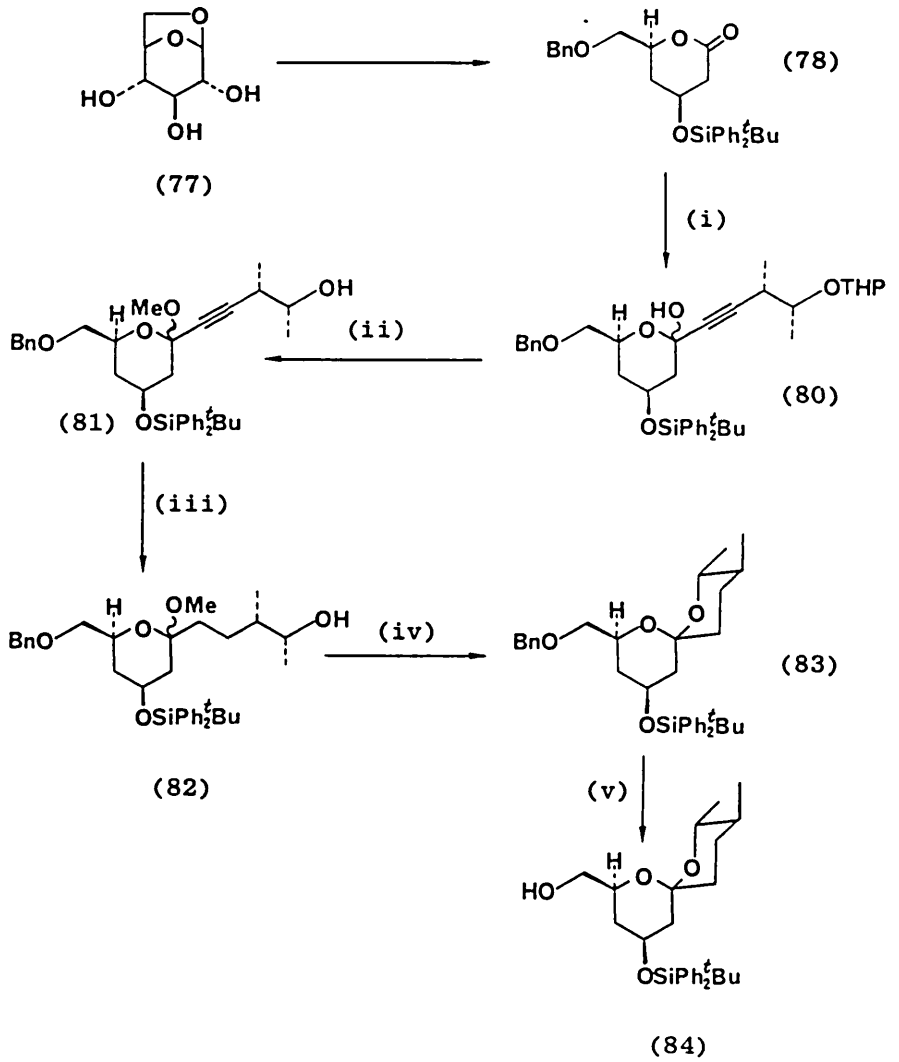
Preparation of the key lactone intermediate (78) was achieved in ten steps from laevoglucosan (77). Treatment of (78) with the lithium acetylide (79), a 67:33 mixture of enantiomers, gave the hemiacetal (80) (Scheme 14). Cleavage of the tetrahydropyranyl ether afforded the acetal (81) which on hydrogenation of the triple bond gave (82). Addition of a catalytic amount of camphorsulphonic acid induced cyclisation to the spiroacetal (83). This compound was deprotected to give the corresponding alcohol (84) in 30% yield from (79).

Cyclisation of (82) can formally yield two diastereoisomers, each of which will be able to exist in two conformations. However, the spiroacetal would prefer to adopt a conformation in which the two vicinal methyl groups are equatorial and the ring oxygens are axial to the adjacent ring, thereby gaining stability from the anomeric effect.[19] Consequently, only one major product, the desired spiroacetal (83), was isolated. The minor enantiomer of (79) undoubtedly forms the equivalent adduct to (80) but following hydrogenation does not undergo cyclisation under the acid conditions employed since the product cannot attain an anomerically stabilised conformation with all four substituents equatorial.

A further approach to the spiroacetal moiety of milbemycin β_1 (16) and β_3 (20) was achieved by Kocienski.[26] This synthesis makes excellent use of an intramolecular Mukaiyama directed aldol reaction[27] to set up the formation of the spiroacetal.

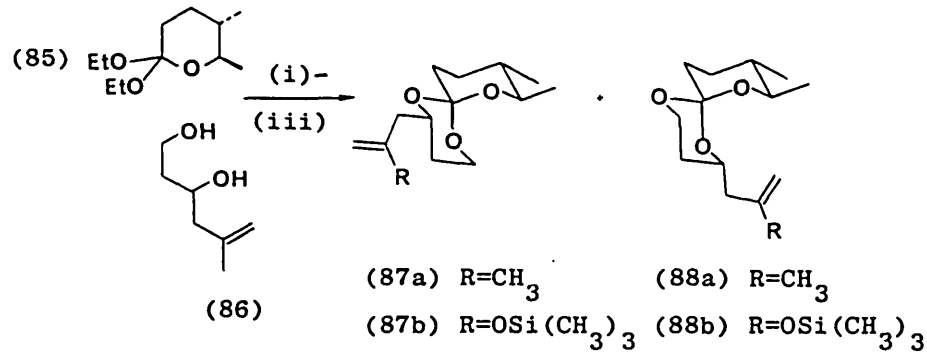
Acid catalysed exchange of ortholactone (85) with diol (86) gave equal amounts of the easily separable isomers (87a) and (88a) in 70% yield. Ozonolysis of the alkene followed by trimethylsilyl enol ether formation gave the spirocyclic ortholactones (87b) and (88b) in 70% overall (Scheme 15).

Scheme 14



Reagents: (i) Li^+ -≡-⟨ ⟩-OTHP (79); (ii) Amberlite AR 118, MeOH; (iii) 10% Pd-C, EtOH, 1h; (iv) CSA (cat), CH_2Cl_2; (v) 10% Pd-C, EtOH, 24h.

Scheme 15



Reagents: (i) H_3O^+; (ii) O_3; (iii) LDA, THF, -78^oC, Me_3SiCl.

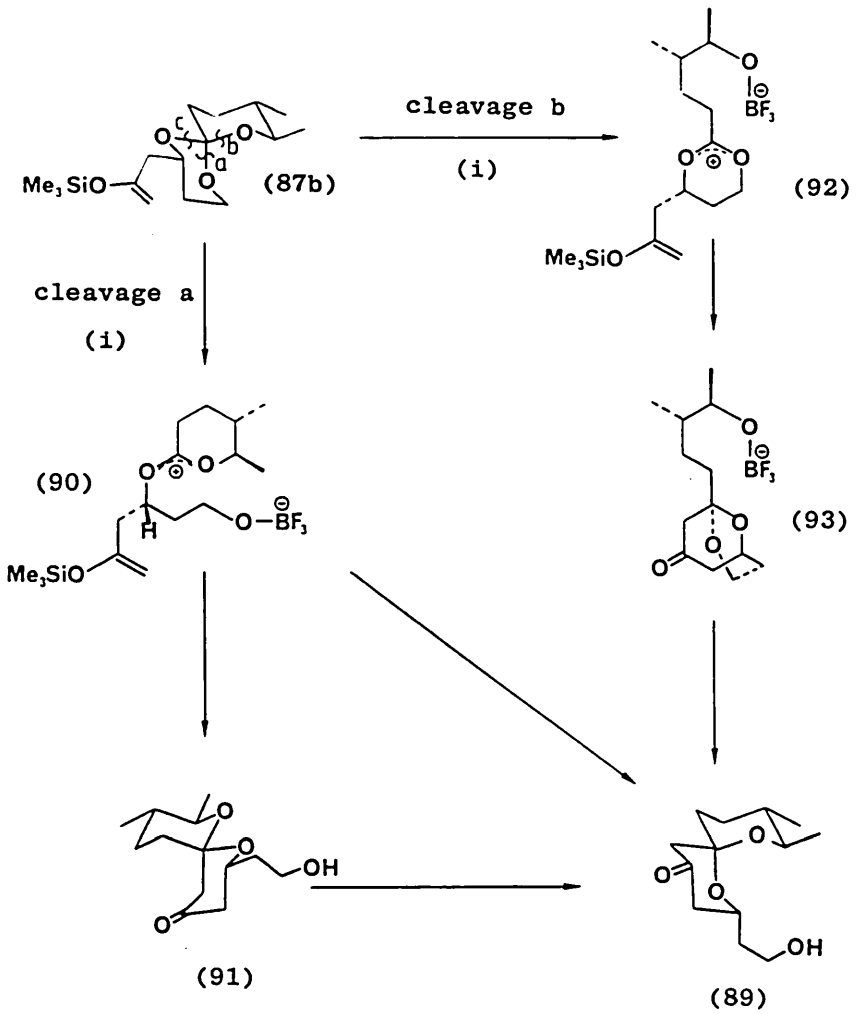
Treatment of (87b) with an acid catalyst afforded the desired spiroacetal (89) in 35% yield. Kocienski postulates that ortholactone cleavage occurs *via* one of the following pathways (Scheme 16).

(1) Dioxonium ion (90), generated by Lewis acid-catalysed cleavage of bond a in (87b), undergoes nucleophilic attack by the silyl enol ether to give the diastereoisomeric spiroacetals (89) and (91). However, since none of (91) was observed he concludes that either a) the annelation may be diastereoselective, or more likely b) that equilibration of the less stable (91) occurs under the given reaction conditions affording the thermodynamically more stable compound (89); or,

(2) Dioxonium ion (92), generated by Lewis acid-catalysed cleavage of bond b in (87b), cyclises to give the bicyclic acetal (93) which in turn undergoes Lewis acid-catalysed acetal exchange to give (89).

Both modes of cleavage should be favoured because bonds a and b both have two adjacent oxygen atoms with antiperiplanar lone pair electrons. Since bond c has only one adjacent oxygen atom with an

Scheme 16



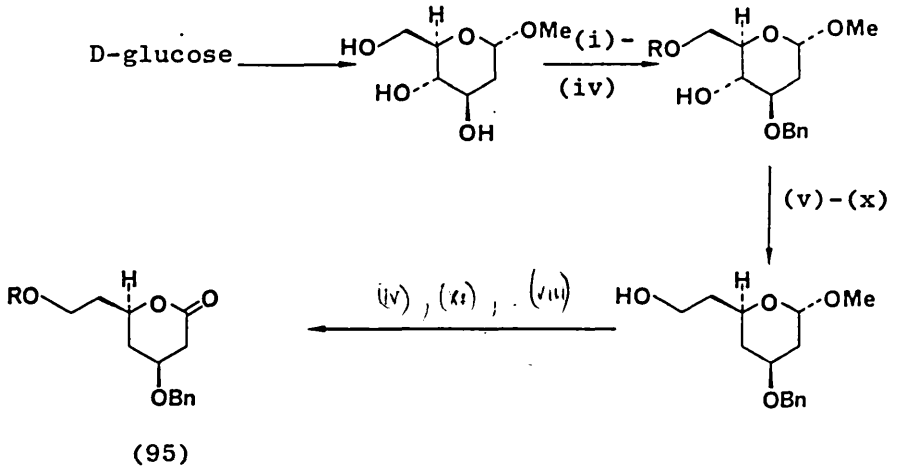
Reagents: (i) $BF_3.Et_2O$.

antiperiplanar lone pair of electrons, its cleavage should not be favoured.

Hanessian[28] has recently reported the synthesis of the spiroacetal unit (94), present in avermectin B_{1a} (26), in optically pure form. In a similar approach to that of Baker, Hanessian generates the spiroacetal by condensation of two "chirons"[29], an acetylide and a lactone, relying on anomeric stereoselection[19] to generate the thermodynamically favoured isomer as found in the natural product. Both "chirons" were prepared from optically active precursors by multistep sequences.

Lactone (95) was prepared *via* two different routes, using either D-glucose or S-malic acid as the optically active starting material (Schemes 17 and 18).

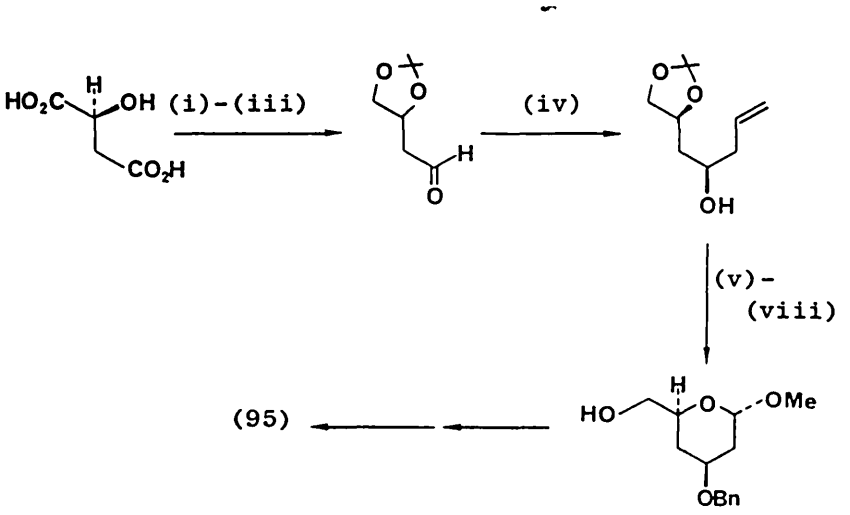
Scheme 17



(95)

Reagents: (i) PhCHO, H^+; (ii) KH, BnBr; (iii) pTsOH, H_2O, MeOH; (iv) $^tBuPh_2SiCl$, py; (v) NaH, CS_2, MeI; (vi) Bu_3SnH; (vii) Bu_4NF; (viii) PCC; (ix) $Ph_3P{=}CH_2$; (x) 9-BBN, NaOH, H_2O_2; (xi) Aq. AcOH, Δ;

Scheme 18



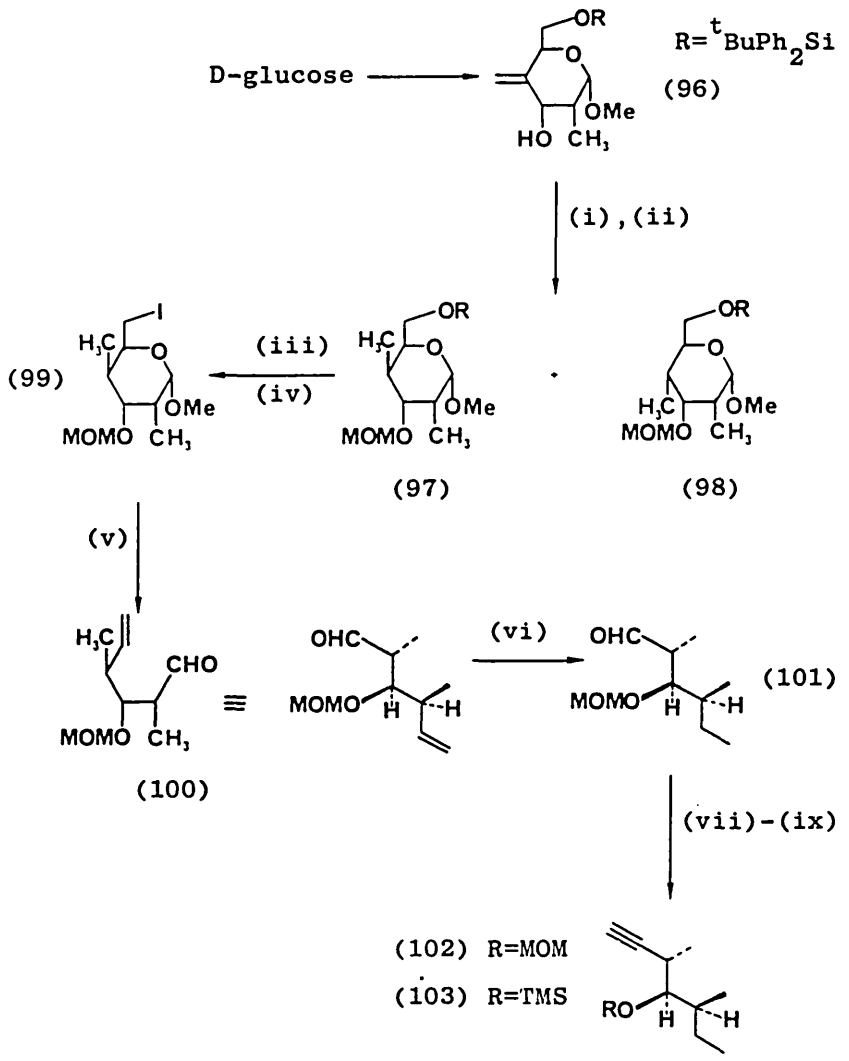
Reagents: (i) $BH_3.Me_2S$; (ii)  , H^+; (iii) PCC; (iv)  ; (v) KH, $C_6H_5CH_2Br$; (vi) TFA; (vii) O_3, Me_2S; (viii) MeOH, $BF_3.Et_2O$

Synthesis of the acetylenic component was accomplished from the intermediate (96), previously employed by Hanessian in the synthesis of (+)-rifamycin S[30], which again is available from D-glucose (Scheme 19). Hydrogenation of (96) gave a 4:1 mixture of axial (97) to equatorial (98) C-4 methyl derivatives. Protection facilitated separation to cleanly afford the required C-4 axial methyl isomer (97). Desilylation, followed by halogenation, gave the primary iodide (99) in 77% overall. The aldehyde (100) was prepared by warming compound (99) in aqueous ethanol containing zinc dust and was subsequently hydrogenated to give (101). Formation of the acetylene (102) from (101) followed by deprotection and re-protection as the trimethylsilyl ether gave the required acetylenic right-hand fragment (103).

Addition of lactone (95) to the lithium acetylide derived from (103) gave hemiacetal (104) in 38% yield (Scheme 20). Hydrolysis and

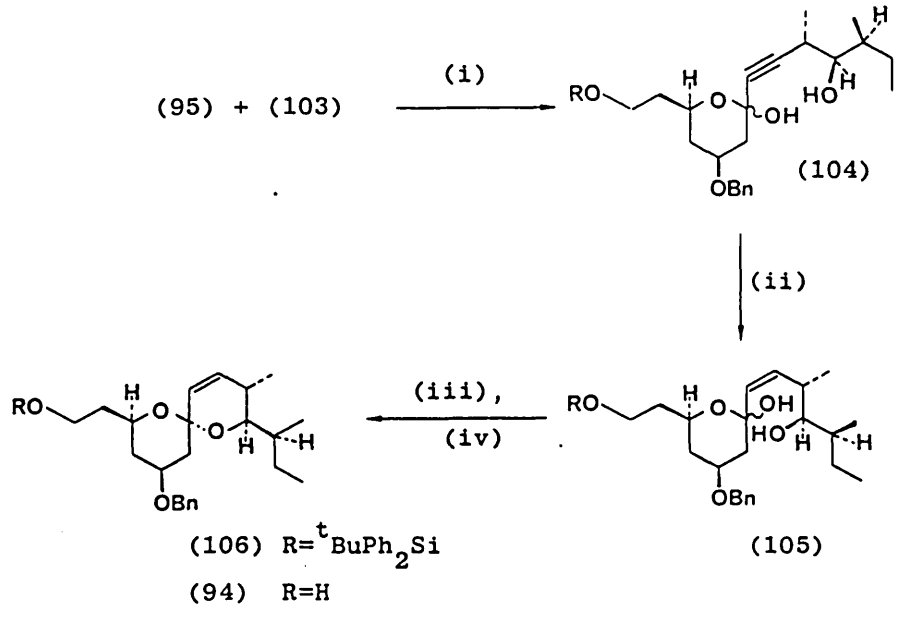
reduction of the acetylenic linkage gave the *cis*-olefin (105) which cyclised on brief exposure to $BF_3.Et_2O$ to afford the desired spiro-acetal (106) desilylation of which produced the alcohol (94).

Scheme 19



Reagents: (i) H_2, $Pd(OH)_2$; (ii) CH_3OCH_2Cl, $^iPr_2NEt$; (iii) $^nBu_4NF$; (iv) Tf_2O, py; $^nBu_4NI$; (v) Zn, EtOH, 45°C; (vi) H_2, Rh/Al_2O_3, C_6H_6; (vii) CBr_4-PPh_3, CH_2Cl_2; ^nBuLi; (viii) Me_3SiBr - CH_2Cl_2, -30°C; (ix) Me_3SiCl, CH_2Cl_2, Et_3N, DMAP.

Scheme 20



Reagents: (i) ^nBuLi, THF, -78°C; BF_3Et_2O, then add ketone; H_3O^+; (ii) H_2, $Pd/BaSO_4$, EtOAc, py; (iii) $BF_3.Et_2O$, THF; (vi) $^nBu_4NF$, THF.

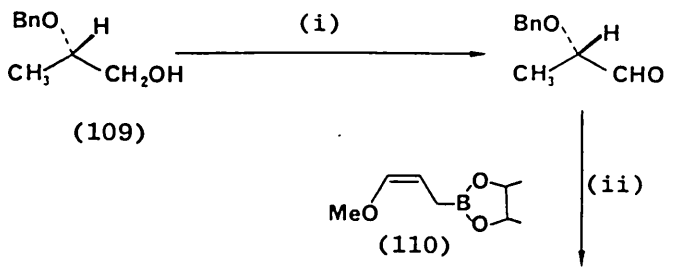
A synthesis of the avermectin disaccharide fragment has recently been published.[31] This was achieved by applying previously developed methodology for the stereospecific synthesis of selectively protected 1,2-diol derivatives.[32] Preparation of oleandrose (107) the key carbohydrate present in the avermectins, and its coupling to form the disaccharide (108) was readily carried out.

Oxidation of the chiral alcohol (109) and treatment with the boronate (110) gave an inseparable mixture of the triol (111a) and two minor isomers (111b) and (111c) in 74% overall. Protection and hydroboration of this mixture gave alcohols (112a)-(112c) which were separated chromatographically (Scheme 21). Oxidation of alcohol (112a) followed by hydrogenolysis gave the desired oleandrose (107) in 85% yield (Scheme 22).

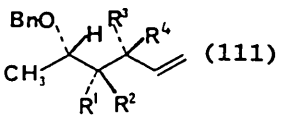
Conversion to the methyl glycoside was straightforward and comparison of spectral data with the methyl glycoside derived by methanolysis of avermectin B_{2a} showed the synthetic and natural materials to be identical.

Coupling of the oleandrose units was achieved by (a) protection of the C-4 hydroxyl and activation of the anomeric centre in one unit, and (b) a free hydroxyl at C-4 and protection of the anomeric centre in the other unit. Benzyl protection of (107) gave a 10:1 mixture of the glycosides (113α) and (113β). Acetylation of the α-isomer gave (114α) which on hydrogenolysis produced the acetates (115α,β). Activation of the anomeric centre by conversion to the 2-pyridylthioglycosides gave (116α) and (116β) respectively as a 1 : 2.4 mixture. Coupling was then achieved by the action of $Pb(ClO_4)_2$ on a mixture of thioglycosides (116α) and (116β) and benzyl-glycoside (113α). This resulted in a 3:1 mixture of αα and αβ di-saccharides in 59% yield, with the natural isomer predominating (Scheme 23). Separation of (116α) and (116β) was not in fact necessary for the coupling reaction since the pure β-isomer gave the same ratio of αα and αβ isomers.

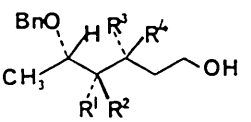
Scheme 21



		R_1	R_2	R_3	R_4
111	a	H	OH	H	OMe
	b	H	OH	OMe	H
	c	OH	H	OMe	H



(iii),(iv)



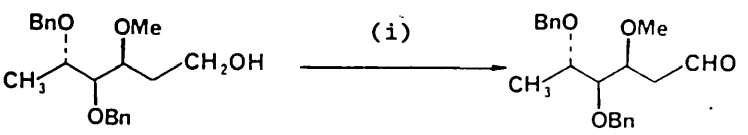
(112)

		R_1	R_2	R_3	R_4
112	a	H	OBn	H	OMe
	b	H	OBn	OMe	H
	c	OBn	H	OMe	H

Reagents: (i) DMSO, $(COCl)_2$; (ii) MeO, ^nBuLi, FB, -78^oC,

(iii) KH, $C_6H_5CH_2Cl$; (iv) a) 0.5M 9BBN, 50^oC, b) H_2O_2.

Scheme 22

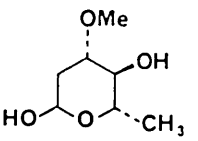


(112a)

(ii)

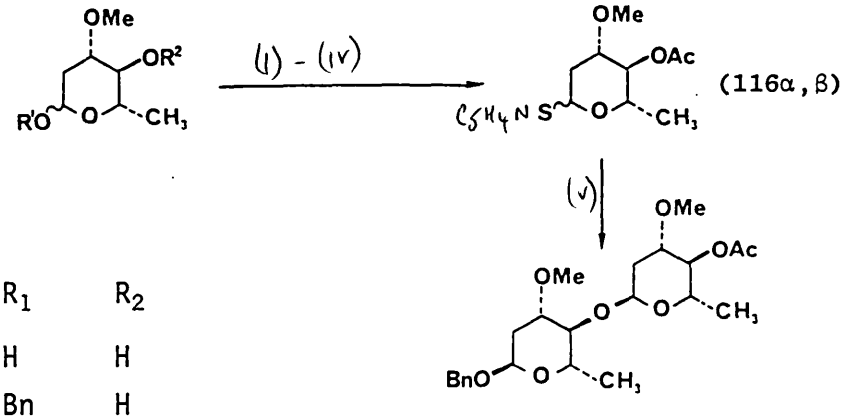
Reagents: (i) PCC;

(ii) 20% $Pd(OH)_2/C$, H_2, 20h



(107)

Scheme 23



(108)

	R_1	R_2
(107)	H	H
(113α)	Bn	H
(113β)	Bn	H
(114α)	Bn	Ac
(115α,β)	H	Ac

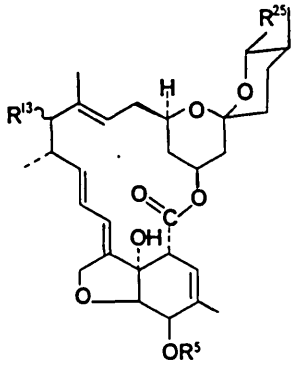
Reagents: (i) $C_6H_5CH_2OH$, HCl; (ii) Ac_2O, py, DMAP; (iii) 20% $Pd(OH)_2/C$, H_2; (iv) 2,2'-dithiopyridine, $(^nBu)_3P$; (v) $Pb(ClO_4)_2$.

Scientists at the Merck Sharp and Dohme research laboratories have recently synthesised milbemycins from the avermectins.[33] Milbemycins α_1 (1) and α_3 (3) can be regarded as lower homologues of 13-deoxy-22,23-dihydroavermectin B_1 aglycone (117) where the C-25 position is substituted by a methyl or ethyl group instead of the sec-butyl or iso-propyl group of (117) (Figure 4).

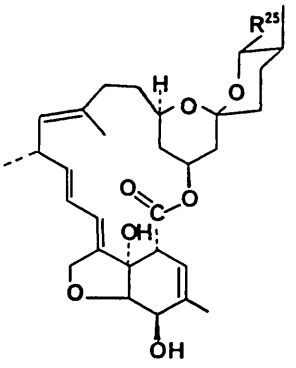
Selective ^{t}butyldimethylsilyl protection of the reactive C-5 hydroxyl group of (117) facilitated easy separation of the C-25 sec-butyl (118) and the C-25 propyl (119) homologues. Reaction of (118)

with 2-nitrobenzenesulphonyl chloride gave the 13-deoxy-13-β-chloro-aglycone (120) directly in 55% yield presumably formed *via* the 13-α-(2-nitrobenzenesulphonate) ester, which reacted under the experimental conditions with the available chloride ions. Reduction of (120) gave the desired 13-deoxy aglycone (121) in 80% yield which on desilylation afforded (122). During the reduction step, a trace amount of the 13,14-double bond isomer (123) appeared as a by-product. This was later separated by reverse phase HPLC. The protected C-25 iso-propyl

Figure 4



	R_5	R_{13}	R_{25}	
(1)	H	H	CH_3	
(3)	H	H	CH_2CH_3	
(117)	H	H	$CH(CH_3)CH_2CH_3$	85%
			$CH(CH_3)_2$	15%
(118)	$SiMe_2{}^tBu$	α-OH	$CH(CH_3)CH_2CH_3$	
(119)	$SiMe_2{}^tBu$	α-OH	$CH(CH_3)_2$	
(120)	$SiMe_2{}^tBu$	β-Cl	$CH(CH_3)CH_2CH_3$	
(121)	$SiMe_2{}^tBu$	H	$CH(CH_3)CH_2CH_3$	
(122)	H	H	$CH(CH_3)CH_2CH_3$	
(124)	H	H	$CH(CH_3)_2$	



(123) R_{25} $CH(CH_3)CH_2CH_3$

(125) R_{25} $CH(CH_3)_2$

aglycone derivative (119) gave, in an identical series of reactions, 13-deoxy-22,23-dihydroavermectin B_{1b} aglycone (124) together with the isomeric (125).

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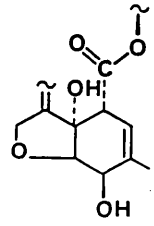
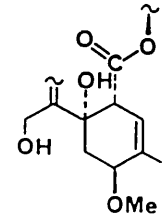
RESULTS AND DISCUSSION

The work presented in this thesis is directed towards the preparation of model compounds for the southern hemispheres (126) and (127) of the avermectins and milbemycins respectively, hopefully utilising methodology which might ultimately be incorporated into the total synthesis of the natural products.

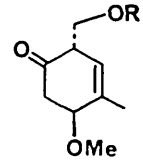


(126)



(127)

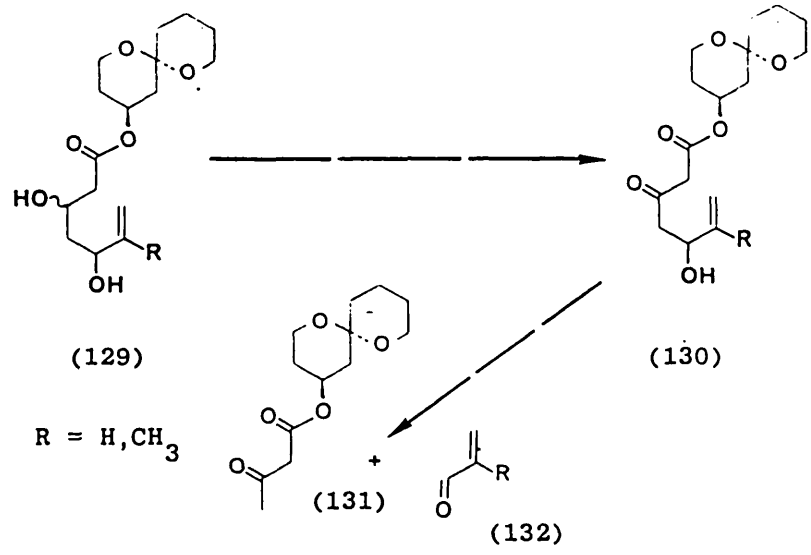
Also included are synthetic efforts towards the preparation of cyclohexenone (128), a key sub-unit necessary for the synthesis of milbemycin β_1 (16).



(128)

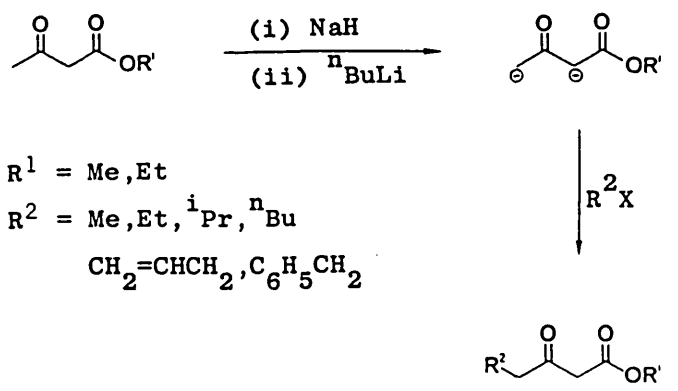
SYNTHESIS OF SECO-MODEL COMPOUNDS

It was envisaged that construction of an acyclic seco-model of structure (129) could be achieved by γ-alkylation of a β-ketoester (131), using an appropriate aldehyde (132), followed by selective reduction of the ketone carbonyl group in (130).

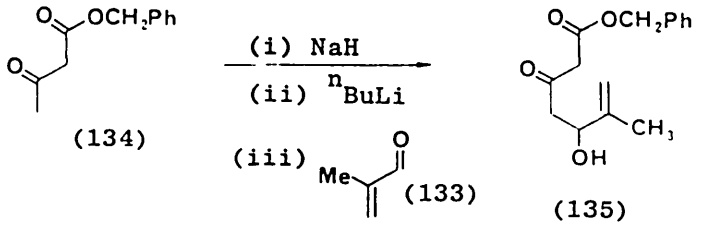


This approach would produce a structure that is flexible but containing essential structural elements common to the avermectin southern hemisphere.

Weiler has already demonstrated the utility of β-ketoester γ-alkylation.[1] He has shown that dianions can be generated from a variety of β-ketoesters, by sequential treatment with sodium hydride and ^{n}BuLi (at 0^{o}C). These dianions subsequently reacted with a wide range of alkylating agents to produce exclusively γ-alkylated products in good yield.



Methacrolein (133) was added at -78°C to the dianion of benzyl-acetoacetate (134), generated according to the Weiler procedure, and used here as a model for the spiroacetal β-ketoester (131). The deep orange colour of the dianion faded immediately on addition of the aldehyde. The mixture, on warming to 0°C over 30 min, was worked-up to give the required aldol product (135) in 45-50% yield.



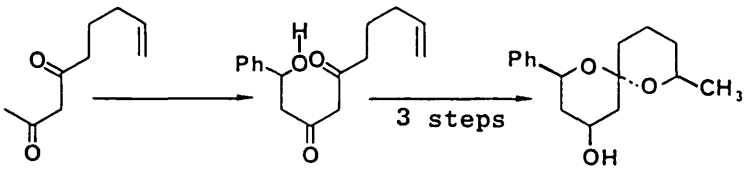
ν_{max}: 3429, 1741, and 1711 cm^{-1}.

δ (250 MHz): 2.76 (2H, d, J 7.2 Hz, *H-4*),
3.57 (2H, s, *H-2*),
4.52 (1H, m, *H-5*).

Spectral evidence clearly supported the assigned structure (135). The presence of the ketone and ester functions was indicated by strong absorptions in the infrared spectrum at 1711 and 1741 cm^{-1} respectively, which would not be the case if O-alkylation had occurred. The high field ^1H n.m.r. spectrum showed a two proton singlet at δ3.57, assigned to the methylene protons at C-2, and the absence of a three proton singlet at *ca.* δ2.30 was evidence that the alkylation had occurred at the γ-carbon as shown.

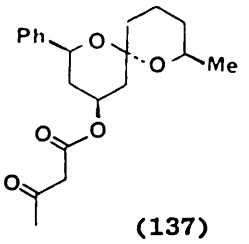
With this result in hand, preparation of a suitable spiroacetal acetoacetate model compound (131) could be undertaken. Concurrent work in these laboratories had resulted in the preparation of (2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-ol (136) *via* an organoselenium-mediated cyclisation reaction (Scheme 24).[2] This compound was chosen as the appropriate spiroacetal appendage for coupling to the desired β-ketoester side chain.

Scheme 24



(136)

Formation of the β-ketoester (137) was achieved using the procedure of Mauz.[3] Addition of excess diketene to a warmed solution of spiroacetal (136) in THF containing triethylamine (0.5 equiv.) and heating to reflux for 1h gave acetoacetate (137) in 89% yield.



(137)

ν_{max}: 1742 and 1717 cm^{-1}

δ (250 MHz):

1.13 (3H, d, J 7.2 Hz, C-8 *Me*)

2.25 (3H, s, *H-4'*)

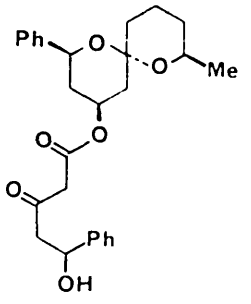
3.41 (1.68H, s, *H-2'*)

3.71 (1H, m, *H-8*)

4.71 (1H, dd, J 2.2, 11.5 Hz, *H-2*)

5.47 (1H, m, *H-4*)

Reaction of the dianion from (137) was attempted using benzaldehyde as a typical reacting aldehyde. Addition of benzaldehyde to the dianion of (137), generated by sequential treatment with sodium hydride (at 0^oC) and ^nBuLi (at -20^oC), in THF at -78^oC and quenching the reaction at 0^oC after 30 min unfortunately gave only a 35% yield of the aldol product (138).

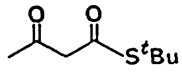


(138)

This result may arise from the β-ketoester (137) containing a relatively acidic position at C-2 and therefore not being particularly stable to the reaction conditions for formation of the dianion. If correct, this observation points out certain difficulties with the

Weiler methodology. An alternative approach for the formation of an acyclic model is therefore desirable.

Recent work in these laboratories has shown that the anions of ^{t}butyl acetothioacetate (139), by analogy with the work of Weiler previously described, will react in a regiospecific manner with a variety of alkylating agents.[4]



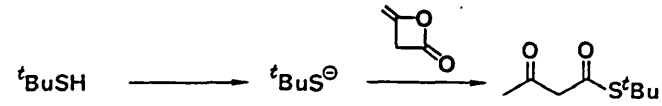
(139)

The β-ketothioester products resulting from these alkylation reactions are remarkably versatile, combining many of the properties of both thioesters[5] and β-ketoesters[1,6], and have been shown to undergo direct and efficient conversion to esters and lactones upon activation in the presence of an alcohol.[7]

Since alkylation of the spiroacetal acetoacetate (137) proceeded in an unacceptable yield, it seemed reasonable that reaction of the dianion of ^{t}butyl acetothioacetate (139) with a suitable aldehyde followed by transesterification with the spiroacetal (136) might offer a superior synthetic route, albeit one step longer. Also, the resulting transesterification methodology may ultimately be applicable as the final coupling step in the formation of the 16-membered lactone present in the avermectins and milbemycins.

^{t}Butyl acetothioacetate (139) was conveniently prepared in 69% yield by treatment of diketene with sodium ^{t}butylthiolate in THF at -10^{o}C over 1h. Use of the thiolate anion in this manner circumvents

the addition of thiol to the double bond of diketene noted elsewhere.[8]



(139)

Data for compound (139)

ν_{max}: 1721, 1676, and 1621 cm^{-1}

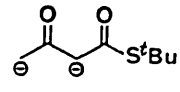
(250 MHz): 1.54 (9H, s, ^{t}Bu)

2.30 (3H, s, *H-4*)

3.57 (2H, s, *H-2*)

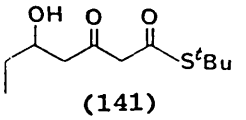
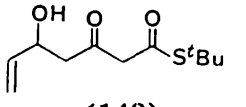
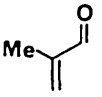
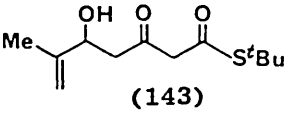
The infrared spectrum of ^{t}butyl acetothioacetate shows three strong carbonyl absorptions at 1721, 1676, and 1621 cm^{-1} for the ketone, thioester, and enolised thioester respectively.

Sequential treatment of (139) with one equivalent of sodium hydride (at 0°C) and one equivalent of ^{n}BuLi (at -20°C) in THF gave the expected dianion (140) as a deep yellow/orange solution.



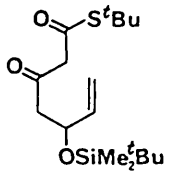
(140)

In a brief study, this dianion was shown to react with a range of aldehydes in good yield.

Aldehyde	Product	Yield
	 (141)	84%
	 (142)	83%
	 (143)	89%

Each product retains strong absorptions in the infrared spectrum at *ca.* 1710 - 1720 and 1670 cm^{-1} indicating the retention of the ketone and thioester functional groups. From the ^1H n.m.r. spectra of the products it is evident that alkylation has again occurred exclusively at the γ-carbon atom. Each product shows a two proton singlet at δ3.61 - 3.63 due to the α-methylene protons and each has lost the three proton singlet at δ2.30. The two protons at C-4 in (142) and (143) now appear as multiplets at δ2.78. The protons at C-4 in (141) each appear as a double doublet, presumably due to the molecule adopting a particular conformation as a result of intramolecular hydrogen bonding in which the C-4 protons now become distinguishable in the ^1H n.m.r.

The allylic alcohol (142) was protected to give the ^{t}butyldimethylsilyloxy derivative (144) in 93% yield.[9]

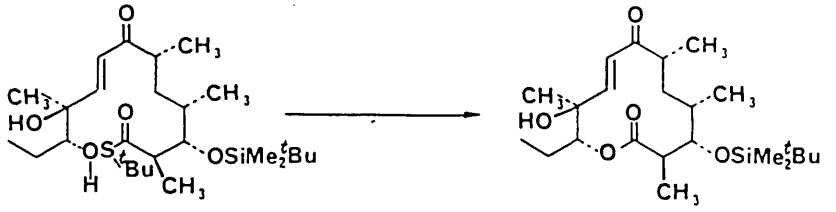


(144)

Compound (144) represents a suitable substrate with which to attempt transesterification reactions. The methodology for the thioester to oxoester conversion was originally developed by Masamune in order to facilitate macrocyclic lactonisation in the synthesis of methymycin.[10] Activation of the 2-methylpropane-2-thiol ester with two equivalents of $Hg^{II}(CF_3CO_2)_2$ in a dilute reaction medium (0.01M in acetonitrile) led to intramolecular lactonisation (Scheme 25).

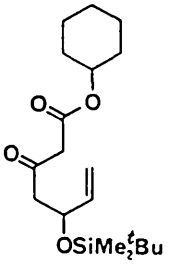
The scope of the reaction was later widened by a study on the variation of the soft metal cation and the acetate counterion with respect to the specific thioester and alcohol concerned.[11]

Scheme 25



However, results obtained in these laboratories had shown that, contrary to the observations of Masamune, silver trifluoroacetate proved to be the reagent of choice as the activating agent for S → O ester conversion.[4]

Using cyclohexanol as a model alcohol, compound (144) was transesterified by stirring as a mixture in THF to which one equivalent of silver trifluoroacetate had been added. This afforded after 18h the oxoester (145) in 67% yield.



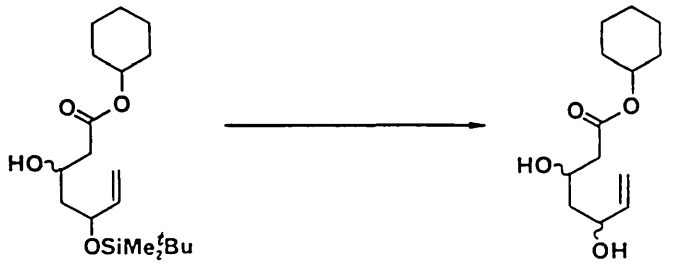
(145)

ν_{max}: 1735 and 1712 cm^{-1}

The infrared spectrum clearly shows the presence of an oxoester with strong absorptions at 1735 and 1712 cm^{-1} for the ester and ketone functionalities respectively.

Selective reduction of the ketone group using sodium borohydride gave the alcohol (146) as a 2:1 mixture of diastereoisomers, which on deprotection using tetra ^{n}butylammonium fluoride[9,12] in THF over 10 min gave the desired diol (147) in 96% overall yield.

Replacement of cyclohexanol in the transesterification reaction by the spiroacetal (136) would therefore provide access to the acyclic seco-model compounds.

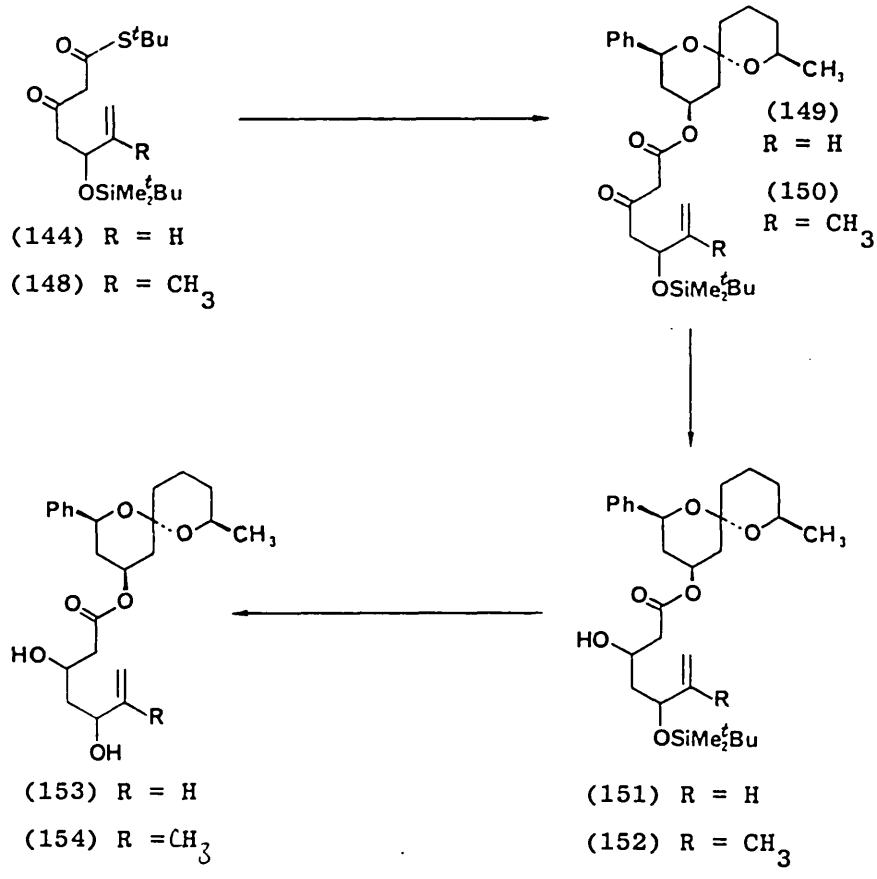


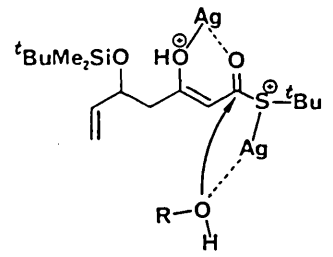
(146) (147)

The ^{t}butyldimethylsilyloxy derivatives (144) and (148) were cleanly transesterified with the spiroacetal (136) and silver trifluoroacetate (2 equiv.) over 18h to give the oxoesters (149) and (150) in 77 and 76% respectively (Scheme 26). Experimentation had shown that the use of two equivalents of silver trifluoroacetate led to increased yields of the desired ester product. This result may indicate that the first equivalent of $AgOCOCF_3$ becomes complexed between the ketone and ester oxygen atoms. In accord with Masamune's postulation, it is thought that the efficient ester and lactone formation, particularly with sterically hindered alcohols, proceeds through coordination of the alcohol with a possible intermediate as shown in (155), which then collapses into the oxoester and silver salts.

As before, selective reduction of the ketones (149) and (150) using sodium borohydride in methanol gave the secondary alcohols (151) and (152), each as a 2:1 mixture of diastereoisomers, in 100 and 97% yield respectively.

Scheme 26





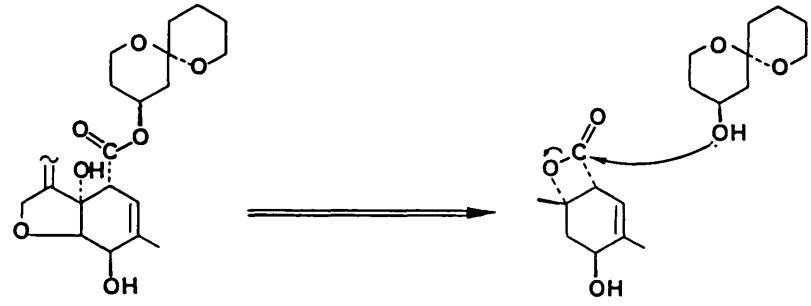
(155)

Remarkably, deprotection of (151) using TBAF/THF over 10 mins gave only a 38% yield of the desired diol (153) as well as a substantial amount of recovered spiroacetal (136). This presumably results from the basic nature of tetra ^{n}butylammonium fluoride causing saponification of the ester. However, using the Roberts' procedure (40% HF/CH_3CN, 5:95)[13], mild and efficient cleavage of the ^{t}butyldimethylsilyl ether to give the diol (153) (97%) was achieved. Similarly, hydroxyester (154) was obtained in quantitative yield from (152).

The seco-model compounds (2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro-[5,5]undecan-4(S)-yl 3',5'-dihydroxyhept-6'-enoate (153) and it's 6'-methyl homologue (154) were submitted for biological screening but were found to be inactive.

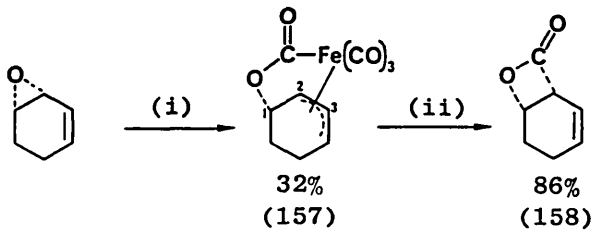
ATTEMPTED SYNTHESIS OF A REACTIVE α-ALKENYL-β-LACTONE MODEL FOR SPIROACETAL COUPLING

A second model study focused on the preparation of a bi-cyclic structure (156) in which the ester carbonyl and the β-hydroxyl functional groups are connected as a reactive β-lactone moiety. Coupling to the spiroacetal would then involve nucleophilic attack by the spiroacetal alcohol on the β-lactone carbonyl generating a β-hydroxyester in which the regiochemistry at these two centres is controlled.



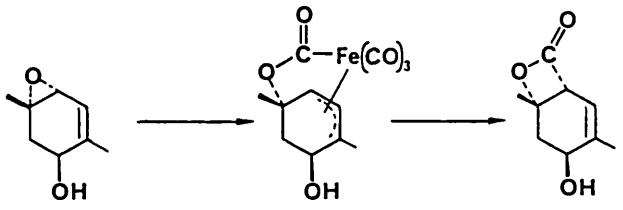
(156)

Methodology developed in these laboratories allows the formation of such α-alkenyl-β-lactone systems by treatment of a suitable alkenyl epoxide with pentacarbonyliron ($Fe(CO)_5$) under photochemical conditions to generate the corresponding π-allyltricarbonyliron lactone complex (157).[14] These π-allyltricarbonyliron complexes are versatile intermediates and upon oxidation with ceric ammonium nitrate, afford β-lactones (158). The product arises from coupling between the lactone carbonyl and C-2 (see diagram), the overall sequence being a formal regioselective $2\pi + 2\pi$ addition of carbon dioxide to a diene.



Reagents: (i) $Fe(CO)_5$; (ii) CAN, EtOH, -5^oC.

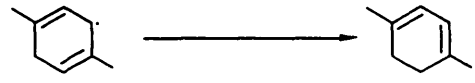
Formation of the π-allyltricarbonyliron lactone complex has since been reinvestigated and two superior practical alternatives to the use of the volatile and toxic pentacarbonyliron have been developed.[15] Treatment of an alkenyl epoxide with nonacarbonyldiiron ($Fe_2(CO)_9$) in either a) benzene under sonochemical conditions[16] or b) as a mixture in THF[17], generally produce the π-allyltricarbonyliron lactone complex in superior yield to the photochemical method. Consequently, it was felt that if a suitable alkenyl epoxide (159) could be prepared, this would then allow access to the corresponding π-allyltricarbonyliron lactone complex (160) and hence the model β-lactone (156).



(159) (160) (156)

Synthetic efforts directed towards the preparation of the alkenyl epoxide (159) began with the Birch reduction of *p*-xylene to give the expected 1,4-dimethyl-1,4-cyclohexadiene (161) in 84% yield. Several

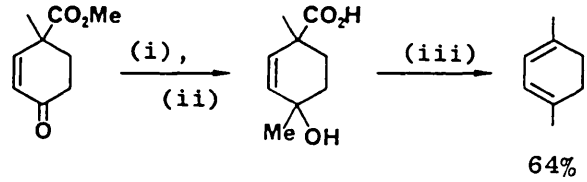
attempts were made to conjugate the double bonds to give the 1,3-cyclohexadiene (162)[18] and thereby facilitate the synthesis of a β-lactone without the free hydroxyl group. However, these attempts only ever resulted in recovered starting material or in inseparable mixtures of the conjugated and non-conjugated isomers in accord with the experimental observations of Birch.[19]



(161) (162)

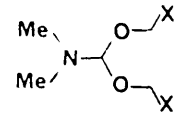
The regiospecific preparation of 1,3-cyclohexadiene derivatives under non-isomerising conditions has been achieved by Eshenmoser.[20] Treatment of a suitable β-γ-unsaturated-δ-hydroxy cyclohexene carboxylic acid (163) with DMF-dineopentylacetal in a non-polar solvent causes a smooth decarboxylative elimination to give the conjugated diene (162) in good yield (Scheme 27). However, this procedure was not attempted.

Scheme 27



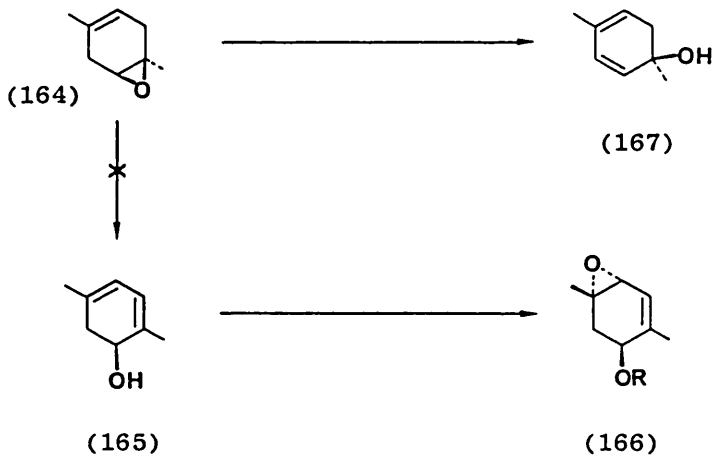
(163) (162)

Reagents: (i) $Zn(BH_4)_2$, MeMgBr; (ii) NaOH; (iii)



X = neopentyl.

Formation of the mono-epoxide (164) was achieved in 84% yield by treating the non-conjugated diene (161) with one equivalent of mCPBA at 0°C. It was hoped that base-induced ring opening[21] of epoxide (164) would give *p*-xylene hydrate (165) which on protection and regiospecific epoxidation from the sterically least hindered face would then afford the alkenyl epoxide (166). However, ring opening of the epoxide (164), using the strongly basic lithium diethylamide at -60°C in Et_2O, gave the tertiary alcohol (167) as the only product.



Data for compound (167)

ν_{max}: 3360, 2970, and 1500 cm^{-1}

δ(250 MHz): 1.32 (3H, s, C-1 *Me*)

1.28 (3H, d, J 2.3 Hz, C-4 *Me*)

1.99 (1H, br s, *OH*)

2.36 (1H, dd, J 2.3, 18.9 Hz, *H-6*)

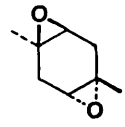
2.46 (1H, ddd, J 1.5, 2.3, 18.9 Hz, *H-6*)

5.55 (1H, m, *H-5*)

5.75 (1H, d, J 9.3 Hz, *H-2*)

5.84 (1H, dd, J 1.5, 9.3 Hz, *H-3*)

Treatment of the mono-epoxide (164) with a second equivalent of mCPBA gave a 7:3 mixture of two highly crystalline diepoxides (168) and (169) in 87% combined yield.



(168)

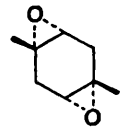
δ(250 MHz):

1.34 (6H, s, C-1,-4 *Me*)

2.18 (2H, d, J 17.0 Hz, *H-3,-6*)

2.35 (2H, dd, J 3.8, 17.0 Hz, *H-3,-6*)

2.93 (2H, d, J 3.8 Hz, *H-2,-5*)



(169)

δ(250 MHz):

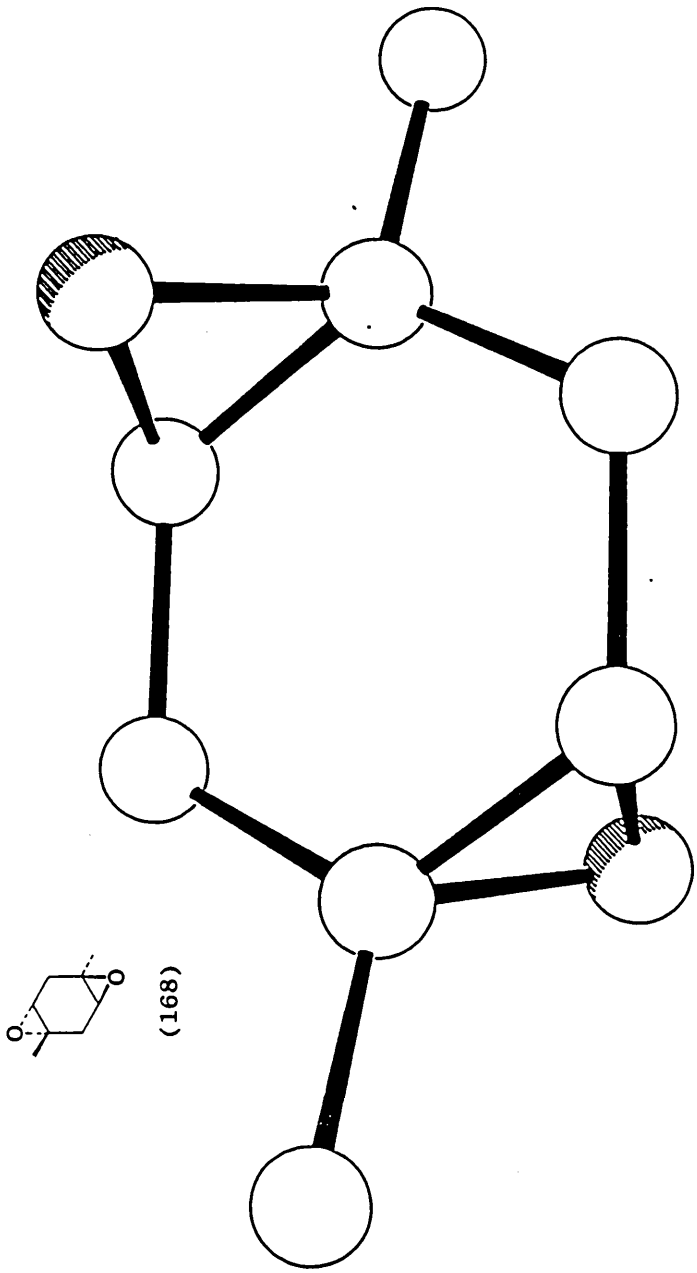
1.30 (6H, s, C-1,-4 *Me*)

2.15 (2H, dd, J 3.4, 17.0 Hz, *H-3,-6*)

2.59 (2H, d, J 17.0 Hz, *H-3,-6*)

2.92 (2H, d, J 3.4 Hz, *H-2,-5*)

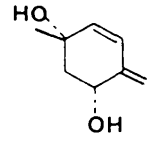
A comparison of the high-field ^1H n.m.r. spectra of the two di-epoxides clearly shows the different environments in which the methylene protons are situated in each compound. In the *cis*-diepoxide, both epoxide oxygens are present on the same face of the molecule. The two pseudo-axial protons at C-3 and C-6 in this isomer are extensively de-shielded by the close proximity of these oxygens and consequently resonate downfield at δ2.59. Conversely, the pseudo-equatorial protons are relatively shielded and resonate upfield at δ2.15. In the *trans*-diepoxide, with the oxygen atoms on opposite faces of the molecule, the above effects are not so pronounced, and all four methylene protons experience some deshielding. Hence the resonances for the pseudo-axial and -equatorial protons in the *trans*-diepoxide occur within the limits set by the *cis*-diepoxide *ie* at δ2.35 and 2.18 respectively. The above observations were confirmed by an X-ray crystal structure obtained on the highly crystalline *trans*-diepoxide (168).



(168)

That the more sterically crowded *cis*-diepoxide is the major isomer implies that the initial mono-epoxide exerts some directing effect on the incoming peroxy acid, presumably by hydrogen bonding, in an analogous manner to the directing and promoting effect of an allylic hydroxyl group.[22] For large scale preparations of the diepoxides, the mono-epoxide was never isolated.

By treating either diepoxide with only one equivalent of base, it was hoped that in each case a single epoxide could be opened in a controlled manner and thereby generate the required alkenyl epoxide. Using the more abundant *cis*-diepoxide (169) for the trial ring opening reactions, treatment with one equivalent of lithium diethylamide in ether, heated at reflux for 1h, gave a mixture of two products (170) and (171) as well as recovered starting material.



(170)

ν_{max}: 3360, 2980, and 1600 cm^{-1}.

δ(250 MHz):

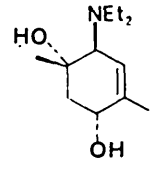
1.32 (3H, s, C-1 *Me*)

5.09 (1H, s, $=CH_2$)

5.15 (1H, s, $=CH_2$)

5.83 (1H, dd, J 1.0, 10.2 Hz, *H-3*)

6.10 (1H, d, J 10.2 Hz, *H-2*)



(171)

ν_{max}: 3400, 2980, and 1665 cm^{-1}.

δ(60 MHz):

1.05 (6H, t, J 7.0 Hz, CH_2CH_3)

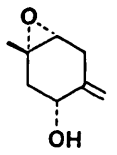
1.18 (3H, s, C-2 *Me*)

1.75 (3H, br s, C-5 *Me*)

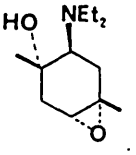
2.55 (4H, q, J 7.0 Hz, CH_2CH_3)

5.50 (1H, m, *H-6*)

Compound (170) results from the initial opening of one epoxide to give the alcohol (172). This compound has acidic protons in the allylic position which are preferentially abstracted by a second equivalent of base to give the tertiary alcohol (170). Amine (171) results from ring opening of the first epoxide by the amide base uncharacteristically acting as a nucleophile. The resulting β-hydroxy amine (173) presumably exerts a directing effect on the incoming amide base so that the second epoxide is regiospecifically opened to give the secondary alcohol (171).



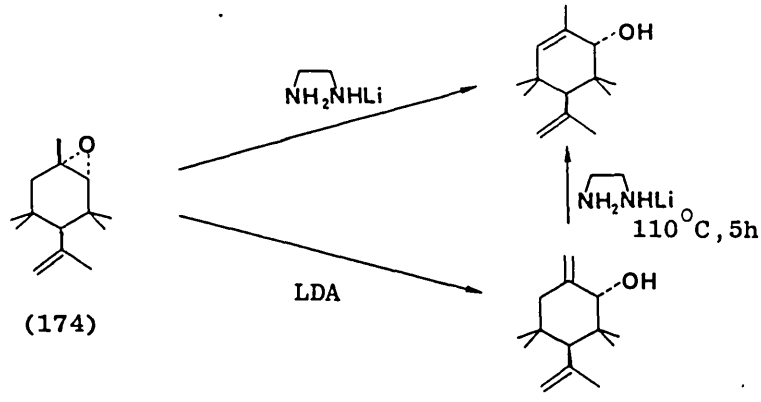
(172)



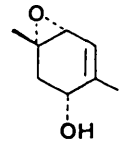
(173)

Hoffmann has shown that the regiochemistry of the E-2 like opening of the *trans*-epoxide (174) can be controlled by the choice of base.[23] The less sterically demanding lithium ethylenediamide base[24] will preferentially form the endocyclic allylic alcohol, presumably by initial proton abstraction to form the exocyclic double bond and then by equilibration, in which the amide acts as a weak protic acid, to give exclusively the olefin of thermodynamic control.

Using this procedure, reaction of *cis*-diepoxide (169) with one equivalent of lithium ethylenediamide in a 4:1 mixture of Et_2O:THF at rt gave after 30 mins the alkenyl epoxide (175) in 76% yield and the diol (170), observed previously, in 12% yield.



(174)



(175)

ν_{max}: 3510, 2940, and 1660 cm^{-1}.

δ(250 MHz):

1.43 (3H, s, C-5 *Me*)

1.78 (1H, dd, J 4.5, 15.2 Hz, *H-6*)

1.86 (3H, d, J 1.4 Hz, C-2 *Me*)

2.30 (1H, dd, J 1.9, 15.2 Hz, *H-6*)

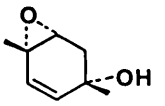
2.55 (1H, d, J 11.4 Hz, O*H*)

3.20 (1H, dd, J 1.6, 4.5 Hz, *H-4*)

3.77 (1H, ddd, J 1.9, 4.5, 11.4 Hz, *H-1*)

5.82 (1H, m, *H-3*)

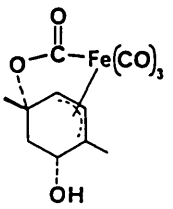
The high-field ^1H n.m.r. shows the product (175) to be contaminated with a small percentage (<5%) of the isomer (176), presumably resulting from ring metalation followed by α-elimination and rearrangement of the resulting carbenoid species. The olefinic protons in (176) appear as a sharp singlet at δ5.90. This minor isomer was inseparable from alkenyl epoxide (175) and consequently was carried through the synthetic sequence.



(176)

Treatment of the alkenyl epoxide (175) with nonacarbonyldiiron ($Fe_2(CO)_9$), stirred as a solution in THF at 20°C for 12h gave the expected π-allyltricarbonyliron lactone complex (177) in 27% yield.

ν_{max}: 3400, 2920, 2080, 2010, and 1660 cm^{-1}



(177)

δ(90 MHz):

1.58 (3H, s, C-1 *Me*)

1.62 (3H, s, C-4 *Me*)

1.80 - 2.25 (3H, m)

3.65 (1H, m, *H-5*)

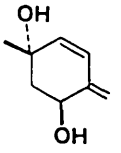
4.98 (1H, d, J 4.4 Hz, *H-2*)

5.02 (1H, d, J 4.4 Hz, *H-3*)

Attempted oxidation of compound (177) using ceric ammonium nitrate in ethanol at -40 → 0°C over 1h did not provide the desired β-lactone. The presence of the free hydroxyl group may be a complicating factor in the decomplexation of the π-allyltricarbonyliron lactone. Hopefully, protection at the π-allyltricarbonyliron lactone stage followed by oxidation and deprotection would afford the desired product.

It was assumed that treatment of the *trans*-diepoxide with the less sterically demanding amide base would produce analogous results to the opening of the *cis*-diepoxide. This, however, was not the case. Inverse addition of lithium ethylenediamide to a THF solution of the

trans-diepoxide and stirring at rt for 1h gave a mixture of three products. The polar *trans*-diol (178), formed by initial proton abstraction from the α-methyl group, was reproducibly formed in 25% yield, a much higher percentage than in the *cis*-diepoxide case.

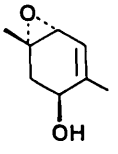


(178)

ν_{max}: 3355, 2970, 2927, 1662, and 1605 cm^{-1}.

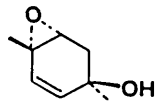
δ(90 MHz):
1.35 (3H, s, C-1 *Me*)
1.71 (1H, d, J 12.9 Hz, *H-6*)
2.12 (1H, dd, J 4.9, 12.9 Hz, *H-6*)
2.37 (2H, br s, O*H*)
4.55 (1H, m, *H-5*)
5.05 (1H, s, =CH_2)
5.30 (1H, s, =CH_2)
5.62 (1H, d, J 10.0 Hz, *H-3*)
6.11 (1H, d, J 10.0 Hz, *H-2*)

The two other products, inseparable by chromatography, resulted from equal proton abstraction from either side of the epoxide, resulting in a 35% yield of each of the required alkenyl epoxide (179) and the isomeric (180).



(179)

δ(90 MHz):
1.40 (3H, s, C-5 *Me*)
1.68 (1H, dd, J 3.9, 16.7 Hz, *H-6*)
1.80 (3H, br s, C-2 *Me*)
2.55 (1H, d, J 16.7 Hz, *H-6*)
3.00 (1H, d, J 4.6 Hz, *H-4*)
4.25 (1H, m, *H-1*)
5.70 (1H, m, *H-3*)



(180)

δ(90 MHz):

1.32 (3H, s, C-4 *Me*)

1.44 (3H, s, C-1 *Me*)

1.68 (1H, br s, O*H*)

1.92 (1H, ddd, J 1.3, 2.0, 15.3 Hz, *H-6*)

2.45 (1H, dd, J 2.6, 15.3 Hz, *H-6*)

3.30 (1H, m, *H-5*)

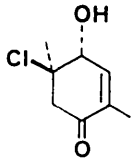
5.77 (2H, s, *H-2,-3*)

Base induced epoxide isomerisations to allylic alcohols require the removal of a *syn*-quasi-axial proton.[25] In the *trans*-diepoxide (168), the experimental observations show that two such protons can be removed, with equal probability, from either side of the epoxide. In the *cis*-diepoxide (169) however, the cyclohexane ring is probably twisted in order to reduce the electronic interaction between the oxygen lone pairs situated on the same face of the molecule. This could result in the increased lability of a single proton on one side of the epoxide and lead to the predominant generation of the single allylic alcohol (175).

Treatment of the mixture of (179) and (180) with nonacarbonyldiiron, with the possibility of separating the two resulting π-allyltricarbonyliron lactones, resulted in a complex mixture of products.

It has been shown that oxidation of the C-5 hydroxyl group in the avermectin southern hemisphere followed by stereospecific reduction of the newly formed enone carbonyl with sodium borohydride gives exclusively the β-hydroxyl.[26] Furthermore, the naturally occurring milbemycins J and K both contain enones in their southern hemispheres.[27] Consequently, if alkenyl epoxide (175) were oxidised to give the enone, this would then represent a suitable compound for both the iron lactone complex formation and the oxidation to the β-lactone.

Attempts to oxidise allylic alcohol (175) using both activated manganese dioxide[28] and Fetizon's reagent[29] gave recovered starting material. Even under heavily buffered conditions, oxidation using PCC[30] repeatedly gave the chlorohydrin enone (181) as the only isolable product in 38% yield.

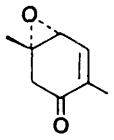


(181)

ν_{max}: 3450, 2980, 1685, and 1618 cm^{-1}.

δ(250 MHz):
1.42 (3H, s, C-5 *Me*)
1.85 (1H, br s, O*H*)
2.03 (3H, d, J 2.0 Hz, C-2 *Me*)
2.96 (1H, dd, J 1.0, 15.1 Hz, *H-6*)
3.11 (1H, d, J 15.1 Hz, *H-6*)
3.69 (1H, m, *H-4*)
6.69 (1H, m, *H-3*)

The infrared spectrum of compound (181) clearly shows the presence of both the free hydroxyl and the enone functionalities with strong absorptions at 3450 and 1685 cm^{-1} respectively. Collin's oxidation[31] did however provide the required epoxy enone (182) in 80% yield.



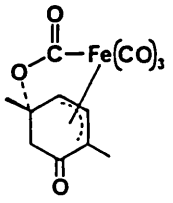
(182)

ν_{max}: 3446, 2963, 2926, 1676, and 1449 cm^{-1}.

δ(90 MHz):
1.50 (3H, s, C-5 *Me*)
1.80 (3H, d, J 1.3 Hz, C-2 *Me*)
2.60 (1H, d, J 19.3 Hz, *H-6*)
3.08 (1H, dd, J 1.3, 19.3 Hz, *H-6*)
3.25 (1H, dd, J 1.3, 3.9 Hz, *H-4*)
6.90 (1H, m, *H-3*)

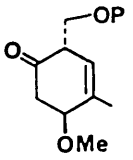
Addition of 1M NaOH solution to the chlorohydrin (181) and stirring for 20 min caused ring closure and the production of enone (182) in 69% yield.

Unfortunately, and despite repeated attempts, treatment of enone (182) with nonacarbonyldiiron at rt for 18h, in either THF or in benzene under sonochemical conditions, failed to produce the corresponding π-allyltricarbonyliron lactone complex (183).



(183)

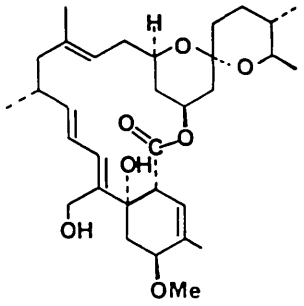
At this stage, it was decided to leave this aspect of the model chemistry and concentrate synthetic efforts on the preparation of cyclohexenone (128), a key sub-unit in our strategy for the synthesis of milbemycin β_1 (16).



(128)

SYNTHESIS OF THE SOUTHERN HEMISPHERE OF MILBEMYCIN β_1

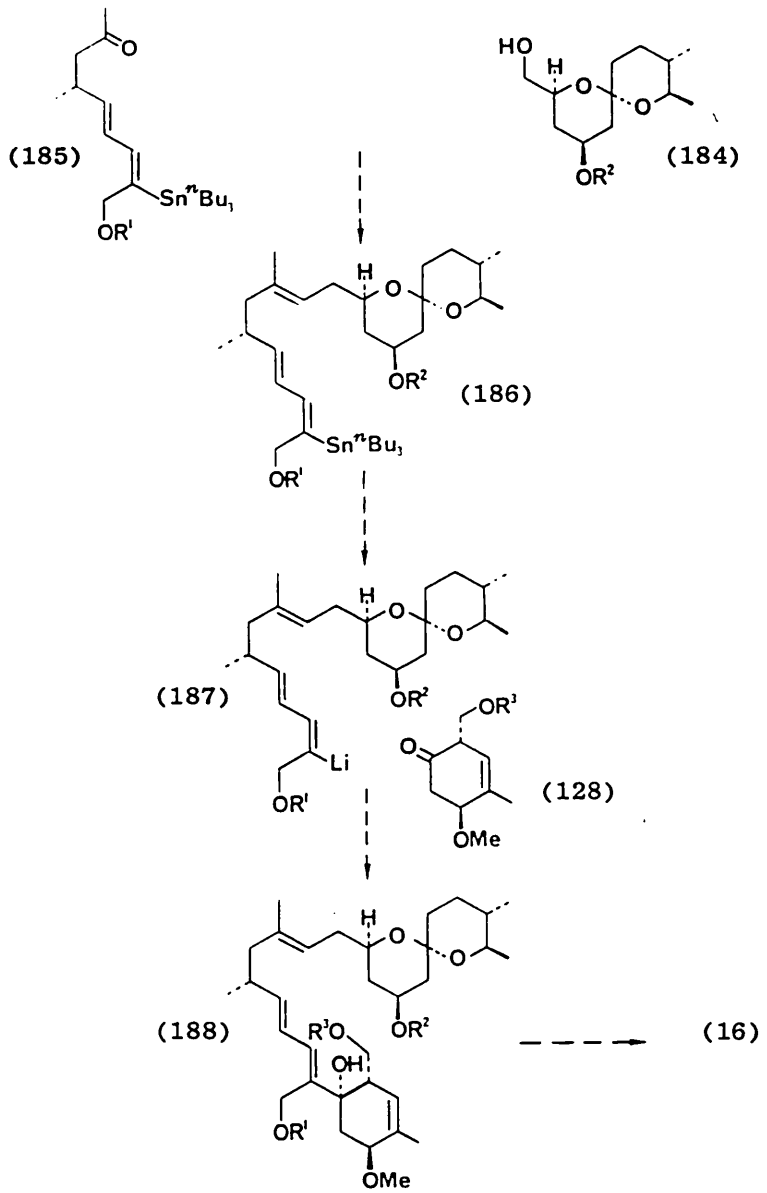
This chapter describes the synthetic efforts directed towards the synthesis of the non-conjugated cyclohexenone (128), one of three sub-units required for the convergent synthesis of milbemycin β_1 (16) presently being studied in our group.



(16)

Our synthetic strategy involves the initial coupling of the individually prepared spiroacetal moiety (184), already produced in its optically pure form[32], and the side chain (185) to give the northern hemisphere of the molecule (Scheme 28). Vinyl stannanes are known to exchange with lithium to give vinyl lithiums in which the geometry of the double bond is retained.[33] Consequently, metalation of the vinyl stannane (186) and its subsequent nucleophilic addition into the ketone carbonyl of cyclohexenone (128) should yield (188). It is hoped that the direction of nucleophilic attack into the ketone can be controlled by use of a sterically demanding protecting group R_3 to shield the α-face of cyclohexenone (128) and thereby force the nucleophilic side-chain to approach from the β-face. Ring closure to give the 16-membered ring lactone could then be achieved by removal of protecting group R_3,

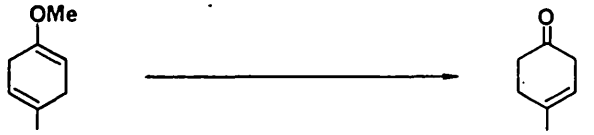
Scheme 28



oxidation of the resulting primary alcohol to the corresponding carboxylic acid, and finally macrocyclic lactonisation[34] onto the deprotected secondary alcohol of the spiroacetal. Conversely, the methyl ester of the intermediate carboxylic acid could be converted to the ^{t}butylthioester[35] and ring closure to give the lactone achieved by transesterification using the methodology already developed in the seco-model study.

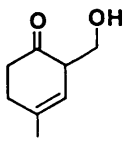
Preparation of the cyclohexenone (128) was undertaken with the intention of utilising some of the intermediate compounds, containing less elaborate though relevant functionalities, for model studies.

Lithium in ammonia reduction of *p*-methylanisole (a more powerful reduction than the sodium in ammonia procedure of Birch) using Et_2O as a co-solvent and adding absolute alcohol as the final step gave the expected dihydro compound (189) in 77% yield.[36] Mild acid hydrolysis of diene (189) using 10 mol % oxalic acid in a 98:2 THF/water mixture over 18h gave the non-conjugated enone (190) in quantitative yield.



(189) (190)

Several attempts were made to kinetically alkylate the enone (190) in the C-2 position and thereby give immediate access to a model on which nucleophilic addition into the ketone carbonyl could be performed. Addition of a THF solution containing excess monomeric formaldehyde (5 equiv.) to the lithium enolate of (190), (generated using 1.1 equiv. LDA and maintained at -78^{o}C), gave a low yield (17%) of the β-hydroxyketone (191).



(191)

ν_{max}: 3410 and 1715 cm^{-1}

δ(90 MHz): 1.80 (3H, br s, C-4 *Me*)

2.26 - 2.70 (4H, m)

3.07 (1H, m, *H-2*)

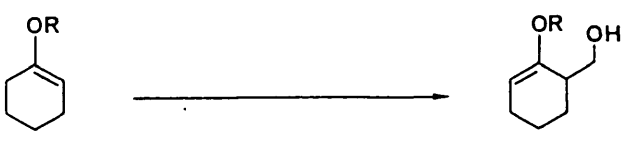
3.70 (2H, m, CH_2OH)

5.31 (1H, m, *H-3*)

Preparation of compound (191), even accepting the poor yield, was not reproducible and despite several attempts could not be prepared in any sizeable quantity. Similarly, attempts to react the lithium enolate of (190) with methyl chloroformate, trimethylorthoformate and finally benzaldehyde were equally unreproducible despite the utilisation of 1→2 equiv. HMPA or DMPU[37] as co-solvents. The possibility of a rapid retro-aldol reaction of the C-alkylated product or the disintegration of an unstable product resulting from O-alkylation of the stabilised enolate are thought to be contributing factors to the lack of success achieved with this reaction. Consequently, this approach to a model compound for cyclohexenone (128) was not pursued.

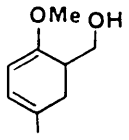
Snider has recently shown that the reaction of formaldehyde and trimethylaluminium, the least strong Lewis acid of the alkyl aluminiums, with an enol ether derived from a ketone will give an ene-type adduct (Scheme 29).[38]

Scheme 29



R	Yield
Me	87%
TMS	82%
TBDMS	81%

Dropwise addition over 10 min of a 1M solution of Me_3Al in hexane (2 equiv.) to a mixture of the enol ether (189) and paraformaldehyde (2 equiv.) in CH_2Cl_2 at 0^oC caused complete dissolution of the paraformaldehyde suspension. The solution was stirred at this temperature for 10 min, Et_2O added, and the reaction then quenched by the cautious dropwise addition of water until gas evolution ceased. Filtration of the mixture through celite under suction to remove the precipitated aluminium salts followed by extraction of the aqueous layer afforded the diene (192) in 61% yield.



(192)

ν_{max}: 3370, 1658, and 1611 cm^{-1}

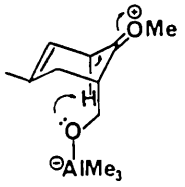
δ(250 MHz): 1.72 (3H, d, J 1.4 Hz, C-4 *Me*)

3.57 (3H, s, O*Me*)

4.93 (1H, d, J 5.7 Hz, *H-2*)

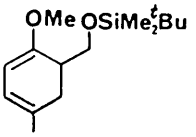
5.51 (1H, m, *H-3*)

The product results from proton abstraction by the oxygen *via* a six-membered ring transition state to give the homoallylic alcohol (ene adduct).



The infrared spectrum of (192) shows two very strong, sharp absorptions at 1658 and 1611 cm^{-1} for the enol ether and conjugated double bond respectively as well as an absorption for the hydrogen bonded hydroxyl group at 3370 cm^{-1}. The resonances for the two olefinic protons are quite distinct in the ^1H n.m.r., as would be expected, with the olefin of the electron rich enol ether appearing as a doublet at δ4.93, coupled to H-3, and the second olefin proton H-3 as a multiplet at δ5.51.

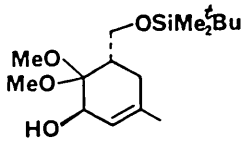
Compound (192) was initially converted to the ^{t}butyldimethylsilyloxy derivative (193)[9], the choice of protecting group being governed by the need for hydrolytic stability and for the shielding effect on one face of the molecule should a suitable ketone product be prepared on which addition reactions could be attempted.



(193)

Epoxidation of the electron rich double bonds of methyl or trimethylsilyl enol ethers using a peracid in an alcoholic solvent has been shown by Frimer to provide convenient access to α-hydroxyacetals.[39] Addition of 1 equiv. mCPBA to a methanolic solution of the enol ether (193) and stirring at rt for 1h gave a complex mixture of products, as expected with a diene of this type, from which careful chromatographic separation afforded the α-hydroxyacetal (194) in 27% yield.

The α-hydroxyacetal (194) is potentially a very useful compound since, whilst remaining within the overall strategy adopted for the synthesis of milbemycin β_1, it could also allow access to the avermectin southern hemisphere (126).



(194)

ν_{max}: 3432, 2929, 1677, and 1463 cm^{-1}

δ(250 MHz): 1.70 (3H, br s, C-5 *Me*)

3.23 (3H, s, O*Me*)

3.35 (3H, s, O*Me*)

3.88 (1H, m, *H-1*)

5.50 (1H, m, *H-6*)

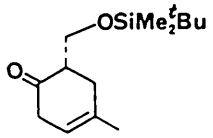
Enantioselective epoxidation of (194) using the Sharpless procedure and ring opening of the resulting epoxide using the less sterically demanding base lithium ethylenediamide, utilised in the preparation of alkenyl epoxide (175), should theoretically provide diol (195) in good yield. Protection of the diol, addition of the vinyl lithium (187) into the free ketone derived from (195), and deprotection would generate a system ideally set-up for ring closure to give the *cis*-fused tetrahydrofuran in the bi-cyclic southern hemisphere of the avermectins. Further elaboration of allylic alcohol (194) in this manner is obviously dependent on the development of viable methodology leading to cyclohexenone (128).

(194) (195)

Mild hydrolysis of the methyl enol ether (193) to give the non-conjugated enone (196) could be achieved using 10 mol % oxalic acid in THF/water (98:2), though the reaction was generally very sluggish. Heating the mixture at reflux or increasing the acidity did increase

the rate of the reaction but unfortunately resulted in some formation of the undesired conjugated enone.

The preferred method for the hydrolysis of the enol ether (193) was to stir with silica-gel, to which 5% H_2SO_4 solution had been adsorbed, as a slurry in CH_2Cl_2.[40] With a maximum loading of 100 mg H_2SO_4 solution per gram of silica and a silica to compound ratio of not less than 10:1, the enol ether was cleanly hydrolysed at rt in 3h to give the non-conjugated enone (196) in 93% yield. Purification of the product was usually not necessary as work-up simply involved filtration and elution from the silica-gel.



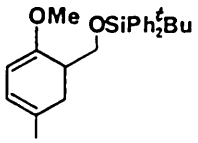
(196)

ν_{max}: 3070, 2931, and 1713 cm^{-1}

Attempted protection of the ketone carbonyl in compound (196) as the dialkyl acetal using (a) triethylorthoformate and an Amberlite resin[41] or (b) trimethylorthoformate adsorbed onto K_{10}[42], or as the 1,3-dithiolane using ethane dithiol and $BF_3.Et_2O$[43] failed to give the required product. It was believed that a possible reason for the failure of these methods was the excessive acidity of the catalyst. It was decided therefore to change the alcohol protecting group for the very hydrolytically stable ^{t}butyldiphenylsilyl moiety.[44] A distinctive feature of the O-^{t}butyldiphenylsilyl group is its compatibility under conditions required for the acid-catalysed formation, and cleavage, of acetals. A further advantage is that the increased size over the ^{t}butyldimethylsilyl group should ultimately favour the

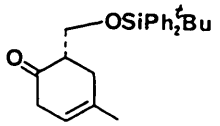
desired regioselectivity of nucleophilic addition into the ketone of the final enone (128).

Protection of (192) was achieved under standard conditions of imidazole, DMF, and a trace of DMAP, heated at 50°C overnight to give the required ^{t}butyldiphenylsilyloxy derivative (197) in 94% yield.



(197)

Mild hydrolysis, under the now standard conditions, by stirring with a CH_2Cl_2 slurry of silica, onto which 5% H_2SO_4 solution had been adsorbed, cleanly gave the non-conjugated enone (198) in quantitative yield.

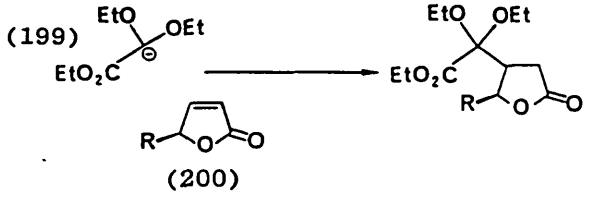


(198)

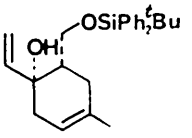
ν_{max}: 3071, 2931, and 1714 cm^{-1}.

The non-conjugated enone (198) represents a suitable compound on which to attempt addition reactions into the ketone carbonyl and thereby test the shielding effect of the bulky ^{t}butyldiphenylsilyl group on the α-face of the molecule. Schlessinger has demonstrated the addition of the latent carbonyl anion (199), generated by addition of 1 equiv. LDA at -78°C in THF under argon, into the butenolide (200).[45] The anion (199) is considerably less stable than its dithioethyl analogue, used

later, but has the advantage of being much easier to hydrolyse into the corresponding carbonyl compound.



However, inverse addition of the anions of both diethoxyethyl acetate at -78°C and dithiane at -30°C gave recovered starting enone (198). Inverse addition of vinylmagnesium bromide at -20°C did give a low yield (29%) of the addition product (201).



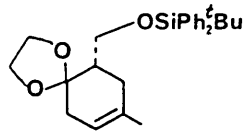
(201)

ν_{max}: 3497, 2930, and 1638 cm^{-1}.

The methylene protons α to the ketone in (198) are doubly activated, both by the ketone itself and by the double bond, and consequently are reasonably acidic. The acidity of these protons may play some part in the poor results observed on the attempted addition into the ketone. If so, a similar effect may be observed in the addition into the ketone carbonyl of the target molecule (128).

Protection of the ketone carbonyl in enone (198) to give the dioxolane (202) was achieved in 61% yield by heating at reflux a

mixture of the enone and ethylene glycol in benzene, to which a small amount of the very mild acid catalyst pyridinium tosylate[46] had been added, under Dean-Stark conditions. The resulting acetal (202) was later produced directly from the enol ether (197), by employing the same reaction conditions, in 81% yield.

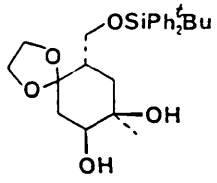


(202)

The next stage in the synthetic sequence requires elaboration of the double bond to allow access to the allylic methoxy group of the target molecule. This can conceivably be achieved by two routes: (a) epoxidation of the double bond followed by base-induced ring opening to give the allylic alcohol or (b) *cis*-hydroxylation of the double-bond using osmium tetroxide[47] followed by preferential elimination of the resulting tertiary alcohol. An important consideration in comparing the two routes is that osmylation will occur from the least hindered face of the molecule and therefore will produce a single product. Epoxidation, on the other hand, will produce two isomers resulting from addition to both the α- and β-faces of the molecule though the isomer resulting from attack on the sterically least hindered face should predominate. Consequently, it was decided to give the *cis*-hydroxylation route priority.

Addition of the olefin (202) to a pyridine solution of osmium tetroxide under argon caused immediate darkening of the solution indicating formation of the osmate ester. After stirring at rt for 8h,

the osmate ester was cleaved by the addition of aqueous sodium bisulphite and the mixture stirred overnight. The granular precipitate was removed by filtration and the reaction worked-up to give the *cis*-diol (203) in 83% yield. The reaction was repeated with only a catalytic amount of the expensive and highly toxic osmium tetroxide, using N-methyl morpholine N-oxide to regenerate the OsO_4, but this method proved to be unsuccessful.[48]



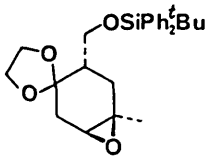
(203)

ν_{max}: 3431, 3071, and 2933 cm^{-1}

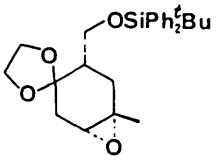
It was anticipated that elimination of the tertiary alcohol in (203) would prove to be a facile process. Unfortunately, the procedure was complicated by the fact that under acidic conditions the acetal would be cleaved thereby rendering the methylene protons α to the resulting ketone acidic and causing preferential loss of the secondary alcohol. Despite repeated attempts to facilitate elimination of the tertiary alcohol, (Burgess' salt[49], $POCl_3$/py[50], $SOCl_2$/py[51], anhydrous $CuSO_4$/heat[52]), all resulted in complete degradation of the starting material. Selective methylation of the secondary alcohol might facilitate dehydration of the tertiary alcohol but was not attempted at this stage.

Turning to the second strategy for double bond elaboration, epoxidation of the olefin (202) with mCPBA at 0^oC in CH_2Cl_2 gave an 82% overall yield of a 76:24 ratio of the predicted β- and α-epoxides (204) and (205). Chromatographic separation of the two isomers was not possible

at this stage and consequently the α-epoxide was carried through to the next stage of the synthetic scheme.

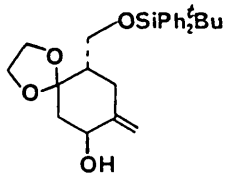


(204)

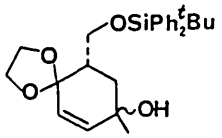


(205)

By analogy with the results obtained in the attempted preparation of a β-lactone model (156), it was envisaged that treatment of the β-epoxide (204) with the sterically demanding base lithium diethylamide would open the epoxide ring to produce the secondary alcohol (206). However, isomerisation of the epoxide mixture with this amide base firstly in THF and then in the more usual Et_2O surprisingly gave on each occasion the tertiary alcohol (207) as the major product in 72% yield.



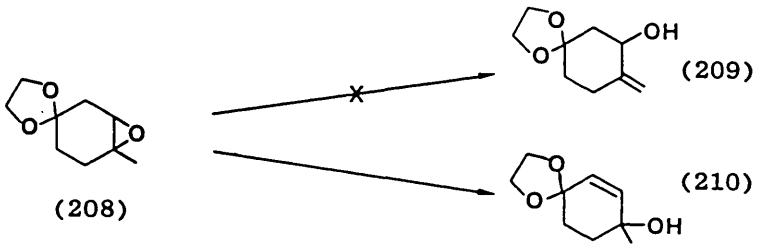
(206)



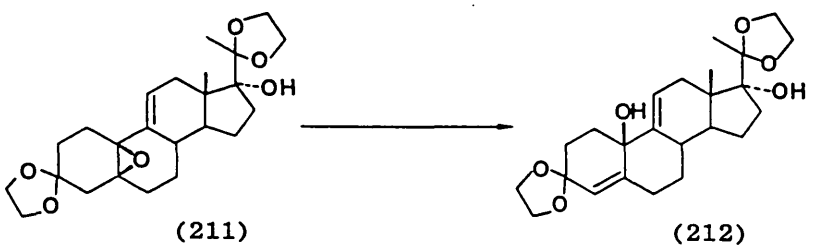
(207)

Base catalysed rearrangement of epoxides to allylic alcohols has been known for a long time and is now well documented especially by the work of Crandall[53] and Rickborn[54]. We were surprised therefore to obtain this unpredicted isomer in such a high reproducible yield. On researching the literature, this unexpected effect has in fact been

recorded on two previous occasions. As part of a terpene synthesis program, Still required the allylic alcohol (209). Treatment of the epoxide (208) with lithium diethylamide however resulted in the preferential production of tertiary alcohol (210).[55]

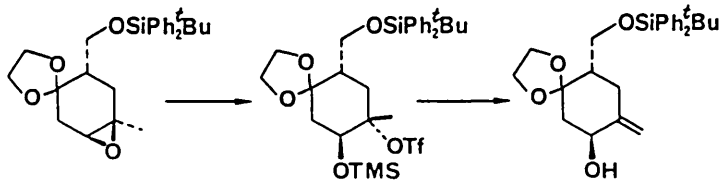


Similarly, Teutsch found base opening of the steroidal α,β-unsaturated epoxide (211) gave exclusively the dienol (212) by proton abstraction at C-4, even though the C-12α proton is in a suitable orientation for a *syn*-opening.[56]



The unexpected regiochemistry of this reaction presumably results from the involvement of the ketal as an alternative site for base coordination. Complexation in this manner would then induce proton removal from the adjacent methylene group.

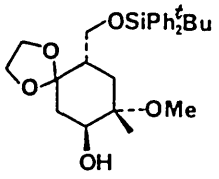
This formation of the tertiary alcohol (207) indicates that a standard lithium amide induced isomerisation of the epoxide (204) will not provide a viable route to the desired allylic alcohol (206). Attempted ring opening using TMSI at $0^{o}C$, prepared *in situ* from hexa methyldisilane and I_2 warmed at $60^{o}C$ for 10 min, and elimination of the resulting tertiary iodide by addition of DBU and heating at reflux in benzene for 12h gave complete degradation of the starting epoxide.[57] Under the less severe conditions of Noyori[58], a 26% yield of the allylic alcohol (206) was achieved by addition of trimethylsilyl trifluoromethanesulphonate and 2,6-lutidine at $-78^{o}C$ to the epoxide mixture and then stirring with DBU at rt for 18h.



(204) (206)

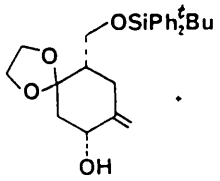
Despite this promising result the method does not facilitate access to any large quantity of the required allylic alcohol (206).

Addition of the mild acid catalyst pyridinium tosylate[46] to a methanolic solution of the epoxide (204) gave a 95% yield of the secondary alcohol (213). However, despite heating at reflux for 24h, no elimination of MeOH could be achieved, presumably due to the methyl ether occupying an equatorial position and consequently requiring a less favoured *syn*-elimination to give the olefin. Similar use of the stronger acid catalyst CSA caused deprotection of the dioxolane and subsequent degradation of the molecule.



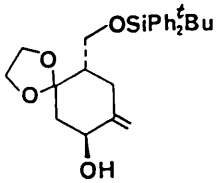
(213)

Treatment of the epoxide (204) with diethylaluminium tetramethylpiperidide (DATMP)[59], prepared *in situ* by the addition of 1 equiv. diethylaluminium chloride to a benzene solution of lithium tetramethylpiperidide formed in the usual manner, and stirring at 0°C for 1h gave a mixture of three products: (a) the α-allylic alcohol (214) in 4% yield, formed by isomerisation of the α-epoxide (205); the β-allylic alcohol (206) in 73% yield; and finally the previously obtained tertiary alcohol in 17% yield.



(214)

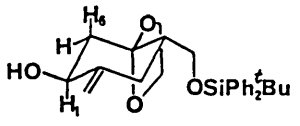
δ(250 MHz): 1.82 (2H, m, *H-6*)
2.04 (1H, m, *H-4*)
2.57 (2H, m, *H-3*)
4.88 (1H, br s, $=CH_2$)
4.99 (1H, br s, $=CH_2$)



(206)

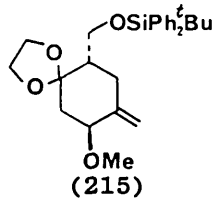
δ(250 MHz):
1.61 (1H, ddd, J 0.9, 8.5, 13.5 Hz, *H-6*)
1.97 (1H, dd, J 4.3, 13.5 Hz, *H-6*)
2.05 (1H, m, *H-4*)
2.33 (1H, dd, J 8.2, 13.6 Hz, *H-3*)
2.80 (1H, dd, J 4.5, 13.6 Hz, *H-3*)
4.88 (1H, br s, $=CH_2$)
5.00 (1H, br s, $=CH_2$)

That the major product contains an equatorial hydroxyl group can be seen from the large coupling constant (J_{aa} = 8.5 Hz) between the *trans*-coplanar protons H-1 and H-6.



Thus the required exocyclic allylic alcohol (206) has been obtained in an isomerically pure state and in 73% yield by a base-promoted isomerisation of the precursor epoxide (204).

Protection of the secondary alcohol (206) was achieved by deprotonation using a slight excess of sodium hydride and the sequential addition of 1 equiv. HMPA (replaced by the less toxic DMPU[37] for large scale reactions) followed by excess freshly distilled methyl iodide to give the methyl ether (215) in 98% yield. The product was isolated in a high state of purity but was routinely passed through a short pad of silica to remove a slight discolouration.



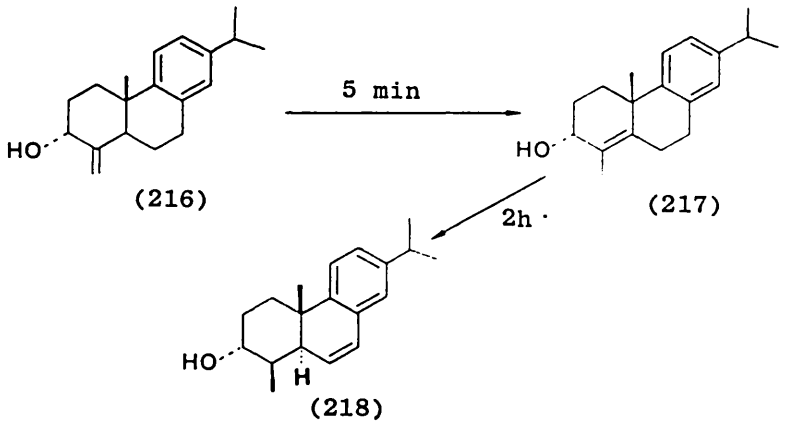
(215)

ν_{max}: 2932, 2885, and 1665 cm^{-1}

δ(250 MHz): 1.54 (1H, dd, J 9.8, 12.6 Hz, *H-6*)
1.96 - 2.21 (3H, m)
2.75 (1H, dd, J 3.8, 12.6 Hz, *H-3*)
3.38 (3H, s, O*Me*)

Isomerisation of the double bond into the ring should theoretically be carried out at this stage, *ie* prior to the introduction of the polyene northern hemisphere (187) of milbemycin β_1. It was initially

envisaged that the isomerisation could be achieved by brief treatment with the lithium salt of ethylenediamine.[60] Cambie has already shown that treatment of the allylic alcohol (216) with lithium ethylenediamide for 5 min gives the isomeric alcohol (217) which itself rearranges to give the thermodynamically favoured product (218) after 2h.[61]



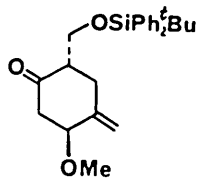
(216) (217) (218)

Compound (215) was similarly treated with lithium ethylenediamide under a wide variety of reaction conditions. ^1H n.m.r. (90 MHz) of each reaction mixture clearly showed the appearance of signals corresponding to a methyl on a double bond (δ 1.72) and a new olefinic proton (δ 5.71). However, even after heating at reflux for 24h, the isomerisation could not be induced to provide more than 20% of the endocyclic isomer. Consequently, other methods for the isomerisation of the exocyclic double bond are currently under investigation.[62,69]

Attempted deacetalisation of the dioxolane (215) by pyridinium tosylate catalysed transacetalisation with wet acetone gave recovered starting material, even after heating at reflux for several hours.[63]

Initial removal of the dioxolane protecting group in (215) was achieved using trityl fluoroborate as a solution in CH_2Cl_2 at 0^oC for

1h.[64] This gave the ketone (219) in 31% yield with substantial, and predicted, deprotection of the ^{t}butyldiphenylsilyl group. Though the method gave access to material for the next step in the synthetic scheme, and could presumably be optimised by either lowering the temperature or reaction time, it was not considered prudent to have such a sensitive reaction at this stage in the synthesis. Consequently, a milder method for the deprotection of the acetal would be desirable.



(219)

ν_{max}: 3071, 2931, 1715, and 1657 cm^{-1}

δ(250 MHz): 2.30 (1H, dd, J 5.5, 13.0 Hz, *H-3*)

2.50 (1H, ddd, J 0.8, 5.7, 14.5 Hz, *H-6*)

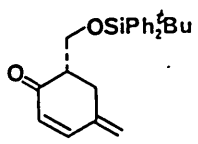
2.61 (1H, dd, J 4.2, 14.5 Hz, *H-6*)

2.64 - 2.81 (2H, m)

3.25 (3H, s, O*Me*)

3.88 (1H, dd, J 4.2, 5.7 Hz, *H-5*)

Regeneration of the ketone (219) was finally achieved in 78% yield by stirring the acetal (215) with a slurry of silica-gel, to which 10% H_2SO_4 solution had been adsorbed, in CH_2Cl_2 for 7h.[40] Increasing the reaction time or concentration of sulphuric acid caused some elimination of the methoxy group to give the surprisingly stable enone (220). Compound (220) could be prepared exclusively in 66% yield by stirring the acetal (215) with the silica slurry for 24h.



(220)

ν_{max}: 3070, 2931, 1672, and 1578 cm^{-1}

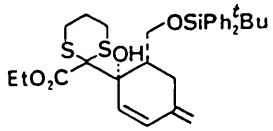
δ(250 MHz): 5.32 (1H, br s, =*CH*$_2$)

5.38 (1H, br s, =*CH*$_2$)

5.92 (1H, d, J 10.2 Hz, *H-2*)

7.07 (1H, d, J 10.2 Hz, *H-3*)

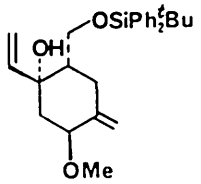
Addition of ketone (219) to the anion of carboethoxydithiane at -20°C in THF, prepared by deprotonation with sodium hydride followed by addition of two equiv. of DMPU, gave a low yield of the diene (221).[65] The anion of carboethoxydithiane surprisingly promotes elimination of the methoxy group by removal of one of the acidic methylene protons α to the ketone. Inverse addition of the anion to the ketone should prevent much of the elimination but was not attempted at this time.



(221)

δ(250 MHz): 1.32 (3H, t, J 7.1 Hz, CH_2CH_3)
4.24 (2H, q, J 7.1 Hz, CH_2CH_3)
5.30 (1H, br s, $=CH_2$)
5.34 (1H, br s, $=CH_2$)
5.97 (1H, d, J 10.1 Hz, *H-3*)
7.02 (1H, d, J 10.1 Hz, *H-2*)

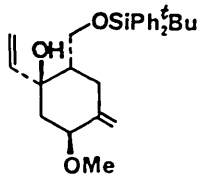
However, inverse addition of excess vinylmagnesium bromide into the ketone (219) gave a mixture of two products (222) and (223) in a 12:1 ratio and in 87% overall yield. It can be seen therefore that the strategy of a sterically demanding protecting group to shield one face of the molecule does indeed influence the direction of attack of the incoming nucleophile.



(222)

ν_{max}: 3482, 3072, 2932, and 1654 cm^{-1}

δ(250 MHz): 4.80 (1H, br s, $=CH_2$)
4.97 (1H, br s, $=CH_2$)
5.21 (1H, dd, J 1.7, 10.1 Hz, *H-2' anti*)
5.57 (1H, dd, J 1.7, 16.8 Hz, *H-2' syn*)
5.82 (1H, dd, J 10.1, 16.8 Hz, *H-1'*)



(223)

ν_{max}: 3489, 3070, 2930, and 1654 cm^{-1}

δ(250 MHz): 4.91 (1H, br s, $=CH_2$)

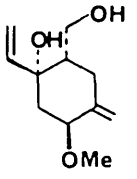
5.00 (1H, br s, $=CH_2$)

5.17 (1H, dd, J 1.8, 10.7 Hz, *H-2' anti*)

5.43 (1H, dd, J 1.8, 16.8 Hz, *H-2' syn*)

5.95 (1H, dd, J 10.7, 16.8 Hz, *H-1'*)

Deprotection of the ^{t}butyldiphenylsilyloxy derivative (222) using the standard conditions of two equiv. tetra ^{n}butylammonium fluoride at 0°C in THF over 20 min gave a quantitative yield of the diol (224).[66]



(224)

ν_{max}: 3374, 3090, 2930, and 1654 cm^{-1}

δ(250 MHz): 1.40 (1H, dd, J 11.5, 13.1 Hz, *H-6*)

1.53 (1H, m, *H-2*)

2.04 (1H, dd, J 5.1, 13.1 Hz, *H-6*)

2.24 (1H, dd, J 4.1, 13.7 Hz, *H-3*)

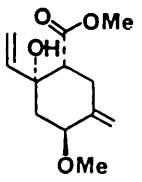
2.75 (1H, dd, J 11.5, 13.7 Hz, *H-3*)

3.63 (1H, dd, J 2.9, 10.8 Hz, *H-7*)

4.00 (1H, dd, J 2.9, 10.8 Hz, *H-7*)

The infrared spectrum of diol (224) shows a strong, sharpened absorption at 3374 cm^{-1}, indicative of intramolecular hydrogen bonding, and supports a six-membered intramolecularly hydrogen-bonded conformation wherein the hydroxyl and hydroxymethyl groups are on the same face of the molecule.

Oxidation of the primary alcohol in compound (224) with PDC in DMF at rt over 48h[67], followed by treatment of the crude reaction mixture with diazomethane[68] afforded the methyl ester (225) in 63% yield.



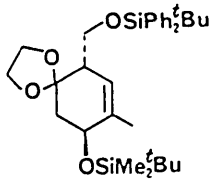
(225)

ν_{max}: 3497, 1714, and 1654 cm^{-1}

δ(250 MHz): 3.41 (3H, s, O*Me*)

3.66 (3H, s, CO_2*Me*)

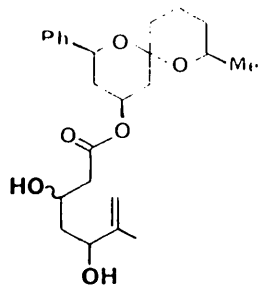
In conclusion, although preparation of the target cyclohexenone (128) has not yet been achieved, literature precedent indicates that ring opening of epoxide (204) using ^{t}butyldimethylsilyl iodide would afford the endocyclic olefin (226)[69], elaboration of which would give the target molecule (128).



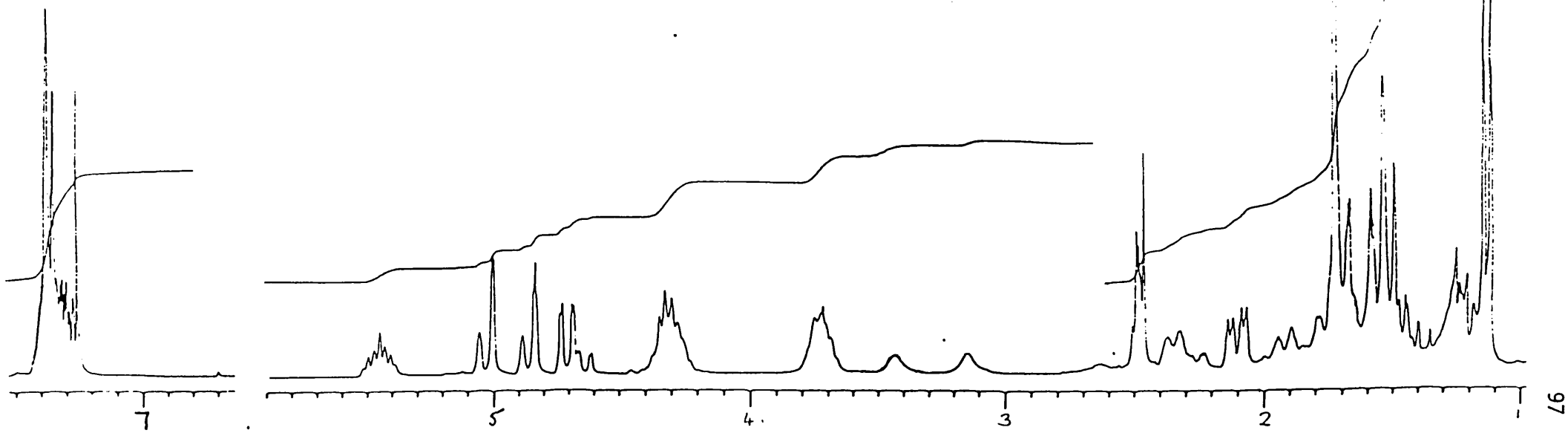
(226)

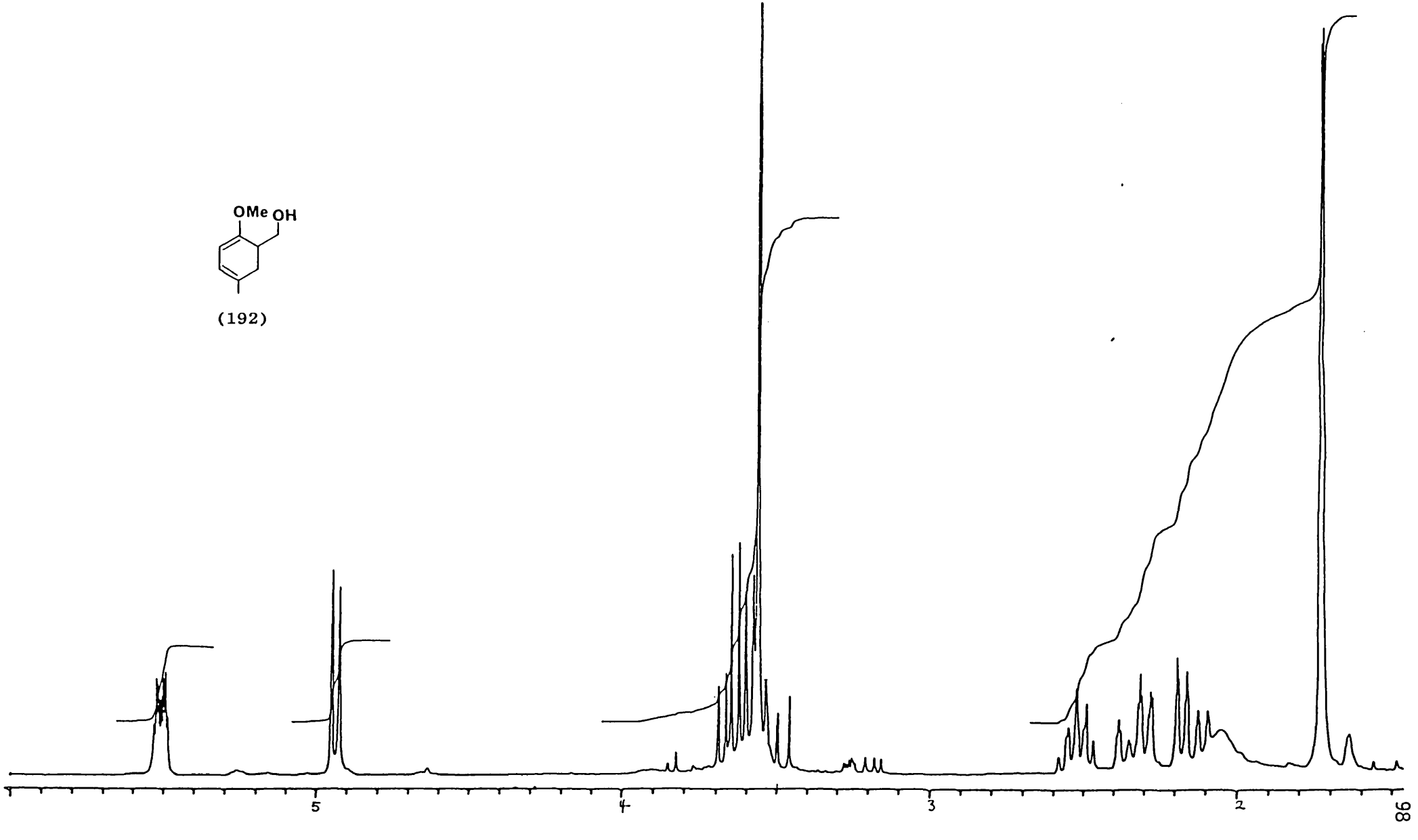
However, preparation of the isomeric (219) has been achieved. Nucleophilic addition into the ketone carbonyl of (219) has been shown to proceed regioselectively with a 12:1 ratio in favour of the desired product (222). Deprotection of the ^{t}butyldiphenylsilyloxy derivative (222) and oxidation of the resulting primary alcohol to facilitate macrocyclic lactonisation has culminated in the preparation of the carboxylic ester (225) in eleven steps and 6.2% overall yield from *p*-methylanisole.

APPENDIX - 250 MHz ^{1}H n.m.r. SPECTRA

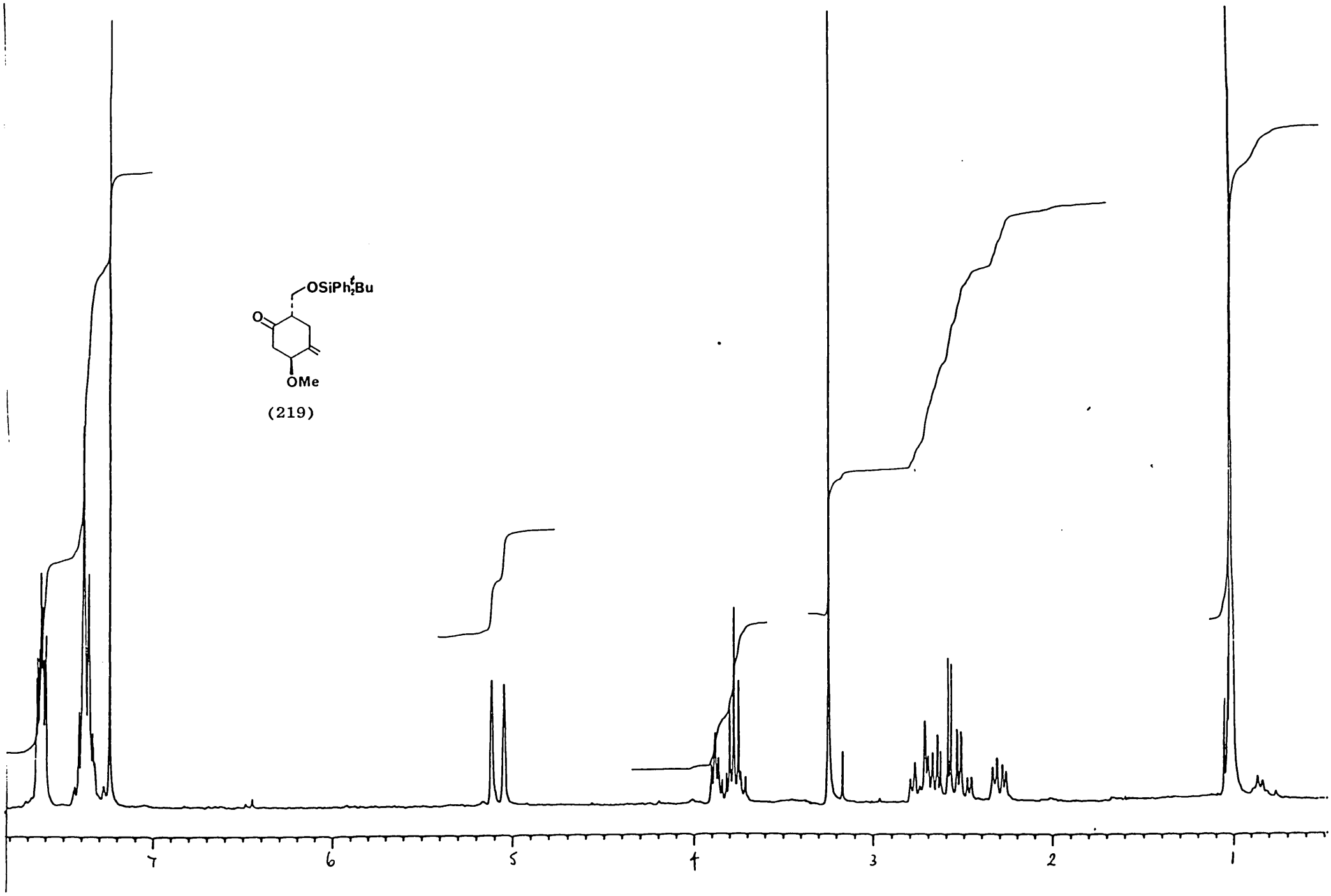


(154)

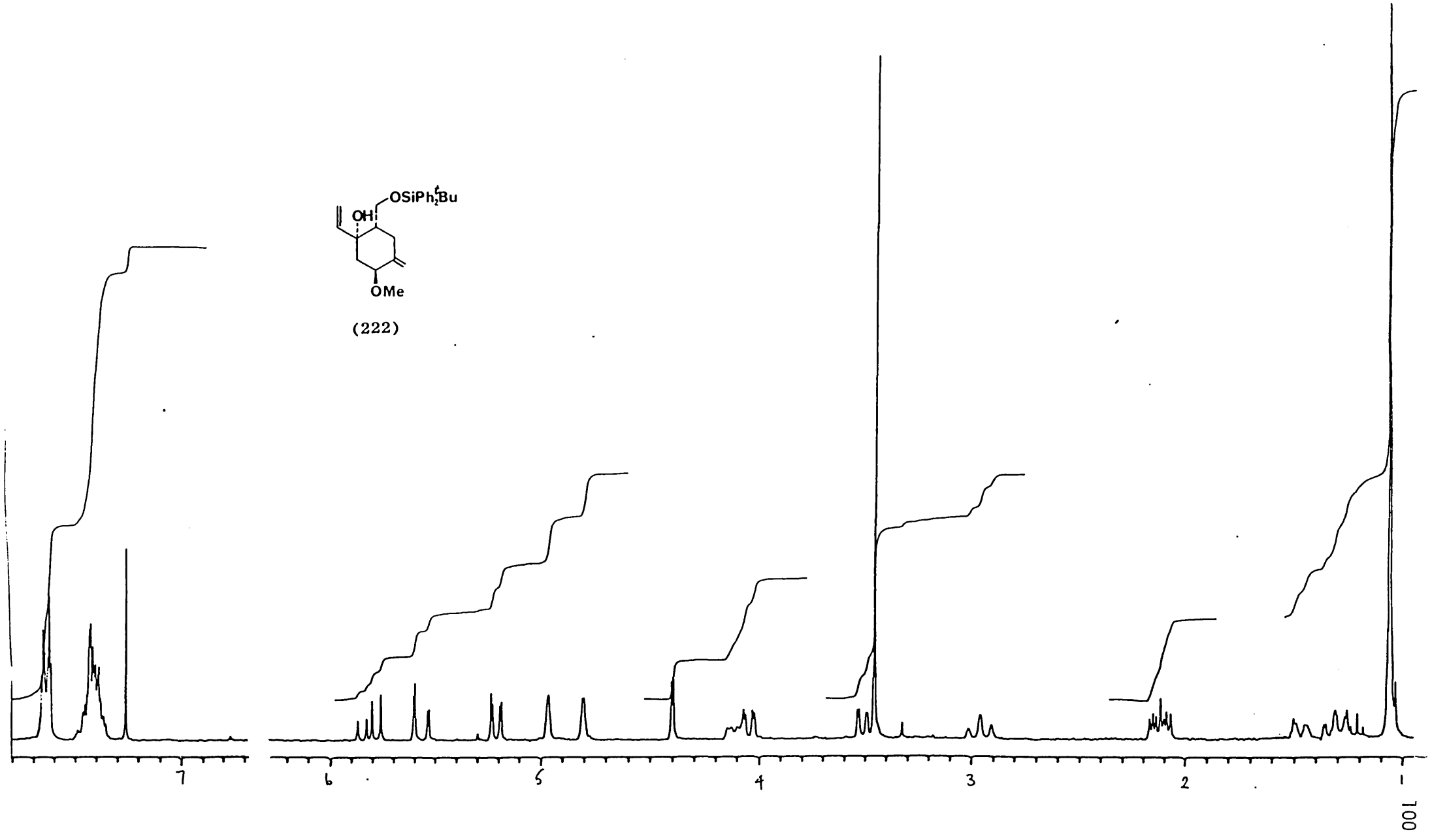




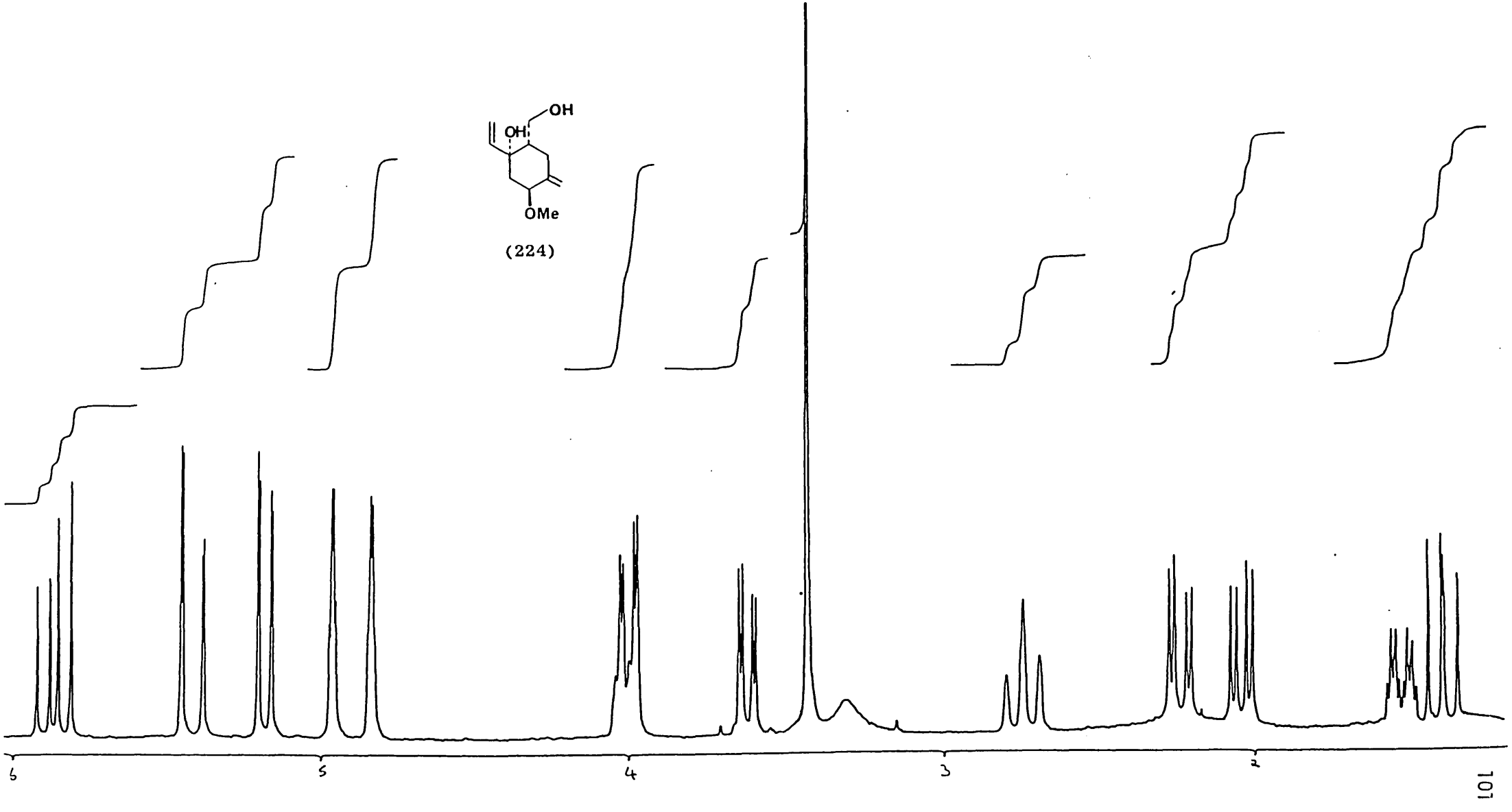
(192)

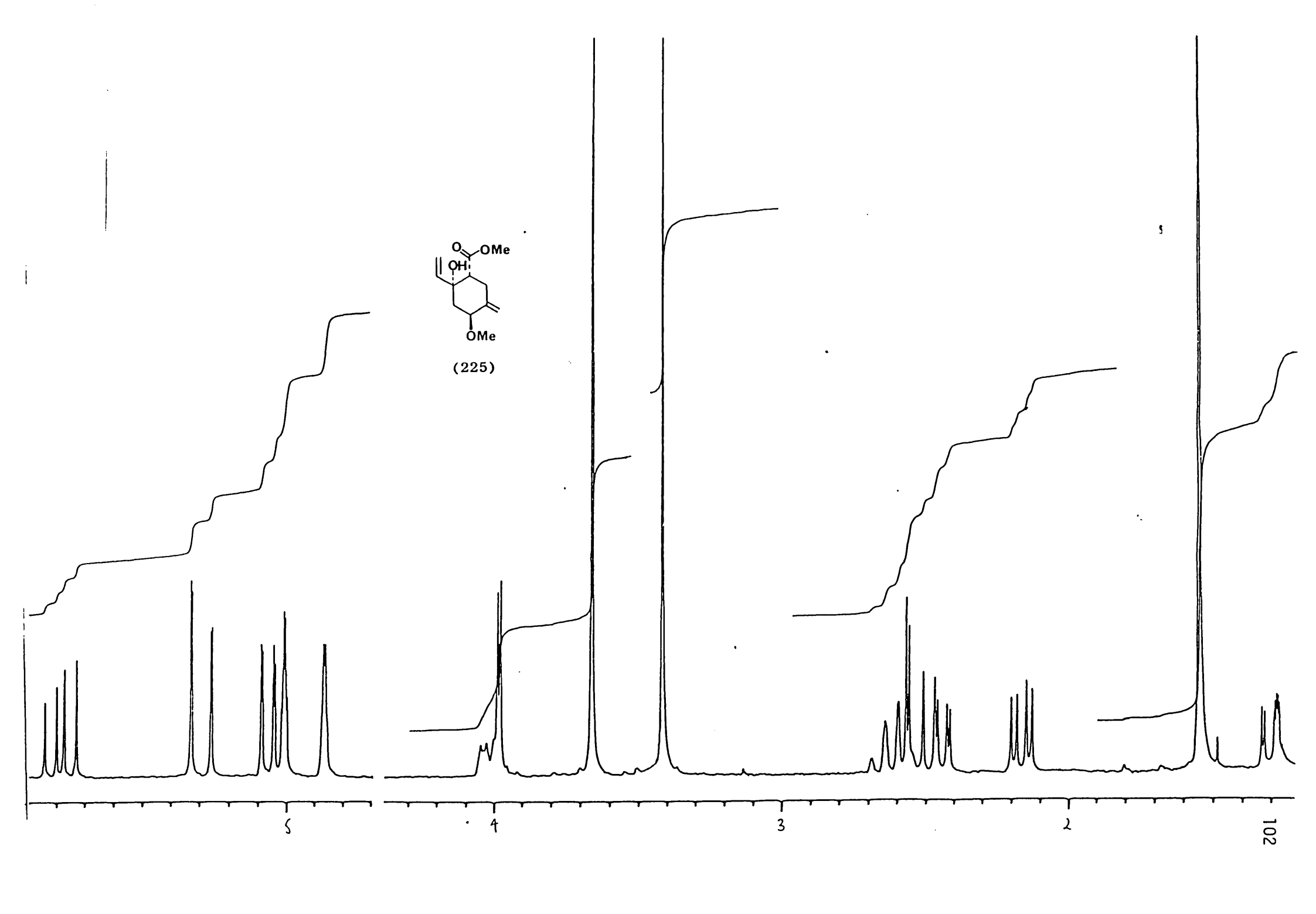


(219)



(222)


OH
OH
OMe
(224)
6
5
4
3
2
1


O
OMe
OH
OMe
(225)
5
4
3
2
1
0

EXPERIMENTAL

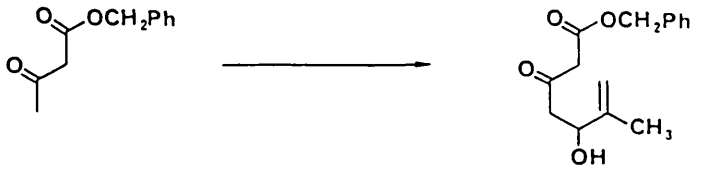
Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 298 grating infrared spectrophotometer using a thin film or solution in $CHCl_3$. ^1H N.m.r. spectra were recorded at 60 MHz on a Varian EM-360A, at 90 MHz on a Joel FX 90Q or at 250 MHz on a Bruker WM-250 machine and are quoted for solutions in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were determined with a VG micromass 7070B instrument. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory.

Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel F_{254} plates and preparative chromatography was conducted under low pressure using Merck Kieselgel 60 (230-400 mesh).

Petrol (b.p. 40-60^{o}C) was redistilled before use. Benzene and diethyl ether were dried over sodium wire. Dimethylformamide (DMF) was dried over 4$\mathring{A}$ molecular sieves. Tetrahydrofuran (THF) was dried by reflux over sodium/benzophenone and distilled before use. Dichloromethane was dried by reflux over phosphorus pentoxide and distilled before use. Solutions were dried over anhydrous magnesium sulphate and evaporated with a rotary evaporator, followed by static evaporation with an oil pump.

SECTION A

Preparation of Benzyl 5-hydroxy-6-methyl-3-oxohept-6-eneoate (135)



(134) (135)

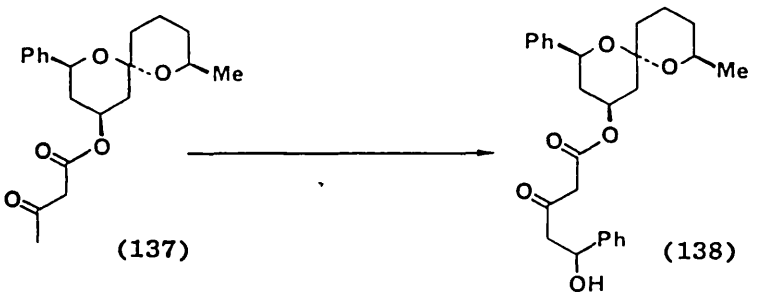
To a stirred suspension of sodium hydride (400 mg, 8.29 mmol, 50% dispersion in oil), prewashed with sodium-dried 40-60° petrol (2 x 3 ml), in THF (5 ml) at 0°C under argon, was added benzyl acetoacetate (134) (1.06g, 5.514 mmol). The solution was stirred at 0°C for 10 min, cooled to -20°C, and ^{n}BuLi (4.8 ml of a 1.26M solution in hexane, 6.069 mmol) added dropwise. The resulting deep orange solution of the dianion was stirred at -20°C for 20 min, cooled to -78°C, and methacrolein (425 mg, 6.069 mmol, freshly distilled to remove inhibitor) added dropwise. The mixture was warmed to 0°C over 30 min, poured into saturated NH_4Cl solution (8 ml) and extracted with Et_2O (3 x 15 ml), each extract being washed with water (10 ml) and brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (25% Et_2O - 40-60° petrol) to give *benzyl 5-hydroxy-6-methyl-3-oxohept-6-eneoate* (135) (643 mg, 45%) as a colourless oil, ν_{max} (film) 3429, 2927, 1741, 1711, and 1648 cm^{-1}; δ(250 MHz) 1.71 (3H, s, C-6 *Me*), 2.61 (1H, d, J 3.6 Hz, *OH*), 2.76 (2H, d, J 7.2 Hz, *H-4*), 3.57 (2H, s, *H-2*), 4.52 (1H, m, *H-5*), 4.87 (1H, s, *H-7*), 5.00 (1H, s, *H-7*), 5.19 (2H, s, $PhCH_2$), and 7.38 (5H, s, *Ph*); *m/z* = 262 (M^+) (Found: C, 68.51; H, 7.09%; M^+ 262.1191. $C_{15}H_{18}O_4$ requires C, 68.67; H, 6.93%; M^+ 262.1205).

Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl acetoacetate (137)

(136) (137)

To a solution of (2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]-undecan-4(S)-ol (136) (98.4 mg, 0.375 mmol) in THF (5 ml) was added Et_3N (20 mg, 0.198 mmol) and the mixture heated at reflux for 10 min. Diketene (41.0 mg, 0.488 mmol) was then added and the mixture heated at reflux for a further 2h before pouring into 1M HCl solution (2 ml). The product was extracted into Et_2O (3 x 10 ml) and the combined organic extracts dried, evaporated under reduced pressure, and chromatographed (20% Et_2O - 40-60° petrol) to give *(2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl acetoacetate* (137) (116 mg, 89%) as a colourless oil, ν_{max} (film) 2935, 1742, and 1717 cm^{-1}; δ(250 MHz) (16% enol form) 1.05 - 2.00 (8H, m), 1.13 (3H, d, J 7.2 Hz, C-8 *Me*), 2.12 (1H, dd, J 3.6, 12.6 Hz, *H-11*), 2.25 (3H, s, *H-4'*), 2.36 (1H, m, *H-5*), 3.41 (1.68H, s, *H-2'*), 3.71 (1H, m, *H-8*), 4.71 (1H, dd, J 2.2, 11.5 Hz, *H-2*), 4.94 (0.16H, s, *H-2' enol*), 5.47 (1H, m, *H-4*), and 7.36 (5H, m, *Ph*); *m/z* = 244 (M^+ - 102) (Found: C, 69.56; H, 7.76%. $C_{20}H_{26}O_5$ requires C, 69.33; H, 7.58%).

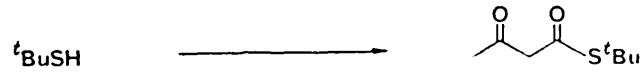
Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 5'-hydroxy-3'-oxo-5'-phenylpentanoate (138)



To a stirred suspension of sodium hydride (12 mg, 0.25 mmol, 50% dispersion in oil), prewashed with sodium-dried 40-60° petrol (1 x 1 ml), in THF (2 ml) at 0°C under argon, was added the β-ketoester (137) (58.5 mg, 0.169 mmol). The solution was stirred at 0°C for 10 min, cooled to -20°C, and ^{n}BuLi (139 μl of a 1.34M solution in hexane, 0.186 mmol) added dropwise. The resulting deep yellow solution of the dianion was stirred at -20°C for 30 min, cooled to -78°C, and benzaldehyde (26.9 mg, 0.254 mmol) added dropwise. The mixture was allowed to warm to 0°C over 30 min, poured into saturated NH_4Cl solution (3 ml), and extracted with Et_2O (3 x 10 ml), each extract being washed with water (5 ml) and brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residual oil chromatographed (30% Et_2O - 40-60° petrol) to give the β-ketoester (138) (26.8 mg, 35%) as a colourless oil, ν_{max} (film) 3428, 2934, 1736, and 1710 cm^{-1}; δ(250 MHz) (10% enol form) 1.13 (3H, d, J 6.8 Hz, C-8 *Me*), 1.15 - 2.00 (8H, m), 2.09 (1H, ddd, J 1.6, 5.0, 12.6 Hz, *H-11*), 2.34 (1H, m, *H-5*), 2.87 (1H, dd, J 3.6, 17.3 Hz, *H-4'*), 2.97 (1H, dd, J 8.5, 17.3 Hz, *H-4'*), 2.98 (1H, s, *OH*), 3.45 (1.8H, s, *H-2'*), 3.70

(1H, m, *H-8*), 4.69 (1H, dd, J 2.5, 11.8 Hz, *H-2*), 5.0 (0.1H, s, *H-2' enol*), 5.17 (1H, m, *H-5'*), 5.43 (1H, m, *H-4*), and 7.32 (10H, m, *Ph*); *m/z* = 452 (M^+).

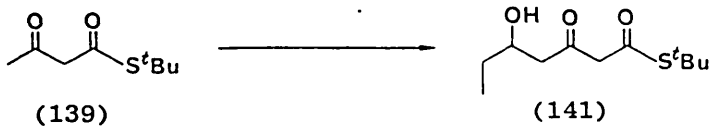
Preparation of ^{t}butyl acetothioacetate



(139)

To a stirred suspension of sodium hydride (2.75g, 68.66 mmol, 60% dispersion in oil), prewashed with sodium-dried 40-60^o petrol (2 x 5 ml), in THF (50 ml) at -10^{o}C under argon, was added 2-methyl-2-propanethiol (5.16g, 57.21 mmol). The solution was warmed to 10^{o}C over 20 min, cooled to -10^{o}C, and diketene (5.77g, 68.66 mmol) added dropwise. The mixture was allowed to warm to rt over 1h before quenching with saturated NH_4Cl solution (25 ml). The product was extracted into Et_2O (3 x 50 ml), each extract being washed with water (10 ml) and brine (10 ml). The combined organic extracts were dried, evaporated under reduced pressure, and chromatographed (5% Et_2O - 40-60^o petrol) to give the thioester (139) (6.88g, 69%) as a pale red oil, ν_{max} (film) 2965, 1721, 1676, 1621, and 1475 cm^{-1}, δ(60 MHz) 1.54 (9H, s, ^{t}*Bu*), 2.30 (3H, s, *H-4*), and 3.57 (2H, s, *H-2*); *m/z* = 174 (M^+).

Preparation of ^{t}Butyl 5-hydroxy-3-oxoheptanthioate (141)



(139) (141)

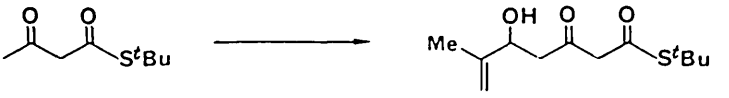
To a stirred suspension of sodium hydride (37.1 mg, 0.773 mmol, 50% dispersion in oil), prewashed with sodium-dried 40-60^{o} petrol (2 x 2 ml), in THF (2 ml) at 0^{o}C under argon, was added ^{t}butyl acetothioacetate (139) (96.6 mg, 0.555 mmol). The solution was stirred at 0^{o}C for 10 min, cooled to -20^{o}C, and ^{n}BuLi (444 µl of a 1.50M solution in hexane 0.666 mmol) added dropwise. The resulting deep yellow solution of the dianion was stirred at -20^{o}C for 10 min, cooled to -78^{o}C, and propionaldehyde (39.0 mg, 0.671 mmol) added dropwise. The mixture was allowed to warm to 0^{o}C over 30 min, poured into saturated NH_4Cl solution (5 ml), and extracted with Et_2O (3 x 10 ml), each organic extract being washed with water (5 ml) and brine (5 ml). The combined extracts were dried, the solvent evaporated under reduced pressure, and the residual oil chromatographed (20 → 30% Et_2O - 40-60^{o} petrol) to give *^{t}butyl 5-hydroxy-3-oxoheptanthioate* (141) (108.5 mg, 84%) as a colourless oil, ν_{max} (film) 3570, 2920, 1710, 1670, and 1620 cm^{-1}; δ(250 MHz) (18% enol form) 0.95 (3H, t, J 7.6 Hz, CH_2CH_3), 1.48 (7.38H, s, *^{t}Bu*), 1.49 (2H, m, CH_2CH_3), 1.51 (1.62H, s, *^{t}Bu enol*), 2.63 (1H, dd, J 8.6, 17.9 Hz, *H-4*), 2.75 (1H, dd, J 2.8, 17.9 Hz, *H-4*), 2.81 (1H, br s, O*H*), 3.61 (2H, s, *H-2*), and 3.99 (1H, m, *H-5*); *m/z* = 232 (M^+) (Found: C, 56.74; H, 8.70%. $C_{11}H_{20}O_3S$ requires C, 56.85; H, 8.69%).

Preparation of ^{t}Butyl 5-hydroxy-3-oxohept-6-enethioate (142)

(139) (142)

To a stirred suspension of sodium hydride (228 mg, 4.74 mmol, 50% dispersion in oil), prewashed with sodium-dried 40-60^{o} petrol (2 x 2 ml), in THF (2 ml) at 0^{o}C under argon, was added ^{t}butyl acetothioacetate (139) (531 mg, 3.05 mmol). The solution was stirred at 0^{o}C for 10 min, cooled to -20^{o}C, and ^{n}BuLi (2.44 ml of a 1.50M solution, 3.66 mmol) added dropwise. The resulting deep yellow solution of the dianion was stirred at -20^{o}C for 10 min, cooled to -78^{o}C, and acrolein (224 mg, 4.00 mmol, freshly distilled to remove inhibitor) added dropwise. The mixture was allowed to warm to 0^{o}C over 30 min, poured into saturated NH_4Cl solution (5 ml) and extracted with Et_2O (3 x 10 ml), each extract being washed with water (5 ml) and brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and chromatographed (25% Et_2O - 40-60^{o} petrol) to give *^{t}butyl 5-hydroxy-3-oxohept-6-enethioate* (142) (584 mg, 83%) as a colourless oil, ν_{max} (film) 3560, 2850, 1708, 1670, and 1620 cm^{-1}; δ(250 MHz) (19% enol form) 1.48 (7.29H, s, *^{t}Bu*), 1.51 (1.71H, s, *^{t}Bu enol*), 2.78 (3H, m, *H-4* and *OH*), 3.61 (1.62, s, *H-2*), 4.60 (1H, m, *H-5*), 5.15 (1H, ddd, J 2.9, 2.9, 10.6 Hz, *H-7 anti*), 5.31 (1H, ddd, J 2.9, 2.9, 17.1 Hz, *H-7 syn*), 5.40 (0.19H, s, *H-2 enol*), and 5.86 (1H, ddd, J 5.5, 10.6, 17.1 Hz, *H-6*); *m/z* = 230 (M^{+}) (Found: C, 57.16; H, 7.71%. $C_{11}H_{18}O_3S$ requires C, 57.35; H, 7.89%).

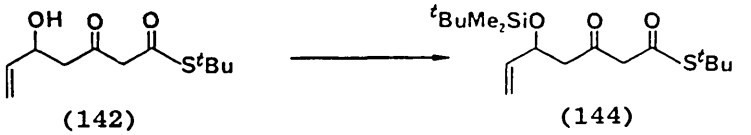
Preparation of ^{t}Butyl 5-hydroxy-6-methyl-3-oxohept-6-enethioate (143)



(139) (143)

To a stirred suspension of sodium hydride (818 mg, 17.25 mmol, 50% dispersion in oil), prewashed with sodium-dried 40-60^{o} petrol (2 x 3 ml), in THF (5 ml) at 0^{o}C under argon, was added ^{t}butyl acetothioacetate (139) (2.0g, 11.48 mmol). The solution was stirred at 0^{o}C for 10 min, cooled to -20^{o}C, and ^{n}BuLi (9.50 ml of a 1.45M solution in hexane, 13.78 mmol) added dropwise. The resulting deep yellow solution of the dianion was stirred at -20^{o}C for 10 min, cooled to -78^{o}C, and methacrolein (886 mg, 12.64 mmol, freshly distilled to remove the inhibitor) added dropwise. The mixture was allowed to warm to 0^{o}C over 30 min, poured into saturated NH_4Cl solution (10 ml) and extracted with Et_2O (3 x 20 ml), each extract being washed with water (10 ml) and brine (10 ml). The combined organic extracts were dried, the solvent removed under reduced pressure, and the residual oil chromatographed (20% Et_2O - 40-60^{o} petrol) to give *^{t}butyl 5-hydroxy-6-methyl-3-oxohept-6-enethioate* (143) (2.50g, 88%) as a colourless oil, ν_{max} (film) 3500, 2940, 1725, 1675, 1625, and 1370 cm^{-1}; δ(250 MHz) (19% enol form) 1.47 (7.29H, s, *^{t}Bu*), 1.51 (1.71H, s, *^{t}Bu enol*), 1.74 (3H, s, C-6 *Me*), 2.73 (1H, br s, *OH*), 2.78 (2H, d, J 5.5 Hz, *H-4*), 3.63 (1.62H, s, *H-2*), 4.52 (1H, m, *H-5*), 4.88 (1H, br s, *H-7*), 5.02 (1H, br s, *H-7*), and 5.41 (0.19H, s, *H-2 enol*); *m/z* = 244 (M^{+}) (Found: C, 59.12; H, 8.55%. $C_{12}H_{20}O_3S$ requires C, 58.97; H, 8.27%).

Preparation of ^{t}Butyl 5-(^{t}butyldimethylsilyloxy)-3-oxohept-6-enethioate (144)



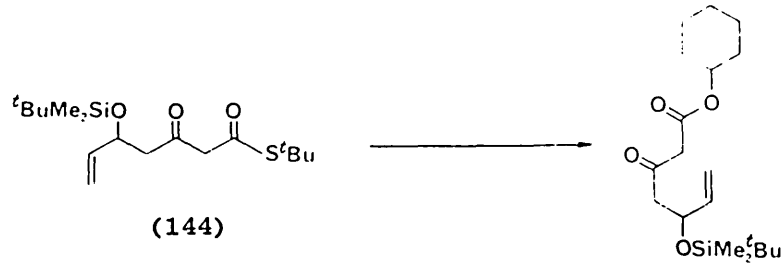
(142) (144)

A solution of allylic alcohol (142) (765 mg, 3.33 mmol), ^{t}butyldimethylsilyl chloride (602 mg, 3.99 mmol), and imidazole (566 mg, 8.31 mmol) in dry DMF (2.5 ml) was stirred overnight at rt. The mixture was poured into Et_2O (50 ml) and washed with water (3 x 10 ml), followed by brine (10 ml). After drying and evaporation of solvent under reduced pressure, the residue was chromatographed (3% Et_2O - 40-60^{o} petrol) to give *^{t}butyl 5-(^{t}butyldimethylsilyloxy)-3-oxohept-6-enethioate* (144) (1.06g, 93%) as a colourless oil, ν_{max} (film) 2855, 1720, 1670, 1618, and 1360 cm^{-1}; δ(250 MHz) (30% enol form) 0.05 (6H, s, Si*Me*$_2$), 0.87 (9H, s, Si^{t}*Bu*), 1.47 (6.3H, s, S^{t}*Bu*), 1.51 (2.7H, s, S^{t}*Bu enol*), 2.62 (1H, dd, J 5.0, 15.1 Hz, *H-4*), 2.80 (1H, dd, J 7.6, 15.1 Hz, *H-4*), 3.58 (1.4H, s, *H-2*), 4.47 (0.3H, m, *H-5 enol*), 4.61 (0.7H, m, *H-5*), 5.07 (1H, ddd, J 2.5, 2.5, 10.3 Hz, *H-7 anti*), 5.22 (1H, ddd, J 2.5, 2.5, 17.0 Hz, H-7 *syn*), 5.37 (0.3H, s, *H-2 enol*), and 5.82 (1H, ddd, J 6.7, 10.3, 17.0 Hz, *H-6*); *m/z* = 287 (M^{+}-^{t}Bu) (Found: C, 59.47; H, 9.40%. $C_{17}H_{32}O_3SiS$ requires C, 59.24; H, 9.38%).

Preparation of Silver Trifluoroacetate

A solution of sodium hydroxide (0.843g, 21.1 mmol) in water (5 ml) was added to a solution of silver nitrate (3.58g, 21.1 mmol) in water (3 ml) and the mixture stirred vigorously for 5 min. The resulting grey/green precipitate was filtered, the receiver changed, and a solution of trifluoroacetic acid (2.30g, 20.2 mmol) in water (100 ml) passed over the filtrate to dissolve it. The colourless solution was evaporated to dryness leaving a white precipitate. This precipitate was dissolved in ether (100 ml), passed through a short pad of charcoal, and the resulting solution evaporated under reduced pressure to give a white crystalline solid (3.44g, 74%).[70]

Preparation of Cyclohexyl 5-(^{t}butyldimethylsilyloxy)-3-oxohept-6-enoate (145)



(144) (145)

To a solution of the thioester (144) (201.7 mg, 0.585 mmol) and cyclohexanol (70.5 mg, 0.704 mmol) in THF (3 ml) was added silver trifluoroacetate (155 mg, 0.705 mmol). The mixture was stirred at rt for

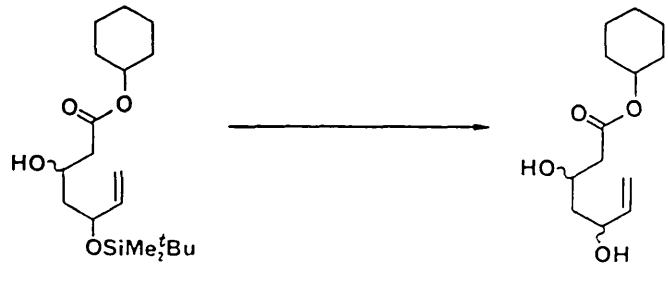
18h. The solution was diluted with Et_2O (50 ml), filtered through a short pad of silica, and washed with saturated $NaHCO_3$ solution (2 x 20 ml) followed by brine (10 ml). After drying and evaporation of the solvent under reduced pressure, the residue was chromatographed (5% Et_2O - 40-60° petrol) to give *cyclohexyl 5-(tbutyldimethylsilyloxy)-3-oxohept-6-enoate* (145) (137.9 mg, 67%) as a colourless oil, ν_{max} (film) 2915, 2850, 1735, 1712, and 1635 cm^{-1}; δ(250 MHz) (22% enol form) 0.04 (4.68H, s, Si*Me*$_2$), 0.05 (1.32H, s, Si*Me*$_2$), 0.87 (7.02H, s, Si^t*Bu*), 0.88 (1.98H, s, Si^t*Bu*), 1.10 - 1.60 (6H, m), 1.70 (2H, m, *H-2'* and *H-6'*), 1.85 (2H, m, *H-2'* and *H-6'*), 2.31 (0.44H, m, *H-4 enol*), 2.60 (0.78H, dd, J 4.4, 15.0 Hz, *H-4*), 2.80 (0.78H, dd, J 6.1, 15.0 Hz, *H-4*), 3.45 (1.56H, s, *H-2*), 4.47 (0.22H, m, *H-5 enol*), 4.61 (0.78H, m, *H-5*), 4.81 (1H, m, *H-1'*), 4.99 (0.22H, s, *H-2 enol*), 5.07 (1H, ddd, J 2.9, 2.9, 10.5 Hz, *H-7 anti*), 5.22 (1H, ddd, J 2.9, 2.9, 16.8 Hz, *H-7 syn*), and 5.82 (1H, ddd, J 5.9, 10.5, 16.8 Hz, *H-6*); *m/z* = 354 (M^+) (Found: C, 64.41; H, 9.69%. $C_{19}H_{34}O_4Si$ requires C, 64.35; H, 9.68%).

Preparation of Cyclohexyl 5-(tbutyldimethylsilyloxy)-3-hydroxyhept-6-enoate (146)

(145) (146)

To a solution of the β-ketoester (145) (99.2 mg, 0.28 mmol) in MeOH (2 ml) was added sodium borohydride (27.0 mg, 0.714 mmol). After stirring at 20°C for 20 min reaction was complete as indicated by TLC and the mixture was poured into saturated NH_4Cl solution (10 ml). The product was extracted into Et_2O (4 x 20 ml), and the combined organic extracts dried, evaporated under reduced pressure, and finally passed through a short pad of silica to give *cyclohexyl 5-(*^{t}*butyldimethylsilyloxy)-3-hydroxyhept-6-enoate* (146) (95.7 mg, 96%) as a colourless oil, ν_{max} (film) 3480, 2935, 2860, 1725, and 1450 cm^{-1}; δ(250 MHz) (2:1 mixture of diastereoisomers) 0.05 (4H, s, Si*Me*$_2$), 0.06 (2H, s, Si*Me*$_2$), 0.88 (6H, s, Si^t*Bu*), 0.89 (3H, s, Si^t*Bu*), 1.15 - 1.90 (12H, m), 2.45 (1H, dd, J 3.0, 7.4 Hz, *H-2*), 2.47 (1H, dd, J 1.0, 7.4 Hz, *H-2*), 4.15 (1H, m, *H-3*), 4.37 (1H, br s, O*H*), 4.48 (1H, m, *H-5*), 4.79 (1H, m, *H-1'*), 5.07 (0.66H, ddd, J 1.4, 2.1, 10.1 Hz, *H-7 anti*), 5.09 (0.33H, ddd, J 1.6, 1.6, 10.1 Hz, *H-7 anti*), 5.17 (0.33H, ddd, J 1.5, 1.5, 17.2 Hz, *H-7 syn*), 5.24 (0.66H, ddd, J 1.5, 1.5, 17.2 Hz, *H-7 syn*), and 5.74 - 5.92 (1H, m, *H-6*); *m/z* = 356 (M^+).

Preparation of Cyclohexyl 3,5-dihydroxyhept-6-enoate (147)



(146) (147)

To a solution of the ^{t}butyldimethylsilyloxy derivative (146) (42.0 mg, 0.118 mmol) in THF (2 ml) at 0^{o}C was added tetra ^{n}butylammonium fluoride (130 µl of a 1.0M solution in THF, 0.130 mmol). After 1h starting material was consumed (TLC), and the mixture was poured into 1M HCl solution (2 ml). The product was extracted into ether (3 x 15 ml), each extract being washed with brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and chromatographed (50% Et_2O - 40-60^{o} petrol) to give *cyclohexyl 3,5-dihydroxyhept-6-enoate* (147) (27.4 mg, 96%) as a colourless oil, ν_{max} (film) 3420, 2950, 2870, 1725, and 1470 cm^{-1}; δ(250 MHz) (2:1 mixture of diastereoisomers) 1.15 - 1.97 (12H, m), 2.50 (2H, m, *H-2*), 2.75 (1H, br s, O*H*), 3.51 (1H, br s, O*H*), 4.22 - 4.52 (2H, m, H_3 and H_5), 4.81 (1H, m, *H-1'*), 5.12 (0.33H, ddd, J 1.5, 1.5, 9.6 Hz, *H-7 anti*), 5.16 (0.66H, ddd, J 1.5, 1.5, 9.6 Hz, *H-7 anti*), 5.28 (0.33H, ddd, J 1.5, 1.5, 16.3 Hz, *H-7 syn*), 5.32 (0.66H, ddd, J 1.5, 1.5, 16.3 Hz, *H-7 syn*), and 5.80 - 6.00 (1H, m, *H-6*); *m/z* = 242 (M^{+}).

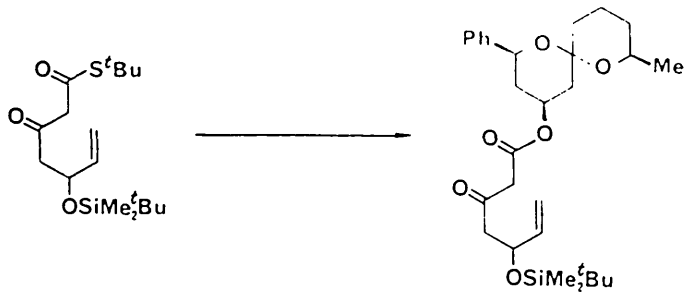
Preparation of ^{t}Butyl 5-(^{t}butyldimethylsilyloxy)-6-methyl-3-oxohept-6-enethioate (148)

(143) (148)

A solution of β-ketoester (143) (1.01g, 4.14 mmol), ^{t}butyldimethylsilyl chloride (781 mg, 5.18 mmol), and imidazole (721 mg, 10.59 mmol)

in dry DMF (3 ml) was stirred overnight at rt. The mixture was poured into Et_2O (50 ml) and washed with water (3 x 10 ml), followed by brine (10 ml). After drying, and evaporation of solvent under reduced pressure, the residue was chromatographed (3% Et_2O - 40-60° petrol) to give *^{t}butyl 5-(^{t}butyldimethylsilyloxy)-6-methyl-3-oxohept-6-enethioate* (148) (1.425g, 96%) as a colourless oil, ν_{max} (film) 2930, 1730, 1680, 1625, and 1370 cm^{-1}; δ(250 MHz) (52% enol form) 0.04 (6H, s, Si*Me*$_2$), 0.86 (9H, s, Si^t*Bu*), 1.47 (4.3H, s, S^t*Bu*), 1.51 (4.7H, s, S^t*Bu enol*), 1.70 (3H, br s, C-6 *Me*), 2.19 (0.52H, ddd, J 1.4, 9.8, 14.7 Hz, *H-4 enol*), 2.29 (0.52H, dd, J 4.6, 14.7 Hz, *H-4 enol*), 2.56 (0.48H, dd, J 4.2, 16.8 Hz, *H-4*), 2.84 (0.48H, dd, J 9.2, 16.8 Hz, *H-4*), 3.58 (0.96H, d, J 2.8 Hz, *H-2*), 4.40 (0.52H, dd, J 4.6, 9.8 Hz, *H-5 enol*), 4.56 (0.48H, dd, J 4.6, 9.8 Hz, *H-5*), 4.79 (1H, br s, *H-7*), 4.95 (1H, br s, *H-7*), and 5.34 (0.52H, s, *H-2 enol*); *m/z* = 301 (M^+-^{t}Bu) (Found: C, 60.20; H, 9.60%. $C_{18}H_{34}O_3SiS$ requires C, 60.27; H, 9.57%).

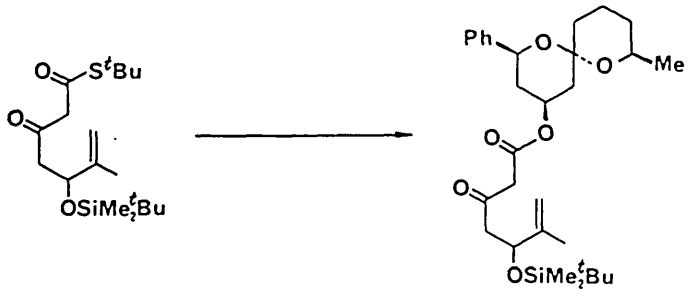
Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 5'-(^{t}butyldimethylsilyloxy)-3'-oxohept-6'-enoate (149)



(144) (149)

To a solution of the thioester (144) (255.8 mg, 0.742 mmol) and (2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-ol (230.0 mg, 0.878 mmol) in THF (5 ml) was added silver trifluoroacetate (463 mg, 1.765 mmol). The mixture was stirred at rt for 18h. The solution was diluted with Et_2O (50 ml), filtered through a short pad of silica, and washed with saturated $NaHCO_3$ solution (2 x 20 ml) followed by brine (10 ml). After drying and evaporation of solvent under reduced pressure, the residue was chromatographed (10% Et_2O - 40-60° petrol) to give *(2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 5'-(^{t}butyldimethylsilyloxy)-3'-oxohept-6'-enoate* (149) as a colourless oil, ν_{max} (film) 2940, 2870, 1740, 1715, 1653, and 1375 cm^{-1}; δ(250 MHz) (28% enol form) 0.04 (4.32H, s, Si*Me*$_2$), 0.05 (1.68H, s, Si*Me*$_2$), 0.86 (6.48H, s, Si^t*Bu*), 0.87 (2.52H, s, Si^t*Bu*), 1.14 (3H, d, J 7.2 Hz, C-8 *Me*), 1.10 - 2.35 (10H, m), 2.51 (1H, dd, J 2.4, 7.6 Hz, *H-4'*), 2.76 (1H, dd, J 3.7, 7.6 Hz, *H-4'*), 3.45 (1.44H, s, *H-2'*), 3.71 (1H, m, *H-8*), 4.47 (0.28H, m, *H-5'*), 4.60 (0.72H, m, *H-5'*), 4.70 (0.72H, dd, J 1.1, 5.8 Hz, *H-2*), 4.72 (0.28H, dd, J 1.1, 5.8 Hz, *H-2*), 4.97 (0.28H, s, *H-2' enol*), 5.07 (1H, ddd, J 1.5, 1.5, 5.3 Hz, *H-7' anti*), 5.22 (1H, ddd, J 1.5, 1.5, 8.4 Hz, *H-7' syn*), 5.46 (1H, m, *H-4*), 5.81 (1H, m, *H-6'*), 7.36 (5H, m, *Ph*), and 10.7 (0.28H, s, O*H enol*); *m/z* = 459 (M^+-^{t}Bu) (Found: C, 67.37; H, 8.71%. $C_{29}H_{44}O_6Si$ requires C, 67.39; H, 8.60%).

Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 5'-(^{t}butyldimethylsilyloxy)-6'-methyl-3'-oxohept-6'-enoate (150)

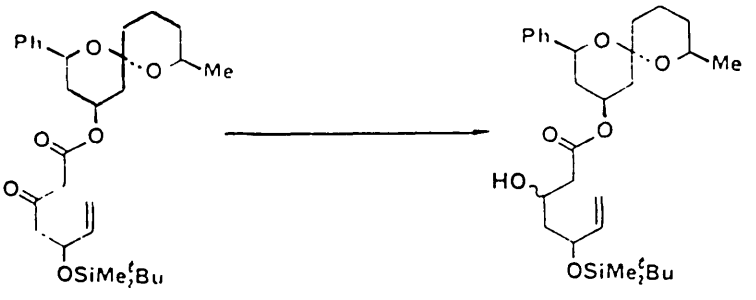


(148) (150)

To a solution of the thioester (148) (470.3 mg, 1.311 mmol) and (2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-ol (354.1 mg, 1.352 mmol) in THF (5 ml) was added silver trifluoroacetate (575.8 mg, 2.617 mmol). The mixture was stirred at rt for 18h before diluting with Et_2O (50 ml) and filtering through a short pad of silica. The ethereal layer was washed with saturated $NaHCO_3$ solution (2 x 20 ml), water (10 ml) and brine (10 ml). After drying and removal of the solvent under reduced pressure the residue was chromatographed (10% Et_2O - 40-60^0 petrol) to give *(2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro-[5,5]undecan-4(S)-yl 5'-(^{t}butyldimethylsilyloxy)-6'-methyl-3'-oxohept-6'-enoate* (150) (529 mg, 76%) as a colourless oil, ν_{max} (film) 2940, 2860, 1745, 1720, 1650, and 1385 cm^{-1}; δ(250 MHz) (20% enol form) 0.02 (4.8H, s, Si*Me*$_2$), 0.04 (1.2H, s, Si*Me*$_2$), 0.84 (1.8H, s, Si^t*Bu*), 0.86 (7.2H, s, Si^t*Bu*), 1.14 (3H, d, J 7.1 Hz, C-8 *Me*), 1.06 - 1.64 (8H, m), 1.69 (3H, s, C-6' *Me*), 2.12 (1H, m, *H-11*), 2.35 (1H, m, *H-5*), 2.50 (1H, dd, J 3.5, 14.3 Hz, *H-4'*), 2.80 (1H, dd, J 8.4, 14.3 Hz, *H-4'*),

3.46 (1.6H, s, *H-2'*), 3.71 (1H, m, *H-8*), 4.41 (0.2H, m, *H-5' enol*), 4.54 (0.8H, dd, J 3.5, 8.4 Hz, *H-5'*), 4.70 (1H, dd, J 2.1, 11.8 Hz, *H-2*), 4.80 (1H, br s, *H-7' anti*), 4.94 (0.2H, s, *H-2' enol*), 4.96 (1H, br s, *H-7' syn*), 5.46 (1H, m, *H-4*), 7.36 (5H, m, *Ph*), and below 11 (0.2H, s, *OH enol*); *m/z* = 473 (M^+-^{t}Bu) (Found: C, 67.97; H, 8.74%. $C_{30}H_{46}O_6Si$ requires C, 67.87; H, 8.75%).

Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 5'(^{t}butyldimethylsilyloxy)-3'-hydroxyhept-6'-enoate (151)

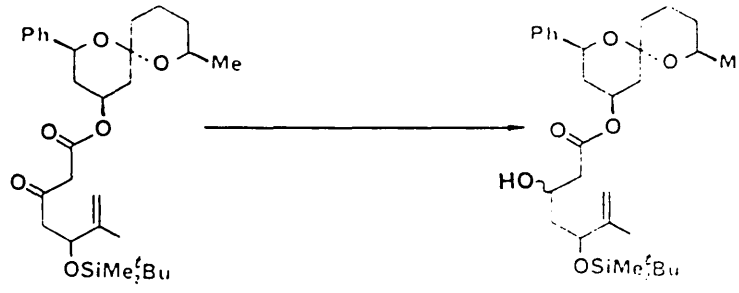


(149) (151)

To a solution of the β-ketoester (149) (200 mg, 0.387 mmol) in MeOH (3 ml) was added sodium borohydride (38 mg, 1.004 mmol). After stiring at rt for 25 min the solution was diluted with Et_2O (50 ml) and washed with water (3 x 10 ml) and brine (10 ml). The organic phase was dried, the solvent evaporated under reduced pressure, and the resulting oil filtered through a short column of silica to give *(2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 5'-(^{t}butyldimethylsilyloxy)-3'-hydroxyhept-6'-enoate* (151) (200 mg, 100%) as a colourless oil, ν_{max} (film) 3520, 2950, 2870, 1740, and 1385 cm^{-1}; δ(250 MHz) (2:1 mixture of diastereoisomers) 0.05 (4H, s, Si*Me*$_2$), 0.07 (2H, s, Si*Me*$_2$),

0.89 (6H, s, Si^{t}*Bu*), 0.90 (3H, s, Si^{t}*Bu*), 1.13 (3H, d, J 7.1 Hz, C-8 *Me*), 1.14 - 2.00 (10H, m), 2.10 (1H, m, *H-11*), 2.35 (1H, m, *H-5*), 2.44 (2H, m, *H-2'*), 3.72 (1H, m, *H-8*), 4.15 (0.66H, m, *H-3'*), 4.28 (0.33H, m, *H-3'*), 4.36 (0.66H, m, *H-5'*), 4.48 (0.33H, m, *H-5'*), 4.70 (1H, dd, J 1.9, 11.6 Hz, *H-2*), 5.07 (0.66H, ddd, J 2.0, 2.0, 10.1 Hz, *H-7' anti*), 5.10 (0.33H, J 2.0, 2.0, 10.1 Hz, *H-7' anti*), 5.17 (0.66H, ddd, J 2.0, 2.0, 17.1 Hz, *H-7' syn*), 5.23 (0.33H, ddd, J 2.0, 2.0, 17.1 Hz, *H-7' syn*), 5.43 (1H, m, *H-4*), 5.72 - 5.93 (1H, m, *H-6'*), and 7.38 (5H, m, *Ph*); *m/z* = 461 (M^{+}-^{t}Bu) (Found: C, 67.21; H, 8.98%. $C_{29}H_{46}O_6Si$ requires C, 67.13; H, 8.96%).

Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 5'-(^{t}butyldimethylsilyloxy)-3'-hydroxy-6'-methylhept-6'-enoate (152)

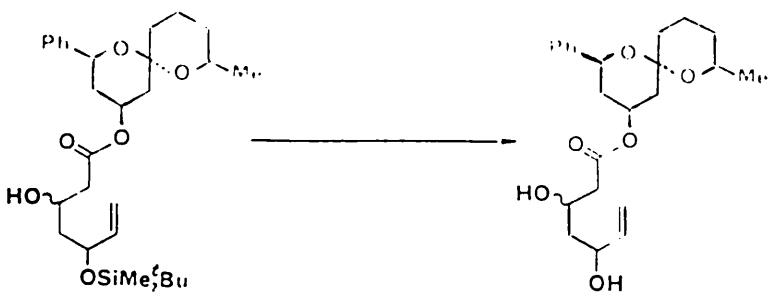


(150) (152)

To a solution of the β-ketoester (150) (203.8 mg, 0.384 mmol) in MeOH (3 ml) was added sodium borohydride (36.0 mg, 0.951 mmol). After stirring at rt for 30 min, the solution was poured into water (5 ml) and extracted into Et_2O (4 x 10 ml). The combined organic extract was dried, evaporated under reduced pressure, and filtered through a short

column of silica to give *(2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]-undecan-4(S)-yl 5'-(^{t}butyldimethylsilyloxy)-3'-hydroxy-6'-methylhept-6'-enoate* (152) (199 mg, 97%) as a colourless oil, ν_{max} (film) 3520, 2940, 2870, 1732, and 1375 cm^{-1}; δ(250 MHz) (2:1 mixture of diastereoisomers) 0.04 (4H, s, Si*Me*$_2$), 0.09 (2H, s, Si*Me*$_2$), 0.89 (6H, s, Si^t*Bu*), 0.90 (3H, s, Si^t*Bu*), 1.14 (3H, d, J 7.1 Hz, C-8 *Me*), 1.16 - 1.98 (10H, m), 1.68 (3H, s, C-6' *Me*), 2.09 (1H, m, *H-11*), 2.35 (1H, m, *H-5*), 2.44 (2H, m, *H-2'*), 3.71 (1H, m, *H-8*), 4.12 (0.66H, m, *H-3'*), 4.20 (0.33H, m, *H-3'*), 4.33 (1H, m, *H-5'*), 4.70 (1H, dd, J 2.0, 11.8 Hz, *H-2*), 4.81 (0.66H, br s, *H-7' anti*), 4.84 (0.33H, br s, *H-7' anti*), 4.93 (0.66H, br s, *H-7' syn*), 5.00 (0.33H, br s, *H-7' syn*), 5.43 (1H, m, *H-4*), and 7.38 (5H, m, *Ph*); *m/z* = 475 (*M*$^+$-^{t}Bu) (Found: C, 67.81; H, 9.19%. $C_{30}H_{48}O_6Si$ requires C, 67.62; H, 9.10%).

Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 3',5'-dihydroxyhept-6'-enoate (153)



(151) (153)

To a solution of the ^{t}butyldimethylsilyloxy derivative (151) (137.6 mg, 0.265 mmol) in THF (2 ml) at 0°C was added tetra ^{n}butylammonium

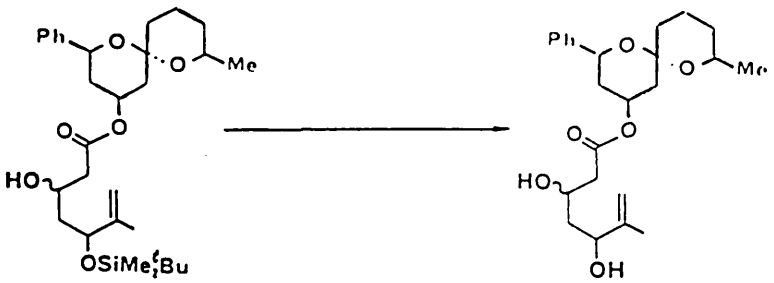
fluoride (292 µl of a 1.0M solution in THF, 0.292 mmol). After 30 min starting material was consumed (TLC) with the production of two polar products. The mixture was poured into 1M HCl solution (5 ml), the product extracted into Et_2O (3 x 20 ml) and the combined organic extracts dried, the solvent evaporated under reduced pressure, and chromatographed (50% Et_2O - 40-60° petrol) to give firstly the spiro-acetal (136) (32.9 mg) and secondly *(2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 3',5'-dihydroxyhept-6'-enoate* (153) (40.4 mg, 38%) as a colourless oil, ν_{max} (film) 3430, 2940, 2870, 1730, and 1385 cm^{-1}; δ(250 MHz) (2:1 mixture of diastereoisomers) 1.13 (3H, d, J 7.1 Hz, C-8 *Me*), 1.14 - 2.00 (10H, m), 2.10 (1H, dd, J 4.6, 11.5 Hz, *H-11*), 2.34 (1H, m, *H-5*), 2.48 (2H, m, *H-2'*), 2.68 (1H, br s, *OH*), 3.15 (1H, br s, *OH*), 3.70 (1H, m, *H-8*), 4.20 - 4.50 (2H, m, *H-3'* and *H-5'*), 4.70 (1H, dd, J 1.9, 11.6 Hz, *H-2*), 5.08 - 5.18 (1H, m, *H-7' anti*), 5.21 - 5.29 (0.33H, m, *H-7' syn*), 5.29 - 5.35 (0.66H, m, *H-7' syn*), 5.45 (1H, m, *H-4*), 5.79 - 6.00 (1H, m, *H-6'*), and 7.35 (5H, m, *Ph*); *m/z* = 404 (M^+) (Found: C, 68.18; H, 8.05%. $C_{23}H_{32}O_6$ requires C, 68.28; H, 7.99%).

Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 3',5'-dihydroxyhept-6'-enoate (153) using CH_3CN/HF

To a solution of the ^{t}butyldimethylsilyloxy derivative (151) (23.2 mg, 4.8 x 10^{-5} mmol) in THF (1 ml) at 0°C was added HF (100 µl of a 0.70M solution of 40% HF in acetonitrile, 7.2 x 10^{-5} mmol). After 15 min, reaction was complete by TLC and the mixture was poured into saturated $NaHCO_3$ solution (2 ml). The product was extracted into CH_2Cl_2 (4 x 10 ml), and the combined organic extracts dried, the solvent evaporated under reduced pressure, and chromatographed (50% Et_2O -

40-60° petrol) to give the diol (153) (17.6 mg, 97%) identical to the previously prepared sample.

Preparation of (2S,8R)-8-Methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 3',5'-dihydroxy-6'-methylhept-6'-enoate (154)



(152) (154)

To a solution of ^{t}butyldimethylsilyloxy derivative (152) (179.0 mg, 0.336 mmol) in THF (2 ml) at 0°C was added HF (500 µl of a 0.70M solution of 40% HF in acetonitrile, 0.35 mmol). After 10 min reaction was complete by TLC and the mixture was poured into saturated $NaHCO_3$ solution (5 ml). The product was extracted into CH_2Cl_2 (4 x 10 ml), and the combined organic extracts dried, the solvent evaporated under reduced pressure, and chromatographed (50% Et_2O - 40-60° petrol) to give *(2S,8R)-8-methyl-2-phenyl-1,7-dioxaspiro[5,5]undecan-4(S)-yl 3',5'-dihydroxy-6'-methylhept-6'-enoate* (154) (140.2 mg, 100%) as a colourless oil, ν_{max} (film) 3420, 2940, 2870, 1732, and 1375 cm^{-1}; δ(250 MHz) (2:1 mixture of diastereoisomers) 1.12 (3H, d, J 7.1 Hz, C-8 *Me*), 1.13 - 2.02 (10H, m), 1.72 (3H, s, C-6' *Me*), 2.10 (1H, dd, J 5.0, 11.9 Hz, *H-11*), 2.34 (1H, m, *H-5*), 2.48 (2H, m, *H-2'*), 3.14 (1H, br s, O*H*), 3.45 (1H, br s, O*H*), 3.73 (1H, m, *H-8*), 4.22 - 4.40

(2H, m, *H-3'* and *H-5'*), 4.64 (0.33H, dd, J 2.0, 11.8 Hz, *H-2*), 4.71 (0.66H, dd, J 2.0, 11.8 Hz, *H-2*), 4.84 (0.66H, br s, *H-7' anti*), 4.88 (0.33H, br s, *H-7' anti*), 5.00 (0.66H, br s, *H-7' syn*), 5.05 (0.33H, br s, *H-7' syn*), 5.45 (1H, m, *H-4*), and 7.38 (5H, m, *Ph*); *m/z* = 418 (M^+) (Found: C, 68.65; H, 8.19%. $C_{24}H_{34}O_6$ requires C, 68.86; H, 8.20%).

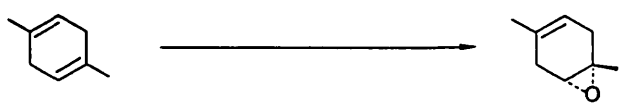
SECTION B

Preparation of 1,4-Dimethyl-1,4-cyclohexadiene (161)

(161)

To a vigorously stirred solution of *p*-xylene (108g, 1.017 mol) in a mixture of anhydrous Et_2O (200 ml), liquid ammonia (800 ml) and absolute ethanol (194 ml) was added sodium (70g) in portions over 5h. On disappearance of the blue colour, the ammonia was allowed to evaporate, the system purged with nitrogen, and an ice-water slurry (300 ml) cautiously added. The organic layer was separated and washed with water (2 x 50 ml) and brine (50 ml) before drying and evaporation of solvent under reduced pressure to give the non-conjugated diene (161) (89.3g, 81%) as a colourless oil, ν_{max} (film) 2980, 2920, 1660, and 1440 cm^{-1}; δ(60 MHz) 1.6 (6H, s), 2.5 (4H, br s), and 5.2 (2H, m); m/z = 108 (M^+).

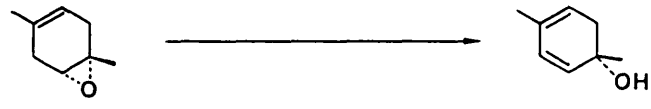
Preparation of 1,4-Dimethyl-4,5-epoxycyclohexene (164)



(161) (164)

To a stirred solution of 1,4-dimethyl-1,4-cyclohexadiene (161) 5.28g, 48.80 mmol) in CH_2Cl_2 (60 ml) at 0^oC was added dropwise a solution of mCPBA (8.99g, 44.28 mmol) in CH_2Cl_2 (100 ml). The mixture was stirred at rt for 18h then poured into 1M NaOH solution (50 ml). The organic layer was separated, washed with water (3 x 40 ml), and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (10% Et_2O - 40-60^o petrol) to give the monoepoxide (164) (5.09g, 84%) as a colourless oil, ν_{max} (film) 2960, 2875, 1680(w), 1445, and 1420 cm^{-1}; δ(60 MHz) 1.35 (3H, s, C-4 *Me*), 1.63 (3H, s, C-1 *Me*), 2.38 (4H, br s), 3.04 (1H, m, *H-5*), and 5.10 (1H, m, *H-2*); *m/z* = 124 (M^+) (Found: M^+ 124.0884. $C_8H_{12}O$ requires 124.0888).

Preparation of 1,4-Dimethyl-2,4-cyclohexadiene-1-ol (167)

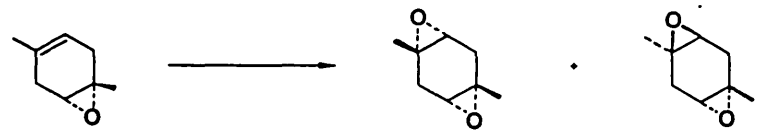


(164) (167)

To a solution of diethylamine (118.1 mg, 1.615 mmol) in Et_2O (5 ml) at -10^oC under argon was added ^nBuLi (1.06 ml of a 1.52N solution in hexane, 1.614 mmol) dropwise. The colourless solution was allowed to warm to rt over 15 min, cooled to -60^oC, and a solution of the epoxide (164) (100 mg, 0.805 mmol) in Et_2O (2 ml) added dropwise. The mixture was stirred at -60^oC for 1h then poured into saturated NH_4Cl solution (10 ml). The aqueous phase was extracted with ether (3 x 20 ml), each extract being washed with water (5 ml) and brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced

pressure, and the residue chromatographed (20% Et_2O - 40-60° petrol) to give the hydrated *p*-xylene (167) (95 mg, 95%) as a colourless oil, ν_{max} (film) 3360, 2970, 2860, 1500, and 1378 cm^{-1}; δ(250 MHz) 1.32 (3H, s, C-1 *Me*), 1.78 (3H, d, J 2.3 Hz, C-4 *Me*), 1.99 (1H, br s, O*H*), 2.36 (1H, dd, J 2.3, 18.9 Hz, *H-6*), 2.46 (1H, ddd, J 1.5, 2.3, 18.9 Hz, *H-6*), 5.55 (1H, m, *H-5*), 5.75 (1H, d, J 9.3 Hz, *H-2*), and 5.84 (1H, dd, J 1.5, 9.3 Hz, *H-3*); *m/z* = 124 (M^+) (Found: M^+ 124.0878. $C_8H_{12}O$ requires 124.0888).

Preparation of *trans*-1,4-Dimethyl-1,2,4,5-diepoxycyclohexane (168) and *cis*-1,4-Dimethyl-1,2,4,5-diepoxycyclohexane (169)



(164) (169) (168)

To a stirred solution of the mono-epoxide (164) (100 mg, 0.805 mmol) in CH_2Cl_2 (5 ml) at 0°C was added a solution of mCPBA (167 mg, 0.823 mmol) in CH_2Cl_2 (20 ml) dropwise. The mixture was stirred for 3h, poured into 1M NaOH solution (10 ml), and the aqueous phase extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (20 → 40% Et_2O - 40-60° petrol) to give firstly the *trans*-diepoxide (168) (33.5 mg, 30%) as white crystals, m.p. 48°C; ν_{max} ($CHCl_3$) 2980, 2930, 1475, and 1425 cm^{-1}; δ(250 MHz) 1.34 (6H, s, C-1,-4 *Me*), 2.18 (2H, d, J 17.0 Hz, *H-3,-6*), 2.35 (2H, dd, J 3.8, 17.0 Hz, *H-3,-6*), and 2.93 (2H, d, J 3.8 Hz, *H-2,-5*); *m/z* = 140 (M^+) (Found:

M^+ 140.0833. $C_8H_{12}O_2$ requires 140.0837), followed by the *cis*-diepoxide (169) (78.0 mg, 69%) as white crystals, m.p. 57°C; ν_{max} ($CHCl_3$) 2980, 2930, 1480, 1455, and 1385 cm^{-1}; δ(250 MHz) 1.30 (6H, s, C-1,-4 *Me*), 2.15 (2H, dd, J 3.4, 17.0 Hz, *H-3,-6*), 2.59 (2H, d, J 17.0 Hz, *H-3,-6*), and 2.92 (2H, d, J 3.4 Hz, *H-2,-5*); *m/z* = 140 (M^+) (Found: M^+ 140.0833. $C_8H_{12}O_2$ requires 140.0837).

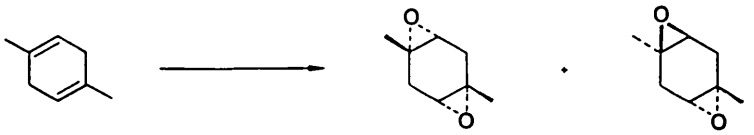
X-Ray Crystallographic Data for (168)

Crystals of (168), $C_8H_{12}O_2$ *Mr* = 140.2, are monoclinic with a = 6.517(2), b = 7.553(2), c = 8.438(2)Å, β = 111.77(2)°, u = 386 Å^3, space group $P2_1/n$, Z = 2, (Cu-K_α) = 7 cm^{-1}, *Dc* = 1.21 gcm^{-3}. 401 independant reflections ($\theta \leq 50°$) were measured with Cu-K_α radiations (graphite monochromator) using the omega-scan measuring routine. Of these 379 had $|F_0|>3\theta(|F_0|)$ and were considered to be observed. The data was corrected for Lorentz and polarisation factors; no absorption correction was applied.

The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The positions of the hydrogen atoms were clearly defined in a ΔF map. The methyl and epoxide hydrogen atoms were refined isotropically; the methylene hydrogen atom positions were idealised and the atoms allowed to ride on their parent carbon atom. Refinement was by block-cascade full-matrix least-squares to R = 0.037.

Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

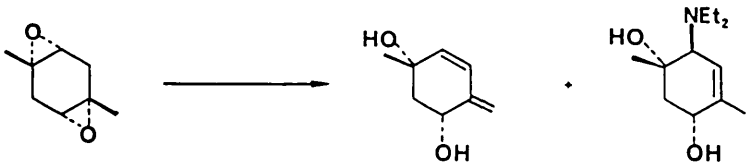
Preparation of *trans*-1,4-Dimethyl-1,2,4,5-diepoxycyclohexane (168) and *cis*-1,4-Dimethyl-1,2,4,5-diepoxycyclohexane (169)



(161) (169) (168)

To a stirred solution of 1,4-dimethyl-1,4-cyclohexadiene (161) (3.0g, 27.73 mmol) in CH_2Cl_2 (100 ml) at 0^oC was added a solution of mCPBA (12.6g, 58.41 mmol) in CH_2Cl_2 (250 ml) dropwise over 3h. The mixture was then stirred at rt for 18h before pouring into 1M NaOH solution (100 ml). The organic phase was separated, washed with water (3 x 50 ml) and then dried. Evaporation of solvent under reduced pressure gave a white crystalline solid which was chromatographed (20 → 40% Et_2O - 40-60^o petrol) to give firstly the *trans*-diepoxide (168) (1.09g, 28%) followed by the *cis*-diepoxide (169) (2.76g, 71%). Each isomer gave spectral data identical to that of the previously prepared material.

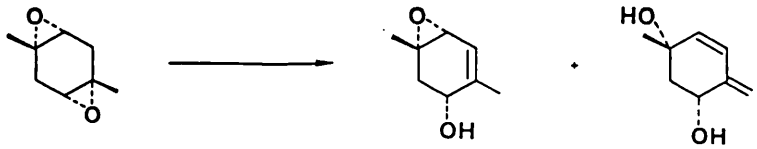
Preparation of 1α,5α-Dihydroxy-1β-methyl-4-methylenecyclohex-2-ene (170) and 2α,4α-Dihydroxy-2β,5-dimethylcyclohex-5-enediethylamine (171)



(169) (170) (171)

To a stirred solution of diethylamine (65.0 mg, 0.889 mmol) in THF (2 ml) at -20°C under argon was added ^{n}BuLi (585 µl of a 1.52N solution in hexane, 0.889 mmol) dropwise. The mixture was warmed to rt over 15 min, then added dropwise *via* a catheter to a solution of the *cis* diepoxide (169) (124.4 mg, 0.887 mmol) in THF (5 ml) under argon. The solution was heated at reflux for 24h, allowed to cool, then poured into saturated NH_4Cl solution (10 ml). The aqueous phase was extracted with Et_2O (3 x 20 ml), each extract being washed with water (5 ml) and brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (50% Et_2O - 40-60° petrol) to give firstly recovered starting material (60.0 mg), then *1α,5α-dihydroxy-1β-methyl-4-methylenecyclohex-2-ene* (170) (32.8 mg, 51% based on unrecovered starting material), ν_{max} (film) 3360, 2980, 2930, 1600, and 1370 cm^{-1}; δ(250 MHz) 1.32 (3H, s, C-1 *Me*) 1.85 (1H, ddd, J 1.0, 3.2, 14.2 Hz, *H-6*), 2.23 (1H, ddd, J 1.6, 4.7, 14.2 Hz, *H-6*), 2.32 (1H, m, C-5 O*H*), 3.48 (1H, s, C-1 O*H*), 4.54 (1H, m, *H-5*), 5.09 (1H, s, =CH_2), 5.15 (1H, s, =CH_2), 5.83 (1H, dd, J 1.0, 10.2 Hz, *H-3*), and 6.10 (1H, d, J 10.2 Hz, *H-2*); *m/z* = 140 (M^+) (Found: C, 68.63; H, 8.74%. $C_8H_{12}O_2$ requires C, 68.53; H, 8.65%), and finally the amine diol (171) (24.8 mg, 25% based on unrecovered starting material), ν_{max} (film) 3400, 2980, 2940, 1665, and 1460 cm^{-1}; δ(60 MHz) 1.05 (6H, t, J 7.0 Hz, CH_2CH_3), 1.18 (3H, s, C-2 *Me*), 1.75 (3H, br s, C-5 *Me*), 1.90 - 2.20 (2H, m), 2.55 (6H, inc.q, J 7.0 Hz, CH_2CH_3, 2 O*H*), 3.18 (1H, m, *H-1*), 4.05 (1H, m, *H-4*), and 5.50 (1H, m, *H-6*); *m/z* = 213 (M^+) (Found: M^+ 213.1729. $C_{12}H_{23}NO_2$ requires 213.1716).

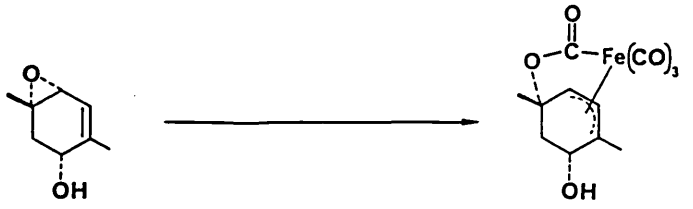
Preparation of 2,5β-Dimethyl-4,5α-epoxycyclohex-2-en-1α-ol (175) and 1α,5α-Dihydroxy-1β-methyl-4-methylenecyclohex-2-ene (170)



(169) (175) (170)

To a solution of ethylenediamine (237 mg, 3.943 mmol) in a 4:1 mixture of Et_2O:THF (2 ml) at 0°C under argon was added ^nBuLi (2.60 ml of a 1.55N solution in hexane, 3.945 mmol) dropwise. The mixture was stirred at this temperature for 20 min before addition of the *cis* diepoxide (169) (502.8 mg, 3.586 mmol) as a solution in THF (2 ml). After stirring at 0°C for 30 min, the solution was warmed to rt over 20 min before pouring into saturated NH_4Cl solution (20 ml). The aqueous phase was extracted with Et_2O (3 x 30 ml), each extract being washed with water (10 ml) and brine (10 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (50% Et_2O - 40-60° petrol) to give firstly *2,5β-dimethyl-4,5α-epoxycyclohex-2-en-1α-ol* (175) (390.3 mg, 78%) as a colourless oil, ν_{max} (film) 3510, 2940, 1660(w), and 1452 cm^{-1}; δ(250 MHz) 1.43 (3H, s, C-5 *Me*), 1.78 (1H, dd, J 4.5, 15.2 Hz, *H-6*), 1.86 (3H, d, J 1.4 Hz, C-2 *Me*), 2.30 (1H, dd, J 1.9, 15.2 Hz, *H-6*), 2.55 (1H, d, J 11.4 Hz, O*H*), 3.20 (1H, dd, J 1.6, 4.5 Hz, *H-4*), 3.77 (1H, ddd, J 1.9, 4.5, 11.4 Hz, *H-1*), and 5.82 (1H, m, *H-3*); *m/z* = 140 (M^+) (Found: C, 68.44; H, 8.83%. $C_8H_{12}O_2$ requires C, 68.53; H, 8.65%), and secondly the diol (170) (60.4 mg, 12%) identical to the sample obtained previously.

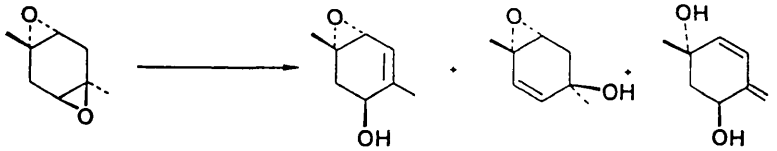
Preparation of 2-4-η^3-(1-Formyloxy-1β,4-dimethyl-5α-hydroxycyclohex-3-enylato)tricarbonyliron (177)



(175) (177)

To a stirred solution of allylic alcohol (175) (31.1 mg, 0.222 mmol) in THF (2 ml) was added nonacarbonyldiiron (92.1 mg, 0.253 mmol) in one portion and the resulting mixture stirred for 24h. The solvent was evaporated under reduced pressure in a cooled water bath (<5°C) and the residue triturated with benzene (1 ml). The triturate was chromatographed (0 → 60% Et_2O - benzene) to give the tricarbonyliron complex (177) (18.2 mg, 27%) as a pale yellow crystalline solid, m.p. 137°C; ν_{max} ($CHCl_3$) 3400, 2920, 2080, 2010, and 1660 cm^{-1}; δ(90 MHz) 1.58 (3H, s, C-1 *Me*), 1.62 (3H, s, C-4 *Me*), 1.80 - 2.25 (3H, m), 3.65 (1H, m, *H-5*), 4.98 (1H, d, J 4.4 Hz, *H-2*), and 5.02 (1H, d, J 4.4 Hz, *H-3*).

Preparation of 2,5β-Dimethyl-4,5α-epoxycyclohex-2-en-1β-ol (179), 1α,4β-Dimethyl-4α,5-epoxycyclohex-2-en-1β-ol (180) and 1α,5β-Dihydroxy-1β-methyl-4-methylenecyclohex-2-ene (178)



(168) (179) (180) (178)

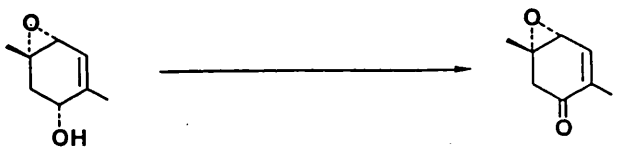
To a solution of ethylenediamine (209 mg, 3.473 mmol) in a 4:1 mixture of Et_2O/THF (5 ml) at 0^oC under argon was added ^nBuLi (2.90 ml of a 1.2N solution in hexane, 3.483 mmol) dropwise. The amide base was stirred at this temperature for 20 min then added dropwise *via* a catheter to a solution of the *trans*-diepoxide (168) (407 mg, 2.903 mmol) in THF (2 ml) at 0^oC under argon. The mixture was allowed to warm to rt over 1h before pouring into saturated NH_4Cl solution (20 ml). The aqueous phase was extracted with Et_2O (3 x 20 ml) and the combined organic extracts dried. The solvent was then evaporated under reduced pressure and the residue chromatographed (20% Et_2O - 40-60^o petrol) to give firstly a 1:1 inseparable mixture of the secondary alcohol (179) (142.0 mg, 35%), δ(90 MHz) 1.40 (3H, s, C-5 *Me*), 1.68 (1H, dd, J 3.9, 16.7 Hz, *H-6*), 1.80 (3H, br s, C-2 *Me*), 2.55 (1H, d, J 16.7 Hz, *H-6*), 3.0 (1H, d, J 4.6 Hz, *H-4*), 4.25 (1H, m, *H-1*), and 5.70 (1H, m, *H-3*), and the tertiary alcohol (180) (142.0 mg, 35%), ν_{max} (film) 3390, 2960, 2920, 1645, and 1450 cm^{-1}; δ(90 MHz) 1.32 (3H, s, C-4 *Me*), 1.44 (3H, s, C-1 *Me*), 1.68 (1H, br s, O*H*), 1.92 (1H, ddd, J 1.3, 2.0, 15.3 Hz, *H-6*), 2.45 (1H, dd, J 2.6, 15.3 Hz, *H-6*), 3.30 (1H, m, *H-5*), and 5.77 (2H, s, *H-2,-3*); and secondly the diol (178) (101.4 mg, 25%), ν_{max} (film) 3355, 2970, 2927, 1662, and 1605 cm^{-1}; δ(90 MHz) 1.35 (3H, s, C-1 *Me*), 1.71 (1H, d, J 12.9 Hz, *H-6*), 2.12 (1H, dd, J 4.9, 12.9 Hz, *H-6*), 2.37 (2H, br s, O*H*), 4.55 (1H, m, *H-5*), 5.05 (1H, s, $=CH_2$), 5.30 (1H, s, $=CH_2$), 5.62 (1H, d, J 10.0 Hz, *H-3*), and 6.11 (1H, d, 10.0 Hz, *H-2*); *m/z* = 140 (M^+) (Found: M^+ 140.0834. $C_8H_{12}O_2$ requires 140.0837).

Preparation of 5β-Chloro-4α-hydroxy-2,5α-dimethylcyclohex-2-enone (181)

(175) (181)

A solution of the allylic alcohol (175) (63.0 mg, 0.449 mmol) in CH_2Cl_2 (2 ml) was added in one portion to a vigorously stirred suspension of pyridinium chlorochromate (161 mg, 0.744 mmol) and excess sodium acetate as buffer in CH_2Cl_2 (3 ml). After stirring for 3h, TLC showed complete removal of starting material with the production of a very u.v. active spot of lower Rf. The mixture was filtered through a short column of silica, eluting with further quantities of CH_2Cl_2. Concentration of the eluate afforded an oil which was re-chromatographed (50% Et_2O - 40-60° petrol) to give *5β-chloro-4α-hydroxy-2,5α-dimethylcyclohex-2-enone* (181) (33.7 mg, 38%) as a colourless oil, ν_{max} (film) 3450, 2980, 2930, 1685, and 1618 cm^{-1}; δ(250 MHz) 1.42 (3H, s, C-5 *Me*), 1.85 (1H, br s, O*H*), 2.03 (3H, d, J 2.0 Hz, C-2 *Me*), 2.96 (1H, dd, J 1.0, 15.1 Hz, *H-6*), 3.11 (1H, d, J 15.1 Hz, *H-6*), 3.69 (1H, m, *H-4*), and 6.69 (1H, m, *H-3*); *m/z* = 174 (M^+) (Found: C, 55.08; H, 6.47%. $C_8H_{11}O_2Cl$ requires C, 55.02; H, 6.36%).

Preparation of 2,5β-Dimethyl-4,5α-epoxycyclohex-2-enone (182)



(175) (182)

To a solution of pyridine (3.385g, 42.79 mmol) in CH_2Cl_2 (60 ml) at 0^oC was added chromium trioxide (2.14g, 21.40 mmol). The burgundy red solution was stirred at this temperature for 5 min and then allowed to warm to rt over 55 min. A solution of the allylic alcohol (175) (507 mg, 3.616 mmol) in CH_2Cl_2 (2 ml) was added in one portion and the mixture stirred for 18h. The suspension was diluted with Et_2O (300 ml) and filtered through a short pad of silica, eluting with a further quantity of Et_2O (200 ml). The eluate was then washed with saturated $CuSO_4$ solution (2 x 50 ml), water (50 ml) and brine (30 ml). The organic phase was dried, the solvent removed under reduced pressure and the residue chromatographed (50% Et_2O - 40-60^o petrol) to give the enone (182) (405 mg, 81%) as a colourless oil, ν_{max} (film) 3446, 2963, 2926, 1676, and 1449 cm^{-1}; δ(90 MHz) 1.50 (3H, s, C-5 *Me*), 1.80 (3H, d, J 1.3 Hz, C-2 *Me*), 2.60 (1H, d, J 19.3 Hz, *H-6*), 3.08 (1H, dd, J 1.3, 19.3 Hz, *H-6*), 3.25 (1H, dd, J 1.3, 3.9 Hz, *H-4*), and 6.90 (1H, m, *H-3*); *m/z* = 138 (M^+) (Found: M^+ 138.0672. $C_8H_{10}O_2$ requires 138.0681).

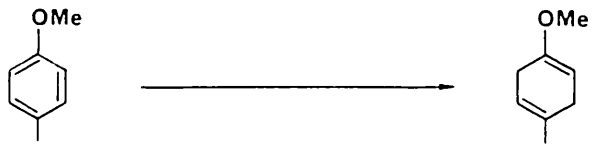
Preparation of 2,5β-Dimethyl-4,5α-epoxycyclohex-2-enone (182)

(181) (182)

To the chlorohydrin (181) (15.0 mg, 8.6 x 10^{-5} mmol) was added 1M NaOH solution (1 ml) and the mixture stirred vigorously for 20 min. The solution was poured into Et_2O (10 ml) and the aqueous phase extracted with further quantities of Et_2O (2 x 5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (50% Et_2O - 40-60^{o} petrol) to give the alkenyl epoxide (182) (8.2 mg, 69%) as a colourless oil (identical to the material prepared previously).

SECTION C

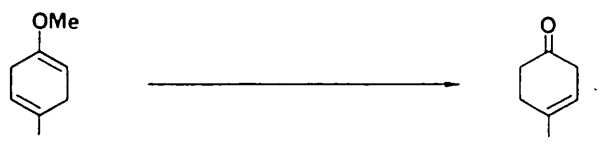
Preparation of 2,5-Dihydro-*p*-methylanisole (189)



(189)

To a solution of *p*-methylanisole (30.0g, 0.250 mol) in Et_2O (60 ml) and liquid ammonia (200 ml) was added lithium shot (7.75g, 1.117 mol) over 15 min. The mixture was stirred for 15 min, absolute alcohol (75.0g) added dropwise, and after the disappearance of the blue colour, the ammonia allowed to evaporate. The residue was cautiously added to water (300 ml) and extracted with Et_2O (3 x 200 ml), each extract being washed with brine (50 ml). The combined organic extracts were dried and the solvent evaporated under reduced pressure in a cold water bath (0^oC) to give the dihydroanisole (189) (22.5g, 73%) as a colourless liquid, ν_{max} (film) 2933, 2906, 1699, and 1667 cm^{-1}; δ(60 MHz) 1.70 (3H, s), 2.70 (4H, br s), 3.59 (3H, s, *OMe*), 4.60 (1H, m, *H-2*), and 5.35 (1H, m, *H-5*); *m/z* = 124 (M^+).

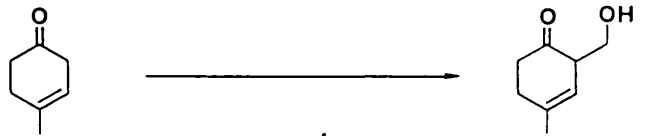
Preparation of 4-Methylcyclohex-3-enone (190)



(189) (190)

A solution of the enol ether (189) (2.0g, 16.10 mmol) and oxalic acid (290 mg, 3.221 mmol) in a 98:2 mixture of THF/water (20 ml) was heated at reflux for 18h. The mixture was cooled, poured into saturated $NaHCO_3$ solution (10 ml) and extracted with Et_2O (3 x 50 ml), each extract being washed with water (20 ml) and brine (10 ml). The combined organic extracts were dried, the solvent removed under reduced pressure, and the residue chromatographed (20% Et_2O - 40-60° petrol) to give the enone (190) (1.684g, 95%) as a colourless oil, ν_{max} (film) 2970, 2930, 2860, 1722, and 1518 cm^{-1}; δ(90 MHz) 1.76 (3H, br s, C-4 *Me*), 2.40 (4H, m), 2.80 (2H, m, *H-2*), and 5.42 (1H, m, *H-3*); *m/z* = 110 (M^+).

Preparation of 2-Hydroxymethyl-4-methylcyclohex-3-enone (191)

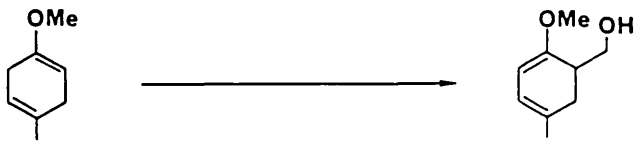


(190) (191)

To a solution of diisopropylamine (90.5 mg, 0.894 mmol) in THF (2 ml) at 0°C under argon was added ^nBuLi (597 µl of a 1.50N solution in hexane, 0.894 mmol) dropwise. The mixture was stirred at this temperature for 10 min, cooled to -78°C, and a solution of the enone (190) (82.0 mg, 0.744 mmol) added. The mixture was warmed to -30°C over 20 min, cooled to -78°C, and a solution of freshly prepared monomeric formaldehyde (112 mg, 3.73 mmol) in THF (10 ml) added. The mixture was warmed to rt over 30 min, poured into saturated NH_4Cl solution (20 ml) and extracted with Et_2O (3 x 50 ml), each extract being washed

with brine (20 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (30% Et_2O - 40-60° petrol) to give the homoallylic alcohol (191) (18.2 mg, 17%) as a colourless oil, ν_{max} (film) 3410, 2940, 2880, and 1715 cm^{-1}; δ(90 MHz) 1.80 (3H, br s, C-4 *Me*), 2.26 - 2.70 (4H, m), 3.07 (1H, m, *H-2*), 3.70 (2H, m, CH_2OH), and 5.31 (1H, m, *H-3*); *m/z* = 140 (M^+).

Preparation of 6-Hydroxymethyl-1-methoxy-4-methyl-1,3-cyclohexadiene (192)

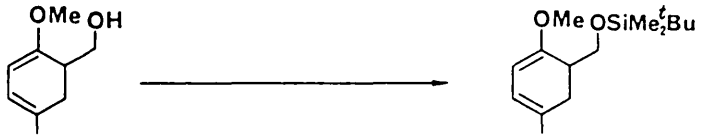


(189) (192)

To a mixture of paraformaldehyde (2.46g, 81.92 mmol) and the enol ether (189) (5.00g, 40.26 mmol) in CH_2Cl_2 (40 ml) at 0°C under argon was added Me_3Al (76.8 ml of a 1.064M solution in hexane, 81.72 mmol) dropwise. The solution was stirred at this temperature for 20 min before addition of Et_2O (100 ml) and cautious addition of water (40 ml). The mixture was filtered through "Celite" under suction, the organic layer separated, and the aqueous phase extracted with more Et_2O (3 x 60 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (30% Et_2O - 40-60° petrol) to give *6-hydroxymethyl-1-methoxy-4-methyl-1,3-cyclohexadiene* (192) (3.79g, 61%) as a colourless oil, ν_{max} (film) 3370, 1658, and 1611 cm^{-1}; δ(250 MHz) 1.72 (3H, d, J 1.4 Hz, C-4 *Me*), 2.05 (1H, br s,

OH), 2.14 (1H, m, *H-5*), 2.33 (1H, m, *H-5*), 2.52 (1H, m, *H-6*), 3.57 (3H, s, O*Me*), 3.50 - 3.70 (2H, m, *H-7*), 4.93 (1H, d, J 5.7 Hz, *H-2*), and 5.51 (1H, m, *H-3*); *m/z* = 154 (M^+) (Found: C, 69.96; H, 9.41%. $C_9H_{14}O_2$ requires C, 70.08; H, 9.17%).

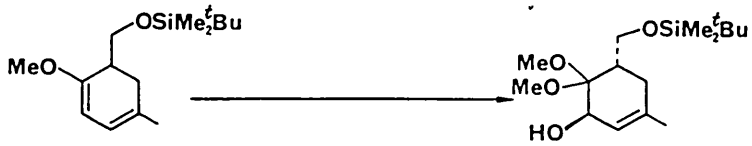
Preparation of 6-^{t}Butyldimethylsilyloxymethyl-1-methoxy-4-methyl-1,3-cyclohexadiene (193)



(192) (193)

A solution of the diene (192) (1.02g, 6.613 mmol), TBDMSCl (1.10g, 7.275 mmol) and imidazole (901 mg, 13.226 mmol) in dry DMF (2 ml) was stirred at rt for 18h. The mixture was poured into Et_2O (80 ml) and washed with water (3 x 20 ml) followed by brine (10 ml). The organic phase was dried, the solvent evaporated under reduced pressure, and the residue chromatographed (2% Et_2O - 40-60^o petrol) to give the ^{t}butyldimethylsilyloxy derivative (193) (1.71g, 96%) as a colourless oil, ν_{max} (film) 3071, 2954, 1652, and 1610 cm^{-1}; δ(250 MHz) 0.05 (6H, s, Si*Me*$_2$), 0.88 (9H, s, ^{t}*Bu*), 1.72 (3H, br s, C-4 *Me*), 2.33 - 2.42 (2H, m, *H-5*), 2.49 (1H, m, *H-6*), 3.51 (3H, s, O*Me*), 3.55 - 3.68 (2H, m, *H-7*), 4.84 (1H, d, J 6.3 Hz, *H-2*), and 5.51 (1H, m, *H-3*); *m/z* = 268 (M^+).

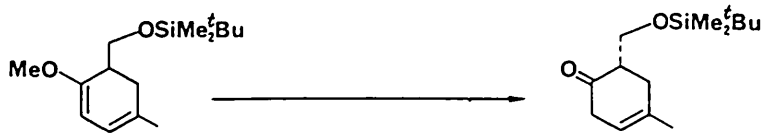
Preparation of 3α-^{t}Butyldimethylsilyloxymethyl-5-methyl-2-oxo(dimethylacetal)cyclohex-5-en-1β-ol (194)



(193) (194)

To a solution of the enol ether (193) (109.4 mg, 0.4074 mmol) in CH_2Cl_2 (5 ml) at 0°C was added a solution of mCPBA (70.3 mg, 0.4074 mmol) in ~~CH_2Cl_2~~ MeOH (20 ml) dropwise over 10 min. The mixture was stirred at this temperature for 1h then poured into 1M NaOH solution (10 ml). The organic phase was separated, the solvent evaporated under reduced pressure, and the residue chromatographed (25% Et_2O - 40-60° petrol) to give *3α-^{t}butyldimethylsilyloxymethyl-5-methyl-2-oxo(dimethylacetal)-cyclohex-5-en-1β-ol* (194) (34.8 mg, 27%) as a colourless oil, ν_{max} (film) 3432, 2929, 1677 and 1463 cm^{-1}; δ(250 MHz): 0.06 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*), 0.88 (9H, s, Si^{t}*Bu*), 1.70 (3H, br s, C-5 *Me*), 1.91 (1H, d, J 16.9 Hz, *H-4*), 2.15 (1H, m, *H-3*), 2.29 (1H, dd, J 8.2, 16.9 Hz, *H-4*), 3.23 (3H, s, O*Me*), 3.35 (3H, s, O*Me*), 3.48 (1H, br s, O*H*), 3.62 (1H, dd, J 3.5, 10.2 Hz, C*H*-O), 3.88 (1H, m, *H-1*), 4.02 (1H, dd, J 4.0, 10.2 Hz, C*H*-O), and 5.50 (1H, m, *H-6*); *m/z* = 316 (M^+) (Found: C, 60.38; H, 10.16%. $C_{16}H_{32}O_4Si$ requires C, 60.70; H, 10.21%).

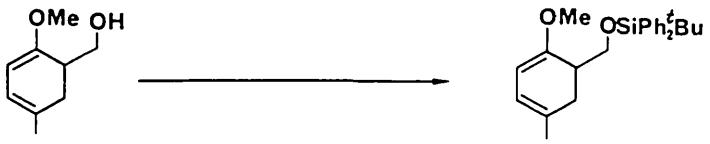
Preparation of 6-^{t}Butyldimethylsilyloxymethyl-4-methylcyclohex-3-enone (196)



(193) (196)

To a slurry of silica-gel (2.5g) in CH_2Cl_2 (7 ml) was added 5% H_2SO_4 solution (130 mg). The mixture was stirred for 20 min during which time the acid solution became adsorbed onto the surface of the silica. A solution of the enol ether (193) (122 mg, 0.454 mmol) in CH_2Cl_2 (2 ml) was added and the slurry stirred at rt for 3h. The mixture was filtered, the filtrate evaporated under reduced pressure, and the residue chromatographed (5% Et_2O - 40-60^{o} petrol) to give the enone (196) (113 mg, 98%) as a colourless oil, ν_{max} (film) 3070, 2931, and 1713 cm^{-1}; δ(250 MHz) 0.05 (6H, s, Si*Me*$_2$), 0.88 (9H, s, ^{t}*Bu*), 1.77 (3H, br s, C-4 *Me*), 2.21 (1H, dd, J 6.1, 11.4 Hz, *H-5*), 2.55 (1H, dd, J 4.6, 11.4 Hz, *H-5*), 2.71 - 2.94 (3H, m), 3.67 (1H, dd, J 8.2, 10.2 Hz, *H-7*), 3.95 (1H, dd, J 5.5, 10.2 Hz, *H-7*), and 5.39 (1H, m, *H-3*); *m/z* = 254 (M^{+}).

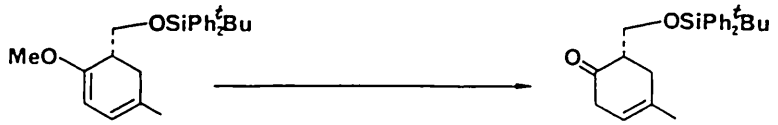
Preparation of 6-^{t}Butyldiphenylsilyloxymethyl-1-methoxy-4-methyl-1,3-cyclohexadiene (197)



(192) (197)

A solution of the diene (192) (2.90g, 18.80 mmol), TBDPSCl (5.69g, 20.70 mmol), and imidazole (2.56g, 37.60 mmol) in dry DMF (6 ml) was heated at 50^{o}C for 18h. The mixture was poured into Et_2O (200 ml) and washed with water (3 x 40 ml) followed by brine (20 ml). The organic phase was dried, the solvent evaporated under reduced pressure, and the residue chromatographed (3% Et_2O - 40-60^{o} petrol) to give *6-^{t}butyldiphenylsilyloxymethyl-1-methoxy-4-methyl-1,3-cyclohexadiene* (197) (6.94g, 94%) as a colourless oil, ν_{max} (film) 3071, 2931, 1658, and 1610 cm^{-1}; δ(250 MHz) 1.07 (9H, s, ^{t}*Bu*), 1.75 (3H, s, C-4 *Me*), 2.36 - 2.48 (2H, m, *H-5*), 2.51 (1H, m, *H-6*), 3.48 (3H, s, O*Me*), 3.56 - 3.70 (2H, m, *H-7*), 4.87 (1H, d, J 6.5 Hz, *H-2*), 5.51 (1H, m, *H-3*), 7.40 (6H, m, *Ph*), and 7.68 (4H, m, *Ph*); *m/z* = 392 (M^{+}). (Found: C, 76.35; H, 8.30%. $C_{25}H_{32}O_2Si$ requires C, 76.47; H, 8.23%).

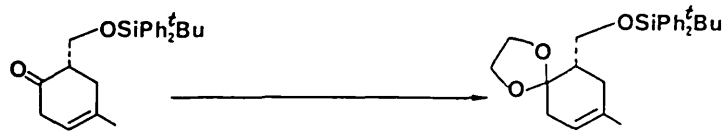
Preparation of 6-^{t}Butyldiphenylsilyloxymethyl-4-methylcyclohex-3-enone (198)



(197) (198)

To a slurry of silica-gel (3.8g) in CH_2Cl_2 (10 ml) was added 5% H_2SO_4 solution (200 mg). The mixture was stirred for 20 min during which time the acid solution became adsorbed onto the surface of the silica. A solution of the enol ether (197) (270 mg, 0.688 mmol) in CH_2Cl_2 (2 ml) was added and the slurry stirred at rt for 3h. The mixture was filtered, the filtrate evaporated under reduced pressure, and the residue chromatographed (5% Et_2O - 40-60^{o} petrol) to give *6-^{t}butyldiphenylsilyloxymethyl-4-methylcyclohex-3-enone* (198) (258 mg, 99%) as a colourless oil, ν_{max} (film) 3071, 2931, 1714, and 1589 cm^{-1}; δ(250 MHz) 1.05 (9H, s, ^{t}*Bu*), 1.76 (3H, br s, C-4 *Me*), 2.13 - 2.22 (1H, m, *H-5*), 2.58 (1H, dd, J 6.6, 17.2 Hz, *H-5*), 2.67 - 2.96 (3H, m), 3.69 - 4.02 (2H, m, *H-7*), 5.37 (1H, m, *H-3*), 7.38 (6H, m, *Ph*), and 7.64 (4H, m, *Ph*); *m/z* = 321 (M^{+}-^{t}Bu) (Found: C, 76.30; H, 8.05%. $C_{24}H_{30}O_2Si$ requires C, 76.13; H, 8.00%).

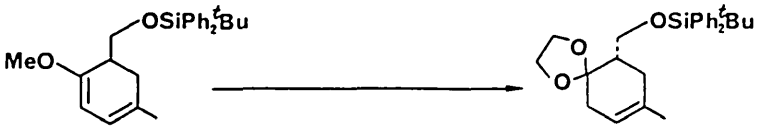
Preparation of 6-^{t}Butyldiphenylsilyloxymethyl-4-methylcyclohex-3-enone 1,3-dioxolane (202)



(198) (202)

A solution of the enone (198) (220 mg, 0.581 mmol), ethylene glycol (144 mg, 2.320 mmol), and pyridinium *p*-toluenesulphonate (trace) in benzene (12 ml) was heated at reflux under Dean-Stark conditions for 2h. The mixture was cooled, the solvent evaporated under reduced pressure, and the residue chromatographed (15% Et_2O - 40-60^{o} petrol) to give starting enone (198) (51.7 mg) and *6-^{t}butyldiphenylsilyloxymethyl-4-methylcyclohex-3-enone-1,3-dioxolane* (202) (114 mg, 61% based on unrecovered starting material) as a colourless oil, ν_{max} (film) 3070 2930, and 1589 cm^{-1}; δ(250 MHz) 1.07 (9H, s, ^{t}*Bu*), 1.71 (3H, br s, C-4 *Me*), 2.03 - 2.50 (5H, m), 3.50 - 3.95 (6H, m), 5.26 (1H, m, *H-3*), 7.39 (6H, m, *Ph*), and 7.66 (4H, m, *Ph*); *m/z* = 365 (M^{+}-^{t}Bu) (Found: C, 74.09; H, 8.14%. $C_{26}H_{34}O_3Si$ requires C, 73.87; H, 8.12%).

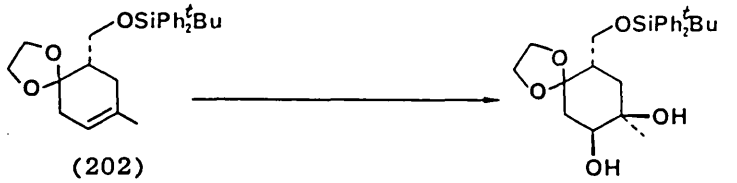
Preparation of 6-^{t}Butyldiphenylsilyloxymethyl-4-methylcyclohex-3-enone 1,3-dioxolane (202)



(197) (202)

A solution of the methyl enol ether (197) (14.60g, 37.18 mmol), ethylene glycol (11.50g, 0.185 mol), and pyridinium *p*-toluenesulphonate (920 mg, 3.661 mmol) in benzene (250 ml) was heated at reflux under Dean-Stark conditions for 6h. The mixture was cooled, the solvent evaporated under reduced pressure, and the residue chromatographed (15% Et_2O - 40-60^{o} petrol) to give the dioxolane (202) (12.73g, 81%) as a colourless oil, identical to the previously prepared material.

Preparation of 4α-^{t}Butyldiphenylsilyloxymethyl-2α-methyl-5-oxo(1,3-dioxolane)cyclohexan-1β,2β-diol (203)

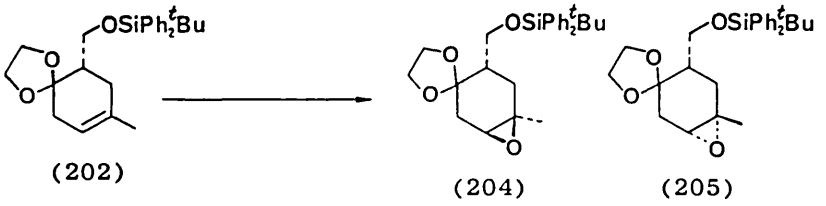


(202) (203)

To a solution of osmium tetroxide (91.2 mg, 0.359 mmol) in pyridine (2 ml) at 0^{o}C under argon was added a solution of the olefin (202) (122.0 mg, 0.289 mmol) in pyridine (2 ml). The black mixture was stirred at

this temperature for 5 min and then at rt for 8h. Aqueous $NaHSO_3$ (3 ml of a 0.72M solution) was then added and stirring continued overnight. The mixture was filtered to remove a granular precipitate and the filtrate then exhaustively extracted with $CHCl_3$ (6 x 20 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (100% Et_2O) to give *4α-^{t}butyldiphenylsilyloxymethyl-2α-methyl-5-oxo(1,3-dioxolane)cyclohexan-1β,2β-diol* (203) (108.7 mg, 83%) as a colourless oil, ν_{max} (film) 3431, 3071, and 2933 cm^{-1}; δ(250 MHz) 1.04 (9H, s, ^tBu), 1.30 (3H, s, C-1 *Me*), 1.42 (1H, m), 1.60 - 1.94 (4H, m, inc. 2 *OH*), 2.16 (1H, m), 2.33 (1H, m, *H-5*), 3.40 - 3.94 (7H, m), 7.37 (6H, m, *Ph*), and 7.64 (4H, m, *Ph*); *m/z* = 441 (M^+-CH_3) (Found: C, 68.14; H, 8.22%. $C_{26}H_{36}O_5Si$ requires C, 68.37; H, 7.96%).

Preparation of 2α-^{t}Butyldiphenylsilyloxymethyl-4β,5β-epoxy-4α-methylcyclohexanone-1,3-dioxolane (204) and 2α-^{t}Butyldiphenylsilyloxymethyl-4α,5α-epoxy-4β-methylcyclohexanone-1,3-dioxolane (205)

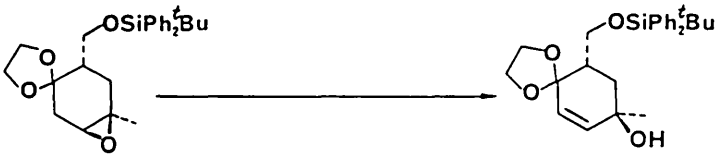


(202) (204) (205)

To a solution of the dioxolane (202) (12.40g, 29.34 mmol) in CH_2Cl_2 (50 ml) at 0°C was added a solution of mCPBA (5.57g, 32.28 mmol) in CH_2Cl_2 (250 ml) dropwise over 30 min. The mixture was stirred at rt for 18h then poured into 1M NaOH solution (60 ml). The organic phase was separated, the solvent evaporated under reduced pressure, and the

residue chromatographed (25% Et_2O - 40-60° petrol) to give *2α-^{t}butyl-diphenylsilyloxymethyl-4,5-epoxy-4-methylcyclohexanone-1,3-dioxolane*, a 76:24 mixture of the β and α epoxides (204) and (205), (10.60g, 82%) as a waxy crystalline solid, ν_{max} ($CHCl_3$) 3070, 2931, 1589, and 1470 cm^{-1}; δ(250 MHz) 1.04 (6.84H, s, *^{t}Bu*), 1.05 (2.16H, s, *^{t}Bu*), 1.33 (0.72H, s, C-4 *Me*), 1.39 (2.28H, s, C-4 *Me*), 1.78 - 2.52 (5H, m), 2.98 (1H, d, J 4.4 Hz, *H-3*), 3.42 - 3.91 (6H, m), 7.39 (6H, m, *Ph*), and 7.65 (4H, m, *Ph*); *m/z* = 439 (M^++1) (Found: C, 71.35; H, 7.87%. $C_{26}H_{34}O_4Si$ requires C, 71.18; H, 7.83%).

Preparation of 5α-^{t}Butyldiphenylsilyloxymethyl-1α-methyl-4-oxo(1,3-dioxolane)cyclohex-2-en-1β-ol (207).



(204) (207)

To a solution of diethylamine (22.6 mg, 0.309 mmol) in Et_2O (1 ml) at 0°C under argon was added ^{n}BuLi (203 μl of a 1.52N solution in hexane, 0.309 mmol) dropwise. The solution was stirred at this temperature for 10 min, cooled to -20°C, and a solution of the epoxide (204) (67.8 mg, 0.155 mmol) in Et_2O (1 ml) added dropwise. The mixture was stirred at rt for 2h, poured into saturated NH_4Cl solution (10 ml) and extracted with Et_2O (3 x 20 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (40% Et_2O - 40-60° petrol) to give the tertiary

allylic alcohol (207) (48.8 mg, 72%) as a colourless oil, ν_{max} (film) 3446, 3070, 2958, 2931, and 1654 cm^{-1}; δ(90 MHz) 1.05 (9H, s, ^{t}Bu), 1.34 (3H, s, C-1 *Me*), 1.60 (1H, br s, O*H*), 1.71 - 2.35 (3H, m), 3.45 - 4.10 (6H, m), 5.55 (1H, d, J 10.4 Hz, *H-2*), 5.75 (1H, dd, J 1.5, 10.4 Hz, *H-3*), 7.40 (6H, m, *Ph*), and 7.66 (4H, m, *Ph*); *m/z* = 438 (M^{+}).

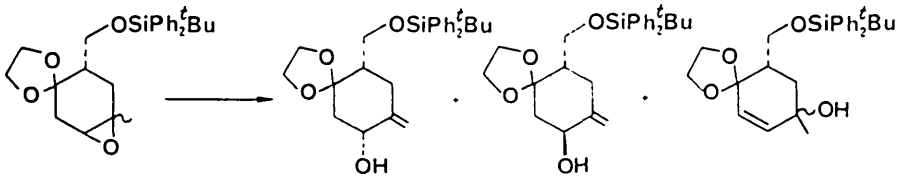
Preparation of 4α-^{t}Butyldiphenylsilyloxymethyl-2-methylene-5-oxo(1,3-dioxolane)cyclohexan-1β-ol (206)

(204) (206)

To a solution of the epoxide (204) (115.7 mg, 0.264 mmol) in benzene (1 ml) at -78°C under argon was added 2,6-lutidine (28.3 mg, 0.264 mmol) followed by trimethylsilyl trifluoromethanesulphonate (58.0 mg, 0.261 mmol) dropwise. The solution was stirred at -78°C for 1h, warmed to 0°C over 1h, and DBU (40.2 mg, 0.264 mmol) added dropwise. The mixture was stirred at rt for 18h, poured into saturated NH_4Cl solution (5 ml) and extracted with Et_2O (3 x 20 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (50% Et_2O - 40-60° petrol) to give *4α-^{t}butyldiphenylsilyloxymethyl-2-methylene-5-oxo(1,3-dioxolane)-cyclohexan-1β-ol* (206) (30.1 mg, 26%) as a colourless oil, ν_{max} (film) 3424, 3071, 2959, 2884, and 1656 cm^{-1}; δ(250 MHz) 1.05 (9H, s, ^{t}Bu), 1.61 (1H, ddd, J 0.9, 8.5, 13.5 Hz, *H-6*), 1.97 (1H, dd, J 4.3, 13.5 Hz,

H-6), 2.05 (1H, m, *H-4*), 2.33 (1H, dd, J 8.2, 13.6 Hz, *H-3*), 2.66 (1H, d, J 7.6 Hz, O*H*), 2.80 (1H, dd, J 4.5, 13.6 Hz, *H-3*), 3.44 - 3.93 (6H, m), 4.21 (1H, m, *H-1*), 4.88 (1H, br s, =CH_2), 5.00 (1H, br s, =CH_2), 7.40 (6H, m, *Ph*), and 7.66 (4H, m, *Ph*); *m/z* = 438 (M^+) (Found: C, 71.23; H, 8.02%. $C_{26}H_{34}O_5Si$ requires C, 71.18; H, 7.83%).

Preparation of 5α-^{t}Butyldiphenylsilyloxymethyl-2-methylene-5-oxo(1,3-dioxolane)cyclohexan-1α-ol (214), 5α-^{t}Butyldiphenylsilyloxymethyl-2-methylene-5-oxo(1,3-dioxolane)cyclohexan-1β-ol (206) and 5α-^{t}Butyldiphenylsilyloxymethyl-1β-methyl-4-oxo(1,3-dioxolane)cyclohex-2-en-1α-ol (207)

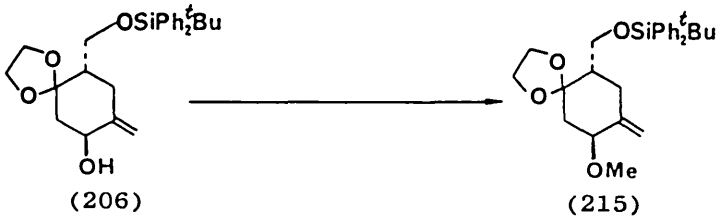


(204) (214) (206) (207)

To a solution of 2,2,6,6-tetramethylpiperidine (1.38g, 9.769 mmol) in benzene (5 ml) at -20°C under argon was added ^{n}BuLi (6.18 ml of a 1.58M solution in hexane, 9.770 mmol) and the mixture warmed to 0°C over 10 min. The solution was cooled to -10°C and diethylaluminium chloride (4.71 ml of a 2.074M solution in hexane, 9.770 mmol) added dropwise. The mixture was warmed to rt over 45 min, cooled to -20°C, and a solution of the epoxide (204) (2.143g, 4.885 mmol) in benzene (5 ml) added. The mixture was allowed to warm to rt over 1h, poured into 1M HCl solution (25 ml) and extracted with Et_2O (3 x 50 ml). The combined organic extracts were dried, the solvent evaporated under

reduced pressure, and the residue chromatographed (50% Et_2O - 40-60° petrol) to give firstly the α-allylic alcohol (214) (86.0 mg, 4%) as a colourless oil, δ(250 MHz) 1.04 (9H, s, ^tBu), 1.82 (2H, m, *H-6*), 2.04 (1H, m, *H-4*), 2.57 (2H, m, *H-3*), 3.10 (1H, d, J 7.9 Hz, *OH*), 3.48 - 3.98 (6H, m), 4.26 (1H, m, *H-1*), 4.88 (1H, br s, $=CH_2$), 4.99 (1H, br s, $=CH_2$), 7.39 (6H, m, *Ph*), and 7.66 (4H, m, *Ph*); secondly the β-allylic alcohol (206) (1.57g, 73%) obtained previously; and finally the tertiary alcohol (207) (364 mg, 17%) also obtained previously.

Preparation of 2α-^{t}Butyldiphenylsilyloxymethyl-5β-methoxy-4-methylene-cyclohexanone-1,3-dioxolane (215)

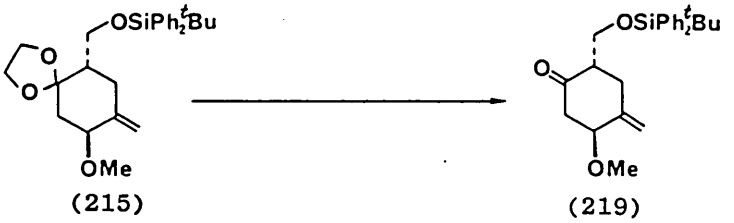


(206) (215)

To a stirred suspension of sodium hydride (317 mg, 6.604 mmol, 50% dispersion in oil), prewashed with sodium-dried 40-60° petrol (2 x 5 ml), in THF (10 ml) at 0°C under argon was added a solution of the allylic alcohol (206) (1.57g, 3.579 mmol) in THF (3 ml). After 15 min, DMPU (1.104g, 8.613 mmol) was added, stirring continued for a further 10 min, and then methyl iodide (3.057g, 21.54 mmol) added. The mixture was stirred at rt for 3h, poured into saturated NH_4Cl solution (30 ml) and extracted with Et_2O (3 x 50 ml), each extract being washed with water (10 ml) and brine (10 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue

chromatographed (25% Et_2O - 40-60° petrol) to give *2α-^{t}butyldiphenylsilyloxymethyl-5β-methoxy-4-methylenecyclohexanone-1,3-dioxolane* (215) (1.592g, 94%) as a colourless oil, ν_{max} (film) 2932, 2885, and 1665 cm^{-1}; δ(250 MHz) 1.05 (9H, s, ^tBu), 1.54 (1H, dd, J 9.8, 12.6 Hz, *H-6*), 1.96 - 2.21 (3H, m), 2.75 (1H, dd, J 3.8, 12.6 Hz, *H-3*), 3.38 (3H, s, *OMe*), 3.43 - 3.98 (7H, m), 4.92 (1H, br s, $=CH_2$), 5.00 (1H, br s, $=CH_2$), 7.38 (6H, m, *Ph*), and 7.66 (4H, m, *Ph*); *m/z* = 452 (M^+) (Found: C, 71.44; H, 8.10%. $C_{27}H_{36}O_4Si$ requires C, 71.63; H, 8.03%).

Preparation of 2α-^{t}Butyldiphenylsilyloxymethyl-5β-methoxy-4-methylenecyclohexanone (219)



(215) (219)

(a) To a solution of the dioxolane (215) (13.8 mg, 3.04 x 10^{-5} mol) in CH_2Cl_2 (1 ml) at 0°C was added triphenylcarbenium tetrafluoroborate (12.0 mg, 3.64 x 10^{-5} mol) in one portion. The mixture was stirred for 1h, poured into water (5 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (15% Et_2O - 40-60° petrol) to give *2α-^{t}butyldiphenylsilyloxymethyl-5β-methoxy-4-methylenecyclohexanone* (219) (3.90 mg, 31%) as a colourless oil, ν_{max} (film) 3071, 2931, 2858, 1715, and 1657 cm^{-1}; δ(250 MHz) 1.00 (9H, s, ^tBu), 2.30 (1H, dd, J 5.5, 13.0 Hz, *H-3*), 2.50 (1H, ddd, J 0.8, 5.7, 14.5 Hz,

H-6), 2.61 (1H, dd, J 4.2, 14.5 Hz, *H-6*), 2.64 - 2.81 (2H, m), 3.25 (3H, s, O*Me*), 3.70 - 3.85 (2H, m, CH_2O), 3.88 (1H, dd, J 4.2, 5.7 Hz, *H-5*), 5.06 (1H, br s, $=CH_2$), 5.12 (1H, br s, $=CH_2$), 7.37 (6H, m, *Ph*), and 7.62 (4H, m, *Ph*); *m/z* = 408 (M^+) (Found: C, 73.44; H, 7.83%. $C_{25}H_{32}O_3Si$ requires C, 73.47; H, 7.91%).

b) To a slurry of silica (1.65g) in CH_2Cl_2 (6 ml) was added 5% H_2SO_4 solution (200 mg). The mixture was stirred for 20 min during which time the acid solution became adsorbed onto the surface of the silica. A solution of the dioxolane (215) (180.8 mg, 0.399 mmol) in CH_2Cl_2 (1 ml) was added and the slurry stirred at rt for 5h. The mixture was filtered, the filtrate evaporated under reduced pressure, and the residue chromatographed (15% Et_2O - 40-60° petrol) to give the ketone (219) (156.7 mg, 96%) identical to the sample prepared previously.

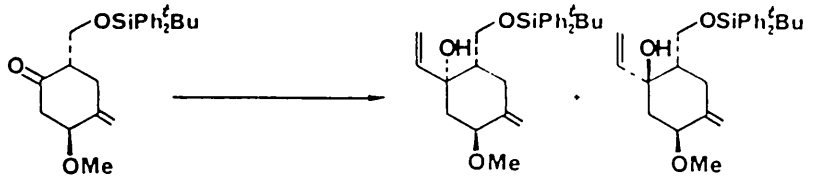
Preparation of 6-^{t}Butyldiphenylsilyloxymethyl-4-methylenecyclohex-2-enone (220)

(215) (220)

To a slurry of silica-gel (2.40g) in CH_2Cl_2 (6 ml) was added 10% H_2SO_4 solution (250 mg). The mixture was stirred for 20 min during which time the acid solution became adsorbed onto the surface of the silica. A solution of the dioxolane (215) (189.2 mg, 0.418 mmol) in CH_2Cl_2 (1 ml) was added and the slurry stirred at rt for 24h. The

mixture was filtered, the filtrate evaporated under reduced pressure, and the residue chromatographed (10% Et_2O - 40-60° petrol) to give *6-^{t}butyldiphenylsilyloxymethyl-4-methylenecyclohex-2-enone* (220) (103.9 mg, 66%) as a colourless oil, ν_{max} (film) 3070, 2931, 2858, 1672, and 1578 cm^{-1}; δ(250 MHz) 1.04 (9H, s, ^tBu), 2.69 (1H, m), 2.76 - 3.00 (2H, m), 3.89 (2H, d, J 5.4 Hz; CH_2O), 5.32 (1H, br s, $=CH_2$), 5.38 (1H, br s, $=CH_2$), 5.92 (1H, d, J 10.2 Hz, *H-2*), 7.07 (1H, d, J 10.2 Hz, *H-3*), 7.40 (6H, m, *Ph*), and 7.69 (4H, m, *Ph*); *m/z* = 319 (M^+-^{t}Bu) (Found: C, 76.72; H, 7.51%. $C_{24}H_{28}O_2Si$ requires C, 76.54; H, 7.51%).

Preparation of 2α-^{t}Butyldiphenylsilyloxymethyl-5β-methoxy-4-methylene-1β-vinylcyclohexan-1α-ol (222) and 2α-^{t}Butyldiphenylsilyloxymethyl-5β-methoxy-4-methylene-1α-vinylcyclohexan-1β-ol (223)

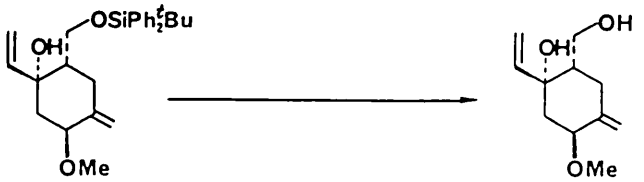


(219) (222) (223)

To a solution of the ketone (219) (330.8 mg, 0.810 mmol) in THF (3 ml) at -30°C under argon was added vinylmagnesium bromide (4.39 ml of a 0.922M solution in THF, 4.047 mmol) and the mixture warmed to 0°C over 30 min. The solution was poured into saturated NH_4Cl solution (10 ml) and extracted with Et_2O (3 x 20 ml), each extract being washed with water (5 ml) and brine (5 ml). The combined organic extracts were dried, evaporated under reduced pressure, and the residue chromatographed (10% Et_2O - 40-60° petrol) to give firstly the α-tertiary

alcohol (222) (282.6 mg, 80%) as a colourless oil, ν_{max} (film) 3482, 3072, 2932, 1654, and 1589 cm^{-1}; δ(250 MHz) 1.06 (9H, s, ^{t}Bu), 1.25 - 1.53 (2H, m), 2.12 (2H, m), 2.96 (1H, m, *H-3*), 3.45 (3H, s, O*Me*), 3.51 (1H, dd, J 1.7, 10.1 Hz, C*H*O), 4.04 (1H, dd, J 2.5, 10.1 Hz, C*H*O), 4.11 (1H, m, *H-5*), 4.40 (1H, d, J 2.0 Hz, O*H*), 4.80 (1H, br s, =CH_2), 4.97 (1H, br s, =CH_2), 5.21 (1H, dd, J 1.7,10.1 Hz, *H-2' anti*), 5.57 (1H, dd, J 1.7, 16.8 Hz, *H-2' syn*), 5.82 (1H, dd, J 10.1, 16.8 Hz, *H-1'*), 7.42 (6H, m, *Ph*), and 7.64 (4H, m, *Ph*); *m/z* = 379 (M^{+}-^{t}Bu); and secondly *2α-^{t}butyldiphenylsilyloxymethyl-5β-methoxy-4-methylene-1α-vinylcyclohexan-1β-ol* (223) (25.0 mg, 7.1%) as a colourless oil, ν_{max} (film) 3489, 3070, 2930, 1654, and 1589 cm^{-1}; δ(250 MHz) 1.06 (9H, s, ^{t}Bu), 1.78 (1H, dd, J 7.9, 13.6 Hz, *H-6*), 1.98 (1H, dd, J 3.6, 13.6 Hz, *H-6*), 2.04 - 2.20 (2H, m), 2.35 (1H, m, *H-3*), 3.32 (3H, s, O*Me*), 3.41 - 3.65 (3H, m), 3.73 (1H, m, *H-5*), 4.91 (1H, br s, =CH_2), 5.00 (1H, br s, =CH_2), 5.17 (1H, dd, J 1.8, 10.7 Hz, *H-2' anti*), 5.43 (1H, dd, J 1.8, 16.8 Hz, *H-2' syn*), 5.95 (1H, dd, J 10.7, 16.8 Hz, *H-1'*), 7.42 (6H, m, *Ph*), and 7.65 (4H, m, *Ph*); *m/z* = 418 (M^{+}-H_2O), 379 (M^{+}-^{t}Bu) (Found: C, 74.56; H, 8.48%. $C_{27}H_{36}O_3Si$ requires C, 74.25; H, 8.33%).

Preparation of 2α-Hydroxymethyl-5β-methoxy-4-methylene-1β-vinylcyclohexan-1α-ol (224)



(222) (224)

To a solution of the ^{t}butyldiphenylsilyloxy derivative (222) (118.0 mg, 0.270 mmol) in THF (2 ml) at 0°C was added TBAF (0.540 ml of a 1.0M solution in THF, 0.540 mmol) and the mixture stirred at this temperature for 30 min. The solution was poured into saturated NH_4Cl solution (10 ml) and extracted with Et_2O (4 x 20 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (50% Et_2O - 40-60° petrol) to give the diol (224) (47.0 mg, 88%) as a colourless oil, ν_{max} (film) 3374, 3090, 2930, and 1654 cm^{-1}; δ(250 MHz) 1.40 (1H, dd, J 11.5, 13.1 Hz, *H-6*), 1.53 (1H, m, *H-2*), 2.04 (1H, dd, J 5.1, 13.1 Hz, *H-6*), 2.24 (1H, dd, J 4.1, 13.7 Hz, *H-3*), 2.75 (1H, dd, J 11.5, 13.7 Hz, *H-3*), 3.32 (1H, br s, O*H*), 3.43 (3H, s, O*Me*), 3.63 (1H, dd, J 2.9, 10.8 Hz, *H-7*), 4.00 (1H, dd, J 2.9, 10.8 Hz, *H-7*), 4.02 (1H, m, *H-5*), 4.84 (1H, br d, J 1.7 Hz, =CH_2), 4.96 (1H, dd, J 1.74, 3.48 Hz, =CH_2), 5.18 (1H, dd, J 1.5, 10.7 Hz, *H-2' anti*), 5.41 (1H, dd, J 1.5, 17.1 Hz, *H-2' syn*), and 5.87 (1H, dd, J 10.7, 17.1 Hz, *H-1'*); *m/z* = 180 (M^{+}-H_2O).

Preparation of 2α-Carboxymethyl-5β-methoxy-4-methylene-1β-vinylcyclohexan-1α-ol (225)

(224) (225)

To a solution of the diol (224) (47.0 mg, 0.237 mmol) in DMF (1.5 ml) was added pyridinium dichromate (357 mg, 0.948 mmol) and the mixture

stirred at rt for 48h. Diazomethane was then bubbled through the crude reaction mixture for 30 min before filtering through a short pad of silica eluting with Et_2O (100 ml). The eluate was then washed with saturated $CuSO_4$ solution (2 x 30 ml), water (2 x 30 ml) and brine 20 ml). The organic phase was dried, the solvent evaporated under reduced pressure, and the residue chromatographed (20% Et_2O - 40-60^o petrol) to give the methyl ester (225) (34.0 mg, 63%) as a colourless oil, ν_{max} (film) 3497, 3091, 2953, 2830, 1714, and 1654 cm^{-1}; δ(250 MHz) 1.30 (1H, dd, J 2.5, 12.7 Hz, *H-6*), 2.17 (1H, dd, J 5.1, 12.7 Hz, *H-6*), 2.40 - 2.71 (3H, m), 3.41 (3H, s, O*Me*), 3.66 (3H, s, CO_2*Me*), 3.98 (1H, d, J 2.5 Hz, O*H*), 4.02 (1H, m, *H-5*), 4.87 (1H, m, =CH_2), 5.01 (1H, m, =CH_2), 5.06 (1H, dd, J 1.5, 10.7 Hz, *H-2' anti*), 5.29 (1H, dd, J 1.5, 17.3 Hz, *H-2' syn*), and 5.79 (1H, dd, J 10.7, 17.3 Hz, *H-1'*); *m/z* = 209 (M^++1 - H_2O).

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