NOVEL METHODS IN NATURAL PRODUCT SYNTHESIS

a thesis presented by

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ABSTRACT

This thesis is divided into two parts. The first section describes the Birch reduction of indole under silylating conditions with ultrasonic agitation, to give, after oxidation, 1,4-bis-(trimethylsilyl)indole. The reactivity of this novel compound was investigated. With electrophiles substitution at the C-3 position occured. Deactivation of the C-3 position by acylation of the indole nitrogen gave, after Friedel-Crafts acylation, 1-4-disubstituted indoles. The extension of this methodology to a synthesis of an ergot alkaloid precursor, such as Uhle's ketone, was thwarted by low yields.

Also described is an extension of the Birch reduction under silylating conditions to a variety of hetero- and carbocyclic aromatic systems to give, after oxidation, various aryl silanes.

The second part of this thesis describes a Diels-Alder approach towards the synthesis of the hexahydrobenzofuran Southern zone of the avermectins and milbemycins. Thus on heating Z-methyl-3-acetoxy-4-oxopent-2-enoate with 3-methyltrimethylsilyloxybutadiene in toluene a 63% yield of (±)-methyl (7α-acetoxy-7β-acetyl-4-methyl-6β-trimethylsilyloxy)cyclohex-4-ene-2α-carboxylate was obtained. Attempts to introduce functionality at the acetyl methyl group, suitable for further elaboration to the tetrahydrofuran moiety, were unsuccessful. However, oxidation of the carbon-carbon double bond gave access to compounds arising from oxid-

ation on the α-face ; initial studies on the further transformation of these compounds to the target structure are reported.

During the course of this work, new methods of chemical synthesis were investigated. For example, a new route to sodium phenylselenide using diphenyldiselenide and ultrasonic agitation proved a markedly superior and convenient method than existing procedures. Furthermore, a novel, stereochemically controlled route to Z-methylvinylselenides based upon the carboselenation of acetylenes is also described.

A review of published work in the avermectin and milbemycin southern zone area is provided.

Full experimental and bibliography are given.

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LIST OF CONTENTS

	page
ABSTRACT	2
ACKNOWLEDGEMENTS	5
DEDICATION	6
ABBREVIATIONS	7
PREPARATION AND REACTIONS OF 4-(TRIMETHYLSILYL)INDOLE	9
PREPARATION OF AN UHLES KETONE DERIVATIVE	22
THE SILYL BIRCH REDUCTION	25
EXPERIMENTAL (PART 1)	34
BIBLIOGRAPHY (PART 1)	60
INTRODUCTION TO PART 2	63
REVIEW	70
REVIEW BIBLIOGRAPHY	93
A DIELS-ALDER APPROACH TO THE HEXAHYDROBENZOFURAN SOUTHERN HEMISPHERE OF THE AVERMECTINS AND MILBEMYCINS	98
STUDIES TOWARDS SOME NOVEL HETEROATOM-CONTAINING DIENES	125
A CYCLOHEXENONE ROUTE TO THE SOUTHERN ZONE OF MILBEMYCIN β_1.	134
AN IMPROVED PROCEDURE FOR THE PREPARATION OF SODIUM PHENYLSELENIDE	140
EXPERIMENTAL (PART 2)	145
BIBLIOGRAPHY (PART2)	193

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TO MY MOTHER

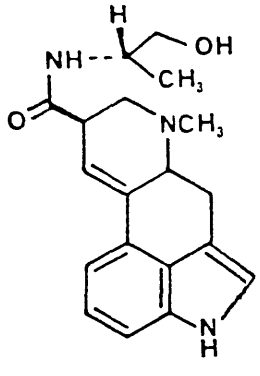
WITH LOVE AND AFFECTION.

ABBREVIATIONS

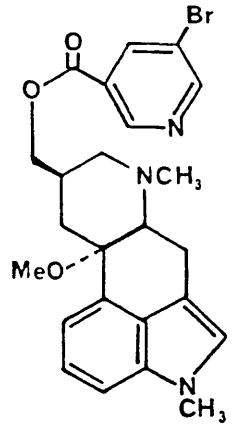
BSA	-	Benzeneseleninic anhydride
^{n}BuLi	-	n-Butyl-lithium
^{t}BuLi	-	*tert*-Butyl-lithium
CSA	-	(dl)-Camphorsulphonic acid
DBU	-	Diazobicyclo[5.4.0]undec-7-ene
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	-	Dihydropyran
DIBAL	-	Diisobutylaluminium hydride
DMAP	-	N,N-Dimethyl-4-aminopyridine
DME	-	1,2-Dimethoxyethane
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulphoxide
eq.	-	equivalent
HMDS	-	Hexamethyldisilazane
HMPA	-	Hexamethylphosphoric triamide
I R	-	INFRA-RED
LDA	-	Lithium diisopropylamine
m-CPBA	-	*m*-Chloroperbenzoic acid
MeLi	-	Methyl lithium
MOM	-	Methoxymethyl
Ms	-	Methylsulphonyl
NBS	-	N-Bromosuccinimide
NCS	-	N-Chlorosuccinimide
NMO	-	N-Methylmorpholine oxide
N.M.R.	-	Nuclear magnetic resonance
N-PSP	-	N-Phenylselenophthalimide
PBQ	-	*p*-Benzoquinone
PCC	-	Pyridinium chlorochromate

PDC	-	Pyridinium dichromate
rt	-	Room temperature
TBAF	-	Tetra-n-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethylsilyl
TBDPS	-	*tert*-Butyldiphenylsilyl
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
THP	-	Tetrahydropyranyl
t.l.c.	-	Thin layer chromatography
TMS	-	Trimethylsilyl
Ts	-	*p*-Toluenesulphonyl (Tosyl)

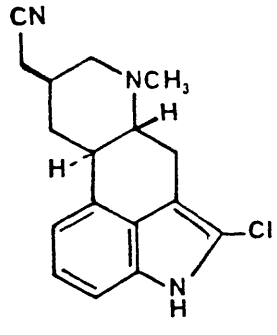
The ergot alkaloids represent a structurally fascinating class of compounds which exhibit a wide range of important biological activity.[1] They are used in the treatment of various illnesses such as postpartum haemorrhage (ergovine) (1), hypertension (nicergoline) (2) and various prolactin-dependent disorders (lergotrile) (3)



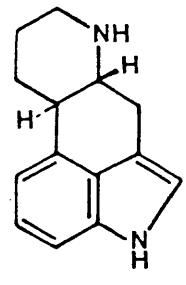
(1)



(2)



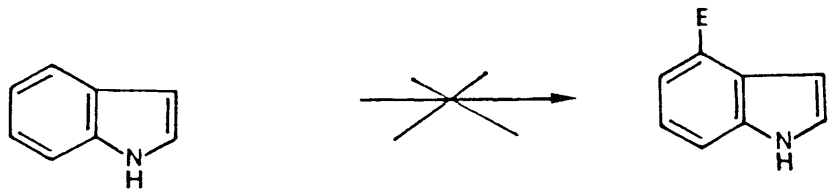
(3)



(4)

The parent unit is the ergoline ring system (4). In any synthesis of the ergot alkaloids the construction of the C-10-C-11 carbon-carbon bond is central to the synthetic plan. The low nucleophilicity of the C-4 position of indole (5) has thwarted the direct use of indole in any total synthesis of the ergot alkaloids to date. (scheme 1)

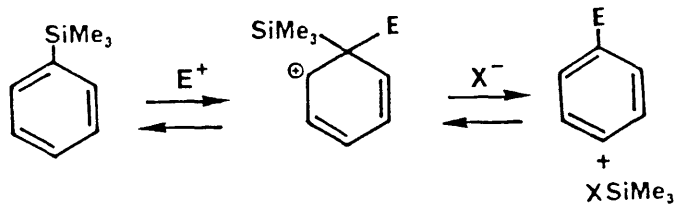
scheme (1)



(5) (6)

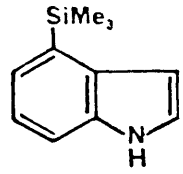
This problem has been overcome classically by either the use of a suitably functionalized C-4 indole[1,2] or via the use of an intramolecular Friedel-Crafts acylation on indoline derivatives.[1,3]

Aryl silanes are well known to undergo *ipso* substitution with electrophiles due to the ability of silicon to stabilize a carbonium ion β to it.[4] (scheme 2)



scheme (2)

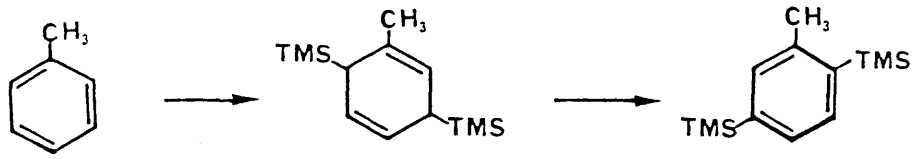
We therefore sought a method to prepare 4-(trimethylsilyl)indole(7) directly from indole(5) and to investigate its reactivity with electrophiles.



(7)

A review of the literature showed that simple aromatic hydrocarbons had been reduced with lithium metal in THF in the presence of TMS-Cl to give 1,4-disilyl derivatives which could be air oxidised to aryl silanes[5] (scheme 3).

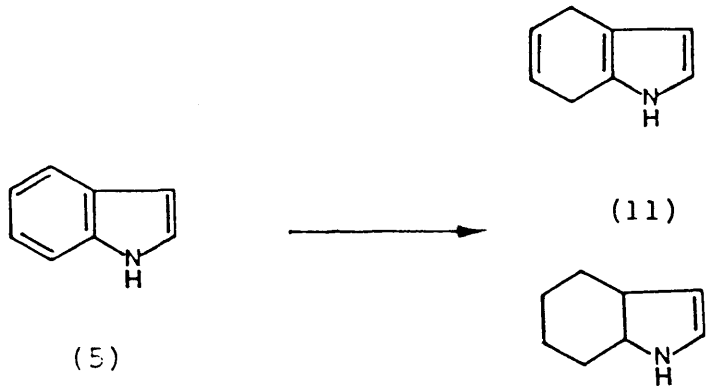
scheme(3)



(8) (9) (10)

In addition, Smith and coworkers had shown that indole(5) was reduced under Birch conditions to produce an inseparable mixture of 4,7-dihydro(11) and 4,5,6,7 tetrahydro indoles[6](12) (scheme 4).

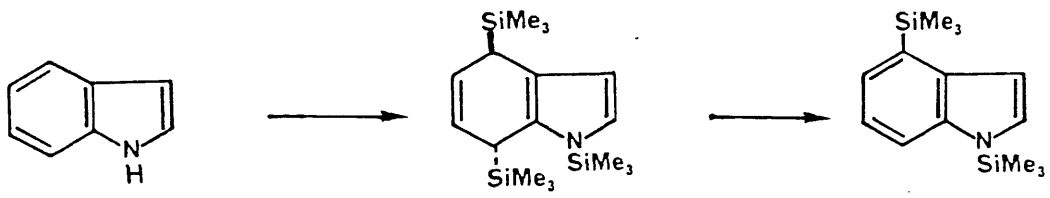
scheme (4)



(5) (11) (12)

Clearly the reduction was giving rise to radical anions centred on the C-4 and C-7[7] positions and the possibility of trapping with TMS-Cl was obvious. Indeed it was found that reduction of indole (5) under silylating conditions followed by *in situ* oxidation of the air sensitive dihydro intermediate (13) with PBQ gave rise to 1,4-bis (trimethylsilyl) indole(14) in 50% yield(scheme5).

scheme(5)

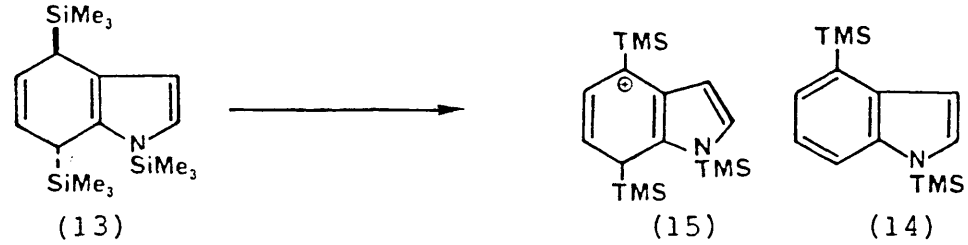


(5) (13) (14)

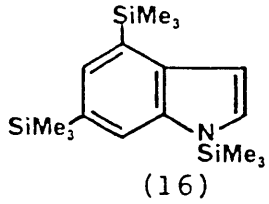
It was found necessary to ultrasonically agitate the reaction mixture to give a satisfactory yield of (14).

Although the dihydro intermediate (13) was not isolated and characterized we assigned the structure shown with the two trimethylsilylgroups *anti*.[5a,b] In the aromatization reaction one hydrogen must be removed from the C-4 and one trimethylsilyl group from the C-7 position (scheme 6), thus electron transfer followed by proton transfer and a second electron transfer from (13) to the quinone should provide (15) and the hydroquinone monoanion.

scheme (6)



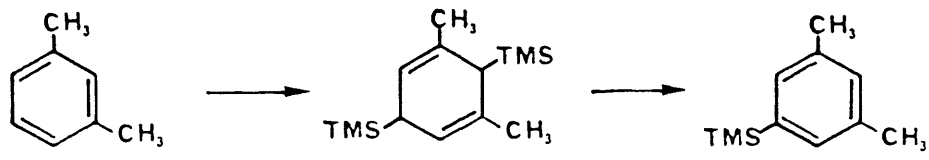
(13) (15) (14)



(16)

In this process it seems reasonable that the less hindered C-4 hydrogen is transferred. Finally the hydroquinone monoanion (15) desilylates at the C-7 position to give (14). Preferential loss of the C-7 trimethylsilyl group follows from release of steric congestion with the N-substituent. In addition, the loss of one hydrogen and one trimethylsilyl group arises from their *syn* disposition in (13). Both these proposals have literature precedent. Laguerre reported that *m*-xylene was converted into 1-(trimethylsilyl)-3,5-dimethylbenzene(17) on reductive silylation and reoxidation (scheme7)[5a].

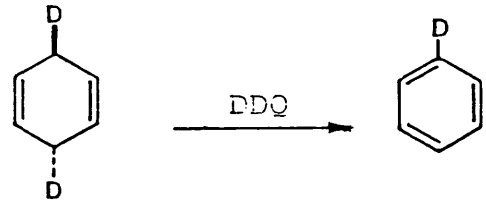
Scheme (7)



(17)

Secondly, Fleming reported that the DDQ oxidation of *trans*-3,6-dideuteric-1,4-cyclohexadiene (18) was *syn* stereospecific giving monodeuteriobenzene (19) only.[8] (scheme 8)

scheme (8)



(18) (19)

In support of the intermediacy of (13) we isolated (16) as a minor product formed during the quinone oxidation *via* a 1,2-(trimethylsilyl) group migration (scheme 6).

The structural assignment of (14) was in agreement with all the spectral and microanalytical data. The ^{1}H high resolution NMR spectrum was especially informative, the chemical shifts and coupling constants for the aromatic protons were fully consistent with the 1,4-disubstitution pattern. Difference n.O.e experiments showed that the N-$SiMe_3$ group was close to the C-2 and C-7 protons, whereas the C-$SiMe_3$ was close to both C-3 and C-5.[9]

As an alternative procedure 1-(trimethylsilyl) indole (20) was reduced by lithium metal in THF in the presence of TMS-Cl followed by PBQ oxidation to give (14) in

55% yield (scheme 9).

Scheme (9)

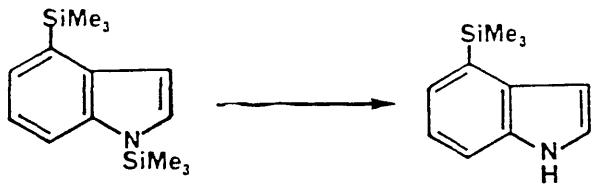


(20) (14)

It should be noted that from a practical point of view these procedures gave easy access to multi gram quantities of (14). With material in hand we set about investigating the properties of (14) towards a variety of electrophiles and the behaviour of the resulting products in further chemical transformations.

For example, on warming in methanol (14) gave 4-(trimethylsilyl) indole (7) in 98% yield (scheme 10).

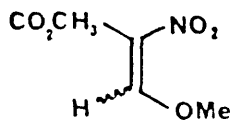
Scheme (10)



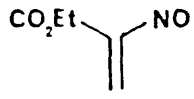
(14) (7)

Both (14) and (7) reacted with electrophiles at the C-3 position and not *via ipso* substitution at C-4. (7) was found to react with methyl 3-methoxy-2-nitro propenoate (21)[10] or ethyl 2-nitrosopropenoate (22)[11] to give (23) and (24) respectively (scheme 11).

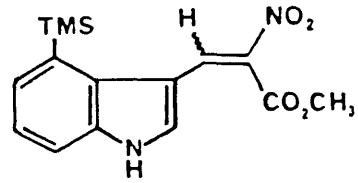
Scheme (11)



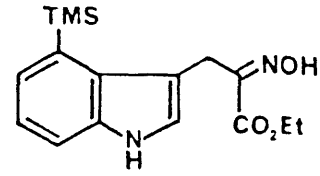
(21)



(22)

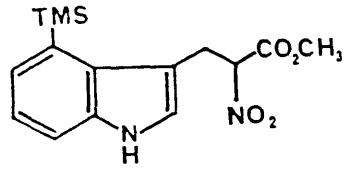


(23)

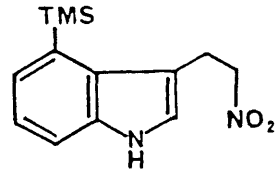


(24)

The reduction of (23) with sodium borohydride to give the saturated nitro ester (25) was not straight forward. (table 1)



(25)



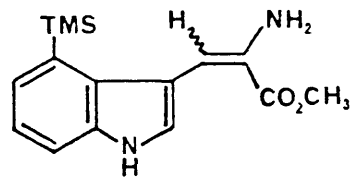
(26)

The basic nature of the reaction medium led to saponification of the methyl ester and subsequent decarboxylation to give the saturated nitro compound (26). This was overcome by the use of sodium borohydride in the presence of silca gel in chloroform/isopropanol[12] which gave a satisfactory 88% yield of (25)

Table (1).

SOLVENT	REACTION CONDITIONS	WORK UP	YIELD (25)	YIELD (26)
CH_3CN	0° 0.5h RT 12h	pH 7 Buffer	46	15
MeOH	RT, 18h	WATER	30	3
MeOH	RT, 18h	pH 5.8 BUFFER	58	13
$CHCl_3/SiO_2$ ISOPROPANOL	RT 5h	pH 5.8 BUFFER	88	-

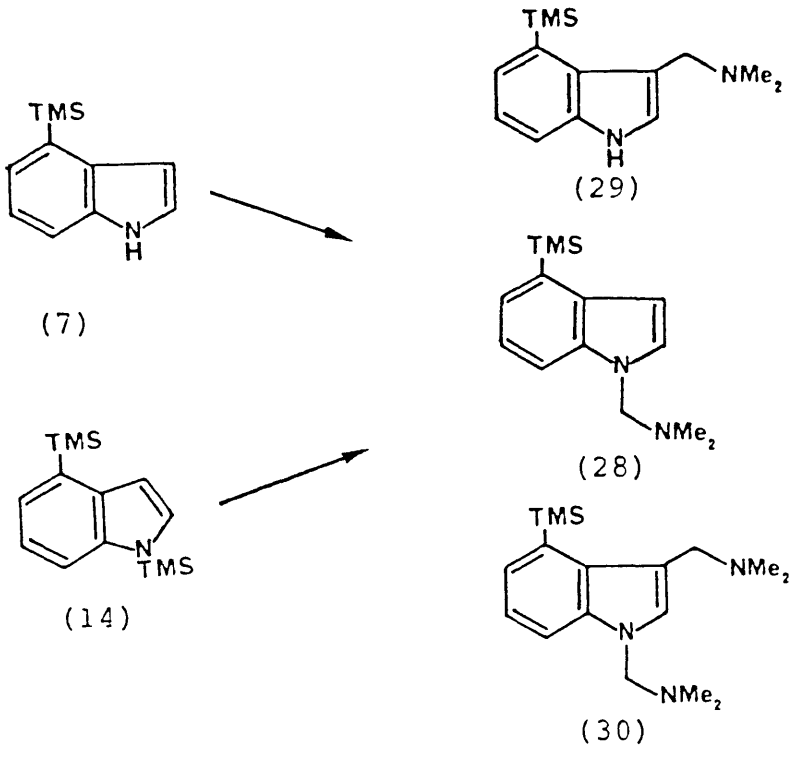
The catalytic hydrogenation of (23) under a wide variety of conditions gave mixtures of (25) and the enamine (27) in low yield. This was in agreement with results of Babievski *et al.*[13]



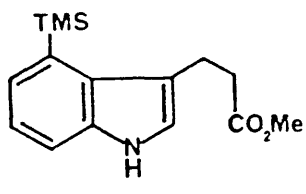
(27)

Both (7) and (14) reacted rapidly with N,N-dimethylmethylene ammonium chloride[14] giving a mixture of 1 and 3 monosubstituted and the 1,3-disubstituted adducts (28), (29) and (30) respectively (scheme 12).

scheme (12)

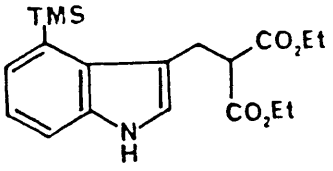


These products were readily separated by column chromatography. The 4-(trimethylsilyl) gramine (29) was transformed by standard indole chemistry[15] into a variety of derivatives. By refluxing (29) with methylnitroacetate[16] in CH_3CN (25) was obtained in 97% yield. Subsequent tri-*n*-butylstannane[17] reduction of nitro ester (25) gave ester(31) in 76% yield



(31)

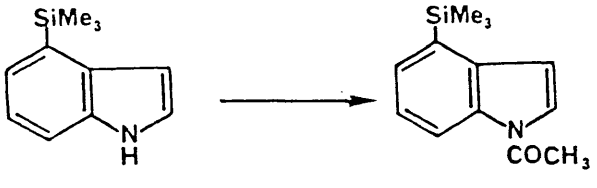
On treatment of (29) with tri-n-butyl phosphine and diethyl malonate[15] at reflux in CH_3CN for 4h an excellent 91% yield of (32) was realized.



(32)

Having investigated the reactivity of (7) and (14) towards a variety of electrophiles we decided to deactivate the C-3 position by placing an electron-withdrawing group on the N-1 position hopefully allowing *ipso* substitution to occur. 4-(Trimethylsilyl)indole (7) was cleanly converted to 1-acetyl-4-(trimethylsilyl) indole(33) in 96% yield by treatment with sodium hydride and acetyl chloride in THF.

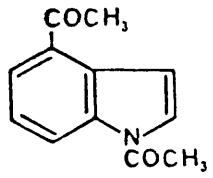
scheme (13)



(7) (33)

Reaction of (33) with acetyl chloride and $AlCl_3$ in dry CH_2Cl_2 gave 1,4-diacetylindole(34) in an excellent 95% yield. The spectral data was completely consistent with N-1, C-4 substitution. (scheme 14)

scheme (14)



(34)

δ_H (250 MHz; $CDCl_3$)

2.66(3H,S, NCO CH_3)

2.71(3H,S, $COCH_3$)

7.41(1H,dd,J=4.0,1.0Hz ,*H-3*)

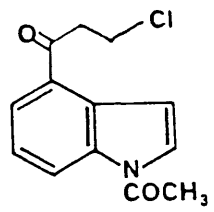
7.44(1H,dd,J=8.5 , 7.5Hz,*H-6*)

7.91(1H,d , J= 4.0Hz ,*H-2*)

7.95(1H, dd,J=7.5 ,1.0Hz ,*H-5*)

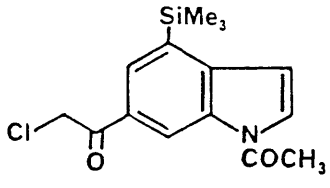
8.66(1H,ddd, J=8.5 , 1.0 ,1.0Hz ,*H-7*)

Under identical Friedel-Crafts conditions(33) reacted with chloropropanoyl chloride and acryoyl chloride to give 1-acetyl-4-(3-chloropropanoyl)indole(35) in 75% and 60% yield respectively.

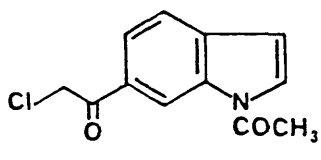


(35)

However when chloroacetyl chloride and (33) were reacted under Friedel Crafts conditions products arising from non-*ipso* substitution were obtained. 1-Acetyl-6-(chloroacetyl)-4-(trimethylsilyl)indole (36) and 1-acetyl-6-chloroacetyl indole (37) were isolated in 37% and 46% respectively. (37) arose presumably *via* protodesilylation of (36).

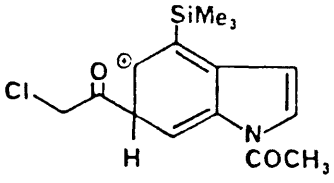


(36)



(37)

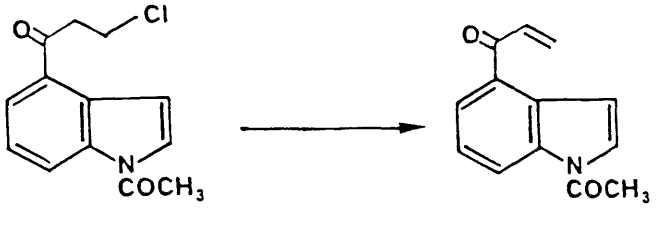
Both (36) and (37) were fully characterized by spectral and microanalytical data. The reaction is likely to have proceeded *via* an intermediate of type (38).



(38)

We feel *ipso* substitution could have been suppressed either by steric congestion or by the nature of the complex formed between chloroacetyl chloride and $AlCl_3$.

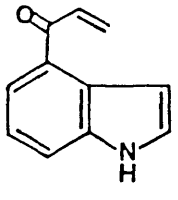
scheme (15)



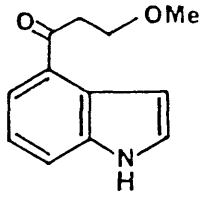
(35) (39)

The conversion of (35) into the acryoyl derivative (39) *via* elimination of HCl was achieved using 1eq of sodium hydroxide in aqueous THF in 84% yield (scheme 15).

Attempts to remove the acetyl deactivating groups in (35) and (39) by treatment with K_2CO_3 in methanol-acetone followed by acidification gave (40) and (41) respectively.



(40)



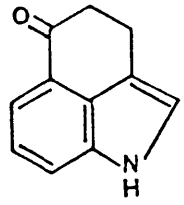
(41)

Attempts to cyclize (40) under basic conditions were unsuccesful.

With these encouraging results from 1,4-bis(trimethylsilyl)indole(14) and 4-(trimethylsilyl)indole(7) it was decided to extend our studies to the synthesis of the ergot alkaloids and their precursors. The work described in this area was carried out by Drs. D.Dauzonne and A.Renaud and although the author played no direct part it is included for completeness.

Preparation of an Uhle's ketone derivative[1,19] from 4-(trimethylsilyl)indole(7).[9]

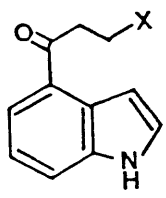
In classical ergot alkaloid syntheses, Uhle's ketone (42)[1] has been used as a key intermediate.



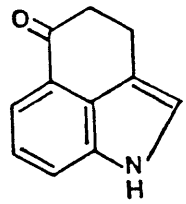
(42)

From 4-(trimethylsilyl)indole(7) we envisaged two distinct approaches. Firstly cyclization of compounds of type(43) was considered. (scheme 16)

scheme(16)



(43)

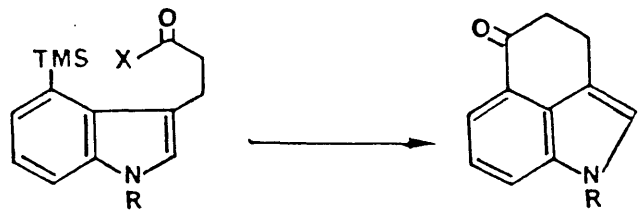


(42)

However our previous studies had indicated that this was not a facile process. We therefore concentrated our efforts on a second approach in which cyclization onto

the C-4 position under Friedel-Crafts conditions with compounds of type (44) was envisaged. (scheme 17)

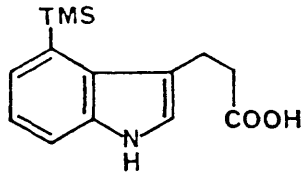
scheme (17)



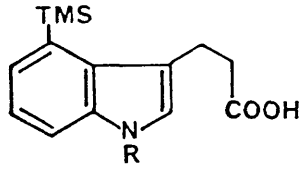
(44) (45)

With this second approach we had to take into account competing cyclization onto the C-2 position of which there was literature precedent. Hence deactivation of the C-2 position by a suitable electron withdrawing substituent on the N-1 position would be necessary. Secondly, there was also the possibility of competing protodesilylation under the Lewis acidic Friedel-Crafts conditions to give 1,3-disubstituted indoles as products.

Preparation of ester (31) from nitro ester (25) was straightforward as previously described. Hydrolysis with sodium hydroxide, followed by careful acidification gave acid (46) in 53% yield.

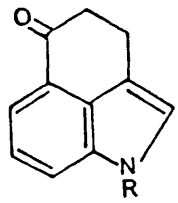


(46)



R $COCF_3$ (47)
SO_2Ts (48)

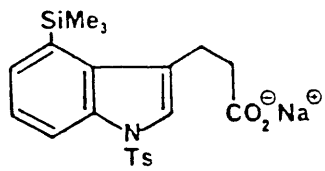
Initially the trifluroacetyl group was chosen to deactivate the C-2 position due to its potent electron withdrawing ability. Treatment of (46) with sodium hydride and trifluroacetic anhydride gave acid (47) in 31% yield. However attempted cyclization of acid (47) using oxalyl chloride followed by $AlCl_3$ did not give isolable quantities of the desired cyclic compound (49).



R=$COCF_3$ (49)

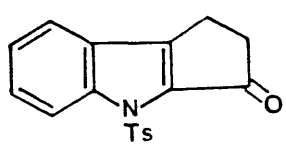
= SO_2TOl (50)

However when the tosyl group was used to deactivate the C-2 position cyclization occured. Ester (31) was treated sequentially with potassium hydride, TsCl and methanolic sodium hydroxide to give the sodium salt(51).



(51)

On reaction with diethylchlorophosphate and $AlCl_3$ (51) was converted into a mixture of compounds. Chromatography gave two cyclic products[18] (50) and (52) in 5% and 34% respectively.



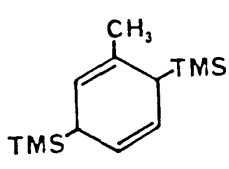
(52)

The desired product(50) was formed in a disappointingly low yield probably due to the ring strain involved during the cyclization.

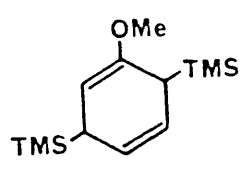
The Silyl Birch Reduction.

As our previous work had successfully illustrated , functionalization of the C-4 position of indole had been achieved by use of the Birch reduction in the presence of TMS-Cl.[19] I shall subsequently refer to this type of reaction as the "silyl Birch reduction".

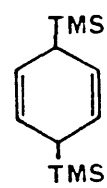
It was decided to investigate the silyl Birch reduction with a variety of carbocyclic and heterocyclic aromatic compounds as substrates. Laguerre and co-workers had reported the use of the silyl Birch on simple mono and di- substituted hydrocarbons such as toluene and xylene[5a] to give 1,4-disilylderivatives which could be reoxidized to the aromatic silanes by refluxing in cyclohexane. In addition an earlier report by Weyenberg and Toporcer[5a] had referred to the reduction of toluene(8) and anisole(53) in the presence of TMS-Cl giving 30-50% yields of 1-methyl and 1-methoxy-3,6-bis(trimethylsilyl)-1,4-cyclohexadiene (9) and (54) respectively.



(9)



(54)

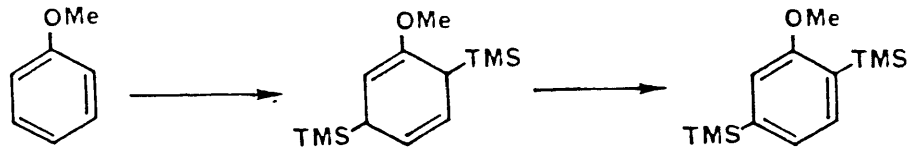


(55)

No experimental detail for either of these later results had been included, however the authors had given details of their reduction of benzene under silylating conditions

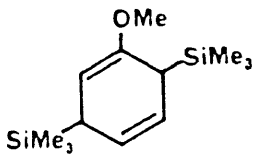
using lithium sand which gave a 30% yield of 1,4-bis-(trimethylsilyl)cyclohexadiene(55) after 8 days at 25 C! We felt our novel use of ultrasound would improve the yields and practicability of these reactions. Indeed we found treatment of anisole (53) with lithium metal, TMS-Cl in THF and ultrasonic agitation of the mixture at 0-5°C for 12h gave after aerial oxidation a satisfactory 69% yield of 2,5-bis(trimethylsilyl)anisole(56) as a white crystalline solid. (scheme 18)

scheme(18)



(53) (54) (56)

Aerial oxidation could be carried out by allowing the crude reaction mixture to stand in the air or more conveniently by boiling in 40-60° petrol. In this case it proved possible to isolate the dihydro intermediate (54) and obtain NMR data, although a small quantity of the oxidized aromatic (56) product was always present.

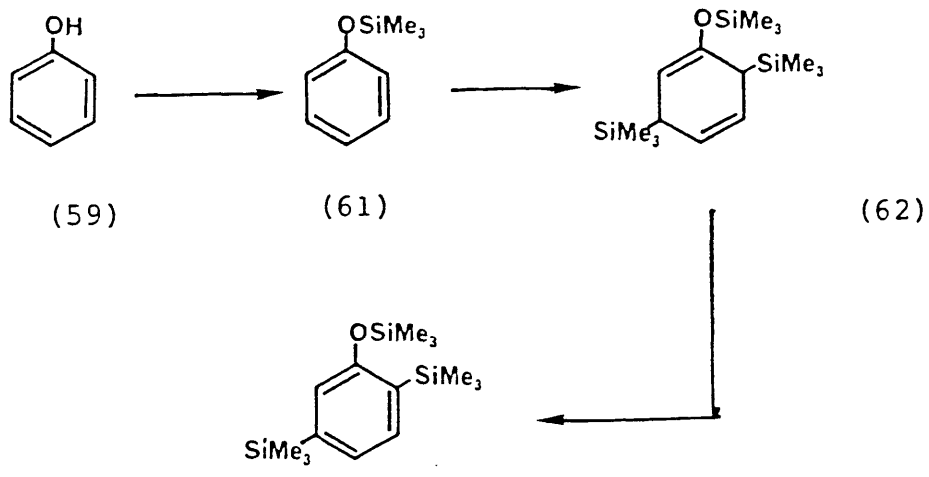


(54)

δ_H(60Hz;$CDCl_3$)
0.10(18H,d,$SiMe_3$)
2.20(2H,m,*H-2*,*H-5*)
3.55(3H,s,OMe)
4.30(1H,s,*H-6*)
5.45(2H,s,*H-3*,*H-4*)

As a result of this we extended the reaction to other carbocyclic substrates the results of which are summarized in table(2). The related *p*-methyl anisole(57) gave 4-methyl-2,5-bis(trimethylsilyl)anisole(58) after oxidative work up. Phenol(59) gave the novel 2,5-bis (trimethylsilyl)siloxybenzene(60). This was formed presumably by initial silylation at the C-1 oxygen to give(61) followed by reduction to give the dihydro intermediate(62). Finally oxidation gave the aromatic product(60) in 72% yield (scheme 19).

scheme (19)



(59) (61) (62)

(60)

Table (2)

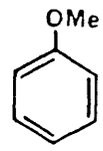
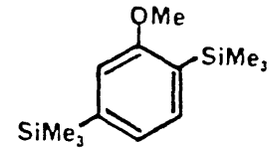
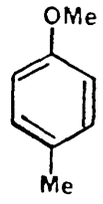
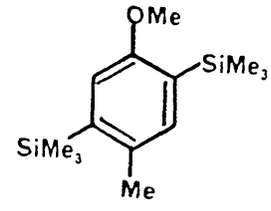
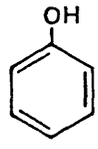
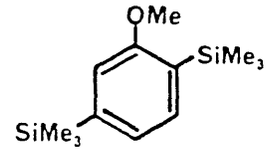
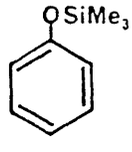
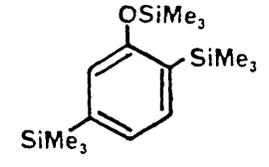
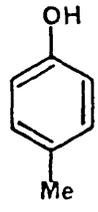
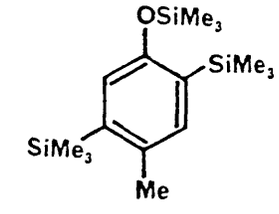
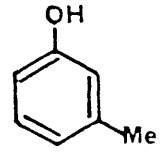
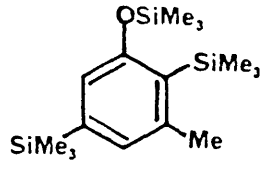
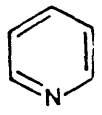
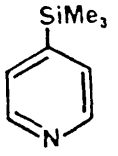
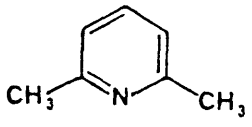
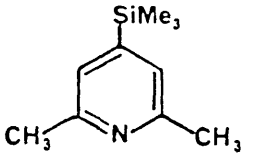
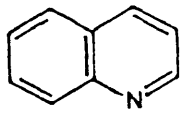
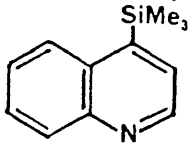
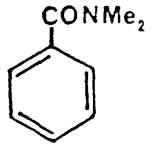
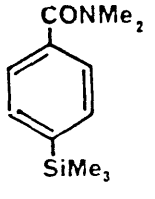
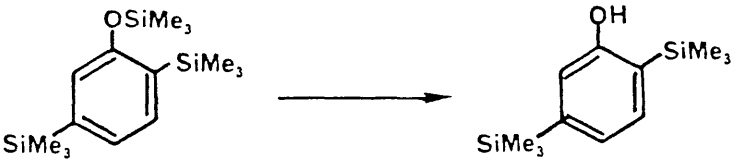
SUBSTRATE	REACTION CONDITIONS	OXIDANT	PRODUCT	% YIELD
 (53)	 0-5°C 12h	△ AIR	 (56)	63
 (57)	 0-5°C 16h	△ AIR	 (58)	64
 (59)	 0-5°C 16h	△ AIR	 (60)	72
 (61)	 0-5°C 16h	△ AIR	 (60)	68
 (63)	 0-5°C 16h	△ AIR	 (64)	58

Table (2) Continued

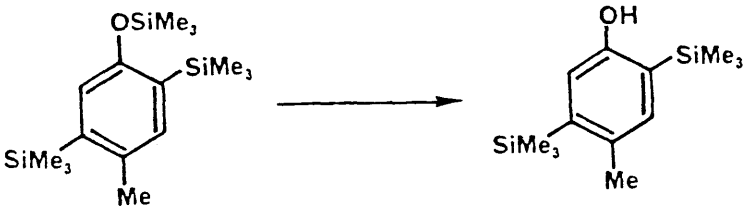
SUBSTRATE	REACTION CONDITIONS	OXD.	PRODUCT	% YIELD
 (67)	 0-5°C 16h	PBQ	 (69)	39
 (80)	0-5°C 4h	DDQ	 (82)	74
 (81)	0-5°C 6h	DDQ	 (83)	42
 (86)	0-5°C 6h	PBQ	 (87)	35
 (75)	 0-5°C 12h	PBQ	 (76)	42

As evidence for this sequence of steps it was found that the siloxy benzene(61) could be reduced under silylating conditions and subsequently air oxidized to give the aromatic silane (60) identical to the previously obtained material. *p*-Methyl-phenol (63) similarly gave 2,5-bis (trimethylsilyl)-4-methyl trimethylsiloxybenzene(64) in 58% yield. Treatment of (60) and(64) with 1 eq of TBAF in THF gave excellent yields of the novel phenols (65) and(66). (scheme 20)

scheme(20)

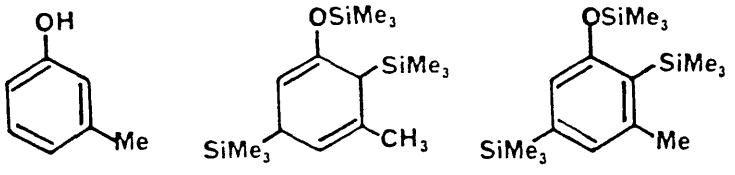


(60) (65)



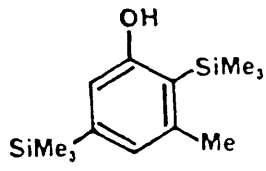
(64) (66)

With *m*-cresol(67) as the substrate,reduction under the silylating conditions gave the dihydrointermediate (68). However even after refluxing in petrol for 72h no aromatic product was obtained and the oxidation step required the use of PBQ to give the aromatic silane (69).



(67) (68) (69)

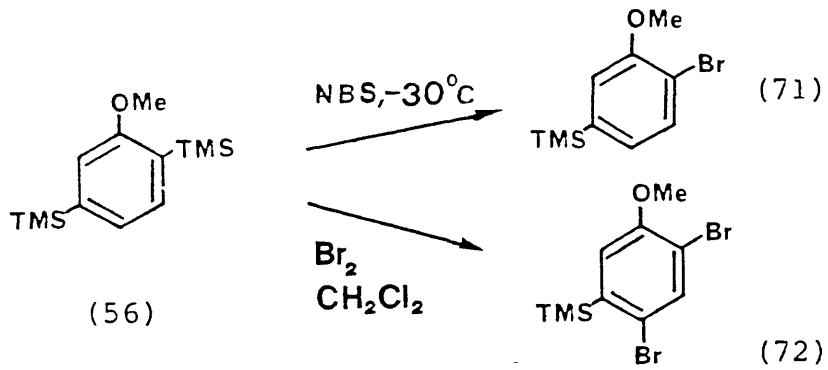
Again treatment of siloxy derivative (69) with 1eq of TBAF in THF gave the phenol (70) in an excellent 87% yield.



(70)

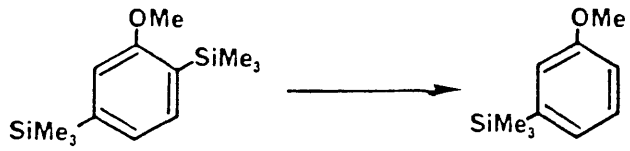
In view of the non-ipso substitution displayed by 4-(trimethylsilyl)indole (7) towards electrophiles we made a brief study of 2,5-bis(trimethylsilyl) anisole (56) and its corresponding reactivity. It was found that the methoxy group directed the reactivity of (56). With NBS at -30°C, monobromide(71) was formed in 73% yield. Treatment of (56) with 2 eq of bromine at 0°C gave the dibromide (72)in 84% yield (scheme 21).

scheme (21)



Selective protodesilylation to give 3-(trimethylsilyl) anisole (73) was achieved by treatment of (56) with 1eq of trifluroacetic acid in THF at 0°C. (scheme 22)

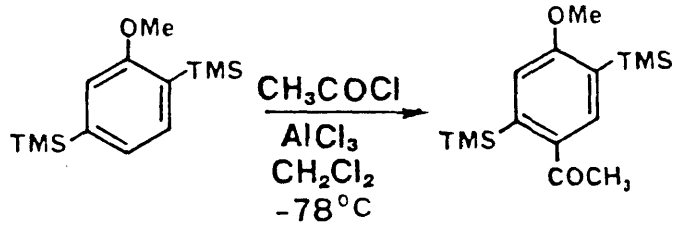
scheme (22)



(56) (73)

Friedel Crafts acylation of (56) using $AlCl_3$ and acetyl chloride at -78^0C in CH_2Cl_2 gave the *non-ipso* product (74) in 67% yield.(scheme 23).

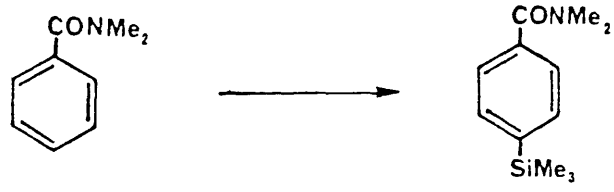
scheme (23)



(56) (74)

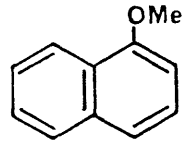
In an attempt to extend this methodology to other substituted carbocyclic systems we examined the reduction of several other systems. N,N-dimethylbenzamide (75) gave 4-(trimethylsilyl) N,N-dimethylbenzamide(76) in overall 42% yield after PBQ oxidation (scheme 24).

scheme (24)

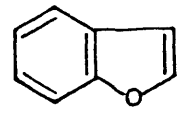


(75) (76)

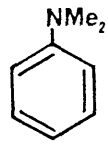
However when 1-methoxynapthalene(77) N,N-dimethyl aniline(78) and benzofuran(79) were examined no recognisable products were obtained. In particular the reduction of (77) gave at least 4 products which contained no *Me*O group by NMR.



(77)

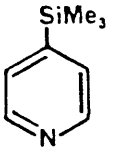


(79)

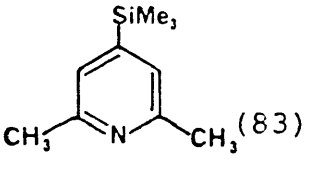


(78)

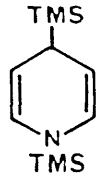
We next turned our attention to the reduction of heterocyclic compounds. Pyridine(80) and2,6-dimethyl pyridine (81)[20] gave 4-(trimethylsilyl)pyridine (82) and 2,6 dimethyl-4-(trimethylsilyl) pyridine (83) in 74 and 42% yield respectively after oxidation. No attempt was made to isolate the dihydrointermediates (84) and (85)



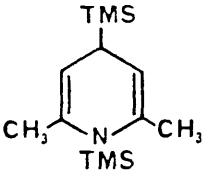
(32)



(83)



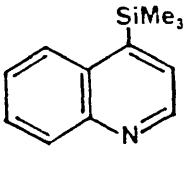
(84)



(85)

which were oxidized *in situ* with DDQ to the aromatic products (82) and (83). The use of DDQ rather than PBQ was found necessary to give satisfactory yields of (82) and (83).

Quinoline (86) gave a 35% yield of 4-(trimethylsilyl) quinoline(86)[21] after *in situ* oxidation with PBQ. These results are also summarized in table (2)



(87)

The reduction of these heterocyclic species was considerably faster than the previously discussed carbocyclic systems reflecting the lower energies of their LUMO's.

EXPERIMENTAL

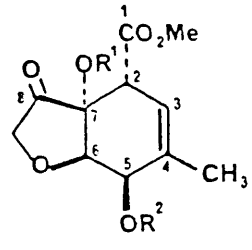
Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 298 and 983G grating infrared spectrophotometers using thin film or as a solution in methylene chloride. ^{1}H N.M.R. spectra were recorded at 60MHz on a Varian EM-360A, at 90MHz on a Jeol FX 90Q and at 250MHz on a Bruker WM-250 and are quoted for solutions in deuteriochloroform with tetramethylsilane as an internal standard. Mass spectra were determined with a VG micromass 7070B instrument. Elemental microanalyses were performed in the Imperial college Chemistry Department microanalytical laboratory.

Analytical thin layer chromatography was performed on precoated glass-backed plates (Merk Kiesegel 60 F_{254}) and preparative chromatography was conducted under low pressure using either MN Kieselgel 60 (230-400 mesh) or BDH Florosil (200-300). Silica gel refers to the Kiesegel.

Petrol 40-60^{o} refers to light petroleum ether with b.p. 40-60^{o}C and was redistilled before use. Diethyl ether, 1,2-dimethoxyethane and tetrahydrofuran were dried by reflux over sodium/benzophenone and distilled before use. Dichloromethane was dried by reflux over phosphorous pentoxide and distilled before use. Benzene and toluene were dried over sodium wire and acetonitrile over calcium hydride and were distilled before use. Pyridine, diisopropylamine and triethylamine were distilled from calcium hydride and stored over potassium hydroxide pellets. All

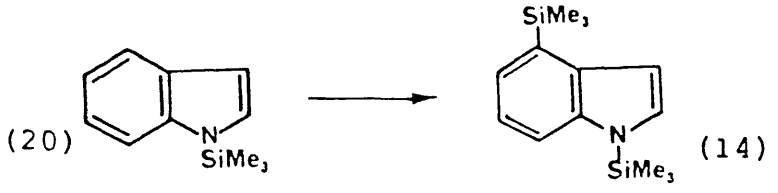
other solvents and reagents were purified by standard techniques. Solutions were dried over anhydrous sodium sulphate and evaporated with a rotary evaporator followed by static evaporation with an oil pump.

The numbering system used throughout the text and the experimental is consistent with the avermectin/ milbemycin system and is illustrated below.



Preparation of 1,4-Bis(trimethylsilyl)indole (14)

Method A:



To a stirred solution of 1-(trimethylsilyl) indole (20) (2.0g, 10.56 mmol) in THF(30ml) at 0°C under argon was added trimethylsilyl-chloride (3.47g, 31.91mmol). Lithium (0.186g 26.80mmol) cut into 20 clean pieces was added and the mixture agitated in an ultrasonic bath at 5-10°C for 4h and subsequently overnight at 45°C. The THF was evaporated under reduced pressure and replaced by CH_2Cl_2 (10ml). It was essential to maintain an argon atmosphere during this solvent change. The mixture was cooled to 0°C and a solution of *p*-benzoquinone(1.72g,15.91mmol) in CH_2Cl_2 (20ml) was added. After the reaction had stirred for 3h the solvent was evaporated under reduced pressure and the residue triturated with 40-60° petrol.

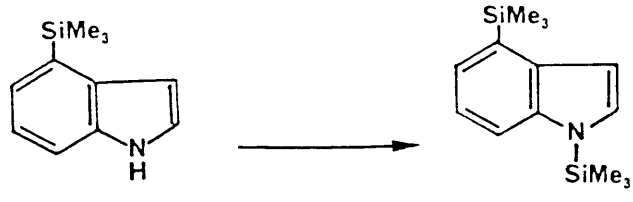
The extract was filtered directly through silica (35g) eluting with 40-60°petrol(60ml) and 10% CH_2Cl_2-40-60°petrol (130ml). The combined filtrates were evaporated under reduced pressure and the residue chromatographed (40-60°petrol → 10% CH_2Cl_2-40-60°petrol) to give *1,4-bis (trimethylsilyl) indole* (14) (1.52g,55%) as white crystals, m.p. 62.5-63.5°C (from 40-60°petrol), ν_{max}(nujol)

1510, 1400, 1290, 1260, 1160, 915, 850, and 760cm^{-1}; δ_H(250MHz; $CDCl_3$) 0.38 (9H,S, N-Si*Me*$_3$),0.53(9H,S,CSi*Me*$_3$), 6.68(1H,dd,J=3.5, Hz,*H-3*), 7.12 (1H,dd,J=8.0 , 9.0Hz,*H-6*) 7.15(1H,d,J=3.5Hz ,*H-2*), 7.25 (1H,dd,J=8.0, 1.0Hz, *H-5*),7.47 (1H,dt,J= 9.0,1.0Hz, *H-7*); *M/Z* =261(M^+) (Found:C, 64.28;H,8.87; N,5.36%. $C_{14}H_{23}NSi_2$requires C,64.28; H,8.93;N,5.33%).

Method B:

When exactly the previous procedure was used, reaction of indole (1.24g,10.58mmol), lithium (0.297g,42.79mmol), trimethylsilylchloride(4.60g,42.34mmol) and *p*-benzoquinone (2.30g,21.28mmol)gave *1,4-bis(trimethylsilyl)indole*(14) (1.39g,50%) identical with the previous sample.

Preparation of 4-(trimethylsilyl)indole(7)



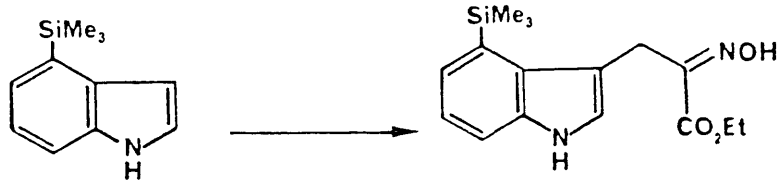
(14) (7)

A solution of 1,4-bis(trimethylsilyl)indole(14) (2.61g,9.98 mmol) in dry MeOH(50ml) was refluxed for 5min. The solvent was evaporated under reduced pressure and the residue re-dissolved in MeOH(50ml), reevaporated and redissolved in 40-60° petrol and reevaporated to give crude *4-(trimethylsilyl) indole*(7). Recrystallization gave pure (7) (1.70g,90%) as white plates, m.p.63.5-64.0°C(from MeOH-H_2O), ν_{max}(CH_2Cl_2) 3400, 1400, 1250, 940, 840, 760, and 735cm^{-1};

δ_H (250 MHz; $CDCl_3$) 0.41 (9H,S, $SiMe_3$), 6.68(1H,m,*H-3*), 7.20(1H,dd,J=8.0, 7.0Hz, *H-6*), 7.23(1H,m,*H-2*), 7.29 (1H,dd,J=7.0, 1.5Hz, *H-5*), 7.40(1H,dt,J=7.0 , 1.5Hz,*H-7*), 8.0-8.3(1H,m, *H-1*); *M/Z*=189(M^+) (Found:C,69.79; H, 8.04; N,7.40%. $C_{11}H_{15}NSi$ requires C,69.76; H,7.99; N,7.40%.

Preparation of Ethyl 2-(hydroxyimino)-3-(4'-(trimethylsilyl) indol-3-yl)-propanoate.

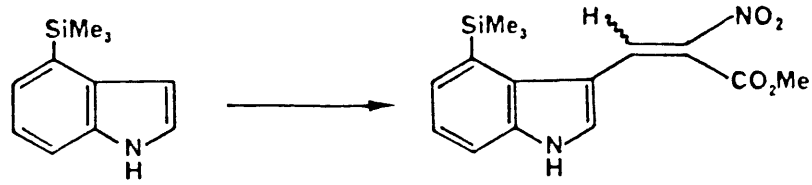
(24)



(7) (24)

To a stirred solution of 4-(trimethylsilyl) indole(7) (0.47g, 2.48mmol) in CH_2Cl_2(60ml) under argon was added ethyl 3-bromo-2-(hydroxyimino) propanoate (0.58g, 2.76mmol) followed by Na_2CO_3 (1.50g, 9.93mmol). The mixture was stirred at rt for 16h, then filtered through celite. The solvent was evaporated under reduced pressure and the residue chromatographed (70% Et_2O-40-60°petrol) to give *ethyl 2-(hydroxyimino)-3-(4'-trimethylsilyl)indol-3-yl)-propanoate*(24) (0.29g, 36%) as white crystals, m.p.201-204°C (fromEtOAc), $\nu_{max.}$ (nujol) 3460, 3250(br), 1720, 1260, 1230,1215, 1130, 1015, 955 and 850cm^{-1}; δ_H(270 MHz; $(CD_3)_2CO$) 0.47(9H,s,Si *Me*$_3$), 1.20(3H,t,J=7.0Hz,*Me*), 4.17(2H,q,J=7.0Hz, CH_2), 4.25(2H,d,J=1.0Hz,*H-2*), 6.88(1H,s,*H-2'*), 7.07(1H,dd, J=7.9, 7.3Hz, *H-6'*), 7.25(1H,dd,J=7.3, 1.3Hz, *H-5'*), 7.42(1H,dd,J=7.9, 1.3Hz,*H-7'*); *M/Z*=301 (M^+-1) (Found: C,60.71; H,7.25; N8.80%. $C_{16}H_{22}N_2O_3Si$ requires C60.35; H,6.96;N,8.80%).

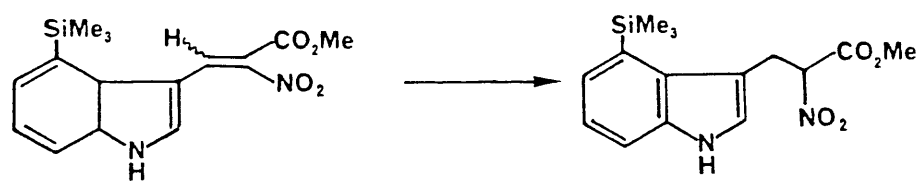
Preparation of Methyl2-nitro-3-(4'-(trimethylsilyl)indol-3-yl) propenoate (23)



(7) (23)

A mixture of 4-(trimethylsilyl)indole (7) (0.189g, 1mmol) and methyl 3-methoxy-2-nitropropenoate(21)(0.161g, 1mmol) were stirred under argon at rt for 24h. A further equivalent of(21) was added and the mixture stirred for a further 24h. The crude material was chromatographed (CH_2Cl_2) to give *methyl 2-nitro-3-(4-(trimethylsilyl)indol-3-yl) propenoate* (23) (0.138g, 43%) as yellow crystals,m.p. 195-202°C (from CCl_4:benzene), $\nu_{max.}$ (nujol) 3390,1710,1615,1520, 1290, 1270, 1250, 1145, 1125, 1105, 835 and 750cm^{-1}; δ_H (250MHz; $CDCl_3$) 0.339, 0.345 (9H, 2s,Si*Me*$_3$) 3.942, 3.975 (3H, 2s,CO_2*Me*)7.275-8.586 (5H, Complex), 8.75, 8.83 (1H,brS, N-*H*); *M/Z* =318(M+) (Found:C,56.65; H,5.79%. $C_{15}H_{18}N_2O_4Si$ requires C,56.56; H, 5.70%).

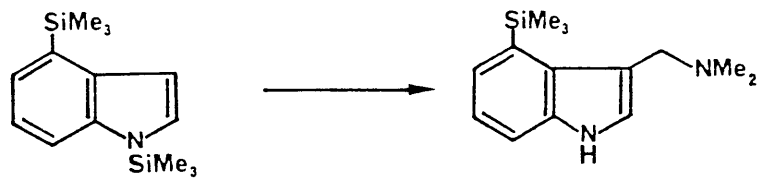
Preparation of Methyl 2-nitro-3-(4'-trimethylsilyl)indol-3-yl)-propanoate. (25)



(23) (25)

To a stirred solution of methyl 2-nitro-3-(4'-(trimethylsilyl)indol-3-yl) propenoate (23) (0.240g, 0.75mmol) in $CHCl_3$:isopropanol (5:1 v/v, 16ml) was added silica gel (1.40g) and sodium borohydride (0.140g, 3.75mmol). The suspension was stirred at rt for 5h, the solvent was evaporated under reduced pressure and the residue triturated with CH_2Cl_2 (3x30ml). The combined organic phase was washed with buffer (pH5.8, 15ml) and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (CH_2Cl_2) to give *methyl 2-nitro-3-(4'-(trimethylsilyl) indol-3-yl)-propanoate* (25) (0.212g, 85%) as a yellow oil, $\nu_{max.}$ (CH_2Cl_2) 3460, 1760, 1570, 1220, 1100, 1015, and 850cm^{-1}; δ_H($CDCl_3$; 60MHz) 0.45(9H,s,Si*Me*$_3$), 3.80(3H,s, CO_2*Me*), 3.85(2H,d,J= 7Hz,*H-3*), 5.43(1H,t, J=7Hz,*H-2*), 6.90 (1H,d,J=3Hz, *H-2'*), 7.1-7.5 (3H,m,*H-5'*, H-6' H-7') 8.0-8.3 (1H,br,N*H*);*M/Z* =320(M^+).

Preparation of 3((Dimethylamino)methyl)-4-(trimethylsilyl) indole (29)

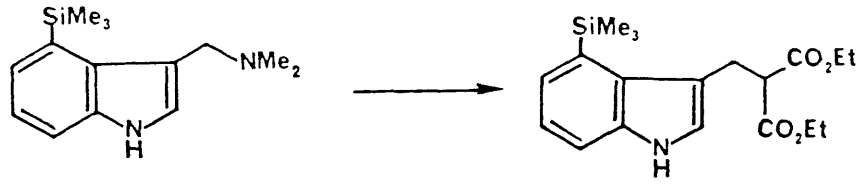


(14) (29)

To a stirred solution of (14) (0.261g,1.00mmol) in dry CH_2Cl_2 (10ml) was added N,N-dimethylmethyleneammonium chloride (0.131g, 1.40mmol). After stirring at rt for 4h, 10% aqueous potassium carbonate (8ml) was added. The organic layer was washed, dried and the solvent evaporated under reduced pressure.

The residue was chromatographed (90%CH_2Cl_2-10% EtoAc then MeOH) to give(28) (0.025g,11%)as an oil, δ_H(60MHz;$CDCl_3$)0.40 (9H,s,Si*Me*$_3$), 2.22(6H,s,N*Me*$_2$), 4.60(2H,s,C*H*$_2$),6.53(1H,d,*H-3*), 7.00-7.55(4H,m,*H-5*,*H-6*,*H-7*) then *3((dimethylamino)methyl)-4-(trimethylsilyl)indole*(29) (0.120g,48%) as a white crystalline solid,m.p.122-133°C (from hexane),$\nu_{max.}$(CH_2Cl_2)3460, 1390, 1100, 1015, 940 and 840cm^{-1}; δ_H(60MHz;$CDCl_3$)0.43(9H,s,Si *Me*$_3$), 2.31 (6H,s,N*Me*$_2$), 3.71(2H,s,C*H*$_2$), 6.98-7.40(4H,m,*H-5*, *H-6*,*H-7*), 8.25-8.65(1H,m,N*H*), *M/z*=246(M^+) (Found:C,68.26; H,8.95;N,11.10%. $C_{14}H_{22}N_2Si$ requires C 68.24;H,8.99;N,11.37%), then (30) (0.035g, 12%) δ_H(60MHz;$CDCl_3$) 0.42(9H,s,Si*Me*$_3$), 2.28(6H,s,N*Me*$_2$), 2.30(6H,s,N*Me*$_2$), 3.70(2H,s,C*H*$_2$), 4.67(2H,s, C*H*$_2$), 7.05-7.58(4H,m,*H-5*,*H-6*,*H-7*).

Preparation of Ethyl 2-(ethoxycarbonyl)-3-(4'-(trimethylsilyl)indol-3-yl)propanoate. (32)



(29) (32)

Gramine derivative (29) (0.105g, 0.43mmol),diethyl malonate (0.082g, 0.51mmol) and tri-*n*-butylphosphine(0.024g,0.12mmol) were dissolved in dry CH_3CN (10ml) and refluxed for 4h. The solvent was evaporated under reduced pressure and the residue chromatographed (CH_2Cl_2) to give *ethyl 2-(ethoxycarbonyl)-3-(4'(trimethylsilyl)indol-3-yl)propanoate*(32)

(0.140g 91%) as a white solid, m.p. 83.5-85.5°C (from hexane), $\nu_{max.}$ (CH_2Cl_2) 3460, 1740, 1725, 1150, 1035, 940 and 840cm^{-1}; δ_H(60MHz;$CDCl_3$) 0.49(9H,s,Si*Me*$_3$), 1.21 (6H,t,J=7Hz,CH_2CH_3), 3.42-3.90 (3H,m,*H-2, H-3*), 4.15 (4H,q, CH_2CH_3, J=7Hz), 6.97 (1H,br d, J=3Hz,*H-2'*), 7.05 (3H,m,*H-5; H-6;H-7'*), 8.05-8.45 (1H, br m, N*H*); *M/Z* =361 (M^+) (Found: C, 63.15; H, 7.58; N, 3.87%. $C_{19}H_{27}NO_4Si$ requires C, 63.13; H,7.53;N,3.87%).

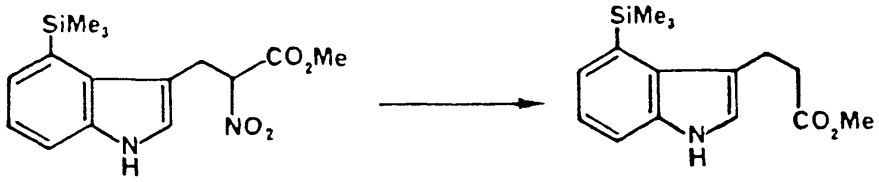
Preparation of Methyl 2-nitro-3-(4'(trimethylsilyl)indol -3-yl) propanoate (25)



(29) (25)

Gramine derivative (29) (0.49g, 2.00mmol) and methyl nitroacetate(0.25g, 2.10mmol) were refluxed in a dry CH_3CN (40ml) under argon for 12h. The solvent was evaporated under reduced pressure and the residue chromatographed to give *methyl 2-nitro-3-(4-(trimethylsilyl)indol-3-yl) propanoate* (25) (0.595g, 97%) as a yellow oil, $\nu_{max.}$ (CH_2Cl_2) 3460, 1760, 1570, 1220, 1100, 1015 and 850cm^{-1}; δ_H (60MHz;$CDCl_3$) 0.45(9H,s, Si*Me*$_3$), 3.80 (3H,s, CO_2Me), 3.85(2H,d, J=7Hz, *H-3*), 5.43 (1H,t,J=7Hz,*H-2*), 6.90 (1H,d, J=3Hz,*H-2'*), 7.10-7.50(3H,m, *H-5; H-6', H-7'*), 8.05-8.30(1H,br m, N*H*); *M/Z*= 320(M^+).

Preparation of Methyl 3-(4'-(trimethylsilyl) indol-3-yl)propanoate (31)



(25) (31)

Nitro ester (25) (1.20g, 3.75mmol), tri-*n*-butyltin hydride (2.31g, 7.94mmol) and AIBN (0.35g, 2.13mmol) were dissolved in dry benzene (100ml) and refluxed for 4h. The solvent was evaporated under reduced pressure and the residue chromatographed on alumina (110g) (50%CH_2Cl_2:hexane) to give *methyl 3(4-(trimethylsilyl)indol-3-yl)propanoate* (31) (0.78g, 76%) as a white solid, m.p. 108-109°C (from cyclohexane), $\nu_{max.}$ ($CHCl_3$) 3490, 1760, 1570, and 1150cm^{-1}; δ_H (60MHz;$CDCl_3$) 0.45(9H,s,Si*Me*$_3$), 2.70(2H,t, J=7.5Hz,*H-3*), 3.25 (2H,t, J=7.5Hz,*H-2*), 3.70(3H,s,CO_2*Me*), 6.90-7.50(4H, m, *H-2'*, *H-5'*, *H-6'*,*H-7'*), 8.10 (1H,br m, N*H*); *M/z*=275(M^+) (Found: C,65.25; H, 7.86; N, 5.11%. $C_{15}H_{21}NO_2Si$ requires C,65.41;H,7.68; N, 5.08%).

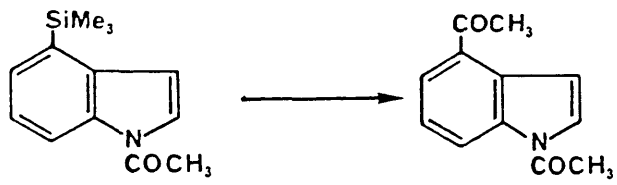
Preparation of 1-Acetyl-4-(trimethylsilyl)indole(33)



(7) (33)

To a suspension of sodium hydride (0.504g, 10.50mmol, 50% dispersion in oil prewashed with sodium dried 40-60°petrol (3x10ml))in THF (30ml)) under argon was added 4-(trimethylsilyl) indole (7) (1.325g, 7.00mmol). The mixture was ultrasonically agitated overnight during which time the temperature increased from 20°C to 40°C. The resulting solution was cooled to -78°C with stirring and acetyl chloride (0.825g, 10.51mmol) in THF(5ml) was added dropwise. The mixture was warmed to rt and the solvent evaporated under reduced pressure to give crude *1-acetyl-4-(trimethylsilyl) indole* (33) (1.550g, 96%). Recrystallization gave pure (33) as needles, m.p. 123-124°C (from 40-60°petrol) $\nu_{max.}$ ($CHCl_3$) 1690, 1530, 1400-1360, 1320, and 1250cm^{-1}; δ_H(250 MHz, $CDCl_3$) 0.39 (9H,s, $CSiMe_3$), 2.64(3H,s,*Me*), 6.77(1H,dd,J=4.0, 0.5Hz, *H-3*), 7.34 (1H,d,J=4.0Hz, *H-2*), 7.43(1H,dd,J=7.5,1Hz, *H-5*), 7.57(H,dd,J=7.5, 0.5Hz,*H-6*), 8.63(1H, br s,*H-7*); *M/Z* =303 (M^+) (Found:C,63.27; H,8.31; N,4.66%. $C_{13}H_{17}NOSi$ requires C,63.31; H,8.30;N,4.61%).

Preparation of 1,4-Diacetylindole(34)



(33) (34)

To a stirred suspension of freshly resublimed $AlCl_3$ (0.667g, 5.00mmol) in CH_2Cl_2 (10ml) under argon was added acetyl chloride (0.39g, 5.00mmol). When all the $AlCl_3$ had been stabilized a solution of 1-acetyl-4-(trimethylsilyl) indole(33) (0.231g,1.22mmol) in CH_2Cl_2 (5ml) was added dropwise. The resulting solution was stirred overnight then

0.25M hydrochloric acid (25ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3x15ml) and the combined organic extracts were washed with water and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (CH_2Cl_2) to give *1,4-diacetylindole* (34) (0.191g, 95%) as pale crystals, m.p. 110-113°C (from cyclohexane), $\nu_{max.}$ (CH_2Cl_2) 1710, 1675, 1580, 1530, 1380, 1320, 1180, 980 and 935cm^{-1}; δ_H (250MHz; $(CD_3)_2$ CO) 2.66 (3H, s, NCO *Me*), 2.71 (3H, s, CO*Me*), 7.41 (1H, d, J=4.0Hz *H-3*), 7.44 (1H, dd, J=8.5, 7.5Hz, *H-6*), 7.91 (1H, d, J=4.0Hz, *H-2*), 7.95 (1H, dd, J=7.5, 1.0Hz *H-5*), 8.66 (1H, dd, J=8.5, 1.0, Hz, *H-7*); *M/Z*=201 (M^+) (Found: C, 71.58; H5.51; N, 6.93%. $C_{12}H_{11}NO_2$ requires C71.63; H, 5.51 N, 6.96%).

Preparation of 1-Acetyl-4-(3'-chloropropanoyl)indole (35)

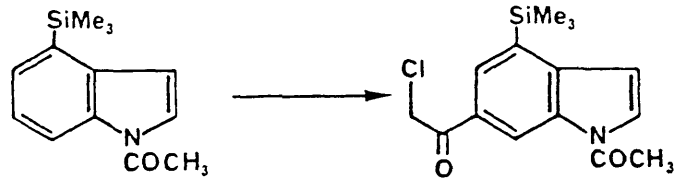


(33) (35)

To a suspension of freshly resublimed $AlCl_3$ (0.667g, 5.00mmol) in dry CH_2Cl_2 (15ml) was added 3- chloropropanoyl chloride (0.635g, 5.00mmol). When all the $AlCl_3$ had been solubilized a solution of 1-acetyl-4-(trimethylsilyl)indole (33) (0.231g 1.22mmol) in dry CH_2Cl_2 (5ml) was added. The solution was stirred at rt overnight, then 0.25M hydrochloric acid (25ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3x20ml) and the combined organic extracts were washed with water (20ml) and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (70% CH_2Cl_2-

40-60°petrol to give *1-acetyl-4-(3-chloropropanoyl)indole* (35) (0.186g, 75%) as a pale yellow solid, m.p. 120-122°C (from cyclohexane), $\nu_{max.}$ (CH_2Cl_2) 1710, 1670, 1580, 1535, 1320, 1170, 1120, 1010 and 930cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.67 (3H,s, COMe), 3.57(2H,t,J=6.5Hz, *H-3'*), 3.97(2H,t,J=6.5Hz, *H-2'*), 7.43 (1H,dd,J=8.0, 8.0Hz *H-6*), 7.51(1H,dd,J=4.0, 0.5Hz, *H-3*), 7.57(1H,d, J=4.0Hz,*H-2*) 7.84(1H,dd, J=8.0, 0.5Hz, *H-5*), 8.74(1H,br d, J=8.0Hz,*H-7*); *M/Z* = 249 (M^+) (Found:C, 62.47; H,5.00; N, 5.38%. $C_{13}H_{12}ClNO_2$ requires C, 62.53; H, 4.84; N,5.61%).

Preparation of 1-Acetyl-6-(Chloroacetyl)-4-(trimethylsilyl) indole (36)



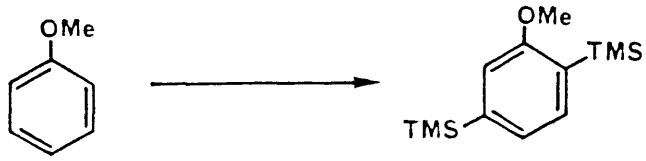
(33) (36)

To a suspension of freshly sublimed $AlCl_3$ (0.667g, 5.00mmol) in CH_2Cl_2 (10ml) under argon was added chloroacetylchloride (0.565g,5.00mmol) with stirring. When all the $AlCl_3$ had been solubilized a solution of 1-acetyl-4-(trimethylsilyl)indole(33) (0.231g, 1.22mmol) in CH_2Cl_2(5ml) was added dropwise. The resulting solution was stirred at rt for 15h, then poured into 0.25 M HCl solution(25ml). The aqueous phase was extracted with CH_2Cl_2 (3x20ml) and the combined organic extracts washed with brine and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (CH_2Cl_2) to give *1-acetyl-6-(chloroacetyl)-4-(trimethylsilyl)indole* (36)

(0.114g, 37%) as pale yellow crystals m.p. 194-196°C, $\nu_{max.}$ (nujol) 1715, 1680, 1585,1515, 1400, 1240, 1190, 1105, 955, 870 and 790cm^{-1}; δ_H(270MHz;$CDCl_3$) 0.42 (9H,s,$SiMe_3$), 2.69 (3H,s,*Me*), 4.83 (2H,s, CH_2), 6.83 (1H,br d, J=4.0Hz,*H-3*), 7.66(1H,d, J=4.0Hz,*H-2*), 8.07 (1H,d, J= .3Hz,*H-5*), 9.09(1H,br d, *H-7*); *M/Z*=307(M^+) (Found: C,58.44; H,5.85; N,4.54%. $C_{15}H_{18}ClNO_2Si$ requires C,58.52; H,5.89; N,4.55%). Further elution with CH_2Cl_2 gave *1-acetyl-6(chloroacetyl)indole*(37)(0.108g, 46%) as a white solid,m.p. 186-188°C, $\nu_{max.}$(nujol) 1715, 1695, 1525, 1340, 1255, 1150, 1040, 950, 835 and 785cm^{-1}; δ_H(270MHz;$CDCl_3$) 2.70(3H,s, *Me*), 4.84(2H,s,CH_2), 6.72(1H, d,J=4.0Hz,*H-3*),7.63(1H,d,J=4.0Hz, *H-2*), 7.67(1H,d,J=8.0Hz,*H-4*), 7.95(1H,dd,J=8.0,1.2Hz,*H-5*), 9.09(1H, brS,*H-7*); *M/Z*=235(M^+)

Preparation of 2,5-Bis(trimethylsilyl)anisole.

(56)



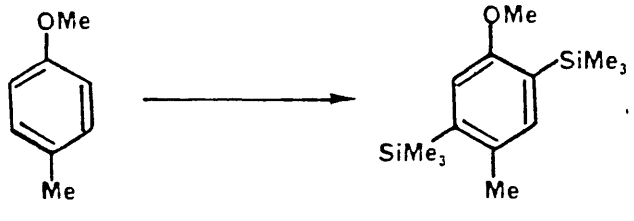
(53) (56)

To a stirred solution of redistilled anisole(53) (1.08g,10.00mmol) under argon at 0°C was added trimethylsilyl chloride(5.43g50.00mmol) followed by lithium(0.347g, 50.00mmol) cut into 50 pieces. The mixture was agitated in an ultrasonic bath at 5-10°C for 3h and subsequently overnight at 45°C The solvent was evaporated under reduced pressure and the residue triturated with 40-60°petrol(4x40ml). The combined extracts were filtered through celite and the solvent evaporated under reduced pressure. The residue was allowed to

air oxidise by standing at rt for 72h. Recrystallization gave *2,5-bis(trimethylsilyl)anisole*(56) (1.55g, 63%) as white crystals, m.p.49-51°C(from MeOH at-20°C), $\nu_{max.}$ (CH_2Cl_2) 2950, 2910, 2860, 1590, 1450, 1230, 1180,1120, 1045 and 850cm^{-1}: δ_H(90MHz; $CDCl_3$) 0.22(9H,s, Si*Me*$_3$), 3.79(3H,s, O*Me*), 6.95(1H,s,*H-6*), 7.15(1H,d, J=7.6Hz, *H-4*), 7.40(1H,d, J=7.6Hz,*H-3*); *M/Z*=252(M^+) (Found:C,61.87;H,9.71%. $C_{13}H_{24}OSi_2$ requires C,61.84; H,9.58%).

Preparation of 2,5-Bis(trimethylsilyl)-4-methyl anisole

(58)

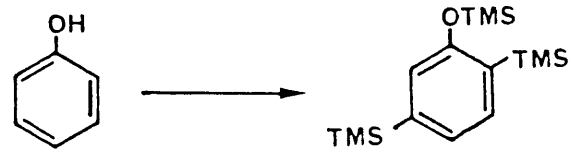


(57) (58)

To a stirred solution of *p*-methyl anisole(57) (1.22g, 10.00 mmol) in THF (30ml) at 0°C under argon was added trimethylsilyl chloride (5.43g, 50.00mmol) followed by lithium metal (0.35g,50.00mmol) freshly cut into approximately 20 pieces. The mixture was agitated in an ultrasonic bath at 0°C for 4h then at 40°C for 16h. The THF was evaporated under reduced pressure and the residue trturated with 40-60°petrol (4x40ml). The combined organic phase was filtered through celite and refluxed for 72h. The solvent was evaporated under reduced pressure and the residue recrystallized from MeOH at -20°C to give *2,5-bis(trimethylsilyl)-4-methyl anisole* (58) (1.70g, 64%) as a white crystalline solid, m.p.76-78°C (from MeOH at -20°C), $\nu_{max.}$ (CH_2Cl_2) 2950, 2915, 2860, 1590, 1430,1230, 1170, 1040 and 840cm^{-1}; δ_H(60 mHz; $CDCl_3$) 0.15

(9H,s,Si*Me*$_3$),0.25(9H,s,*Me*$_3$), 2.32(3H,s,C*H*$_3$), 3.71(3H,s,O*Me*), 6.90(1H,s, *H-6*), 7.13(1H,s,*H-3*); *M/Z*=266(M^+) (Found:C,62.90; H,10.01%. $C_{14}H_{26}OSi_2$ requires C,63.09; H,9.83%).

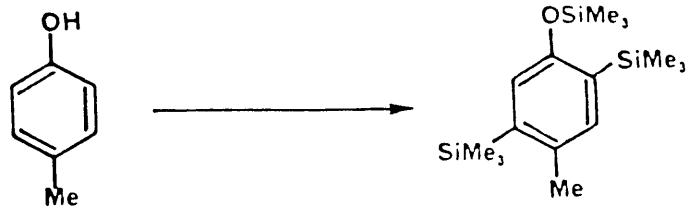
Preparation of 2,5-Bis(trimethylsilyl)-O-(trimethylsilyl) phenol(60)



(59) (60)

To a stirred solution of phenol(59) (0.94g,10.00mmol) at 0°C in dry THF (30ml) under argon was added trimethylsilylchloride (5.43g, 50.00mmol) followed by lithium metal (0.35g, 50.00mmol) cut into 20 pieces. The mixture was agitated in an ultrasonic bath at 0-5°C for 3h then at 40°C for 12h. The THF was evaporated under reduced pressure and the residue triturated with 40-60°petrol(4x40ml). The combined organic phase was filtered through celite and then gently refluxed for 72h. The solvent was evaporated under reduced pressure and the residue chromatographed. (40-60°petrol) to give *2,5-bis(trimethylsilyl)-O-(trimethylsilyl) phenol* (60) (2.72g, 72%) as a colourless oil, $\nu_{max.}$ (film) 3034, 2955, 2898, 1583, 1521, 1405, 1368, 1252, 1231, 1116, 966 and 838cm^{-1}; δ_H(90MHz;$CDCl_3$) 0.30(18H,s, Si*Me*$_3$), 0.38(9H,s, OSi*Me*$_3$), 6.95(1H,s,*H-6*), 7.12(1H,d, J=7.7Hz,*H-4*), 7.41(1H,d,J=7.7Hz,*H-3*); *M/Z*=310(M^+), 295 (M^+-Me) (Found: C,58.23; H,10.00% $C_{15}H_{30}OSi_3$ requires C,57.99; H,9.73%).

Preparation of 2,5-Bis(trimethylsilyl)-4-methyl-O-(trimethylsilyl) phenol (64)

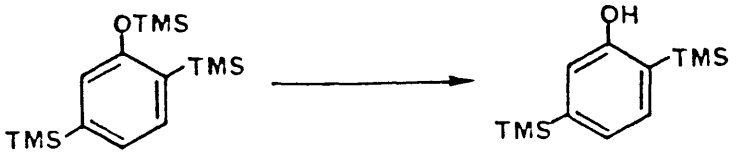


(63) (64)

To a stirred solution of *p*-cresol(63)(1.08g, 10.00mmol) at 0°C in dry THF (30ml) under argon was added trimethylsilylchloride (5.43g,50.00mmol) followed by lithium metal (0.35g, 50.00mmol) cut into approximately 20 pieces. The mixture was agitated in an ultrasonic bath at 0-5°C for 6h then at 40°C for 16h. The THF was evaporated under reduced pressure and the residue triturated with 40-60° petrol (4x40ml). The combined organic phase was filtered through celite then refluxed gently for 48h. The solvent was evaporated under reduced pressure and the residue chromatographed (40-60°petrol) to give *2,5-bis(trimethilsilyl)-4-methyl-O-(trimethylsilyl) phenol*(64) (1.88g, 58%) as a colourless oil $\nu_{max.}$(film) 2955, 2898, 1465, 1337, 1251, 1237, 1116, 891 and 837cm^{-1}; δ_H(90MHz; $CDCl_3$) 0.27(9H,s,OSi*Me*$_3$) 0.33(18H,s,Si*Me*$_3$), 2.40(3H,s,*Me*), 6.91(1H,s,*H-6*), 7.15 (1H,s,*H-3*); *M/Z*=324(M^+) (Found:C,59.06; H,10.18%. $C_{16}H_{32}OSi_3$ requires C,59.19; H,9.93%).

Preparation of 2,5-Bis(trimethylsilyl) phenol.

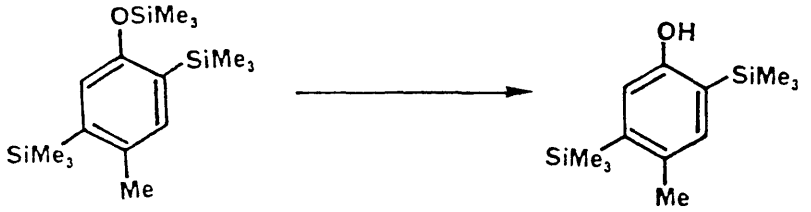
(65)



(60) (65)

To a solution of 2,5-bis(trimethylsilyl)-O-(trimethylsilyl)phenol (60) (0.90g, 2.90mmol) in THF (10ml) was added tetra-butylammonium fluoride (2.90ml of a 1.0M solution in THF, 2.90mmol). The solution was stirred for 1h at rt, poured into saturated $NaHCO_3$ solution (10ml) and extracted with Et_2O (3x20ml). The combined extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (2%Et_2O-40-60°petrol) to give *2,5-bis(trimethylsilyl)phenol* (65) (0.64g,92%) as a white solid, m.p. 70-73°C (from MeOH at -60°C), $\nu_{max.}$ (CH_2Cl_2) 3574, 2949, 2897, 1592, 1530, 1491, 1375, 1225, 1190, 1144, 1112, 1060 and 828cm^{-1}; δ_H(90MHz;$CDCl_3$) 0.25(9H,s, Si*Me*$_3$) 0.27(9H,s,Si*Me*$_3$), 4.75(1H,s,O*H*), 6.78 (1H,s,*H-6*), 7.06(1H,d,J=7.5Hz,*H-4*), 7.38(1H,d,J=7.5Hz,*H-3*); *M/Z*=238(M^+), 223(M^+-15) (Found:C,60.52; H,9.59%. $C_{12}H_{22}OSi_2$ requires C,60.44;H,9.30%).

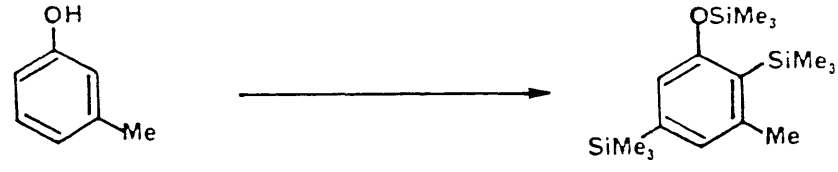
Preparation of 2,5-Bis(trimethylsilyl)-4-methyl phenol(66)



(64) (66)

To a stirred solution of the trimethylsilylenol ether (64) (0.324g, 1.00mmol) in dry THF (5ml) at 0°C was added TBAF (1.10ml of 1.0M solution in THF, 1.10mmol). The resulting solution was stirred at rt for 30min, poured into sat.$NaHCO_3$ solution and extracted with Et_2O (3x20ml). The combined ethereal extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (3%Et_2O-40-60°petrol) to give *2,5-bis(trimethylsilyl-4-methylphenol* (66) (0.229g, 92%) as a white solid, m.p. 69-70°C, $\nu_{max.}$(CH_2Cl_2) 3580,2952, 2898, 1589, 1446, 1379, 1353, 1228, 1180, 1113, 1032 and 839cm^{-1}; δ_H(90MHz; $CDCl_3$) 0.30(18H,s,Si*Me*$_3$), 2.40(3H,s,*Me*), 4.61(1H,s,*OH*), 6.78(1H,s,*H-6*), 7.12(1H,s,*H-3*); *M/z*=254(M^+) (Found:C,61.76; H,9.65%. $C_{13}H_{24}OSi_2$ requires C,61.84; H,9.58%).

Preparation of 2,5-Bis(trimethylsilyl)-3-methyl-O-(trimethylsilyl)phenol(69)

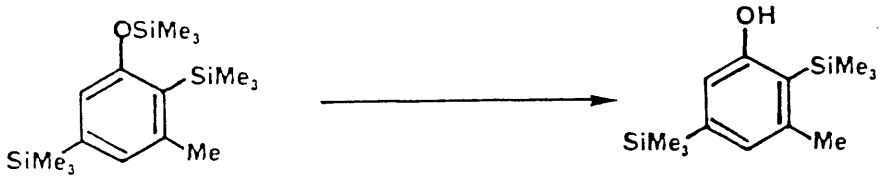


(67) (69)

To a stirred solution of *m*-cresol(67) (1.08g, 10.00mmol) in dry THF (30ml) at 0°C under argon was added trimethylsilyl chloride (5.43g, 50.00mmol) followed by lithium metal (0.35g, 50.00mmol) freshly cut into approximately 20 pieces. The resulting mixture was agitated in an ultrasonic bath at 0°C for 6h then at 40°C for 18h. The THF was evaporated under reduced pressure and the residue triturated with 40-60°petrol(4x40ml).The combined organic phase was filtered through celite and the solvent evaporated

under reduced pressure. The residue was redissolved in dry CH_2Cl_2 (20ml) and PBQ (1.62g, 15.00mmol) was added. The resulting solution was stirred at rt for 72h,the solvent evaporated under reduced pressure and the residue triturated with 40-60°petrol(3x30ml). The solvent was evaporated under reduced pressure and the residue chromatographed (40-60°petrol) to give *2,5-bis(trimethylsilyl)-3-methyl-O-(trimethylsilyl) phenol*(69) (1.26g, 39%) as a colourless oil, $\nu_{max.}$(film)2955, 2897, 1579, 1518, 1405, 1371, 1273, 1251, 1046, 911 and 842cm^{-1}; δ_H(60MHz;$CDCl_3$) 0.30(9H,s,Si*Me*$_3$), 0.35(18H,s,Si*Me*$_3$), 2.45(3H,s,*Me*),6.85 (1H,s,*H-6*), 6.95(1H,s,*H-4*); *M/Z*=324(M^+)

Preparation of 2,5-Bis(trimethylsilyl)-3-methylphenol (70)

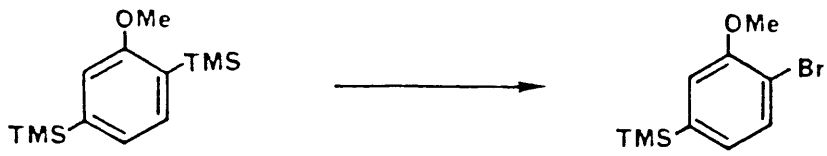


(69) (70)

To a stirred solution of the trimethylsilyl ether(69) (0.324g,1.00mmol) in THF(10ml) at 0°C was added TBAF(1.10ml of a 1.0M solution in THF, 1.10mmol). The resulting solution was stirred at rt fo 50 min, poured into saturated $NaHCO_3$ solution(20ml) and extracted with Et_2O(3x20ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed(3% Et_2O -40-60°petrol) to give *2,5-bis(trimethylsilyl)-3-methyl phenol* (70) (0.22g,87%) as a white solid, $\nu_{max.}$(CH_2Cl_2) 3590, 3530, 2954, 2897, 1588, 1526, 1443, 1369, 1248, 1159, 908, 836 and 755cm^{-1}; δ_H(60MHz;$CDCl_3$) 0.20(9H, s,C-2 Si*Me*$_3$), 0.30(9H,s,C-5Si*Me*$_3$), 2.40(3H,s,*Me*),4.85(1H,s,O*H*),

6.65(1H,s,*H-6*)6.90(1H,s,*H-4*);M/z=252(M^+) (Found: C,61.54;H,9.58%. $C_{13}H_{24}OSi_2$ requires C,61.48;H9.58%)

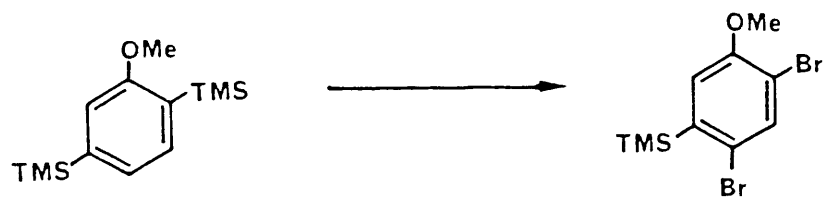
Preparation of 2-Bromo-5-(trimethylsilyl)-anisole(71)



(56) (71)

To a stirred solution of 2,5-bis(trimethylsilyl)anisole(56) (0.252g 1.00mmol) in dry CH_2Cl_2 (10ml) under argon at -30°C was added N-bromosuccinimide(0.179g, 1.00mmol) in one portion. The solution was stirred at -30°C for 20min then warmed to rt. The solvent was evaporated under reduced pressure and the residue triturated with 40-60°petrol (3x20ml). The combined extracts were washed with brine (10ml) and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (40-60°petrol) to give *2-bromo-5-(trimethylsilyl)anisole*(71) (0.218g,82%) as a colourless oil, $\nu_{max.}$ (film) 3004, 2954, 2845, 1570, 1481, 1461, 1371, 1247, 1185, 1106, 1044, 885, 837 and 754cm^{-1}; δ_H(90MHz;$CDCl_3$) 0.30(9H,s,Si*Me*$_3$), 3.75(3H,s,O*Me*), 6.85(1H,s,*H-6*), 7.05(d,J=7.0Hz,*H-4*), 7.30(1H,d,J=7.0Hz, *H-3*); *M/Z*=260, 258 (M^+) (Found:C, 46.52; H,5.95%. $C_{10}H_{15}$ BrOSi requires C, 46.33; H, 5.83%).

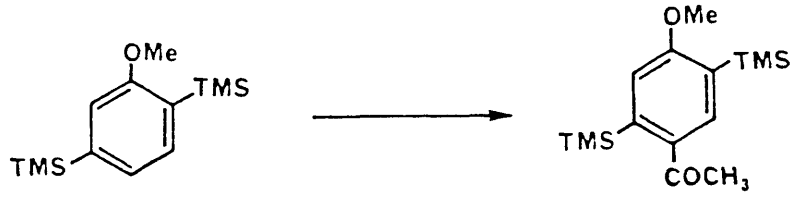
Preparation of 2,4-Dibromo-5-(trimethylsilyl)anisole (72)



(56) (72)

To a stirred solution of 2,5-bis(trimethylsilyl) anisole (56) (0.126g, 0.50mmol) in dry CH_2Cl_2(5ml) was added bromine (0.160g, 1.0mmol) dropwise. The resulting solution was stirred for 1h at rt, washed with saturated sodium thiosulphate (2ml) and brine(2ml). The solvent was evaporated under reduced pressure and the residue chromatographed (40-60°petrol) to give *2,4-dibromo-5-(trimethylsilyl)anisole* (72) (0.141g, 84%) as white crystals, m.p. 91-93°C (from 40-60°petrol), $\nu_{max.}$(KBr) 2960, 2910, 2840, 1560, 1455, 1330, 1245, 1050, 840 and 755cm^{-1}; δ_H(90MHz;$CDCl_3$) 0.35 (9H,s,Si*Me*$_3$), 3.80(3H,s,O*Me*), 6.85(1H,d,J=2.0Hz,*H-6*),7.55 (1H,d,J=2.0Hz,*H-3*); *M/z*=335 (M^+-1) (Found:C,35.80; H,4.05%. $C_{10}H_{14}Br_2OSi$ requires C,35.52; H,4.17%).

Preparation of 2,5-Bis(trimethylsilyl)-4-methoxyacetophenone. (74)

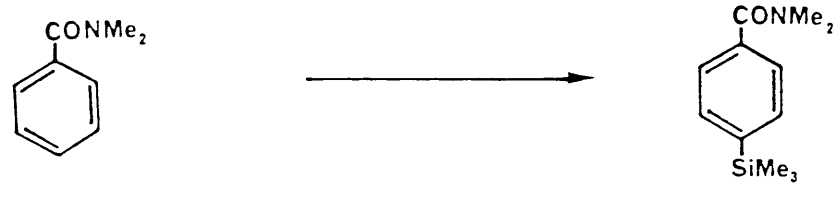


(56) (74)

To a stirred suspension of $AlCl_3$(0.667g,5.00mmol) in CH_2Cl_2 (10ml) under argon was added acetyl chloride(0.39g, 5.00 mmol). When all the $AlCl_3$ had solubilized the solution was cooled to -78°C and a solution of 2,5-bis(trimethylsilyl) anisole(56) (1.23g,5.00mmol) in dry CH_2Cl_2 (5ml) was added rapidly. The resulting solution was stirred at -78°C for 30min, allowed to warm to 0°C and poured into sat $NaHCO_3$(15ml). The aqueous phase was extracted with CH_2Cl_2 (3x15ml), the combined organic phase was dried and the solvent evaporated under reduced pressure. The residue

was chromatographed (10% Et_2O-40-60°petrol) to give to give *2,5-bis(trimethylsilyl)-4methoxy-acetophenone* (74) (0.98g, 67%) as a white solid, m.p.101-102°C, $\nu_{max.}$ (CH_2Cl_2) 2947, 2899, 1671, 1576, 1511, 1456, 1358, 1335, 1227, 1121 and 1041cm^{-1}; δ_H(90MHz;$CDCl_3$) 0.27(18H,s,Si*Me*$_3$), 2.59(3H,s,CO*Me*), 3.88(3H,s,O*Me*), 7.18(1H,s,*H-6*), 7.95 (1H,s,*H-3*); *M/Z*=279(M^+-*Me*) (Found:C,61.10; H,8.95%. $C_{15}H_{26}O_2SO_2$ requires C,61.17; H,8.90%).

Preparation of N,N-Dimethyl-4-(trimethylsilyl) benzamide(76)



(75) (76)

To a stirred solution of N,N-dimethyl benzamide(75) (1.49g 10.00mmol) in THF (30ml) under argon at 0°C was added trimethylsilylchloride(3.26g, 30.00mmol) followed by lithium(0.210g 30.26mmol) cut into 10 pieces. The mixture was ultrasonically stirred at 0°C until all the metal had dissolved. The solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2(20ml) with the careful exclusion of air. The solution was cooled to 0°C and a solution of PBQ(1.08g, 10.00mmol) in CH_2Cl_2(20ml) was added. The resulting solution was stirred at 0°C for 3h then warmed to rt. The solvent was evaporated under reduced pressure, the residue triturated with 40-60°petrol (3x40ml) and the combined extracts filtered through celite. The solvent was evaporated under reduced pressure and the residue chromatographed.

(80%Et_2O-40-60°petrol)to give *N,N-dimethyl-4-(trimethylsilyl) benzamide*(76) (0.98g, 42%) as white crystals,m.p. 45-47°C (fromEt_2O at-60°C), $\nu_{max.}$(KBr) 3040, 2985, 2885, 1645, 1515, 1465, 1255, 1150, 1080,860 and 750cm^{-1}; δ_H (90MHz;$CDCl_3$) 0.32(9H,s,Si*Me*$_3$), 3.05(6H,s,*Me*), 7.25(2H,d, J=7.0Hz,*H-6*),7.65(2H,d,J=7.0Hz,*H-3*,*H-6*); *M/Z*=221(M^+) (Found: C,64.91; H,8.69%. $C_{12}H_{19}NOSi$ requires C,65.09;H,8.67%).

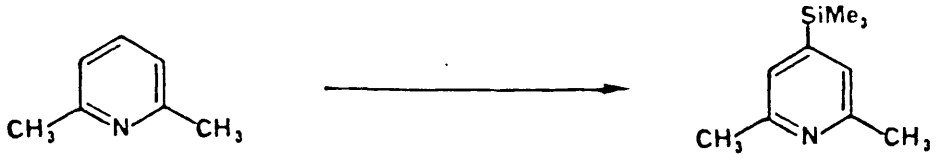
Preparation of 4-(Trimethylsilyl) pyridine(82)



(80) (82)

To a stirred solution of dry pyridine(80) (0.79g, 10.00mmol) in THF (130ml) at 0°C under argon was added trimethylsilyl-chloride (2.72g, 25.04mmol). Lithium(0.146g, 21.04mmol), freshly cut into 30 pieces,was added. The mixture was ultrasonically stirred at 0°C until the metal had dissolved. A solution of DDQ (2.26g,9.95mmol) in THF (20ml) was added dropwise and the resulting solution stirred at 0°C for 15 min. The solvent was evaporated under reduced pressure , the residue was extracted with Et_2O (4x40ml) and the extracts filtered through alumina (5g). The solvent was removed under reduced pressure to give *4-(trimethylsilyl) pyridine* (82) (1.11g, 74%) as a colourless oil, b.p.68°C (8mmHg), $\nu_{max.}$(film) 3050,2950, 2900, 1580, 1400, 1315, 1250, 1125, 840, 800 and 755 cm^{-1}; δ_H(90MHz;$CDCl_3$) 0.35 (9H,s,Si*Me*$_3$), 7.40(2H,dd,J=7.0,2.0Hz, *H-3*, *H-5*), 8.60(2H, dd,J=7.0Hz, 2.0Hz, *H-2*, *H-6*), *M/Z*=151(M^+)

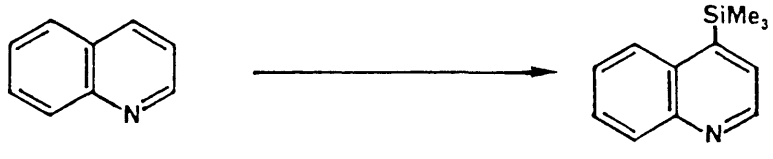
Preparation of 2,6-(Dimethyl-4-(trimethylsilyl)pyridine (83)



(81) (83)

To a stirred solution of redistilled 2,6-dimethyl-pyridine (81)(1.07g, 10.00mmol) in THF (30ml) under argon at 0°C was added trimethylsilylchloride(2.72g, 25.04mmol) followed by lithium (0.146g, 21.04mmol) cut into 25 pieces. The mixture was ultrasonically stirred at 0°C until all the metal had dissolved. A solution of DDQ (2.26g, 9.95mmol) in THF (20ml) was added dropwise and the resulting solution stirred at 0°C for 15 min. The solvent was evaporated under reduced pressure and the residue extracted with Et_2O (4x40ml). The organic extracts were combined and the solvent evaporated under reduced pressure. The residue was chromatographed on alumina (15g, neutral grade 3) (75% Et_2O-40-60°petrol) to give *2,6-dimethyl-4-(trimethylsilyl) pyridine* (83)(0.75g, 42%) as a colourless oil, $\nu_{max.}$ (CH_2Cl_2) 2910, 1585,1530, 1375, 1135, 1030, 980 and 940cm^{-1}; δ_H(90MHz; $CDCl_3$) 0.48 (9H,s,Si*Me*$_3$), 2.75 (6H,S, *Me*), 7.22(2H,s,*H-3*); *M/Z*=179(M^+). A sample was converted into its toluene-4-sulphonate salt, m.p. 124-126°C (Found:C,58.27; H,7.19%. $C_{17}H_{25}NO_3SSi$ requires C,58.06; H,7.17%).

Preparation of 4-(trimethylsilyl)quinoline (87)



(86) (87)

To a stirred solution of redistilled quinoline(86) (2.58g,19.97mmol) in THF(60ml) under argon at 0°C was added trimethylsilylchloride (6.79g, 62.50mmol)followed by lithium (0.430g, 61.96mmol) cut into 100 pieces. The mixture was stirred at 0°C until all the metal had dissolved. The solvent was evaporated under reduced pressure and the residue taken up in CH_2Cl_2 (40ml) with the careful exclusion of air. The solution was cooled to 0°C and a solution of PBQ (2.38g, 22.02mmol) in CH_2Cl_2 (40ml) was added. The solution was stirred at 0°C for 3hr then allowed to warm to rt. The solvent was removed under reduced pressure and the residue triturated with 40-60°petrol (4x50ml). The combined extracts were filtered through celite and the solvent removed under reduced pressure. The residue was chromatographed (30%Et_2O-40-60°petrol to give *4-(trimethylsilyl) quinoline* (87)(1.47g, 35%) as a pale yellow oil, b.p. 102-104°C (0.2mmHg), $\nu_{max.}$(film) 3100, 2970, 2900, 1560, 1475, 1260, 1210, 1140, 1065, 990, 850 and 805cm^{-1}; δ_H(90MHz;$CDCl_3$) 0.48(9H,s,Si*Me*$_3$), 7.50-8.20(5H,m,*aromatic*), 8.85(1H,d,*H-2*); *M/Z*=201(M^+).

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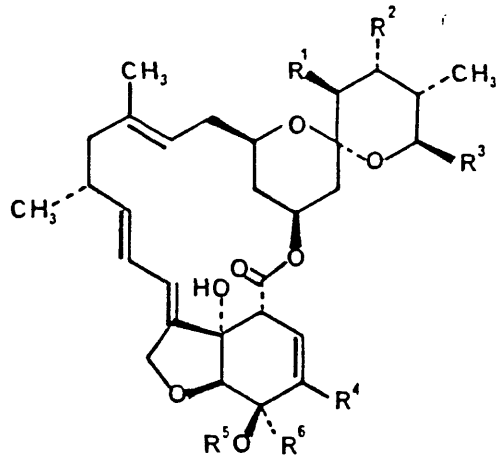
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INTRODUCTION

Since the discovery of penicillin there has been intensive investigation for antibacterial compounds of microbial origin. More recently it has become common to exploit these microbial metabolites for other therapeutic properties. In 1975, Japanese workers isolated and elucidated the structures of the milbemycins[1], a group of fermentation products from *Streptomyces hygroscopicus aureolacrimosus* which show potent, broad spectrum anthelmintic, insecticidal and acaricidal activity[2]. All the milbemycins so far isolated are tetra or pentacyclic 16-membered macrocyclic lactones containing a fused [5.5] spiroacetal ring. They were originally divided into two groups known as the α and β series. The α-series incorporates a tetrahydrofuran ring cis-fused to the cyclohexene ring, whereas the β-series is derived by a formal opening of the tetrahydrofuran ring. More recently the discovery of milbemycins D-K[3] has been announced. X-ray analysis unambiguously defined the absolute stereochemistry and conformation of the milbemycins as shown in Figures 1 and 2.

Figure 1

	Milbemycin	R_1	R_2	R_3	R_4	R_5	R_6
(88)	α_1	H	H	CH_3	CH_3	H	H
(89)	α_2	H	H	CH_3	CH_3	CH_3	H
(90)	α_3	H	H	CH_2CH_3	CH_3	H	H
(91)	α_4	H	H	CH_2CH_3	CH_3	CH_3	H
(92)	α_5	OH	$OCOCH(CH_3)C_4H_9$	CH_3	CH_3	H	H
(93)	α_6	OH	$OCOCH(CH_3)C_4H_9$	CH_3	CH_3	CH_3	H
(94)	α_7	OH	$OCOCH(CH_3)C_4H_9$	CH_2CH_3	CH_3	H	H
(95)	α_8	OH	$OCOCH(CH_3)C_4H_9$	CH_2CH_3	CH_3	CH_3	H
(96)	α_9	H	H	CH_3	CH_2OCOP	H	H
(97)	α_{10}	H	H	CH_2CH_3	CH_2OCOP	H	H
(98)	D	H	H	$CH(CH_3)_2$	CH_3	H	H
(99)	F	H	H	$CH(CH_3)_2$		H	H
(100)	G	H	H	$CH(CH_3)_2$	CH_3	CH_3	H
(101)	J	H	H	CH_3	CH_3	=O	
(102)	K	H	H	CH_2CH_3	CH_3	=O	



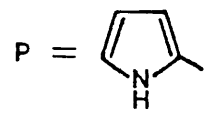
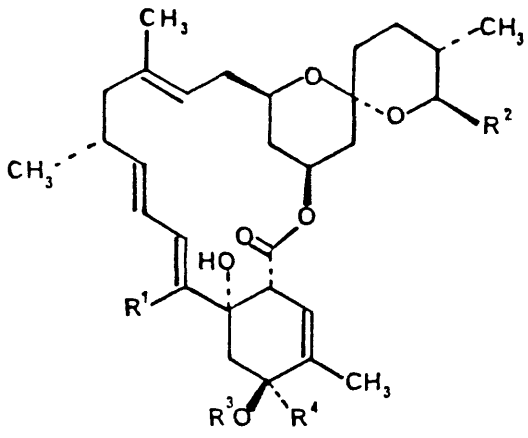
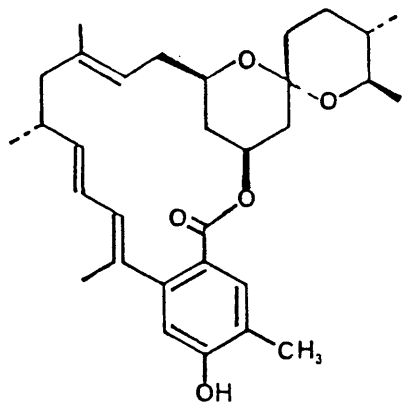


Figure 2



	Milbymecin	R_1	R_2	R_3	R_4
(103)	β_1	CH_2OH	CH_3	CH_3	H
(104)	β_2	CH_2OH	CH_2CH_3	CH_3	H
(105)	E	CH_2OH	$CH(CH_3)_2$	CH_3	H
(106)	H	CH_3	$CH(CH_3)_2$		=O



(107)

In 1978 the discovery of eight highly potent anti-parasitic compounds of closely related structures and designated avermectin $A_{1\alpha}$ through to $B_{2\beta}$ was announced. The avermectins were isolated as fermentation products of *Streptomyces avermitilis*, they are glycoside derivatives containing a α-L-oleandrosyl-α-L-oleandrosyl moiety at the C-13 position of the milbemycin series.

The avermectins were first seperated chromatographically into four major components,[46] 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.

Extensive ^{1}H and ^{13}C NMR and mass spectral investigations [4c] showed that the avermectins shared many common structural features with the milbemycins.[16] It was possible to interpret the complex avermectin spectral data convincingly by considering three structural changes when compared to the milbemycins;

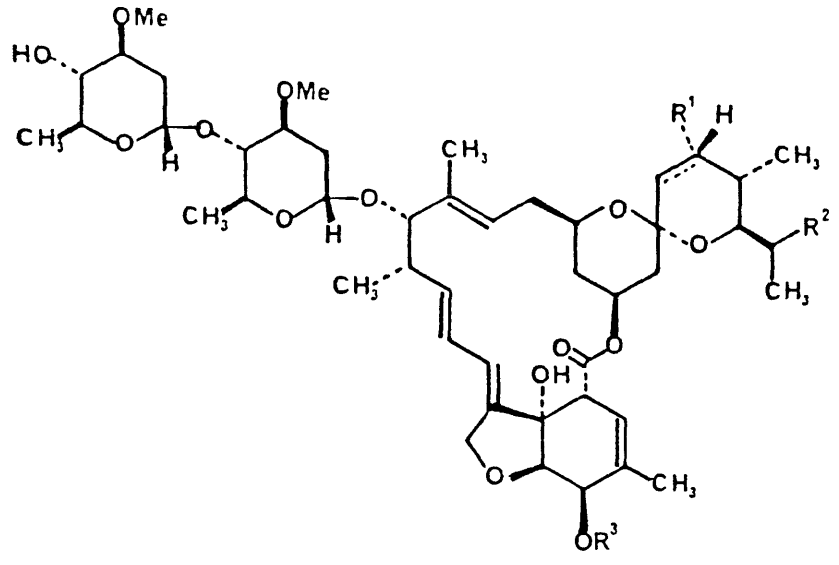
(1) a disaccharide substituent is attached *via* a new C-13 hydroxyl function,

(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 the usual methyl or ethyl substituents.

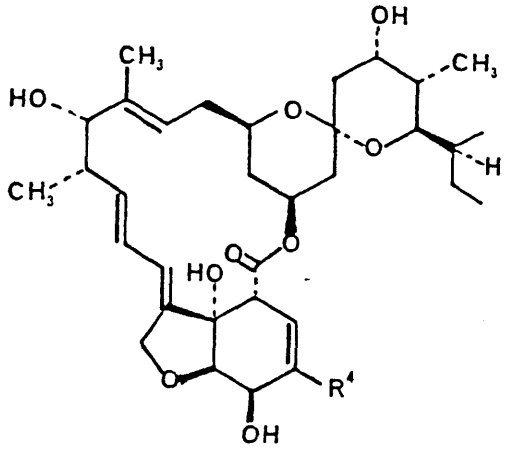
X-ray analysis of the avermectin B_{2a} aglycone (116) and avermectin B_{1a} (112) confirmed the eight avermectins to possess the gross structure shown in Figure 3.[4d]

Figure 3



	Avermectin	R_1*	R_2	R_3
(108)	A_{1a}	-	CH_2CH_3	CH_3
(109)	A_{1b}	-	CH_3	CH_3
(110)	A_{2a}	OH	CH_2CH_3	CH_3
(111)	A_{2b}	OH	CH_3	CH_3
(112)	B_{1a}	-	CH_2CH_3	H
(113)	B_{1b}	-	CH_3	H
(114)	B_{2a}	OH	CH_2CH_3	H
(115)	B_{2b}	OH	CH_3	H

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

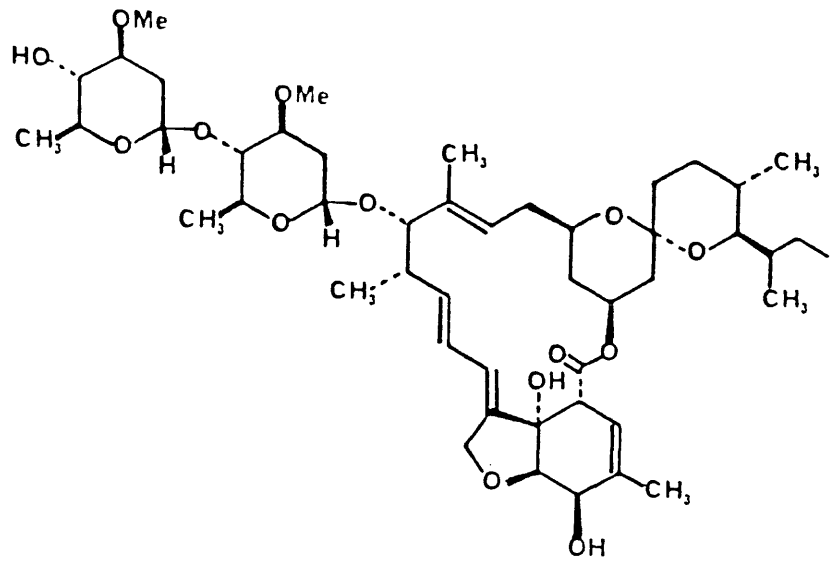


(116)

The avermectins are extraordinarily active against a wide range of parasitic helminths[5], arachnids and ecto-parasites[6] in doses as low as $10\mu g\ kg^{-1}$ yet they are devoid of antibacterial or antifungal activity[7]. The antiparasitic activities of the a and b series are virtually identical and hence the need for separation does not exist although compounds of the b-series are generally more potent than those of the a-series.

In structure-activity studies it was found that protection of the C-5 hydroxyl group as the 5-O-^{t}butyl-dimethylsilyl derivative resulted in complete loss of biological activity indicating the possible importance of the C-5 hydroxyl group for biological activity. Removal 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.[8]

Selective hydrogenation of avermectin B_1[9] using Wilkinson catalyst gave the 22, 23- dihydroavermectin B_1 (117) in 85% yield, together with 3,4,22,23-tetrahydro-avermectin B_1 (3%). Reduction of the C-3-C-4 double bond causes considerable lowering of anthelmintic activity. On the basis of its overall efficacy *via* oral and parental routes in sheep and cattle[10] and for its safety profile (117) is currently marketed under the non- proprietary name "ivermectin."[9]



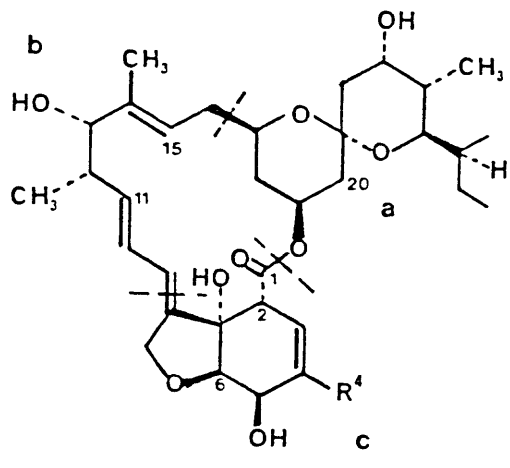
(117)

Studies on the mode of action have been carried out with avermectin B_1, but it is presumed that all the avermectins share a common mechanism.[11,12] The avermectins paralyse worms as do many other anthelmintics, although they appear to do so in a unique way. It is believed they behave as agonists for γ-amino butyric acid (GABA), the neurotransmitter involved in sending inhibitory signals from the interneurons to the motorneurons.[11,12,13] 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.

REVIEW

The milbemycins[1,2,3] and avermectins[4] are as previously described two closely related classes of tetra or penta-cyclic lactones which exhibit extremely potent biological activity.[4e,5,6] Synthetically and structurally they can both be divided into three distinct zones (scheme 25).

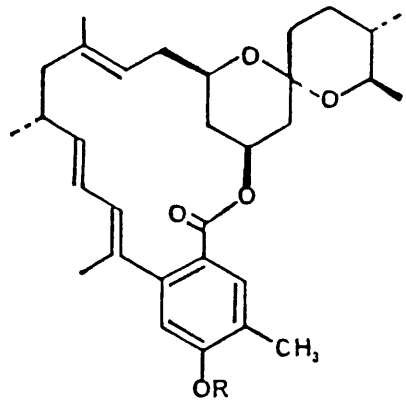
scheme (25)



(116)

Zone (a) - a spiroacetal moiety. Zone (b) - a hydroxylated carbon chain bearing two chiral centres and finally zone (c), a dihydroxy hexahydrobenzofuran unit which in some cases is found to be a cyclohexene ring derived by a formal opening of the C-6-O bond in the tetrahydrofuran ring. In this review the various synthetic approaches towards the southern (c) zone, which have been published, will be discussed and evaluated.

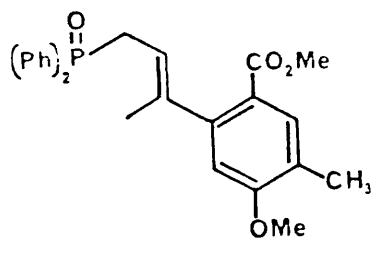
Milbemycin β_3[1a] (107) is the simplest member of the milbemycin series and in contrast to the more complex members contains an aromatic southern zone.



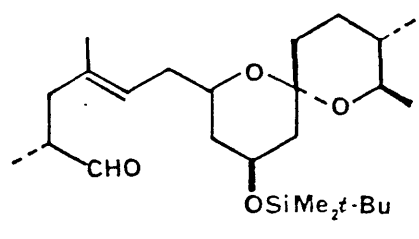
R=H(107)

Me(118)

In 1982 Smith and coworkers published the first total synthesis of (107) in its racemic form.[14] Their approach to the southern zone relied upon the Wittig-Horner[15] coupling of phosphine oxide(119) to a suitably functionalised aldehyde(120) followed by macrocyclic lactonization.[16]



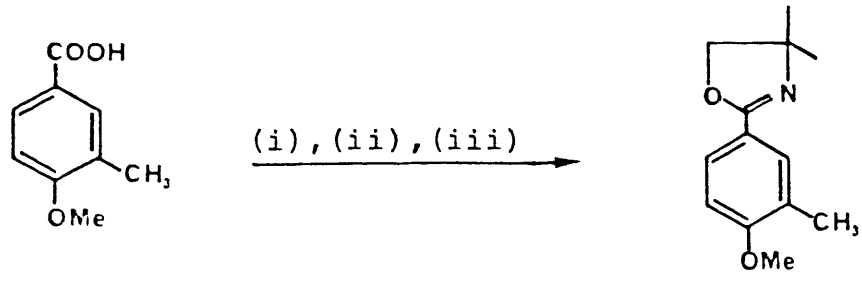
(119)



(120)

The key phosphine oxide (119) was prepared using a novel S_N2' displacement employing lithium diphenyl phosphide.[17] Thus 3-methyl-*p*-anisic acid (121) was converted to oxazoline (122) by standard methodology (scheme 26).

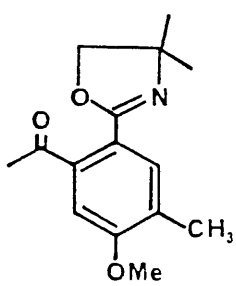
scheme (26)



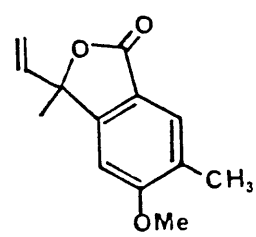
(121) (122)

Reagents: (i) $SOCl_2$, 96%; (ii) 2-amino-2-methyl-1-propanol, CH_2Cl_2, 95%; (iii) $SOCl_2$, 95%.

Metalation of (122) with *sec*-Buli at 0°C followed by inverse addition to acetic anhydride gave methyl ketone (123) in 45-50% yield as a single regioisomer. Subsequent condensation with vinyl magnesium bromide followed by acid hydrolysis gave the key lactone (124) in 74% yield.

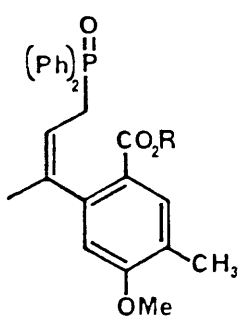


(123)

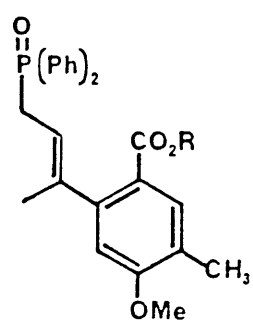


(124)

Treatment of vinyl lactone (124) with lithium diphenylphosphide in THF at -22°C gave a 3:1 mixture of isomeric phosphine oxides (125) and (126) respectively after aerial oxidation.

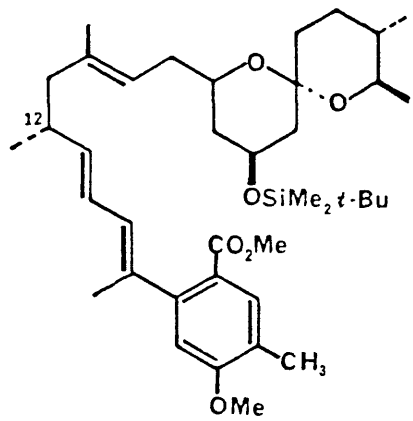


R=H (125)



R=H (126)
Me (119)

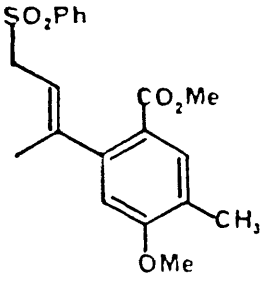
These isomers were separable by chromatography however the ratio of Z to E isomers could be converted to a more favourable 1:1 by treatment with KOH in ethylene glycol at 140°C. Reaction of acid (126) with diazomethane gave methyl ester (119). Deprotonation of phosphine oxide (119) was achieved using sodium hexamethyldisilazide at -78°C and the resulting anion added into aldehyde (120) to give the required diene (127) in 85-95% yield, after work up, as a 7:1 mixture of E/Z isomers. Importantly no epimerization at C-12 occured.



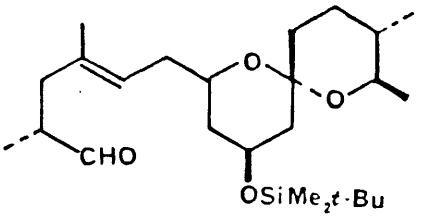
(127)

Removal of the silyl protecting group using TBAF was followed by treatment with potassium hydride to give milbymecin β_3 methyl ether (118). Demethylation of the methyl ether was achieved using excess NaSEt in refluxing DMF to give racemic milbemycin β_3 (107).

More recently Kocienski and coworkers disclosed details of their synthesis of optically pure milbemycin β_3.[18,19] Kocienski chose to use the sulphone (128), clearly analogous to Smiths phosphine oxide (119), to exploit the well established *trans*-selectivity of the Julia olefination.[20]

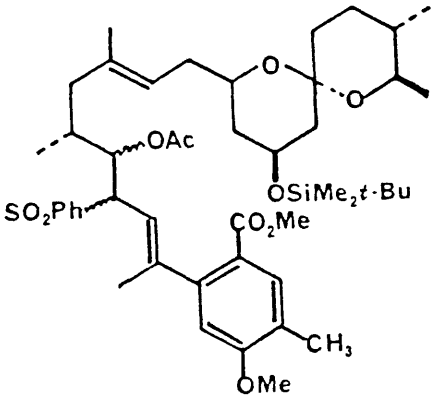


(128)



(120)

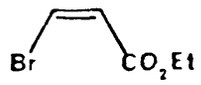
Union of the lithio anion of (128) with chiral aldehyde (120) followed by acetylation proceeded smoothly but subsequent reductive elimination of the mixture of diastereoisomeric-β-acetoxysulphones (129) was described as "capricious" and gave a poor 4:1 ratio of E/Z isomers.



(129)

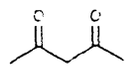
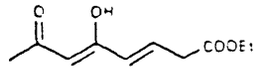
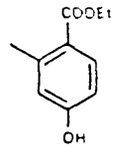
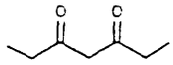
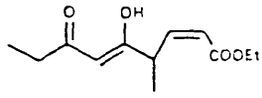
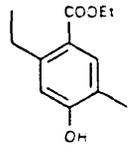
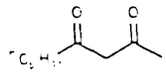
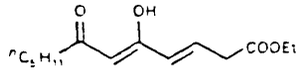
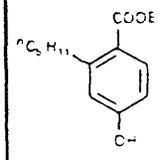
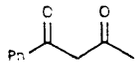
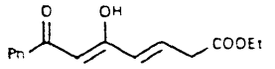
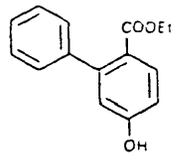
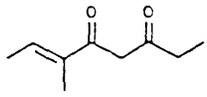
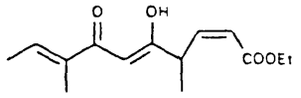
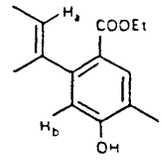
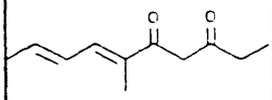
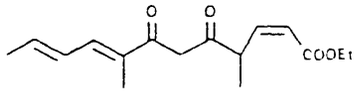
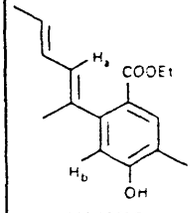
Separation of the resulting dienes was impossible, however removal of the silyl protecting group using TBAF in THF followed by macrolactonization using KHMDS gave only chiral (118). The undesired Z isomer being unable to undergo cyclization and readily separable

Smith[21] has extended his work in this area with the publication of a novel two-step preparation of *p*-hydroxybenzoates (113). Lithium dianions of 1,3-diketones (130) derived by treatment with LDA at -78°C reacted with Z-ethyl-3-bromopropenoate (131) to afford substituted 5,7-dioxoheptenoates (132) in moderate yield.

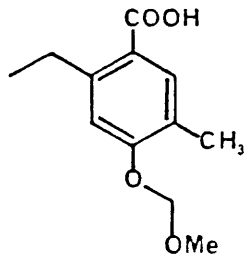


(131)

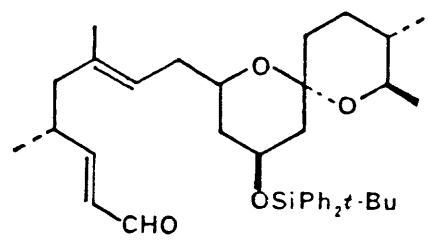
Treatment of the initial addition-elimination products with dilute ethanolic sodium ethoxide at r.t. gave the corresponding *p*-hydroxybenzoate (133) in good yield. These results are summarised in table (3)

Diketone	Diarylpentenoate	Yield °	Hydroxybenzoate Imp	Method	Yield°
		39	 (85-90° C)	A	64
		42	 (75.5 76° C)	A	80
		38		A	58
		41	 (77 78° C)	A B	0 70
		55	 (88.5 89° C)	A B	57 20
		41	 (108 109° C)	A	68

Shortly after the initial disclosure of Smith's total synthesis, Williams and his coworkers published an elegant synthesis of milbemycin β_3 (107) in its chiral form.[22] Although both syntheses were similar in that they were convergent and involved the coupling of two or three major components, the choice of components and their construction was totally different. Williams chose to couple the substituted benzoic acid (134) to chiral enal (135)

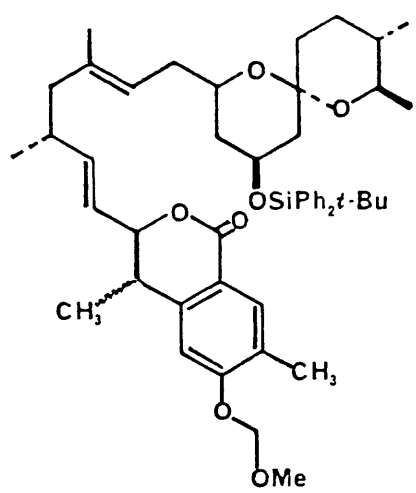


(134)



(135)

Treatment of benzoic acid derivative (134) with sodium hydride in THF, then *tert*-butyl lithium at -78°C gave a burgundy coloured benzylic dianion which afforded the lactone (136) as a diastereoisomeric mixture on addition of enal (135). The diastereoisomers were readily separable.

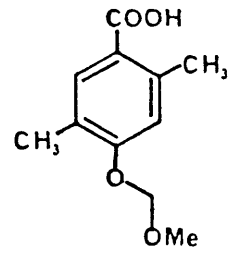


(136)

Removal of the silyl protecting group from each diastereoisomer followed by elimination with potassium hydride gave a single dienecarbocyclic acid which was readily

cyclized and further elaborated to chiral mibemycin β_3 (107).

Acid (134) was prepared from 4-(methoxymethyleneoxy)-2,4-dimethylbenzoic acid (137). Treatment of (137) with

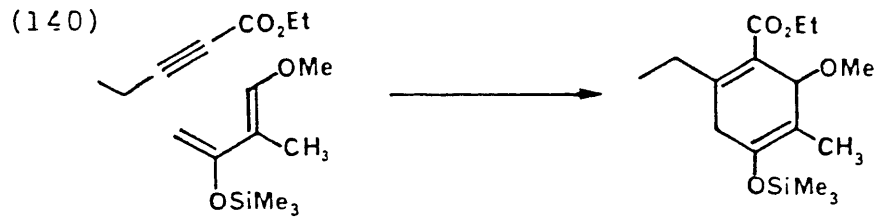


(137)

sodium hydride in THF then *tert*-butyllithium at -78°C followed by dimethylsulphate gave (134) in 85% yield.

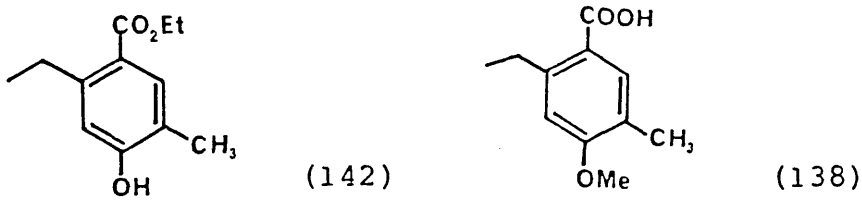
Barrett et al[23] have reported a convergent synthesis of acid (138) *via* a Diels-Alder approach. On refluxing silyloxy diene[24,25] (139) with ethyl 2-pentynoate (140) in xylene, ester (141) was obtained (scheme 27).

scheme (27)



(140) (139) (141)

Ester (141) was not isolated; acidification of (141) with hydrochloric acid in THF gave phenol (142) in 52% yield. Subsequent methylation with iodomethane-potassium carbonate

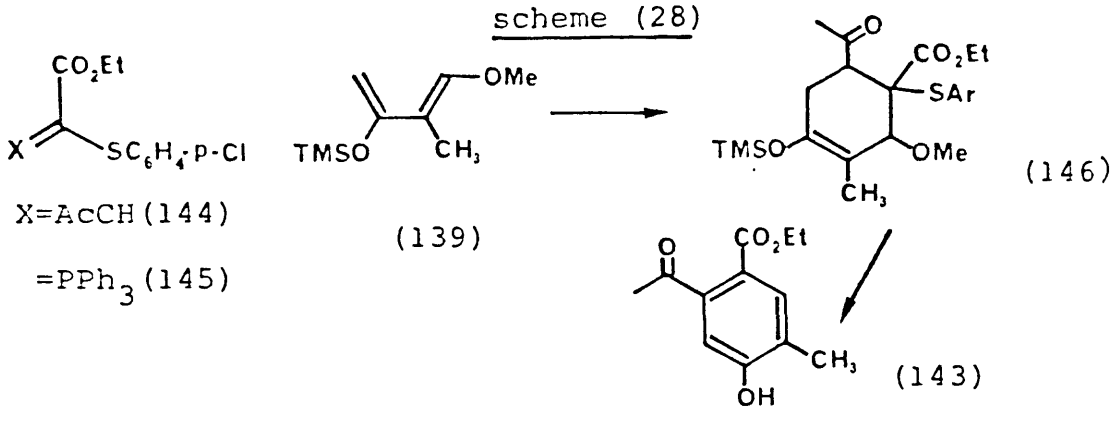


(142) (138)

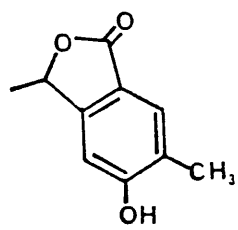
in acetone followed by saponification with sodium hydroxide in methanol gave on acidification the acid (138) in 67% yield.

This work was extended to a synthesis of keto ester (143) (scheme 28)

scheme (28)



Diene (139) and dienophile (144) condensed smoothly in refluxing benzene to give (146). Sequential reaction of (146) with ethanolic hydrochloric acid and sodium hydroxide gave the keto ester (143) in 48% overall yield. Dienophile (144) was readily available from pyruvaldehyde and ylide (145) in 72% yield. As proof of the structure of (143) sodium borohydride reduction of (143) gave the phthalide (147) in quantitative yield.

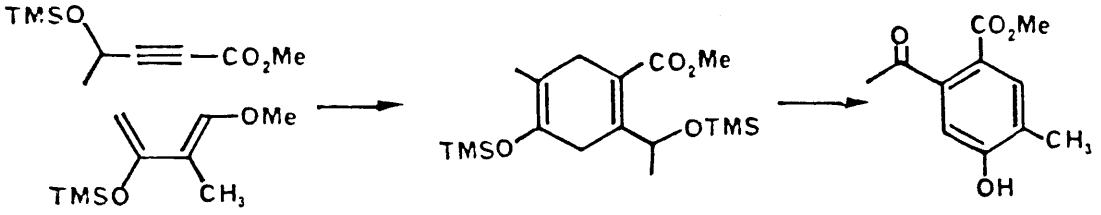


(147)

More recently, Baker and his coworkers have published a very similar approach to (143).[26] Diels-Alder reaction between diene (139) and dienophile (148) in refluxing xylene gave adduct(149) which on treatment with Jones reagent[27] at 0°C gave keto ester(143) in 39% overall yield. (scheme 29)

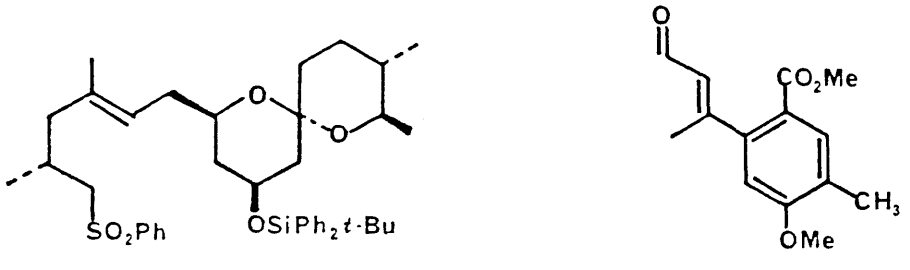
scheme (29)

(148)



(139) (149) (143)

In the syntheses of milbemycin β_3 (107) discussed so far, the important coupling of the southern zone has involved the use of a suitable aromatic portion containing an anionic centre. Baker et al[28] have published a synthesis of milbemycin β_3 (107) in its optically pure form which reverses this protocol by reacting the lithioanion of chiral sulphone (150) with enal (151).

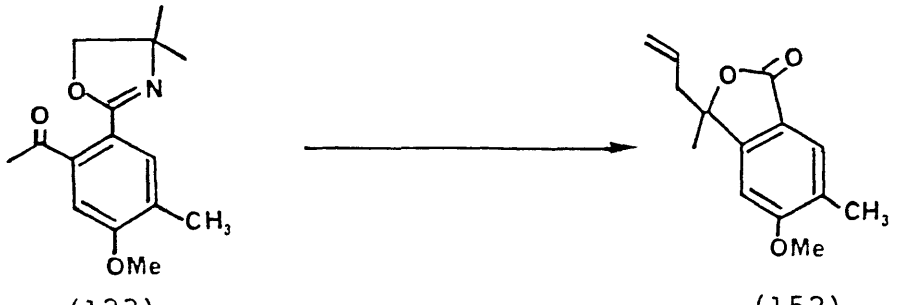


(150) (151)

Addition of benzoyl chloride to the reaction gave a mixture of diastereomeric benzoates which yielded the required *trans* butadienyl system on reductive elimination with sodium amalgam.

Enal (151) was readily prepared from the lactone (152) prepared in a manner analogous to Smith's work[14] (scheme 30).

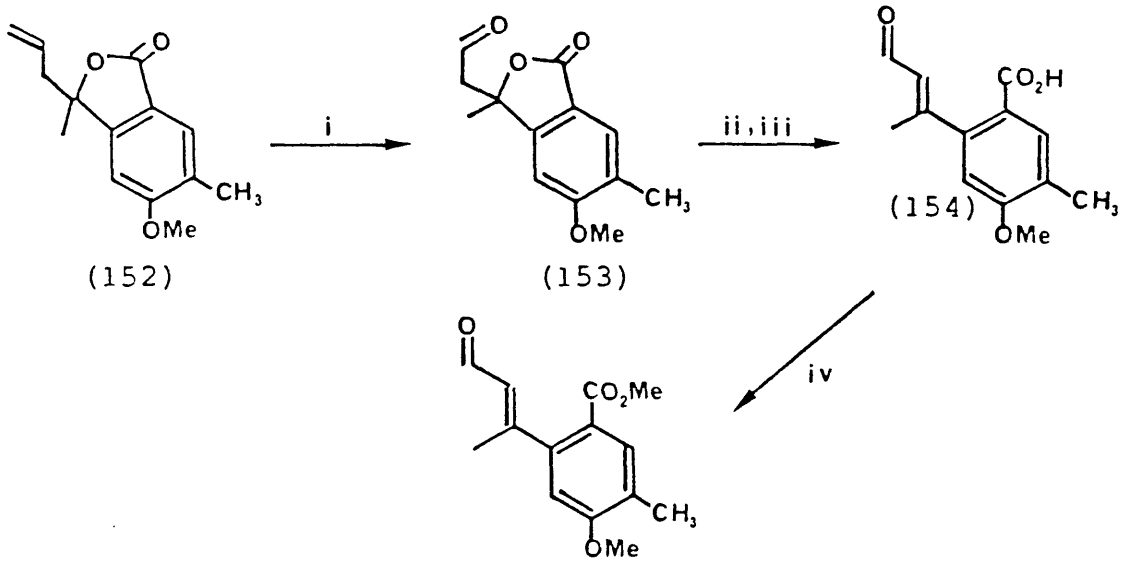
scheme (30)



(123) (152)

Ozonolysis of (152) followed by elimination with DBU gave acid (154) which was methylated to the required enal(151) (scheme 31).

scheme(31)



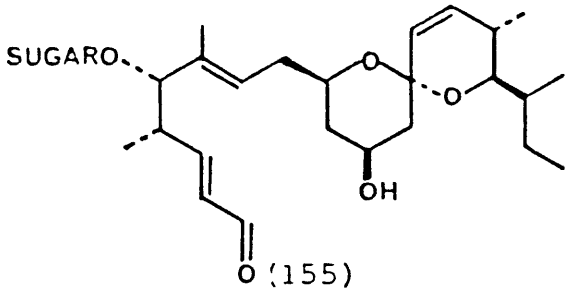
Reagents:(i) O_3,CH_2Cl_2,-78°C; (ii)NEt_3 (iii)DBU,C_6H_6,10 min; (iv) MeI, 5 min.

Enal(151) was formed as a 3:1 mixture of Z : E isomers which were readily separated by chromatography. The undesired Z isomer was isomerized to a 2:1 mixture of Z:E isomers by treatment with DBU in refluxing benzene for 5h with an 80% recovery of material.

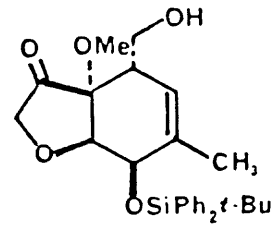
In contrast to the large number of publications related to the aromatic portion of milbemycin β_3 little work has been published on the hexahydrobenzofuran portion of related milbemycins and avermectins. This undoubtedly reflects the much greater synthetic challenge posed by this fragment.

Smith and his coworkers have recently disclosed details of their degredative work on the avermectins.[29,30] After extensive experimentation,conditions were developed which gave enal (1550 and ketone (156) from the controlled

degradation of avermectin B_{1a}. Enal (155) was subsequently

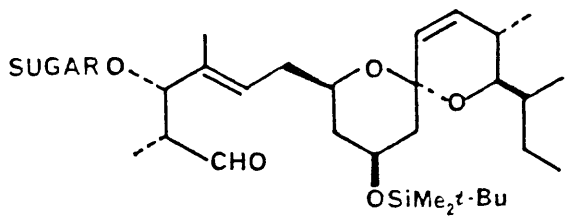


(155)



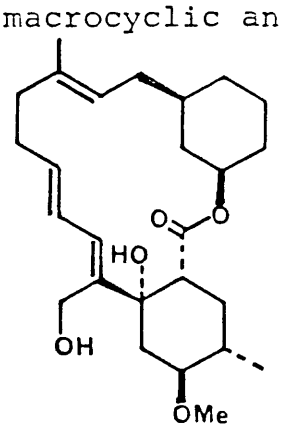
(156)

converted to aldehyde (157) which was coupled to the previously reported phosphine oxide[14] (119) to give, after macrolactonization, a novel milbemycin-avermectin hybrid.



(157)

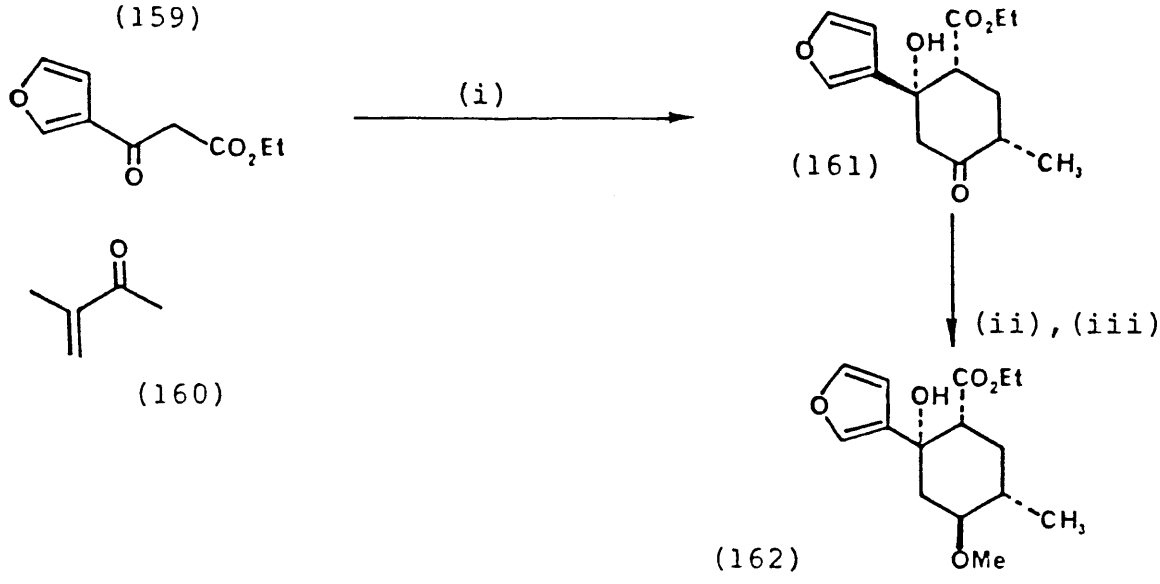
Thomas and his coworkers[31] at Oxford have published a synthesis of a macrocyclic analogue of milbemycin β_7 (158).



(158)

Condensation between keto ester (159), readily available from furan-3-carboxylic acid, and propen-2-yl methylketone (160) gave hydroxy ester (161) as a single diastereoisomer in 65% yield. (scheme 32)

scheme (32)

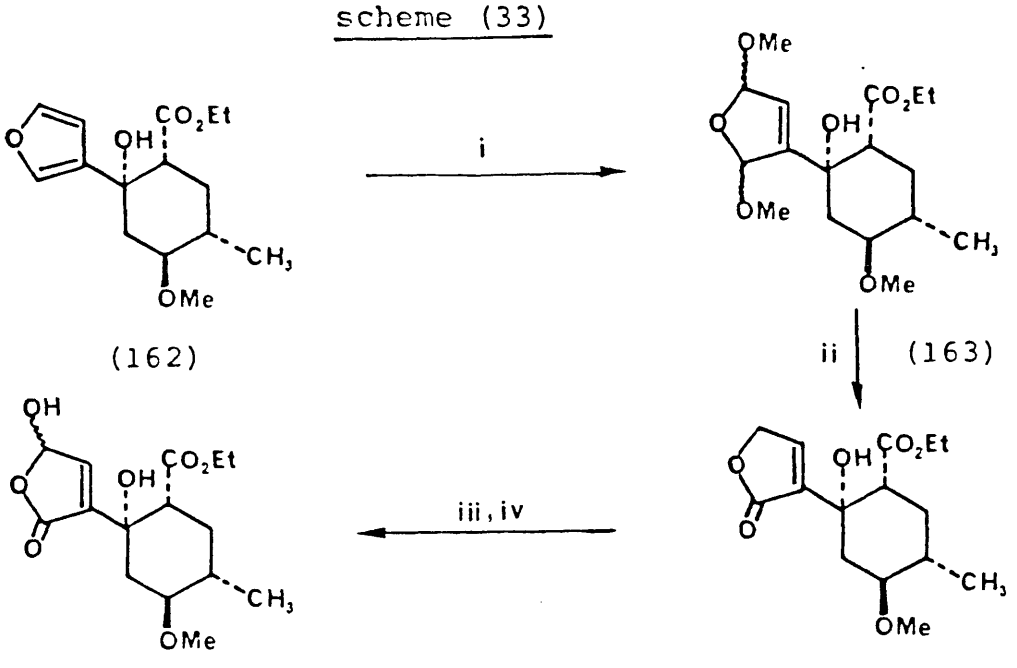


Reagents: (i) NaOH, EtOH, 65%; (ii) $NaBH(OAc)_3$, CH_3CO_2H, 95%; (iii) $Me_3O^+BF_4^-$, K_2CO_3, 70%.

Selective reduction of the ketone (161) with sodium triacetoxyborohydride[32] in acetic acid gave the *trans* diol in 95% yield. Preferential methylation of the secondary alcohol was achieved using trimethyloxonium tetrafluoroborate to give ester (162) in 70% yield

The latent 1,4-dicarbonyl functionality of the furan moiety was then exploited (scheme 33). Treatment of (162) with bromine-methanol gave a mixture of 2,5-dimethoxydihydrofurans (163) which were hydrolysed to 3-substituted 5H-furan-2-one (164) in 80% yield. Oxidation gave the 5-hydroxy-5H-furan-2-one (165) which was readily elaborated to the milbemycin analogue (158) using standard Wittig[33] methodology.

scheme (33)



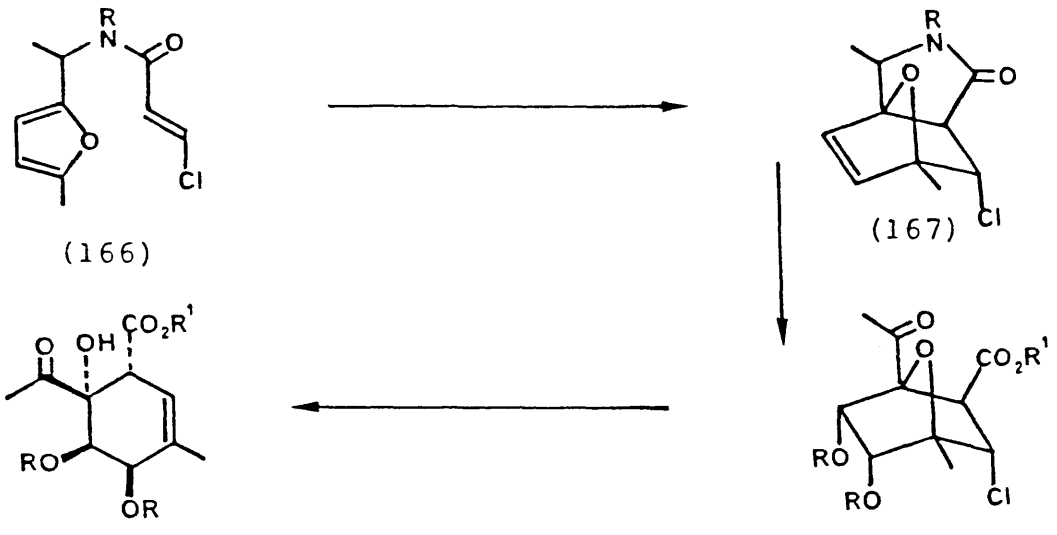
(162) (163) (164) (165)

Reagents: (i) Br_2, MeOH; (ii) HCl, THF, H_2O, 80%; (iii) NBS, CCl_4, Δ, 3h; (iv) Me_2CO, H_2O, Δ, 6h, 75%.

Although this work provides model compounds in a short and efficient manner, the lack of the C-3-C-4 double bond detracts considerably from the synthetic achievement. This is particularly so as removal of the C-3-C-4 double bond in naturally derived milbemycins causes a serious loss of biological activity.[9]

Jung and Street[34] have recently disclosed details of their intramolecular Diels-Alder approach to the bottom part of the avermectins. Scheme(34) illustrates their planned route. The pivotal steps are an intramolecular [4+2] *cis endo* cycloaddition of a N-furfuryl-β-chloroacrylamide(166) followed by an oxidation and reductive elimination to give adduct (169).

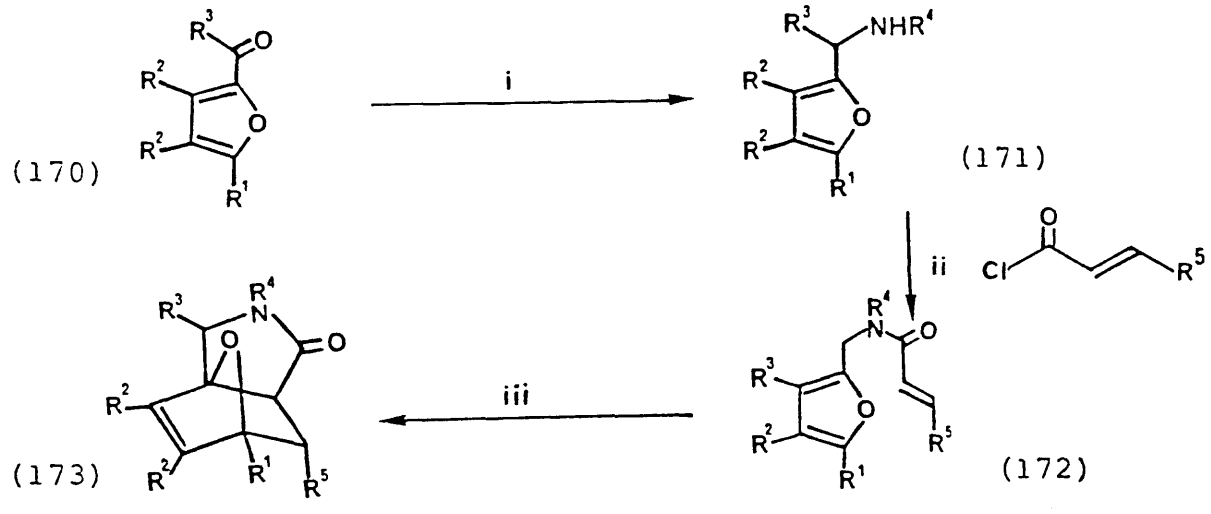
scheme (34)



(166) (167) (168) (169)

A variety of tertiary N-furfurylacrylamides (172) were prepared by a simple two step route in good yields. (scheme 35).The behaviour of these compounds on heating

scheme (35)



(170) (171) (172) (173)

Reagents: (i) R^4NH_2, $NaCNBH_3$, MeOH, HCl; (ii) Et_3N, CH_2Cl_2; (iii) Δ, 110°C.

to 110°C in toluene is summarized in table (4). Two points are worth noting. Firstly, the presence of a R' methyl group on the side chain greatly enhanced the rate and selectivity of the cycloaddition. Secondly, only tertiary

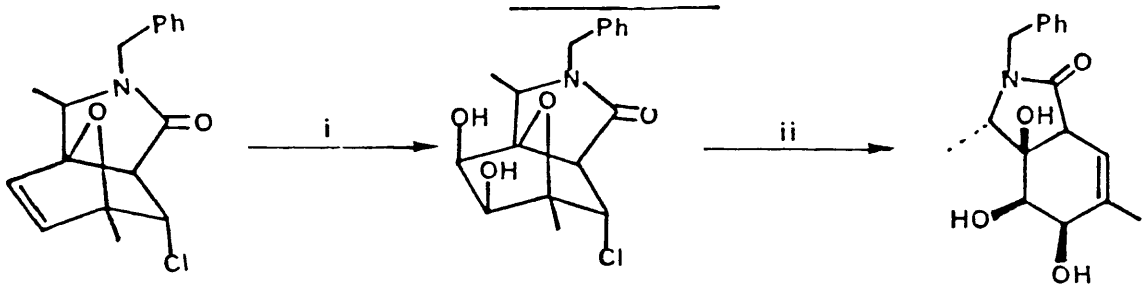
TABLE (4). diaster. ratio is ratio of endo R^3 to exo R^3

Compound (172)	R_1	R_2	R_3	R_4	R_5	time, h	Yield %	Diaster. Ratio.
a	Me	H	Me	o-HOC_6H_4	Cl	12.0	74	5:1
b	Me	H	Me	CH_2Ph	Cl	1.1	100	>95:<5
c	Me	H	Me	CH_2Ph	H	1.0	100	>95:<5
d	H	H	H	CH_2Ph	Cl	1.0	100	>95:<5
e	Me	H	H	CH_2Ph	Cl	8.0	67	
f	Me	OMe	Me	CH_2Ph	Cl	<0.2	100	1:1
g	Me	H	Me	H	Cl	48	0	
h	Me	H	Me	Ac	Cl	4	100	>95:<5

substituted amides underwent the Diels-Alder reaction.

Oxidation of adduct (172b) gave diol (174) in which hydroxylation occured on the undesired -face. However treatment of (174) with sodium in THF gave elimination product (175). (Scheme 36)

scheme (36)

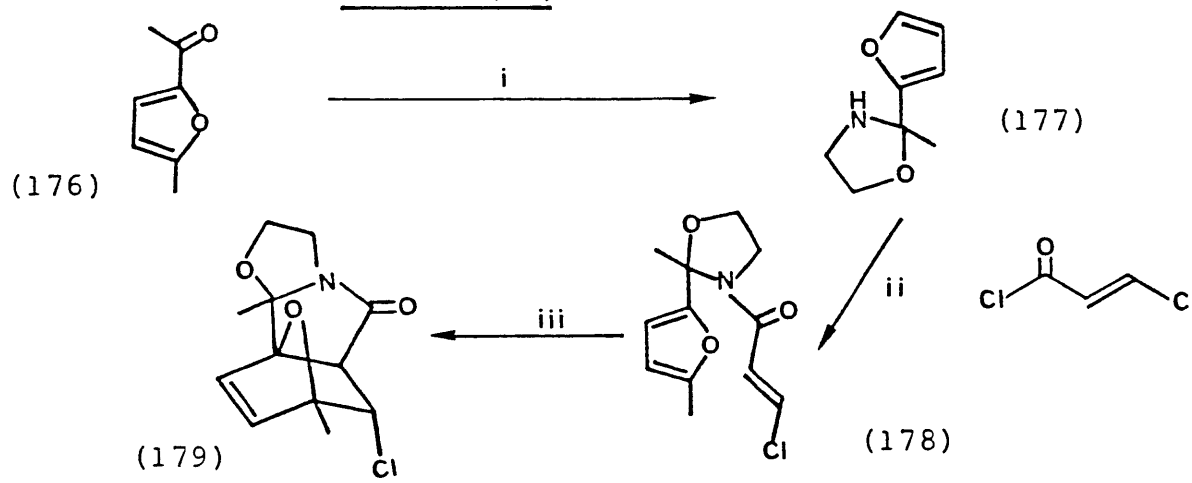


(172b) (174) (175)

Reagents: (i) OsO_4, py, $NaHSO_3$, py, H_2O, 97%; (ii) Na, THF, 78%.

In order to introduce the required C-8 oxygen atom, aminal (177) was prepared from 2-acetyl-5-methylfuran (176). Acylation of (177) with β-chloroacryoyl chloride gave (178) which underwent an intramolecular Diels-Alder reaction on heating to give (179) as a single diastereoisomer in 90% yield (scheme 37).

scheme (37)

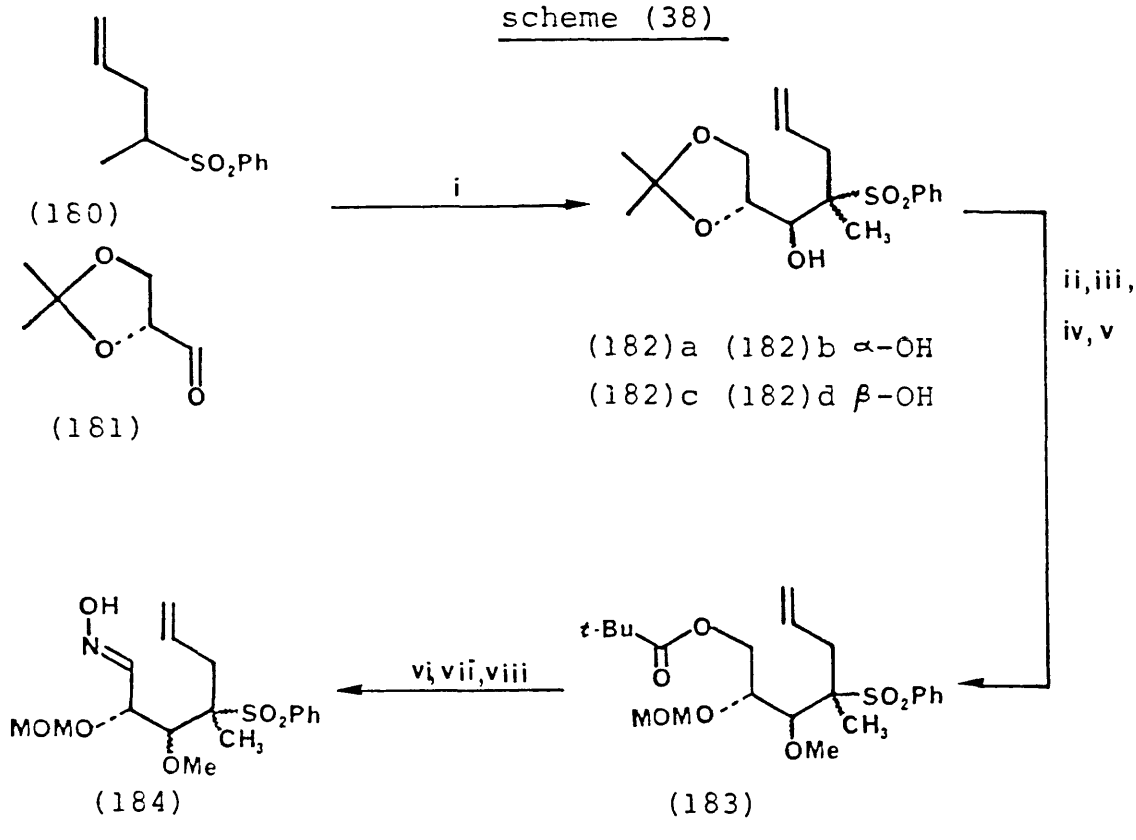


(176) (177) (178) (179)

Reagents: $HO(CH_2)_2NH_2$, $HC(OEt)_3$, TsOH, 79%; (ii) 62%; (iii) 110°C, $PhCH_3$, 3.5h, 90%.

Two recent publications have used an intramolecular nitrile oxide cycloaddition (INOC) as the pivotal step in their approach to the hexahydrobenzofuran fragment of the milbemycins and avermectins. In Kozikowski's[36] work, oximes (184) were prepared from sulphone (180) by standard methodology. (scheme 38)

scheme (38)



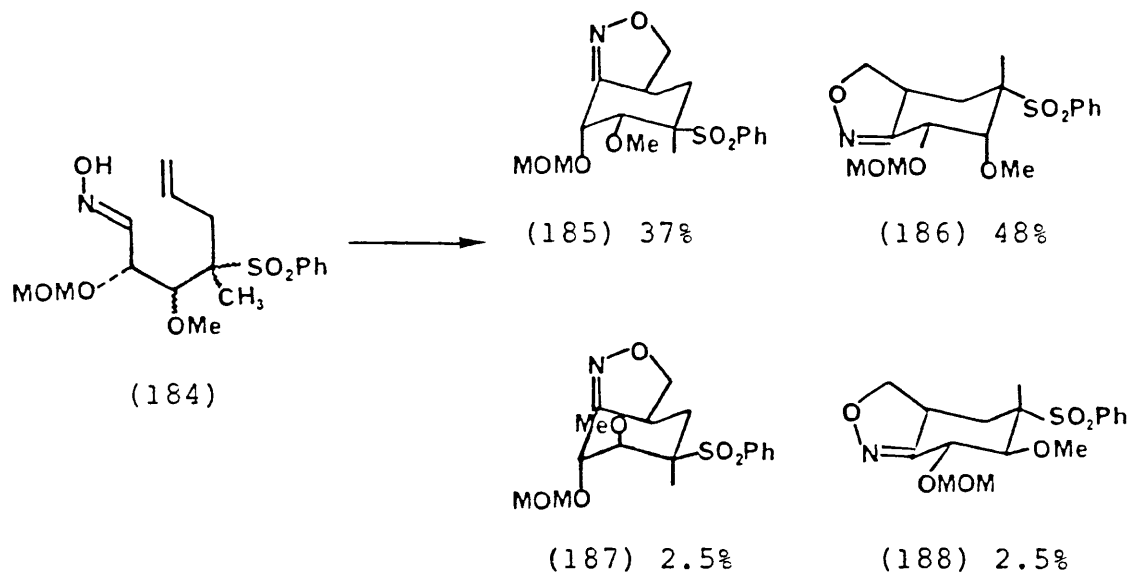
Reagents: (i) *n*-Buli, 73%; (ii) NaH, MeI, 78%; (iii) MeOH, HCl, H_2O, 96%; (iv) ^tBuCOCl, py, 96%; (v) $(MeO)_2CH_2$, P_2O_5, 89%; (vi) EtMgBr, Et_2O, 96%; (vii) PCC, NaOAc, 95%; (viii) $NH_2OH.HCl$, NaOAc, 70%.

Although the initial addition of sulphone (180) into chiral aldehyde (181) gave a mixture of diastereoisomers, the stereochemistry of the new hydroxyl bearing centre

was found to correspond primarily to addition *via* a Felkin like transition state.[37]

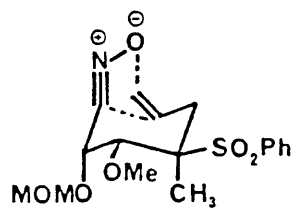
An INOC cyclization was then brought about by treating oximes (184) with sodium hypochlorite. The resulting isoxazolines were readily separated to give two major (185), (186) and two minor isomers (187), (188). (scheme 39).

scheme (39)



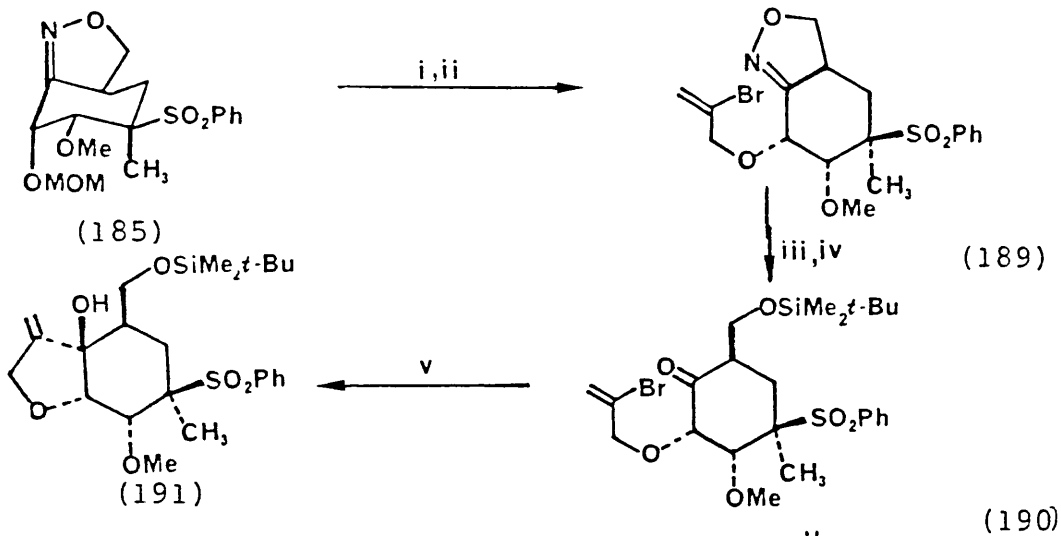
X-ray analysis was used to determine the structure of the major isomers (185) and (186). These results led Kozikowski to postulate that the high selectivity is a consequence of the chair-like transition state in which the sterically demanding sulphone group occupies a pseudo equatorial position.[38] (scheme 40)

scheme (40)



The two minor isomers (187) and (188) arose from a small amount of *anti*-Felkin product generated in the initial condensation of sulphone (180) with aldehyde (181). Elaboration of isoxazoline (185) to the *cis* fused adduct(191) was achieved using standard methodology. Removal of the MOM protecting group followed by alkylation of the resulting alcohol gave vinyl bromide (189). Opening of the isoxazoline ring was accomplished using the conditions of Torsell[39]. Protection of the primary alcohol gave (190) which on treatment with di-*n*-butylcopper lithium under the conditions of Corey[40] gave the cis fused reduced furan ring system (191) (scheme 41).

scheme (41)



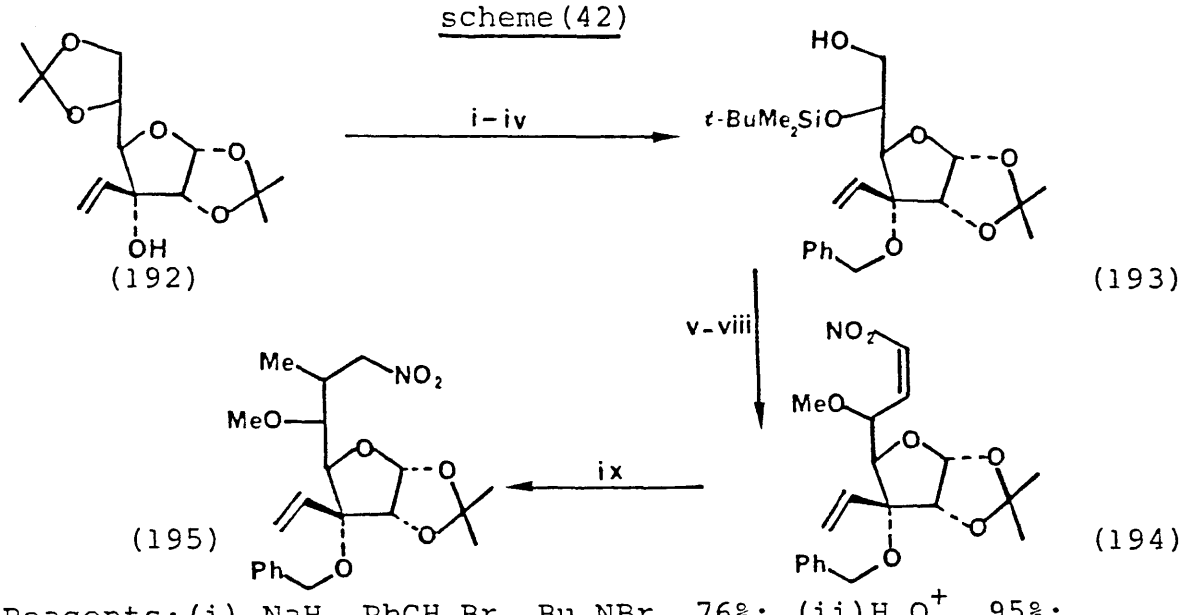
(185) (189) (190) (191)

Reagents (i) HCl, MeOH, 91%; (ii) NaH, Br ⟨ Br, 73%; (iii) Tl^{3+}, MeOH, H_2O, 67%; (iv) $^tBuMe_2SiCl$, imid, DMF, 80%; (v) Bu_2CuLi, pentane, Et_2O, 74%.

No details of attempts to install the C-3-C-4 double bond by elimination of sulphinic acid from (191) were given, however the authors indicated that investigations are being carried out using a 1,3-diene rather than an alkene in the INOC so that the required C-3-C-4 double bond is present at the start of the synthesis.

The second approach utilizing an INOC and undoubtedly the most elegant synthesis to date is by Fraser-Reid and Prashad.[41] Glucose was converted to the allylic alcohol[42] (192) *via* diacetone glucose using literature procedures. Benzylation followed by a protection-deprotection sequence afforded the primary alcohol(193). Swern oxidation[43] gave the aldehyde which underwent a Henry reaction with nitromethane to give, after mesylation and elimination, nitroalkene(194). Conjugate addition of methyl lithium afforded an epimeric mixture of (195) (scheme 42)

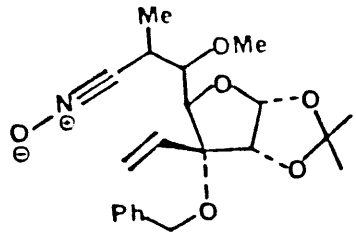
scheme(42)



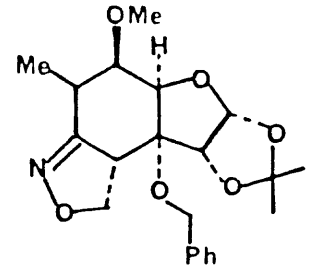
(192) (193) (194) (195)

Reagents:(i) NaH, $PhCH_2Br$, Bu_4NBr, 76%; (ii)H_3O^+, 95%; (iii) TBDMS-Cl, NEt_3, 98%; (iv) MeI, NaH, Bu_4NI, 98%; (v)Bu_4NF, 98%; (vi) $(COCl)_2$, Me_2SO, NEl_3, 90%; (vii) CH_3NO_2, ^tBuOK, 77%; (iii)MsCl,77%; (ix) MeLi, 60%.

Treatment of nitroalkane (195) with phenyl isocyanate[44] gave nitrile oxide (196) which underwent an INOC to give (197) as a single isomer in 74% yield.

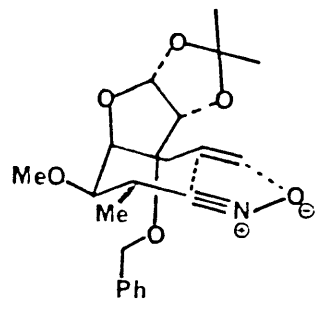


(196)



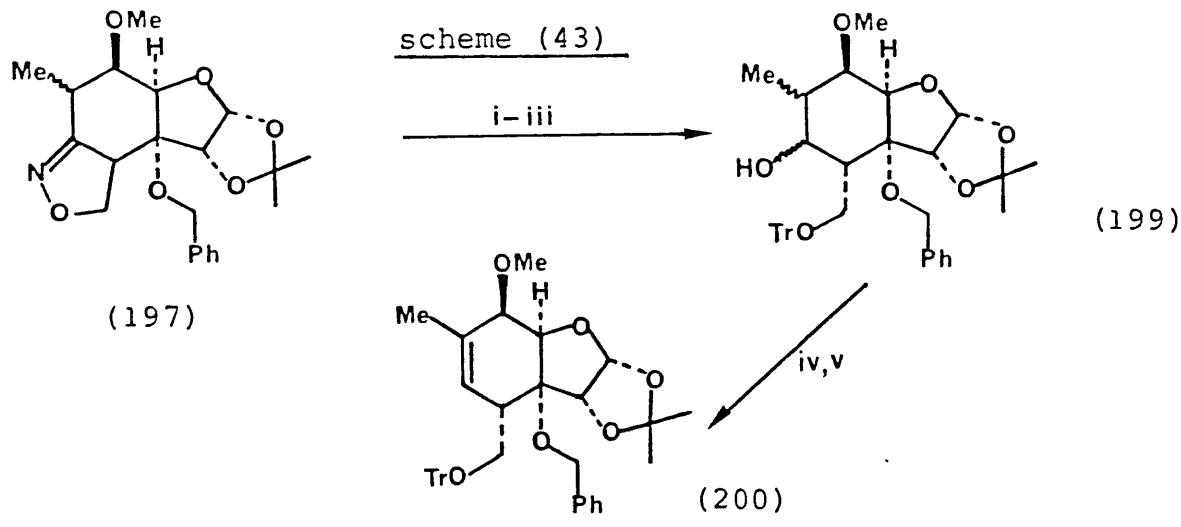
(197)

The extremely high selectivity of the INOC is a consequence of the chair like transition state (198) through which the reaction proceeds.



(198)

Reduction of the isoxazoline (197) followed by treatment with LAH and protection gave the secondary alcohol (199). Mesylation occured smoothly and elimination gave a single olefin (200) with the double bond in the ring (scheme 43).

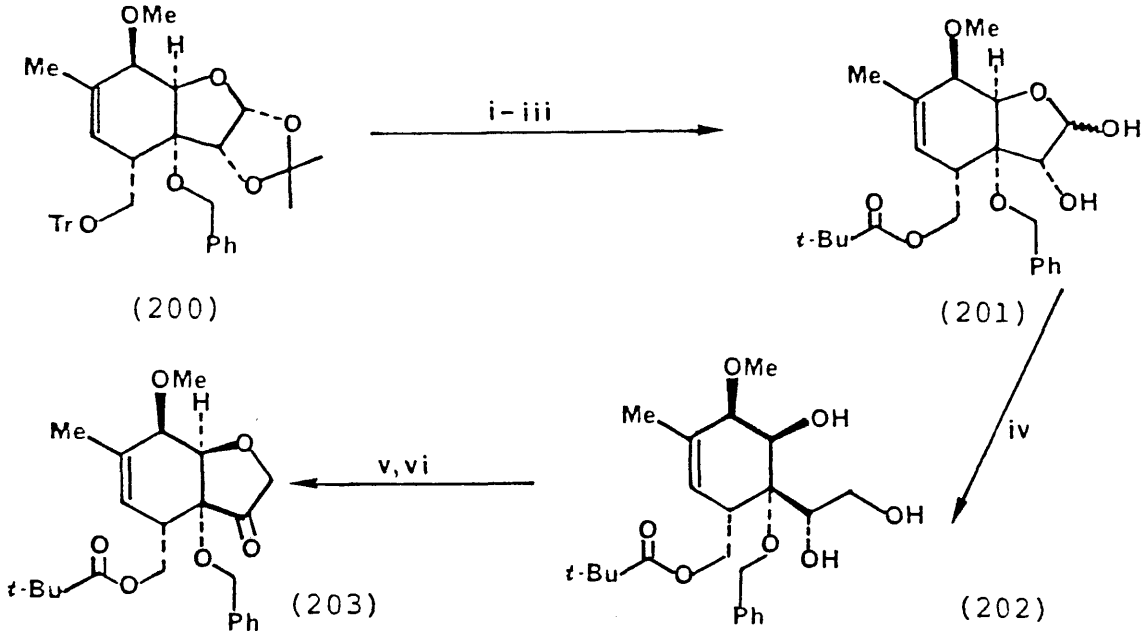


(197) (199) (200)

Reagents: (i) H_2, Ni, 67%; (ii) LAH, 65%; (iii)Ph_3CCl, 90%; (iv) MsCl, 86%; (v) NaOAc, HMPA, 100°C, 3-4 days, 50-55%.

Deprotection and reprotection of the primary hydroxyl group followed by removal of the acetonide gave lactol (201) which was reduced with sodium borohydride to give triol (202). Ring closure was achieved using tosyl chloride and the resulting primary alcohol oxidised under Swern[43] conditions to give the requisite ketones (203) (scheme 44).

scheme (44)



Reagents: (i) CSA, MeOH, rt , 94%; (ii) ^{t}BuCOCl, 80%; (iii) 0.5% H_2SO_4, 85%; (iv) $NaBH_4$, 60%; (v) TsCl, 70%; (vi) $(COCl)_2$, Me_2SO, NEt_3, 70%.

To date this is the only synthesis of the southern hemisphere of the avermectins which provides optically pure material suitable for coupling to other fragments.

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42. D.C.Baker, D.K.Brown, D.Horton, and R.G.Nickol, *Carbohydr.Res.*,1974,*32*,299.

43. K.Omura and D.Swern, *Tetrahedron.*, 1978, *34*, 1651.

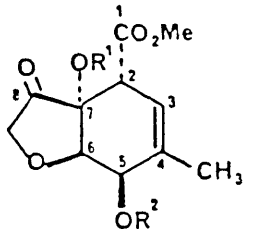
44. T.Mukaiyama and T.Hoshino, *J.Am.Chem.Soc.*, 1960, *82*, 5339.

The current high level of interest in the avermectins and milbemycins is reflected by the large number of publications and synthetic effort in this area. To date 5 total syntheses of the simplest member of the series milbemycin β_3, have been published along with considerable work directed towards the spiroacetal moiety of these systems. There has been, however, with several notable exceptions little work published on the hexahydrobenzofuran southern hemisphere of the avermectins and milbemycins α_1-α_{10} and β_1-β_2. Since our group is involved in synthesis in this area, the problem clearly needed addressing. The remainder of this thesis deals with some of the studies that have been carried out in our laboratories towards the synthesis of the southern hemisphere of the avermectins and milbemycins.

RESULTS AND DISCUSSION

A Diels-Alder approach to the hexahydrobenzofuran southern hemisphere of the avermectins.

Our strategy towards the southern hemisphere was targeted on the sub unit (204) where R^1 and R^2 were



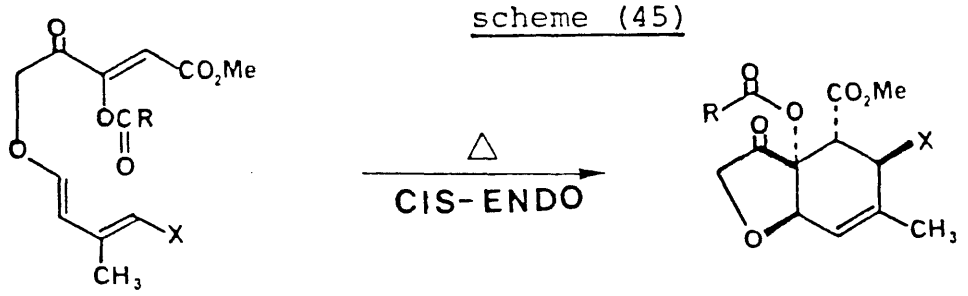
(204)

suitably chosen protecting groups. In order to achieve the total synthesis of an avermectin it would be necessary to couple (204) to a suitably functionalized alkene side chain[1] and a spiroacetal moiety[2]. The coupling of the alkene side chain was proposed *via* either a Wittig-Horner reaction,[3] a Wadsworth-Emmons reaction[4] or a Julia reaction[5] with the C-8 carbonyl group. Coupling of the resulting methyl ester to the spiroacetal moiety could be acieved by one of several routes. Firstly saponification would give the carboxylic acid which could be coupled using standard techniques.[5] Access to the required acid could also be

obtained by a reductive/oxidative procedure.[6] Secondly, transesterification of the methyl ester to the ^{t}butylthio-ester followed by silver catalysed ring closure would yield the requisite lactone.[7]

Of several possible Diels-Alder[8] approaches the intramolecular Diels-Alder reaction illustrated was chosen as the key step in our synthetic strategy. (scheme 45)

scheme (45)

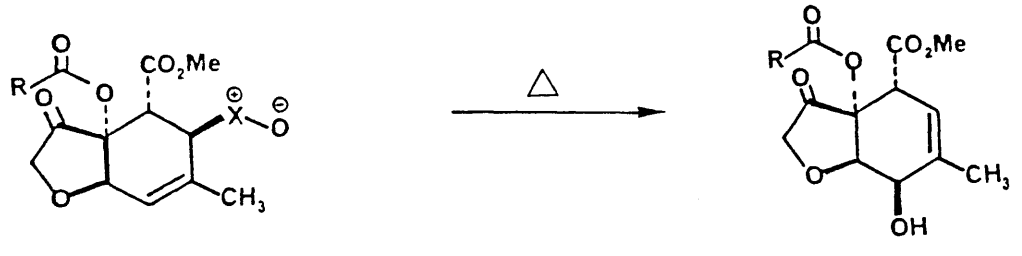


X =SePh (205)
SPh (206)
$SiMe_3$ (207)

X= SePh (208)
SPh (209)
$SiMe_3$ (210)

When X=SePh and SPh it was envisaged that selective oxidation of (208) and (209) at low temperature would give selenoxide[9] (211) and sulphoxide[10] (212) respectively. Literature precedent indicated that on warming, both (211) and (212) would undergo a [2,3] sigmatropic rearrangement[11] to give the allylic alcohol (213) as product (scheme 46).

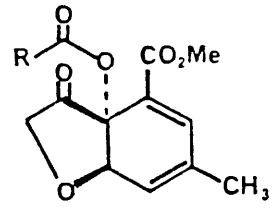
scheme (46)



X=SePh (211)
SPh (212)

(213)

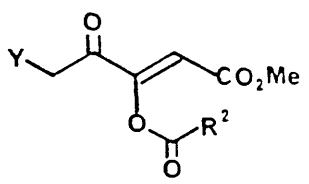
In both the selenoxide (211) and sulphoxide (212) there exists the possibility of competing *syn* elimination to give diene (214), however the [2,3] rearrangement is a kinetically much faster process and occurs at temperatures 20-30°C lower than those required for the *syn* elimination.



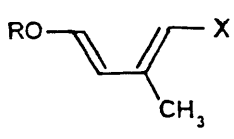
(214)

When X=$SiMe_3$, oxidation of the C-4-C-5 double bond, in the Diels-Alder adduct (210), *via* epoxidation[12] or osmium mediated *cis* hydroxylation[13], followed by elimination of the resulting β-hydroxysilane formed in a Peterson type[14] process should again give allylic alcohol (213). With these approaches it would be necessary to develop methodology for the construction of the required selenide (205), sulphide(206) and silane(207).

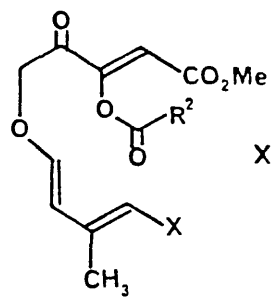
The desired Diels-Alder substrates (205) → (207)



(215)

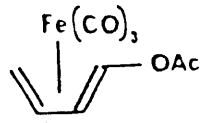


(216)



X = SePh (205)
SPh (206)
$SiMe_3$ (207)

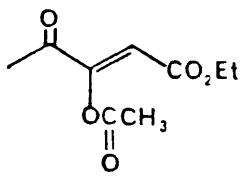
could be accessible *via* a displacement of a leaving group Y from the α-enone (215) by a suitable oxy-diene (216). Although dienes of the type (216) are unknown, tricarbonyl iron complexes of dienes such as (217) are well documented in the literature.[15] Thus substrates of the type (215)



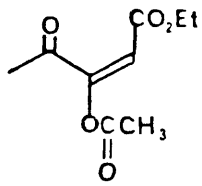
(217)

and (216) became the targets of our synthetic effort.

Before embarking on such a synthesis it was decided to carry out some simpler model studies using an intermolecular Diels-Alder approach. Acetate (218) was chosen as our dienophile



(218)



(219)

Although (218) was unknown, Battersti and coworkers[16] had reported the equilibrium ratio between diketone (220) and its enol form (221) is 1:1 in CCl_4, furthermore the enol form (221) exists entirely as the required Z isomer. (scheme 47)

scheme(47)

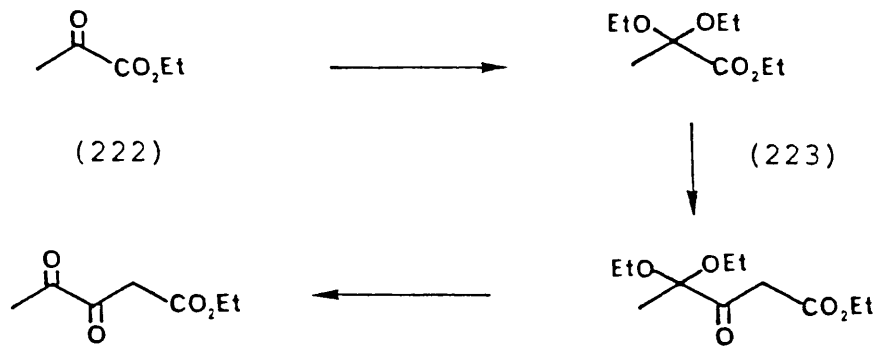


(220) (221)

Acylation of the enol (221) should give the required acetate (218). Treatment of the diketone (220) in Et_2O or CH_2Cl_2 with 1.2eq of acetyl chloride in the presence of 1.2eq of pyridine as base gave a 1:1 mixture of the isomeric acetates (218) and (219) in a combined 67% yield, which were separable by chromatography. However if the reaction was carried out in pyridine at 0°C a 48% yield

of the required acetate,(218) only,was obtained. This was a pleasing result as diketone (220) was readily prepared on a mole scale from ethyl pyruvate *via* a three step procedure. (scheme 48). Thus protection of ethyl pyruvate (222) as its diethyl acetal (223) was smoothly carried out using triethylorthoformate with *p*TSA as an acid catalyst giving (223) in a 92% yield. Claisen condensation of (223) with ethyl acetate using sodium as

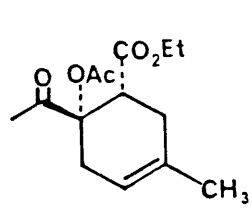
scheme(48)



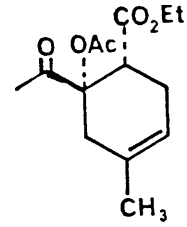
(222) (223) (220) (224)

the base gave a 76% yield of ethyl ester (224) after distillation; finally, removal of the diethylacetal protecting group with conc. HCl at 0°C gave the required diketone (220) in 93% yield as a yellow oil.[16]

Having developed a satisfactory synthesis of acetate (218), we investigated its properties in Diels-Alder reactions. On heating with excess isoprene at 140°C in a sealed tube for 48h a mixture of adducts (225) and (226) was obtained in a combined 15% yield.

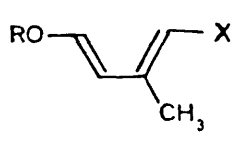


(225)

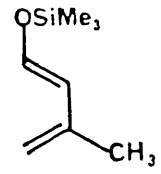


(226)

Although esters (225) and (226) were inseparable by chromatography the 250 MHz NMR spectrum clearly showed the two isomers were present in a 1:1 ratio. After this success siloxydiene[17] (227) was the logical choice in our investigations as it more closely resembled our target dienes (216). Diene (227) was prepared in an overall 48%



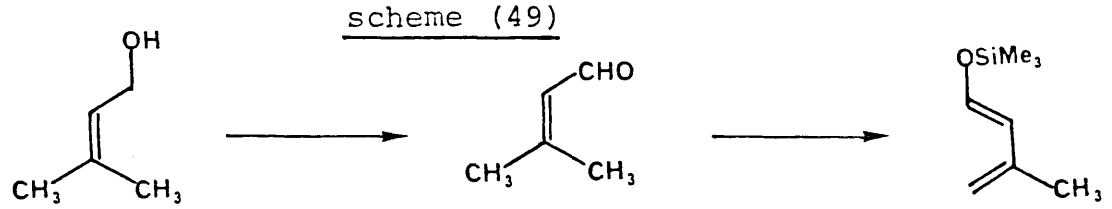
(216)



(227)

yield from the comercially available 4-methyl-but-2-en-1-ol (228) *via* oxidation with PDC[18] followed by treatment with NEt_3, TMS-Cl and $ZnCl_2$ at 40°C. (scheme 49). On heating diene (227) with acetate (218) for 72h in dry

scheme (49)

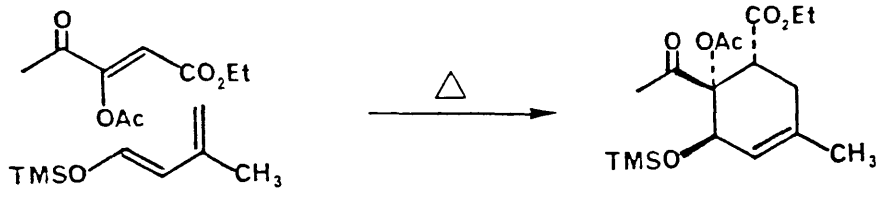


(228) (229) (227)

toluene at 115°C a 47% yield of ester (230) was obtained. (scheme 50)

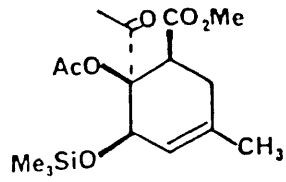
scheme (50)

(218)



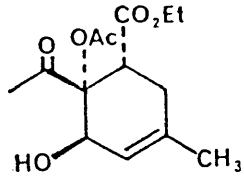
(227) (230)

The 250MHz NMR data of (230) was fully consistent with the proposed structure. However reaction *via* a *cis-exo* addition to give (231) could have resulted in an almost identical spectrum.

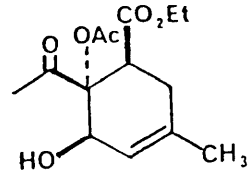


(231)

A derivative of (230) suitable for X-ray analysis was sought as more conclusive evidence of the structure. Treatment of (230) with HF/CH_3CN[19] gave alcohol (232) in a 92% yield as an oil. However on reaction with TBAF[20] in THF, (230) gave a completely different alcohol (233) which was isomeric with (232) from microanalytical data. The 250MHz NMR spectra of the two alcohols did, however,



(232)

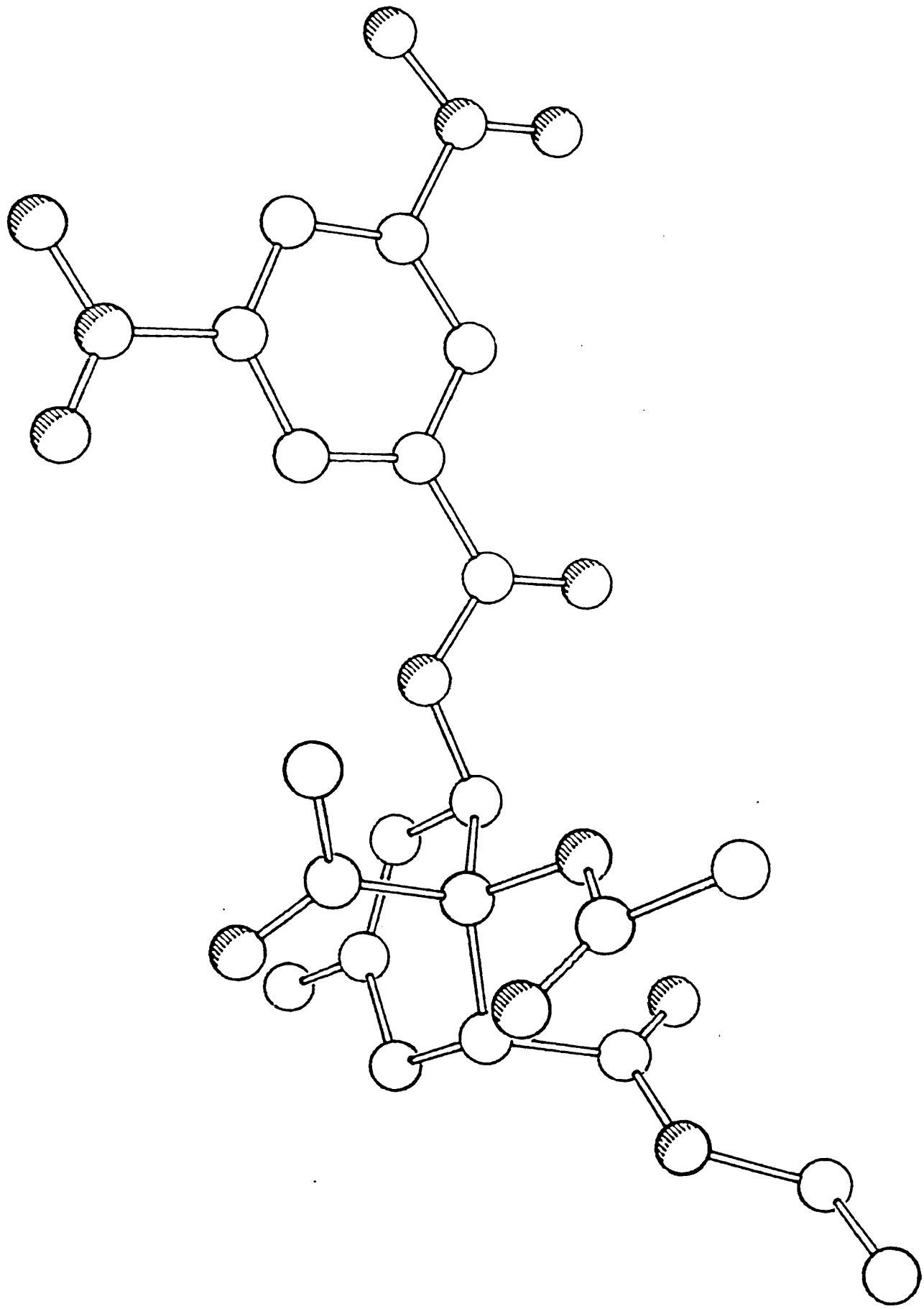


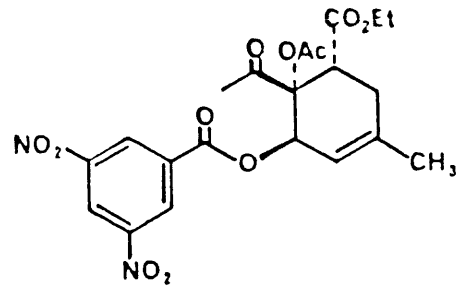
(233)

show some distinct differences. In alcohol(232) the δ values of the acetyl and acetoxy methyl groups were 2.04 and 2.13ppm respectively. In alcohol (233), derived using TBAF, the δ values of the same groups were 2.05 and 2.37 ppm respectively. This led us to postulate that the basic nature of TBAF had caused epimerization at the C-2 position to give (233). There is literature precedent for this idea. On treatment with sodium methoxide in methanol at rt, ivermectin is partly converted to 2-epiivermectin.[21]

Preparation of the crystalline 3,5-dinitrobenzoate derivative (234) from alcohol (232) gave unambiguous evidence that *cis-endo* addition had occured during the Diels-Alder reaction (Figure 4).

Figure 4.

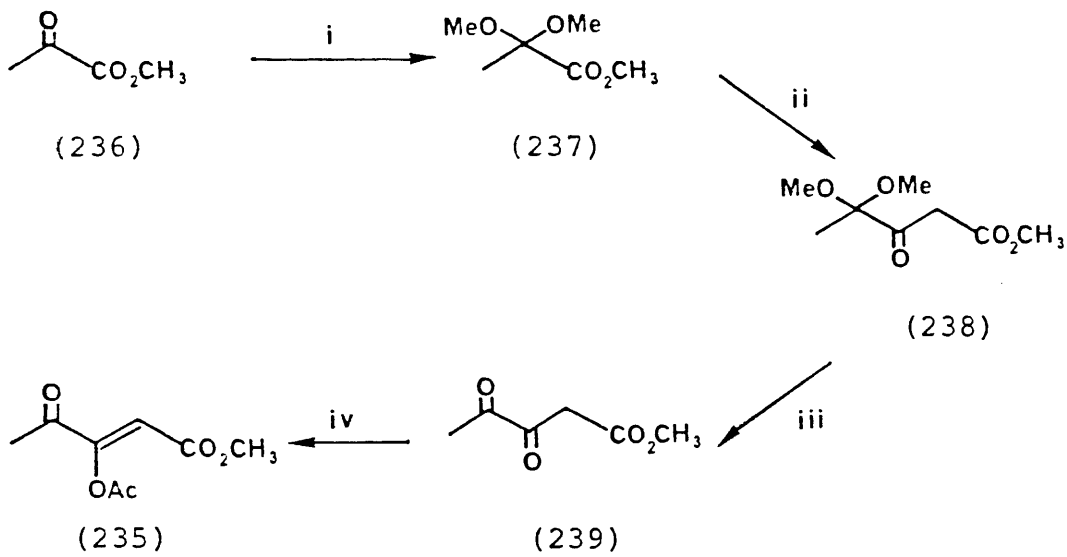




(234)

Thus in a very short sequence the relative stereochemistry of three out of the four required centres in our target molecule (204) had been established. In view of the ease of cleavage of methyl esters under hydrolytic conditions,[22] acetate (235) was prepared in a manner similar to that previously described. (scheme 51)

scheme (51)



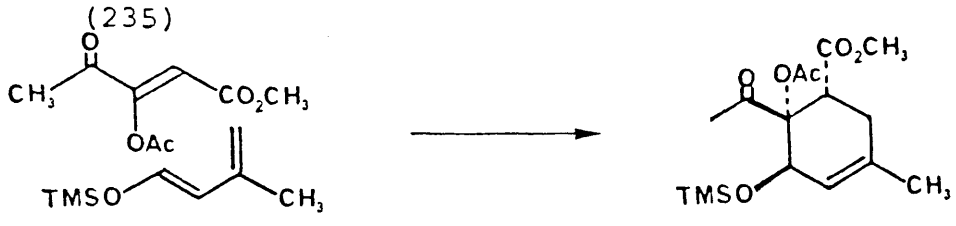
(236) (237) (238) (239) (235)

Reagents: (i) $(MeO)_3CH$, PTSA, MeOH, Δ, 87%; (ii) Na, CH_3CO_2Me, 69%; (iii) Conc. HCl, 0°C, 0.5h, 95%; (iv) AcO, CSA, 85°C, 6h, 72%.

Various attempts were made to improve the yield of the final step. The use of Ac_2O in pyridine at 0°C gave a 56% yield of (235), however it was found that heating diketone (239) with isopropenyl acetate in the presence of CSA[23] for 6h at 85°C gave a 72% yield of the required acetate (235) after chromatography.

On heating acetate (235) with silyloxy diene (227) in dry toluene at 115°C for 72h a 65% yield of ester (240) was obtained. (scheme 52)

scheme (52)



(235) (227) (240)

On treatment with HF/CH_3CN[19] and TBAF[20] (240) gave the isomeric alcohols (241) and (242), in 91% and 23% yield respectively in accordance with our previous observations.



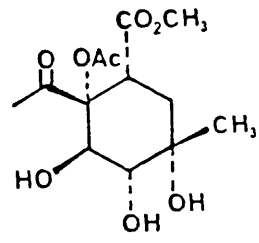
(241) (242)

In view of the accessibility of alcohol (241) it was decided to attempt to convert it to our target molecule (204). This presented us with two distinct problems. Firstly, oxidation of the C-5 position on the β-face and the introduction of the C-3-C-4 double bond. Secondly, formation of the tetrahydrofuran ring. Initially effort was focused on the first of these problems. Oxidation of allylic alcohol (241) with *m*-CPBA gave a single epoxide (243). Literature precedent indicated epoxidation [24] should



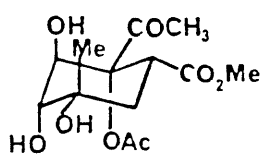
(243) (244)

be directed by the C-6 hydroxyl group onto the β-face. Treatment of (243) with lithium diethylamide[25] failed to give the desired ring opened product (244). Catalytic osmium mediated *cis* hydroxylation of allylic alcohol (241) with N-methylmorpholine oxide[13] as a stoichiometric oxidant, gave a triol whose structure was subsequently determined to be (245).

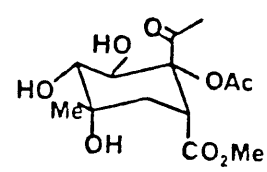


(245)

The osmium mediated *cis*-hydroxylation of olefins is known to be particularly sensitive to steric factors, hence it was important to determine on which face of the olefin oxidation had occurred. The application of high field NMR was of use in solving this problem. Oxidation of the α-face would give a single triol which could exist in the two chair conformers (246) and (247).

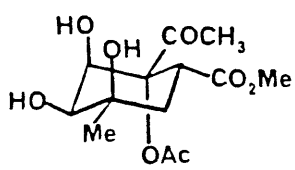


(246)

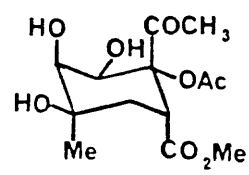


(247)

Similarly oxidation on the β-face would give a single triol which could again exist in two chair conformers (248) and (249).



(248)



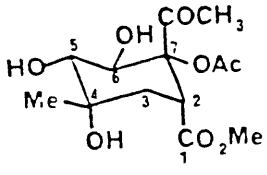
(249)

Examination of molecular models suggested that in each of the four possible chair conformers there was a hydrogen bond between the C-6 hydroxyl group and the methyl ketone. Since intramolecular bonding is known to frequently cause dramatic low-field chemical shifts,[26] it was anticipated that the C-6 hydroxyl proton would be at very low field and would not be involved in vicinal coupling. Further examination of the molecular models indicated that in the three conformers (246), (248) and (249), the dihedral angle between the C-5 and C-6 protons was approximately 60°. However, in (247), the C-5 and C-6 protons are in a *trans*-diaxial orientation with a dihedral angle of 180°. Application of the Karplus equation[26] gave a coupling constant of 6Hz or less between the C-5 and C-6 protons in conformers (246), (248) and (249). In (247) the 180° dihedral angle between the C-5 and C-6 protons is characterized by a much larger coupling constant, usually in the order of 8-12 Hz.

The 250 MHz spectrum of triol(245) was consistent with conformer (247) suggesting that oxidation had occured on the α-face. Of particular interest was a doublet at δ 2.68 with a coupling constant of 10.9 Hz, a triplet at δ3.15 with a coupling constant of 10.9 Hz and a doublet at δ 4.12 again with a coupling constant of 10.9 Hz. The resonance at δ2.68 was assigned to the C-6 proton which was coupled to the C-5 proton with a 10.9 Hz coupling constant, charateristic of the *trans*-diaxial relationship between them. The C-5 proton appeared as a triplet at δ 3.15 although it is most likely that it is an overlapping double doublet due to coupling to the C-5 proton and the C-5 hydroxyl proton. The resonance at δ4.12 was assigned to

the C-5 hydroxyl proton. The C-6 secondary hydroxyl proton was a characteristic singlet at δ5.30. The NMR data for triol (245) is summarized in scheme (53).

scheme (53)



(245)

δ_H (250 MHz; $CDCl_3$)

1.28(3H,S,*Me*)

2.04(1H,dd,J=17.4, 1.6Hz,*H-3*)

2.14(3H,s, OCO*Me*)

2.21(3H,s, CO*Me*)

2.61(1H,dd,J=17.4, 7.3Hz, *H-3*)

2.68(1H,d,J=10.9Hz, *H-6*)

2.96(1H,s, C-4 O*H*)

3.15(1H,t,J=10.9Hz, *H-5*)

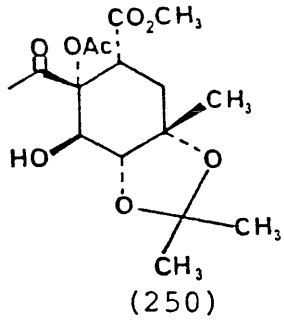
3.73(3H,s,CO_2 *Me*)

3.85(1H,dd,J=7.3,1.6Hz, *H-2*)

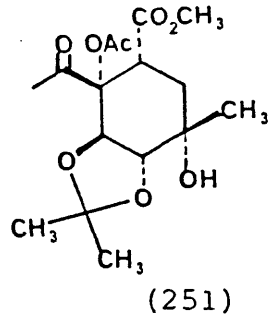
4.12(1H,d,J=10.9Hz, C-5 O*H*)

5.30(1H,s, C-6 O*H*)

On treatment with 2,2-dimethoxypropane, triol (245) gave a mixture of acetonides (250) and(251) in a 3:1 ratio respectively. The 250 MHz NMR of both (250) and (251) was



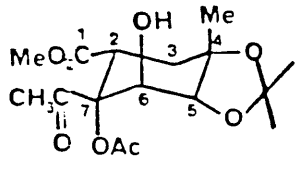
(250)



(251)

consistent with their proposed structures (scheme 54).

scheme (54)



(250)

δ_H(250 MHz; $CDCl_3$)

1.34(3H,s,*Me*)

1.45(3H,s,C*Me*)

1.51(3H,s, C*Me*)

1.88(1H,dd,J=14.1, 3.1Hz, *H-3*)

2.12(3H,s,OCO *Me*)

2.16(3H,s,CO*Me*)

2.51(1H,t, J=14.1Hz, *H-3*)

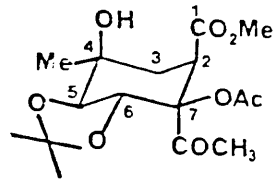
3.33(1H,dd,J=14.1, 3.1Hz *H-2*)

3.68(3H,s,CO_2*Me*)

3.83(1H,d,J=3.4Hz, *H-5*)

4.78(1H,d,J=1.7Hz, C-6 O*H*)

5.09(1H,dd,J=3.4,1.7Hz, *H-6*)



(251)

δ_H(250MHz; $CDCl_3$)

1.34(3H,s,C*Me*)

1.38(3H,s,C*Me*)

1.51(3H,s,*Me*)

2.06(1H,d,J=15.3Hz,*H-3*)

2.14(3H,s,OCO *Me*)

2.21(3H,s, CO *Me*)

2.33(1H,dd,J=15.3, 6.6Hz, *H-3*)

3.32(1H,d,J=10.9Hz,H-5/6)

3.73(1H,s,CO_2 *Me*)

3.90(1H,d,J=6.6Hz, *H-2*)

4.40(1H,d,J=10.9Hz, H-5/6)

4.93(1H,s,C-4 O*H*)

Several points of interest are worth noting here. In (250) the C-6 secondary hydroxyl group is hydrogen bonded to the methyl ketone, however this hydroxyl proton exhibits a small 1.7Hz coupling to the C-6 proton. The C-6 proton also shows a 3.4Hz coupling to the C-5 proton characteristic of the 60° dihedral angle between the two protons. This coupling pattern was extremely useful in determining which resonance corresponded to the C-5 proton and which one corresponded to the C-6 proton, since the C-4 and C-7 were both quaternary centres.
Indeed in acetonide (251) both the C-5 and C-6 protons appeared as doublets with a 10.9Hz coupling. Their assignment was thus somewhat ambiguous.

The conformational rigidity of these systems allowed a more rigorous assignment of the C-3 protons. In (250) the C-3 β proton appears as a triplet, arising from an overlapping double doublet showing a 14.1 Hz geminal coupling and a 14.1 Hz vicinal coupling to the C-2 proton. In acetonide (251) the C-2 proton is coupled only to C-3 β proton with a 6.6 Hz coupling constant reflecting the 60° dihedral angle between these two protons. The C-3 α proton is at almost 90° to the C-2 proton and in accordance with the Karplus equation exhibits no observable coupling.

The interpretation of the high field NMR data was confirmed by X-ray analysis of the highly crystalline acetonides (250) and (251).(Figures 5 and 6). It was disappointing to find that the oxidation had occurred on the α-face of alkene (241) as selective protection of the resulting secondary alcohols arising from oxidation on the β-face (252) followed by elimination of the carbinol[27] would have given easy access to the required alkene.(253)

Figure 5.

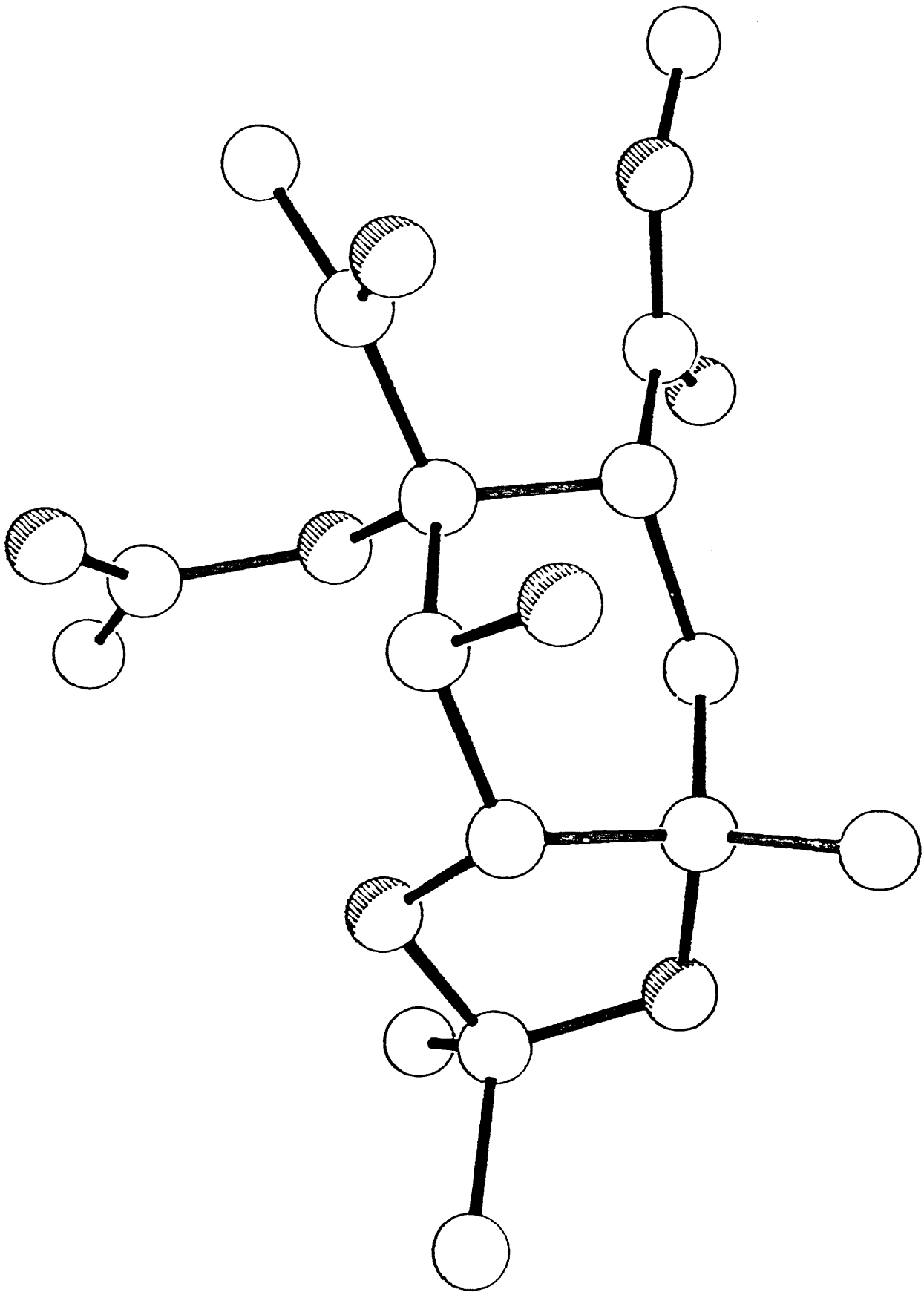
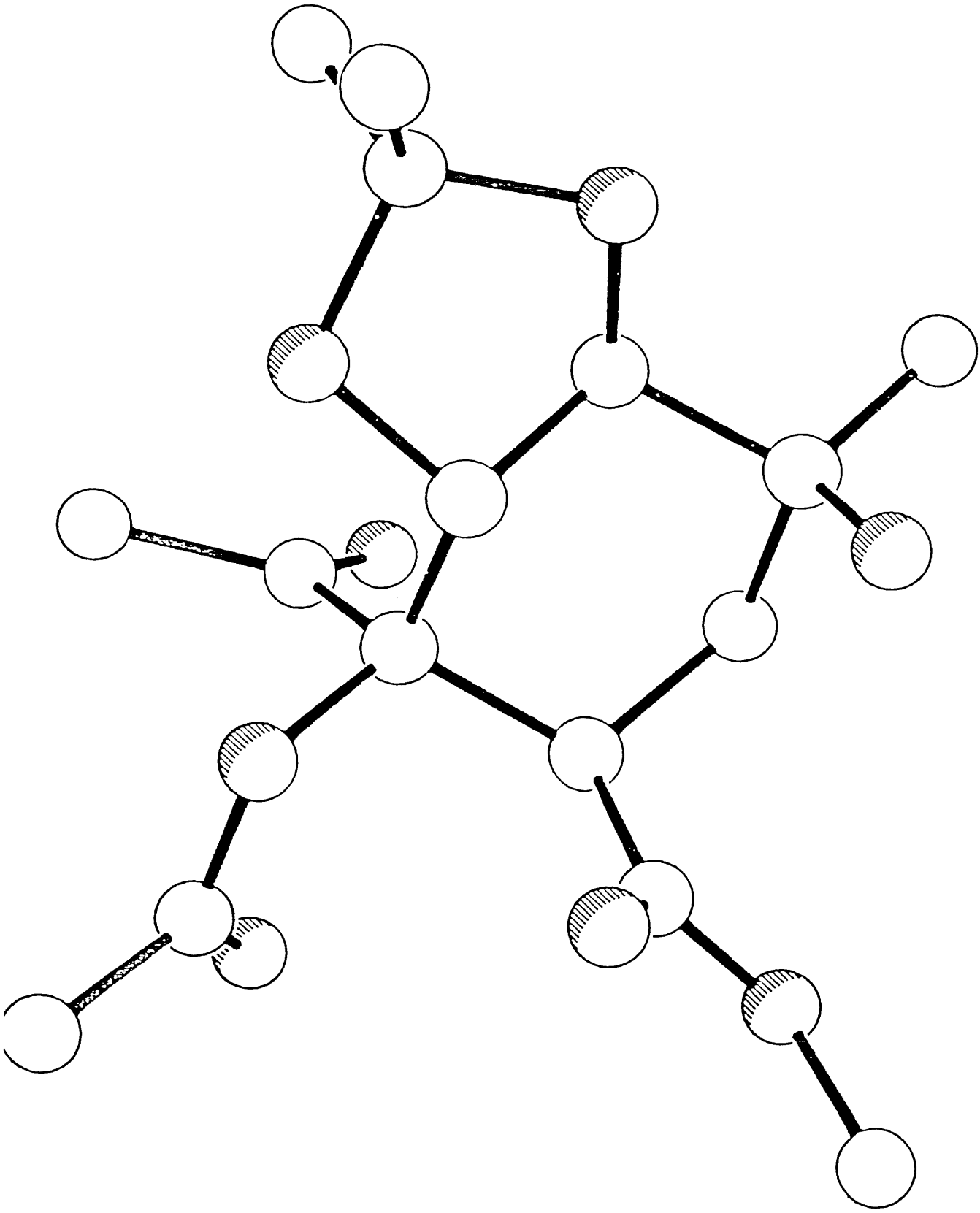
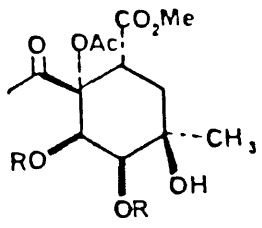
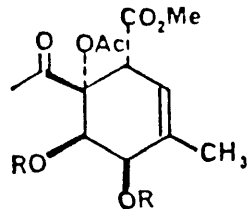


Figure 6.



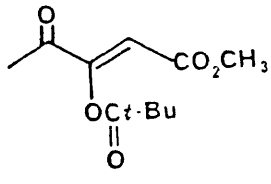


(252)

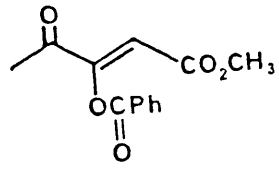


(253)

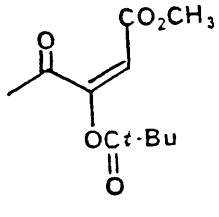
It was then attempted to promote *cis* hydroxylation of the β-face by increasing the steric hindrance on the α-face replacing the acetoxy group with a more bulky group. Hence the dieneophiles (254) and (255) were prepared by treatment of diketone (239) with pivaloyl chloride and benzoyl chloride in pyridine at 0°C in 46% and 35% yield respectively. It was found that the isomeric adducts



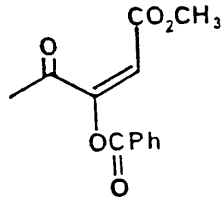
(254)



(255)

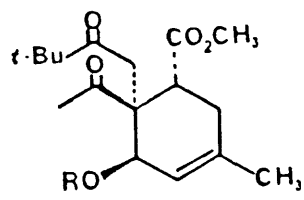


(256)



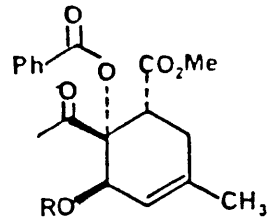
(257)

(256) and (257) were isolated after short reaction times. Extended reaction periods led to almost exclusive formation of (254) and (255). Both (254) and (255) underwent *cis-endo* addition with silyloxy diene (227) at 115°C in toluene to give esters (258) and (260) in unoptimized 48% and 32% yields respectively.



R=TMS (258)

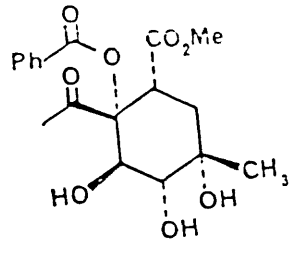
=H (259)



R=TMS (260)

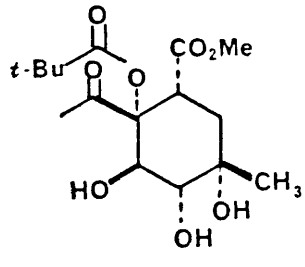
=H (261)

Removal of the trimethylsilyl group from (258) and (260) was acieved using HF/CH_3CN giving alcohols (259) and (261) in 89% and 93% yield respectively. Osmium mediated *cis*-hydroxylation[13] of alkene (260) gave triol (262) in 68% yield. The NMR. data was consistent as previously described with hydroxylation on the α face.

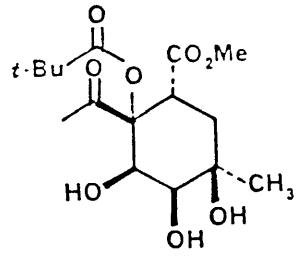


(262)

With alkene (259), hydroxylation gave a 6:1 mixture of two triols (263) and (264) in a combined 56% yield. Again NMR analysis indicated the major isomer (263) was a result of oxidation on the α-face. The minor isomer



(263)



(264)

was tentatively assigned the structure (264). Clearly the use of bulkier substituents was not successful in forcing hydroxylation from the β-face.

Corey[28] has reported a procedure for the *cis*-hydroxylation of olefins from the either the less or the more hindered π-face.

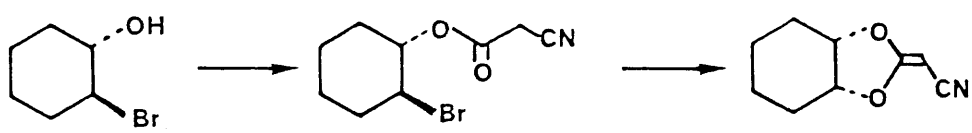
Trans 1,2-bromohydrins are prepared from the alkene by two stereochemically complementary routes;

(i) Reaction of the olefin with hypobromous acid which adds oxygen to the more hindered π-face.

(ii) Peracid epoxidation followed by cleavage with HBr which adds oxygen to the less hindered face.

Corey treated the *trans* 1,2 bromohydrin (265) with cyano-acetic acid in the presence of TsCl to give cyanoester (266). Reaction of (266) with Sodium hydride in THF generated the enolate which underwent internal nucleophilic displacement to give the cyanoketene (267) (scheme 55)

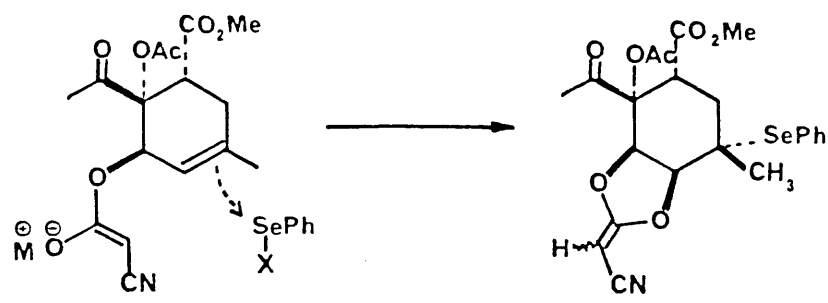
scheme (55)



(265) (266) (267)

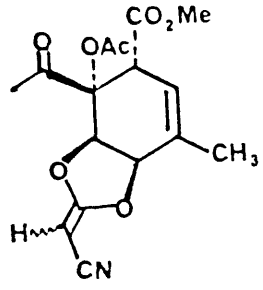
Previous work in our laboratories[29] suggested that a further extension of this work might be possible.

scheme (56)

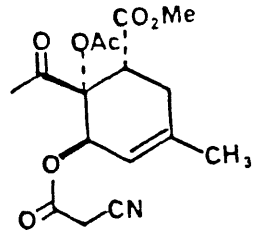


(268) (269)

Treatment of enolate (268) with a suitable selenium electrophile should give selenide (269) (scheme 56). Selective oxidation of (269) to the selenoxide[9] followed by *syn* elimination[11] would give alkene (270).



(270)

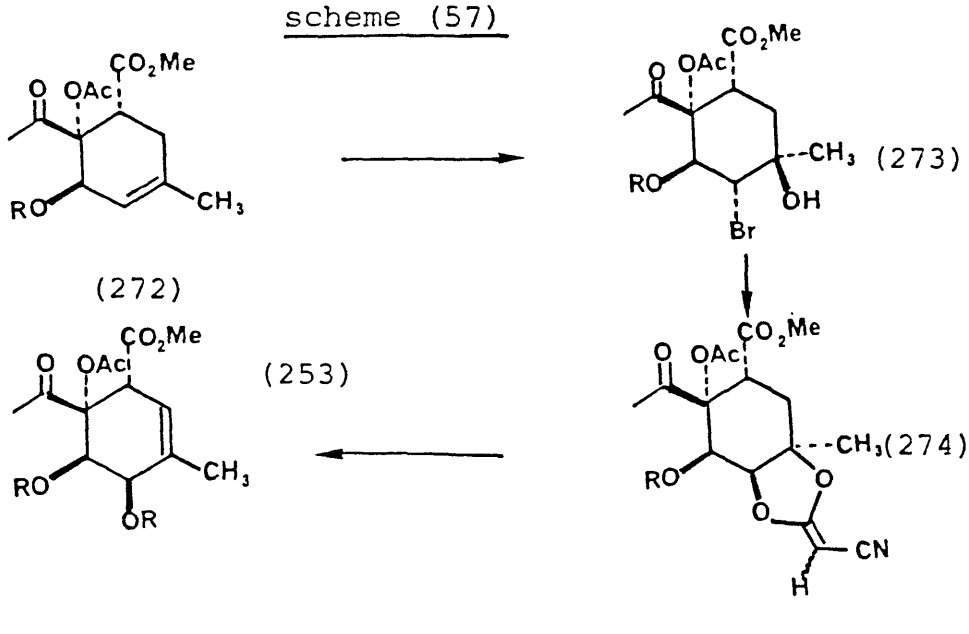


(271)

Cyanoester (271) was prepared from alcohol (241) in 81% yield. However sequential treatment of (271) with sodium hydride and either NPSP[30] or PhSeCl led to several poly-selenated products and the reaction was found to be of no synthetic use.

Research in our laboratories is currently focussed on the direct use of the Corey procedure. Thus preparation of a suitably protected substrate (272), followed by reaction with NBS in DME/H_2O should give bromide (273). Reaction of (273) with cyanoacetic acid in the presence of TsCl and treatment with sodium hydride should yield cyanoketene (274). Hydrolysis, selective protection of

scheme (57)



(272)

(253)

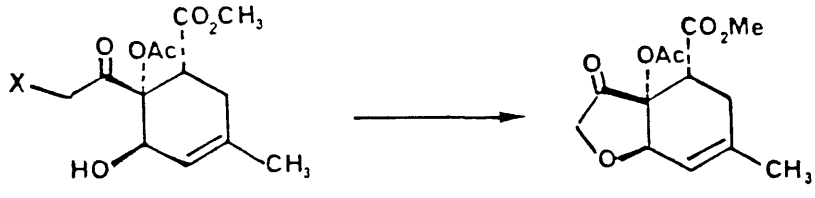
(273)

(274)

the resultant secondary alcohol and finally elimination of the tertiary alcohol should yield a compound of type (253).

Attention was then turned to investigating the second of our problems, the formation of the tetrahydrofuran ring. For this it could be necessary to substitute a leaving group X, α to the ketone which could be readily displaced by the C-6 alcohol to give the required bicyclic system (276) (scheme 58).

scheme (58)



(275) (276)

The leaving group X could be any one of a range such as Cl, Br, I, OTs, OMs or OH. Many methods for the preparation of α-substituted ketones were investigated. Attempts to form the enolate (277) from (240) *via* deprotonation using a variety of bases gave alcohol (241) or polymeric material as products .



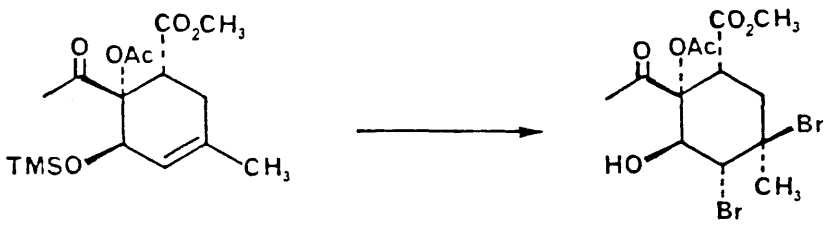
(277) (278)

The use of LDA, KH, KHMDS at -78°C again gave no deprotonation or led to extensive decomposition. It was felt that part of these failures was due to competing deprotonation of the acetoxy group since its chemical shift in the NMR spectrum was almost identical to that of the methyl ketone.

Equally unfruitful were the attempts to form the trimethylsilyl enol ether (278). LDA/TMS-Cl/-78°C, LDA/TMS-Cl/NEt_3/-78°C, LHMDS/TMS-Cl/NEt_3/-78°C, TMS-triflate/DME/-30°C-0°C all failed to give trimethylsilyl enol ether (278).

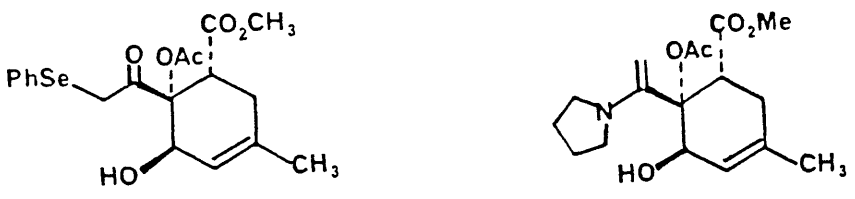
Because of the presence of an allylic double bond in (240), direct halogenation of the carbonyl group with the more reactive brominating reagents was ruled out. Pyrrolidone hydrotribromide (PHT) has been reported to brominate ketones in the presence of double bonds.[31] On treatment with 1eq of this reagent, alkene (240) gave the dibromide (279) (scheme 59) whose structure was determined by X-ray analysis. Figure (7)

scheme (59)



(240) (279)

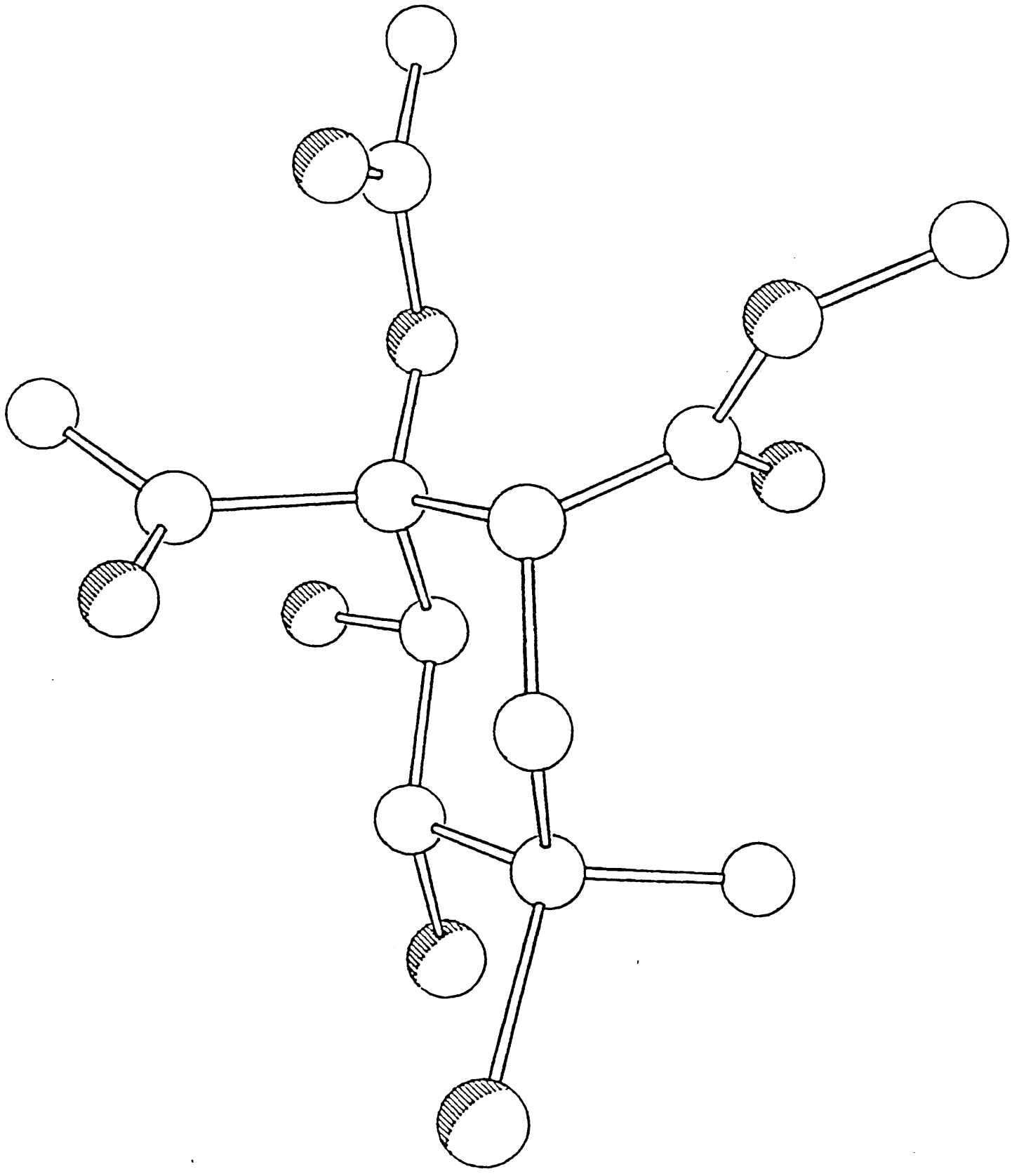
With PhSeCl[32] in ethyl acetate at rt, ketone (240) gave a low yield of α-selenated ketone (280) along with many



(280) (281)

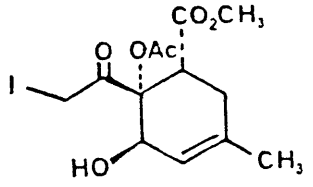
other polyselenated products. Attempts to protect the carbonyl group in (240) as its dioxalane were unsuccesful as was the attempt to prepare enamine (281) by reaction of (241) with pyrrolidine under acidic conditions which gave epimerized ester (242) as the product. Clearly the carbonyl

Figure 7.

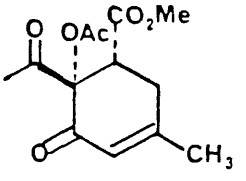


group in (240) was extremely unreactive under a variety of acidic and basic conditions.

Attention was turned to the use of radical chemistry to achieve the required C-O bond formation. Literature precedent[33] suggested that the use of N-iodosuccinimide on alcohol (241) would give the α-iodo ketone (282) which should cyclize under the reaction conditions.



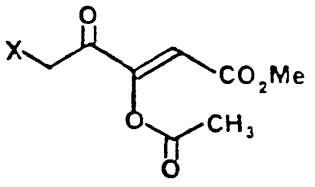
(282)



(283)

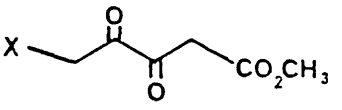
However on treatment with NIS in benzene, alcohol (241) gave enone (283) as the major product.

As a result of the extremely unreactive nature of the carbonyl group in (240) and (241) synthetic effort was focused on the construction of a dieneophile (284) which posessed a suitably functionalized ketone for subsequent ring closure after the Diels-Alder reaction. Diketone (284) became our target.Work by La Mattina[34]and



x=Br(284)

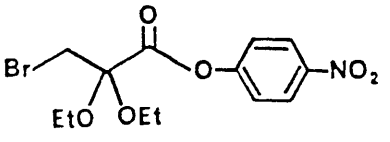
=$OSiMe_3$(285)



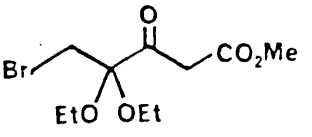
X=Br (286)

=$OSiMe_3$ (287)

Mularski has shown that simple enolates readily react with the activated ester (288).



(288)

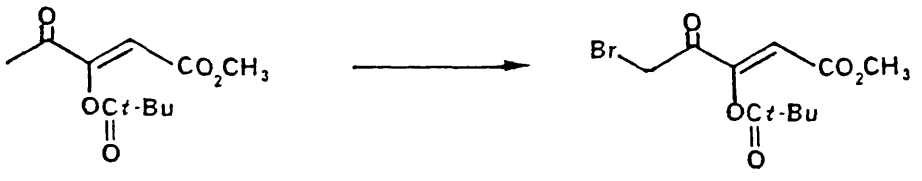


(289)

Ester (288) was readily prepared in three steps from ethyl pyruvate in 55% yield. Treatment of ester (288) with the lithium enolate of methyl acetate at -60°C gave the desired bromo ester (289) in 69% yield after chromatography. Removal of the diethyl acetal was achieved by the use of aqueous formic acid at 80°C which gave a very low yield of the required diketone (286). All attempts to convert diketone (286) to the enol acetate (284) as previously described were unsuccesful.

In the light of these results our efforts were turned to the direct modification of the dienophiles (235) and (254). Treatment of both (235) and (254) with LDA at -78°C gave deep red coloured solutions, however attempts to quench with halogens or halogenating agents gave only polymeric material. Direct bromination of the acetate (235) and pivaloate (254) with bromine or NBS[35] were also unsuccesful, however on treatment with PHT at rt for 72h, pivaloate (254) gave the α-bromoketone (290) in almost quantitave yield (scheme 60).

scheme (60)

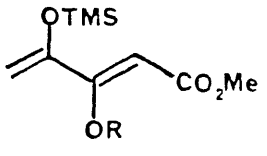


(254) (290)

Bromide (290) was found to be somewhat unstable and could not be purified by chromatography. On heating with siloxy diene (227) at 115°C, bromide (290) gave only polymeric material after 72h. At 2 kbr and 40°C again polymeric material was obtained with diene (227). It was felt that

an oxygenated analogue of bromide (290) would be more stable to the Diels-Alder reaction conditions.

The reaction of trimethylsilyl enol ethers with a variety of oxidants is well known to give α-hydroxyketones,[36] with this in mind we attempted to prepare trimethylsilyl enol ethers (291) and (292) from the enones (235) and (254).



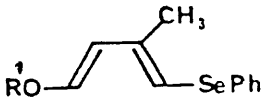
R=Ac (291)

= COt-Bu (292)

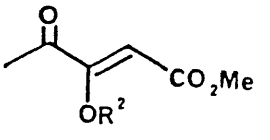
With acetate (235) NEt_3/TMS-triflate in either Et_2O or THF failed to give any of the required product, but treatment with $ZnCl_2$/TMS-Cl/NEt_3 did give a low yield of (291) along with unreacted enone (235). However the reaction of enone (254) with NEt_3/TMS-triflate [37] in DME at rt for 48h gave an excellent 89% yield of trimethylsilyl enol ether (292). The oxidation of this compound is currently being investigated in our laboratories.

Studies towards some novel heteroatom containing dienes.

As has been previously discussed, dienes of type (293) were required in our Diels-Alder approach to the hexahydrobenzofuran portion of the avermectins and milbemycins. To establish both the C-5 hydroxyl in its

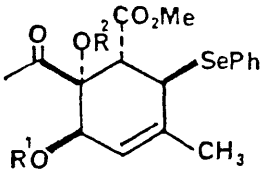


(293)

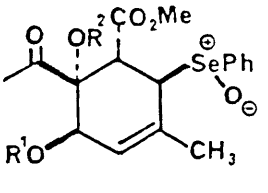


(294)

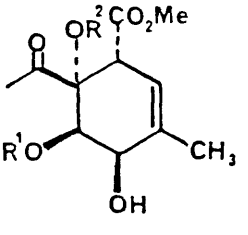
correct relative stereochemistry and the C-3-C-4 double bond, it was proposed to use a [2,3] sigmatropic shift on a selenoxide (296) derived from selenide (295) by selective oxidation.



(295)



(296)

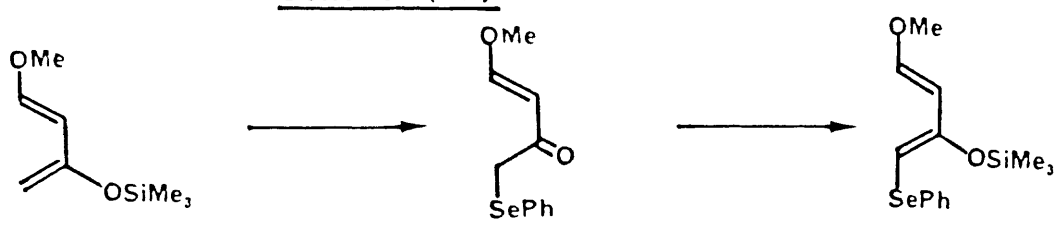


(297)

Since thermal [2,3] sigmatropic rearrangements are known to be suprafacial processes[11] it would be necessary to prepare selenide (295) with the indicated relative stereochemistry, this arising from a thermal [4+2] *cis-endo* cycloaddition of a selenodiene (293) with E,E geometry and the indicated dienophile (294). Hence it was essential to prepare selenodiene (293) and its sulphur analogues with the E,E configuration.

A search of the literature revealed that Danishefsky had prepared a selenodiene (300) by treating silyoxydiene (298) with PhSeCl to give enone (299).[38] Reaction of (299) with $ZnCl_2$, TNS-Cl and NEt_3 gave (300). (scheme 61)

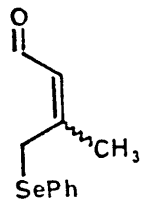
scheme (61)



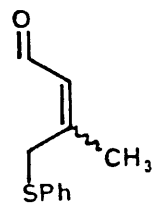
(298) (299) (300)

Diene (300) was found to undergo [4+2] *cis-endo* cycloadditions with a variety of common dieneophiles.

In a similar manner it was found that siloxydiene (227) gave enals (301) and (302) as E/Z mixtures on treatment with PhSeCl and PhSCl respectively.



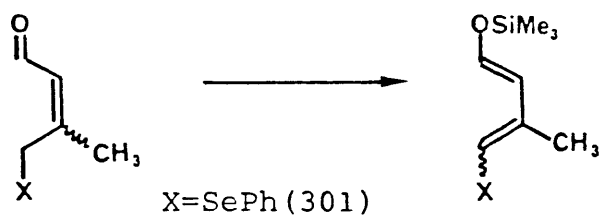
(301)



(302)

As expected, reaction of these E/Z mixtures under standard Danishefsky conditions[38] gave complex mixtures of dienes (303) and (304) usually with two predominant isomers (scheme 62). A more controlled synthesis was clearly required.

scheme (62)

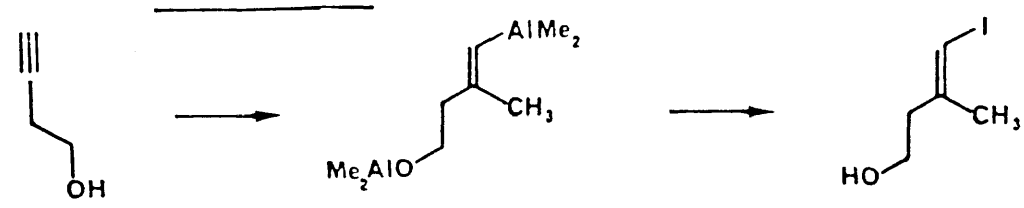


X=SePh (301) X=SePh (303)

=SPh (302) =SPh (304)

Negishi and coworkers[39] have reported that the carboalumination of 3-butyn-1-ol (305) in the presence of bis—(cyclopentadienyl) zirconium dichloride occurs with > 98% *syn* selectivity and that the resulting vinyl alane (306) could be quenced with iodine to give geometrically pure E vinyl iodides (307). (scheme 63)

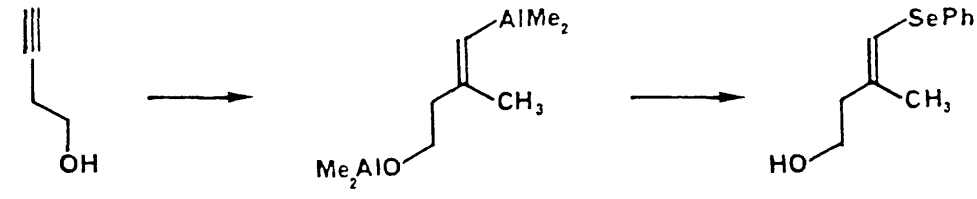
scheme (63)



(305) (306) (307)

It seemed reasonable that iodine would not be unique as an electrophile in this procedure. Consequently vinyl alane (306) was prepared as described and quenched with diphenyl diselenide at -30°C. To our delight vinyl selenide (308) was isolated as a single geometric isomer in 46% yield after chromatography.(scheme 64)

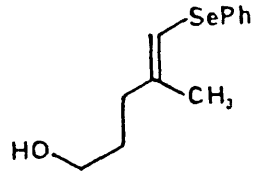
scheme (64)



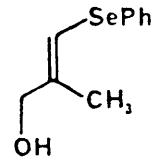
(305) (306) (308)

The E geometry of (308) was determined by use of the difference n.O.e technique. Thus irradiating the olefinic proton at δ6.24 produced clear undistorted enhancements of the two ortho protons of the phenyl ring (δ7.44 and 7.47) and of the unsubstituted methylene at δ2.42. Since some enhancement of the methyl group at δ1.83 was also observed, the reverse experiment was carried out. Irradiation of the methyl signal produced only an INDOR response at δ6.24, a combination INDOR/n.O.e response in the unsubstituted methylene signal at δ2.42. Thus the olefinic proton and the unsubstituted methylene are *cis* in this compound. This novel and efficient synthesis of vinyl selenides was investigated further. 4-pentyn-1-ol (309) and propargyl alcohol (310) gave vinyl selenides (311) and (312) in 66% and 31% yield respectively after carboalumination and

quenching with PhSeCl as previously described. Again both (311) and (312) were found to be single geometric isomers and the E geometry



(311)

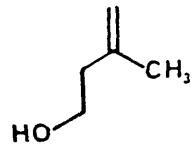


(312)

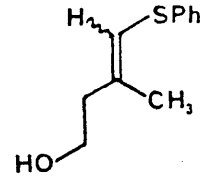
was assigned after difference n.O.e. studies.

The hydrolysis of vinyl selenides under very mild conditions is well documented in the literature, thus in principle this procedure gives a convenient route for preparing aldehydes from acetylenes.[40]

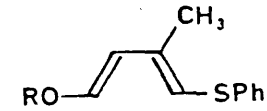
Since sulphur containing dienes such as (313) had also been proposed in our our synthesis the use of various sulphur electrophiles in quenching vinyl alanes was investigated. Treatment of vinyl alane (306) with diphenyldisulphide gave alcohol (314) after aqueous work up, however using PhSCl as the electrophile vinyl alane (306)



(314)



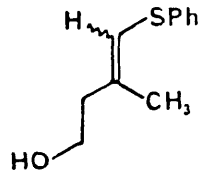
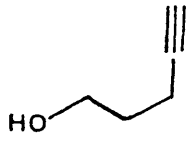
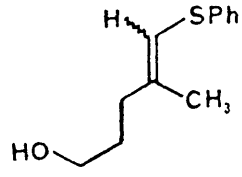
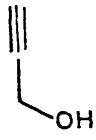
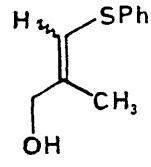
(315)



(313)

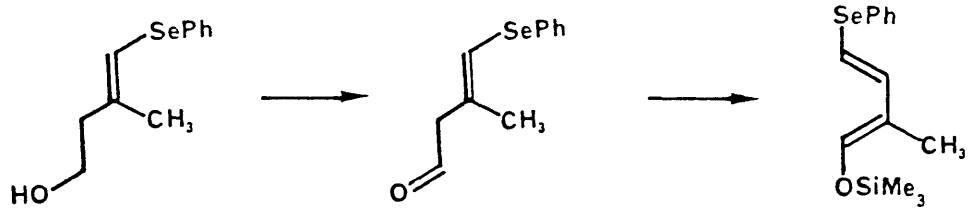
gave vinyl sulphide (315) as an E/Z mixture in a 52% overall yield. Similar results were obtained using propargyl alcohol (310), 4-pentyn-1-ol (309); these are summarised in table (5).

Table (5)

SUBSTR ATE	PRODUCT	E/Z	% YIELD
 (305)	 (315a)	2:1	52
 (309)	 (315b)	1:1	72
 (310)	 (315c)	1:1	33

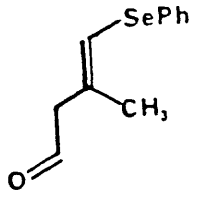
In view of these results attention was focused on the synthesis of selenodiene (317) from vinyl selenide (308) *via* aldehyde (316). (scheme 65)

scheme (65)



(308) (316) (317)

Selective oxidation of alcohol (308) proved to be an extremely difficult task. A wide range of oxidants including PCC,[41] PCC on alumina,[42] PDC,[43] Swern,[44] $py.SO_3$,[45] Collins,[46] Ph_3BiCO_3,[47] BSA,[48] DDQ[49] and NCS/Me_2S[50] all failed to give any of the required aldehyde. Limited success was found with mesityl seleninic anhydride[51] which gave a 15% yield of (316).



(316)

δ_H(60MHz;$CDCl_3$)

1.86(3H,s, *Me*)

3.20(2H,d,J=2.OHz, *H-2*)

6.32(1H,s, *H-4*)

7.35(5H,m, aromatic)

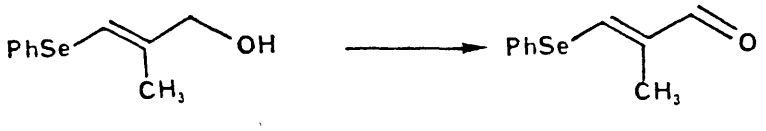
9.85(1H,t,J=2.OHz, C*H*O)

$\nu_{max.}$ (film) 1723 cm^{-1}

M/Z=240 (M^+)

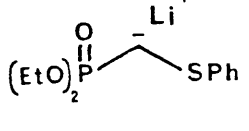
Attempts to improve this oxidation are currently being investigated in our laboratories. In contrast the oxidation of alcohol (312) with MnO_2 proceeded smoothly to enal (318) in an excellent 95% yield.(scheme 66)

scheme (66)

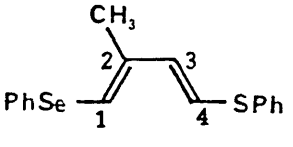


(312) (318)

Enal (318) was found to undergo Wittig-Horner coupling with suitable phosphonate anions (319)[52]. Enal (318) at -78°C gave, after work up, diene (320) as a 10:1 mixture of E/Z isomers separable by chromatography.

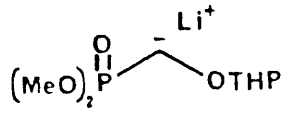


(319)

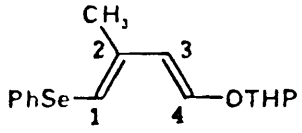


(320)

The 250 MHz NMR spectrum clearly indicated the E geometry of the major isomer by a 15.3 Hz coupling between H-3 and H-4. With the THP protected phosphonate anion (321)[53] enal (318) gave a 48% yield of diene (322) after work up and chromatography.



(321)

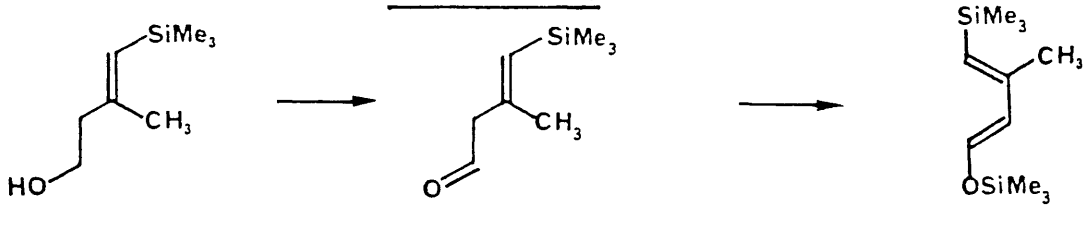


(322)

Although homogeneous by tlc, the NMR spectrum of (322) showed one major isomer which had a 12.0Hz coupling constant between H-3 and H-4 along with small amounts of other geometric isomers. Diene (322) is clearly suitable for use in the proposed Diels-Alder approach to the hexahydrobenzofuran portion of the avermectins and milbemycins. Studies on the Diels-Alder reactivity of (322) are currently being investigated in our laboratories.

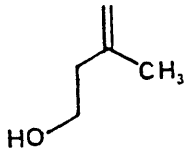
For the synthesis of silyl diene (325) a route similar to that used for seleno diene (317) was envisaged (scheme 67). Preparation of vinyl silane (323) was attempted *via*

scheme (67)

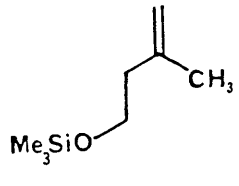


(323) (324) (325)

trapping of vinyl alane (306), prepared by the carboalumination of 3-butyn-1-ol (305),[39] with a silicon electrophile. Unfortunately, despite using a wide range of silicon electrophiles, the reaction was unsuccessful and alkenes (326) and (327) were the only products isolated after work up.



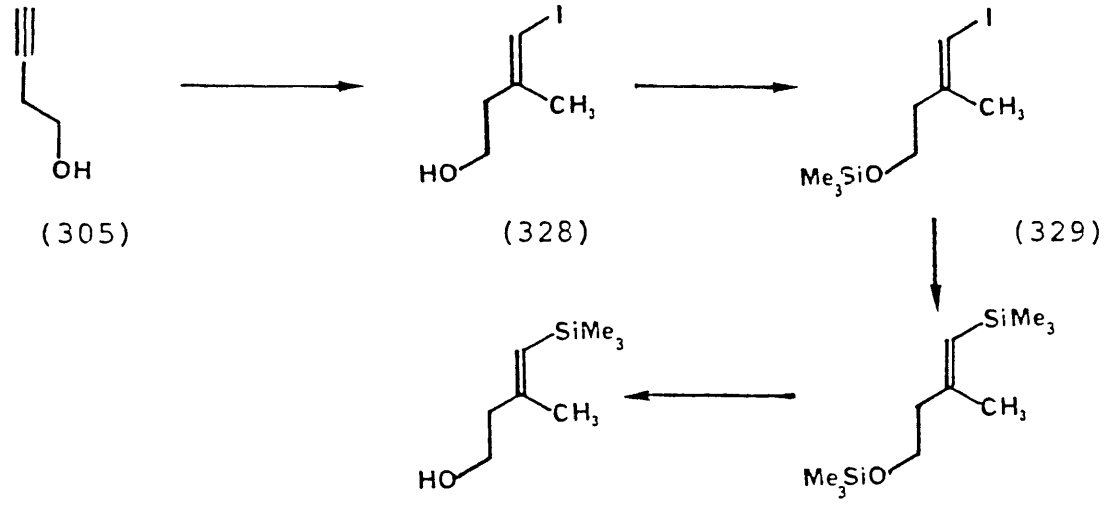
(326)



(327)

Access to (323) was gained by the route shown in scheme (68).

scheme (68)



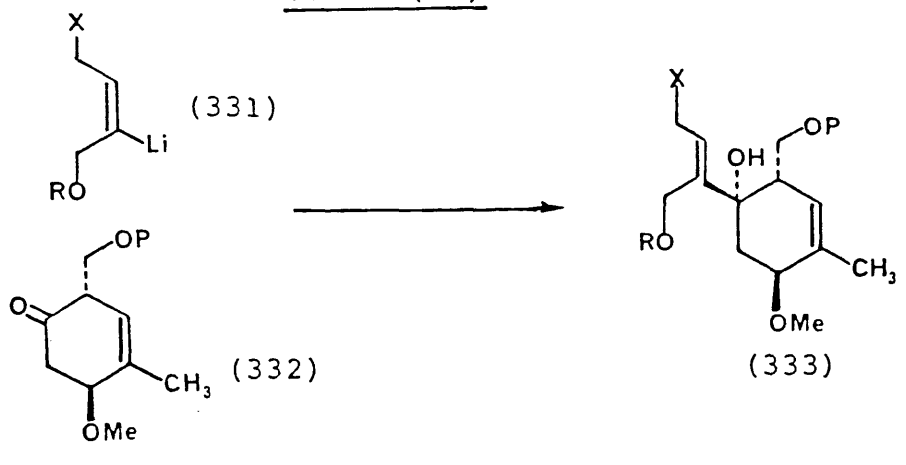
(305) (328) (329) (330) (323)

Hence carboalumination of 3-butyn-1-ol (305) followed by treatment with iodine gave vinyl iodide(328) in 72% yield. Protection of the primary alcohol (328) proceeded smoothly to give (329) in 83% yield. Metal-halogen exchange of the vinyl iodide (329)[54] with nBuli at -60°C in Et_2O followed by treatment with TMS-Cl/NEt_3 gave the vinyl silane (330) as a single geometric isomer in a satisfactory 71% yield after chromatography. Finally selective removal of the trimethylsilyl protecting group using TBAF in THF gave an 84% yield of vinyl silane (323). The oxidation of alcohol (323) to the required aldehyde (324) was not achieved despite the use ofa wide variety of oxidants.[41-50] In most cases tlc analysis showed at least 4 products and attempts to isolate the components by chromatography was unsuccesful.

A cyclohexenone route to the southern zone of milbemycin β_1

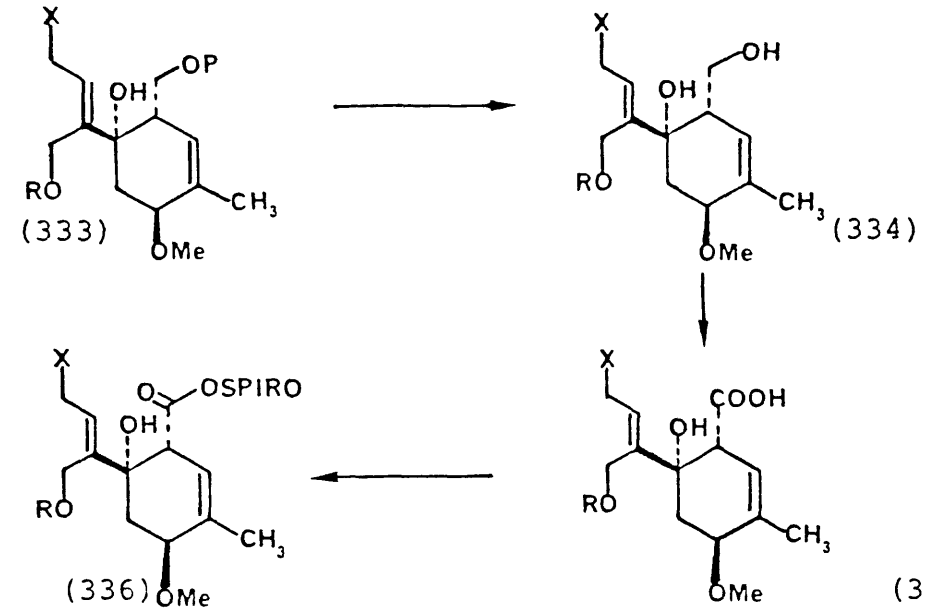
Examination of our synthetic target for the southern zone of the avermectins and milbemycins led us to propose an alternative strategy to the previously described Diels-Alder route. In this approach the key reaction involved the addition of a suitable vinyl anion (331) to a ketone (332). The direction of attack was postulated to be controlled by interaction of the vinyl anion (331) with a sterically demanding protecting group P forcing

scheme (69)

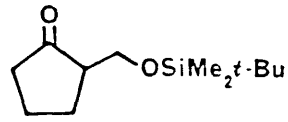


the nucleophilic side chain to approach the ketone from the β face (scheme 69). Ring closure to give the 16 membered ring lactone could then be achieved by removal of the protecting group P followed by oxidation of the resulting primary alcohol (334) to the corresponding carboxylic acid (335) and finally macrocyclic lactonization. (scheme 70)

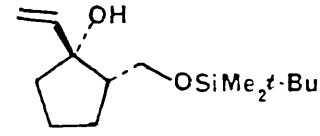
scheme (70)



To test this hypothesis the addition of vinyl anions into ketone (337) was examined.

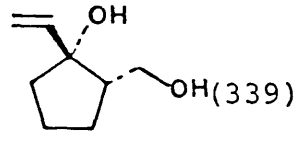


(337)

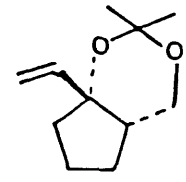


(338)

With vinyl magnesium bromide a 52% yield of tertiary alcohol (338) was obtained. Only one diastereoisomer was detected by high field NMR. With vinyl lithium the reaction was much cleaner and gave an excellent 87% of the alcohol (338). Removal of the silicon protecting group was achieved using TBAF to give the diol (339) in 84% yield.



(339)



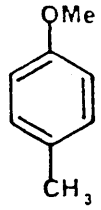
(340)

Treatment of diol (339) with 2,2-dimethoxypropane in the presence of CSA gave the acetonide (340) confirming that the vinyl anion had indeed added on the face opposite the bulky silicon protecting group.

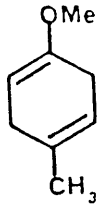
In ketone (332) it was anticipated that the C-2

protons would be relatively acidic being both allylic and α to carbonyl group and hence a vinyl anion could promote the migration of the C-3-C-4 double bond into conjugation. Thus ketone (343) was prepared from *p*-methyl anisole (341) *via* a two step procedure and its reaction with simple vinyl anions studied. Birch reduction of (341)[55] with lithium in liquid ammonia gave vinyl ether (342) which was readily hydrolized[56] to ketone (343) in an overall 62% yield (scheme 71).

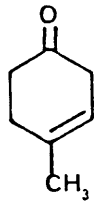
scheme (71)



(341)

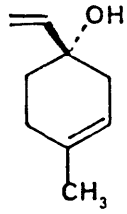


(342)

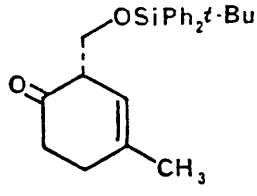


(343)

Treatment of (343) with vinyl magnesium bromide in THF gave a 59% yield of the addition adduct (344) in which no double bond migration had occured.



(344)

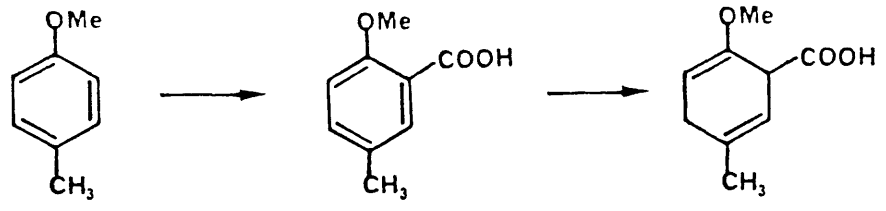


(345)

In the light of these results ketone (345) became the synthetic target. Although (345) lacked the C-5 oxygen functionality it was hoped to introduce this after the addition of the vinyl anion by the use of selenium dioxide.[57] The *tert*-butyldiphenylsilyl group was chosen to protect the primary hydroxyl group as it was both bulky and readily removable with TBAF. The pivotal step in the preparation of ketone (345) was the Birch reduction[58] of acid (346) with sodium in liquid ammonia to give the dihydro intermediate(347) .

Acid (346) was prepared from *p*-methyl anisole (341) by treatment with *n*-Buli followed by quenching with CO_2 and acidification (scheme 72).

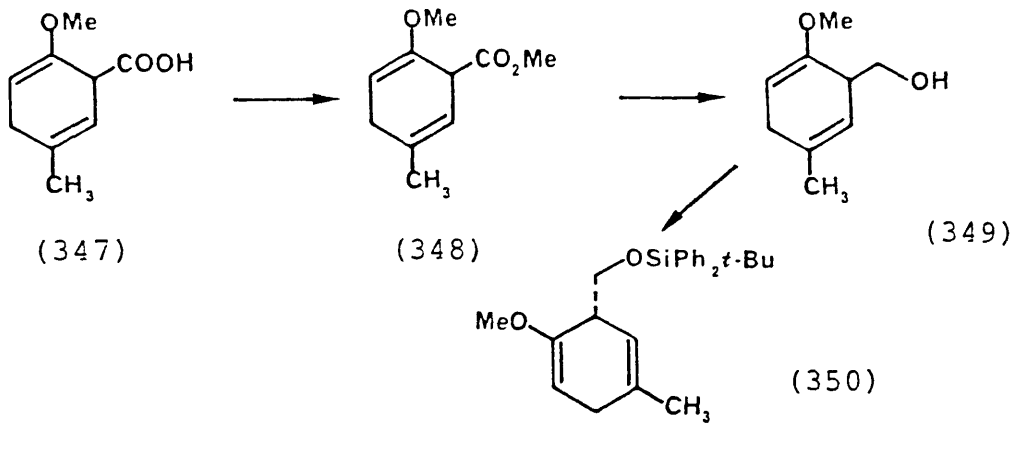
scheme (72)



(341) (346) (347)

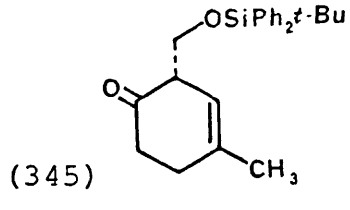
The dihydro intermediate (347) was not routinely isolated but treated with diazomethane to give the methyl ester (348). Subsequent reduction of the ester (348) followed by the protection of the resultant primary alcohol (349) gave the key intermediate (350). (scheme 73)

scheme (73)



(347) (348) (349) (350)

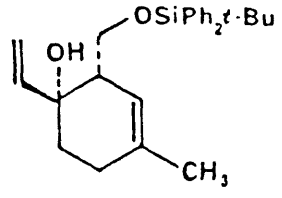
Hydrolysis of the vinyl ether (350) with acid adsorbed onto silica gel[59] gave an excellent 96% yield of the required ketone (345). The NMR spectrum clearly showed that no



(345)

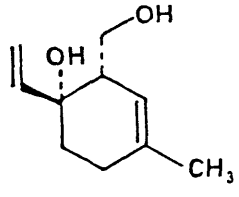
double bond migration had occured. On reaction with 5 eq of vinyl magnesium bromide at -30° C in THF, ketone (345) gave the tertiary alcohol (351). High field NMR spectroscopy

indicatedthat only one diastereoisomer was present. Removal of the silyl protecting group proceeded smoothly using

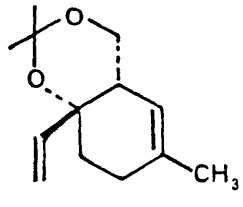


(351)

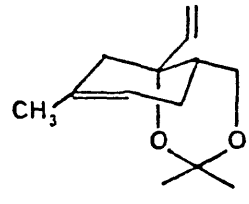
TBAF to give diol (352) in 89% yield. On treatment with 2,2-dimethoxypropane, with acidic catalysis, acetonide (353) was isolated in 66% yield. The formation of acetonide (353) gave clear evidence that the *tert*-butyldiphenylsilyl group had effectively controlled the addition of the vinyl anion. Examination of molecular models suggested that the β-face of acetonide (353) was sterically less hindered and oxidation at the C-5 position should occur on this face.



(352)

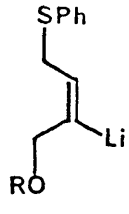


(353)



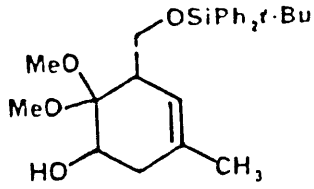
(353)

The addition of a more highly functionalized vinyl anion such as (354) would yield more synthetically useful intermediates.



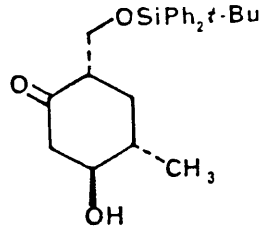
(354)

As many of the avermectins and milbemycins are oxygenated at the C-6 position, the oxidation of vinyl ether was briefly examined. On reaction with *m*CPBA in MeOH[60], (350) gave an unoptimized 27% yield of acetal (355).



(355)

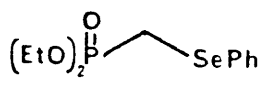
Again the *tert*-butyldiphenylsilyl group promoted attack by the *m*CPBA on the least hindered β face, the intermediate epoxide undergoing ring opening with methanol to give the observed product. An extension of this work with compounds of the type (356) is currently being carried out in our laboratories.[61]



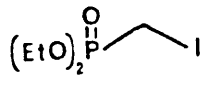
(356)

An improved procedure for the preparation of sodium phenylselenide.

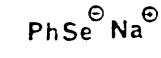
During the course of studies related to the synthesis of the hexahydrobenzofuran portion of the avermectins and milbemycins, quantities of the phosphonate (357) were required. The literature cited two methods for its



(357)



(358)



(359)

preparation;[62] firstly, treatment of diethyl iodomethylphosphonate (358) with sodium phenylselenide (359), generated by the treatment of phenyl selenol with sodium hydride in THF, and secondly, reaction of diphenyldiselenide with hypophosphorous acid followed by the addition of iodide (358).

Neither of these procedures appealed to us. The use of selenols is socially unacceptable due to their unpleasant odours and we wished to avoid the use of strongly acidic conditions.

The first procedure involved the generation of sodium phenylselenide (359), a search of the literature indicated alternative procedures have been used for its preparation. A comprehensive paper by Liotta[63] reviewed the various methods and listed a reactivity gradient for the phenylselenide anion according to its method of preparation.

Least reactive is the phenylselenide-borane complex prepared by the treatment of diphenyl diselenide with sodium borohydride in EtOH/THF[64] (scheme 74).

scheme (74)

$$PhSeSePh + 2NaBH_4 \longrightarrow 2NaSePh + 2BH_3 + H_2$$

Attempts to generate sodium phenylselenide by the reaction of diphenyl diselenide with sodium metal in dry refluxing THF result in the formation of a copious precipitate over a period of 3-4h. However on addition of HMPA, the precipitate is solubilized and the resulting solution is a powerful source of sodium phenylselenide. The use of the highly toxic HMPA is clearly undesirable and a procedure which avoided it's addition would be welcome.

With these thoughts in mind it was reasoned that the use of ultrasound could assist the formation of sodium phenylselenide from sodium metal and diphenyldiselenide. This proposal was borne out by experimental observation. Ultrasonic agitation of diphenyl diselenide (10.00mmol) with sodium metal (21mmol) (cut into approximately 10 pieces) in dry THF(40ml) at $0^{\circ}C$ for 72h under argon gave a very pale yellow colloidal suspension. The reactivity of this suspension towards a variety of electrophiles was investigated and it was found to be an excellent source of the phenyl selenide anion. The results of the studies are listed in table (6). Iodides, bromides and tosylates were readily displaced to give the corresponding selenides. A wide variety of additional functionality including lactones, esters, THP ethers, ketones and dioxanes were all tolerant to the reaction conditions. In addition it was found that allyl bromide (366) reacted completely by an S_N2 process, no products arising from S_N2' displacement could be detected.

A brief study of the behaviour of epoxides was made. Primary epoxides (372) and (374) were attacked at the

Table (6).

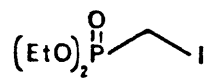
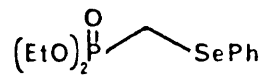
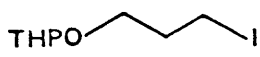
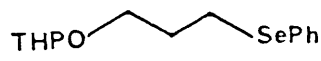
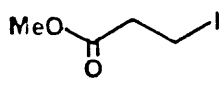
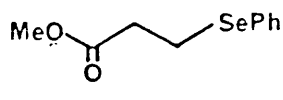
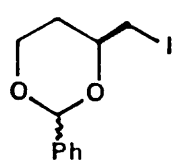
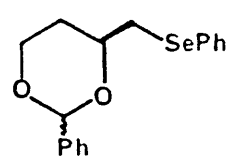
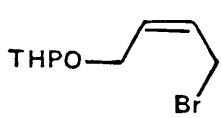
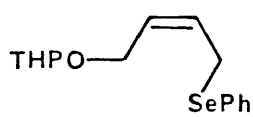
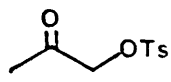
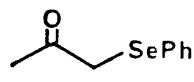
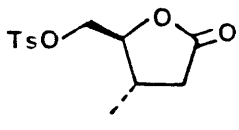
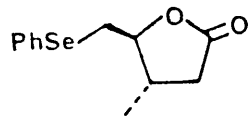
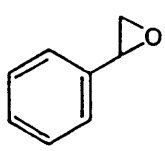
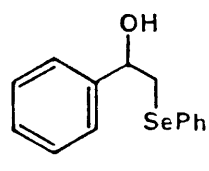
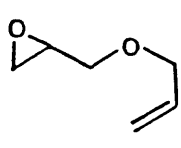
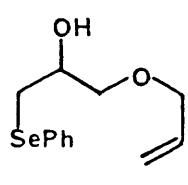
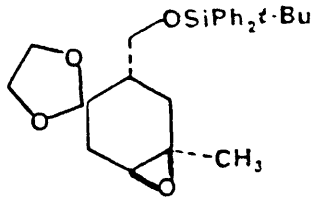
SUBSTRATE	PRODUCT	% YIELD
 (358)	 (357)	92
 (360)	 (361)	86
 (362)	 (363)	88
 (364)	 (365)	84
 (366)	 (367)	94

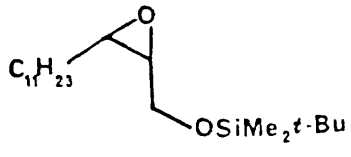
Table (6) continued

SUBSTRATE	PRODUCT	% YIELD
 (368)	 (369)	93
 (370)	 (371)	83
 (372)	 (373)	78
 (374)	 (375)	86

least substituted carbon atom to give the β-hydroxy selenides (373) and (375) respectively. The secondary epoxides (376) and (377) failed to react even after refluxing for 24h.



(376)



(377)

From a practical point of view this procedure offers several advantages. Firstly as previously discussed the use of the highly toxic HMPA is avoided. Secondly the suspension of sodium phenylselenide is readily transferred by a syringe or *via* a canular. It can be stored at rt for at least one week under argon without any apparent deterioration in its reactivity.

Preparation of z-Ethyl 3-acetoxy-4-oxo-pent-2-enoate (218)



(220) (218)

To a stirred solution of diketone (1.44g 10.00mmol) in dry pyridine (10ml) under argon at 0°C was added acetyl chloride (0.942g, 12.00mmol) dropwise. The resulting solution was stirred at 0°C for 30 min then at rt for 1.5h. The reaction mixture was poured into 1.0M hydrochloric acid (20 ml), the aqueous phase was extracted with Et_2O (4x30 ml) and the combined organic phase dried. The solvent was evaporated under reduced pressure and the residue chromatographed (30% Et_2O-40-60°petrol) to give *Z-ethyl 3-acetoxy-4-oxo-pent-2-enoate* (218) (0.960g,48%) as a pale yellow oil, $\nu_{max.}$(film) 3090, 3010, 2950, 2877, 1770, 1730, 1708, 1653, 1433, 1370, 1160, 1090 and 970cm^{-1}; δ_H(90 MHz;$CDCl_3$)1.30 (3H,t,J=7.3Hz,CH_2CH_3), 2.32(3H,s, OCO *Me*), 2.36(3H,s,CO *Me*), 4.23(2H,q,J=7.3Hz,CH_2), 6.51 (1H,s, *H-2*); *M/Z*=200(M^+)

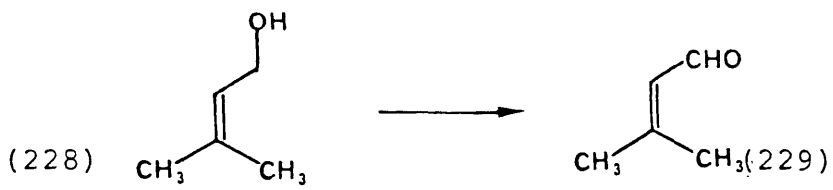
Preparation of (±) Ethyl (7α-acetoxy-7β-acetyl-4-methyl) cyclohex-4-en-1α-carboxylate (225) and (±) Ethyl (7α-acetoxy-7β-acetyl-5-methyl) cyclohex-4-en-2α-carboxylate (226)

A mixture of ester (218) (0.61g,3.05mmol) and isoprene (1.36g, 20.00mmol) was sealed in a Carius tube under dry argon and heated at 140°C for 96h. The tube was cooled to rt, the contents removed and chromatographed (10%Et_2O-40-60°petrol) to give an inseparable mixture of (±)*ethyl (7α-acetoxy-7β-acetyl-4-methyl)cyclohex-4-en-1α-carboxylate* (225) and *(±) ethyl (7α-acetoxy-7β-acetyl-5-methyl)cyclohex-4-en-2α-carboxylate* (226) as a colourless oil, $\nu_{max.}$(film)

2979, 2931, 1738, 1438, 1370, 1242, 1202, 1071, 1034 and 858cm^{-1}; δ_H(250 MHz;$CDCl_3$) 1.22(2H,t,J=8.1Hz, CH_2CH_3), 1.66(3H, brS, C-4 *Me*,C-5 *Me*), 2.05(3H,s,OCO*Me*), 2.16(1.5H, s, CO *Me*), 2.18(1.5H,s,CO*Me*), 2.25-2.50 (2H,m,*H-6*), 2.59-2.91 (2H,m,*H-3*), 3.00(0.5H,t,J=8.0Hz,*H-2*), 3.14(0.5H,t, J=8.0Hz, *H-2*), 4.03(2H,m, CH_2CH_3), 5.23(0.5H,brS, *H-5*), 5.36(0.5H,br S, *H-4*); *M/Z*=268 (M^+)

(Found:C,62.47; H,7.75%. $C_{14}H_{20}O_5$ requires C, 62.67; H, 7.51%).

Preparation of 4-Methyl but-2-enal (229)

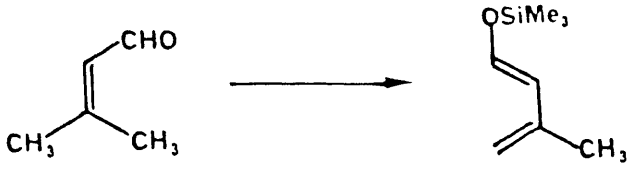


(228) (229)

To a stirred solution of allylic alcohol (228) (8.60g,100.0mmol) in dry CH_2Cl_2(200ml) at 0°C was added PDC (56.40g, 150.0mmol) in 5g portions over a period of 30 min. After the addition was complete the reaction was warmed to rt and stirred for 16h. The crude mixture was poured into the Et_2O(500ml) and the resulting suspension filtered through a pad of florosil. After eluting with Et_2O (2x200ml) the combined organic extracts were washed with 1.0 M HCl(100ml), brine (200ml) and dried. The solvent was carefully evaporated under reduced pressure and the residue distilled to give *4-methyl but-2-enal* (229) (8.20g, 95%) as a colourless oil, $\nu_{max.}$(film) 2978, 2938, 1674, 1633, 1581, 1379, 1199, 1047 and 835 cm^{-1}: δ_H(60MHz;$CDCl_3$) 2.05(3H,s,*Me*), 2.20(3H,s, *Me*), 5.90(1H,d,J=8.0Hz, *H-2*), 9.95(1H,d,J=8.0Hz, *H-1*); *M/Z*=84(M^+).

Preparation of *E*-3-Methyl-1-(trimethylsilyloxy) butadiene

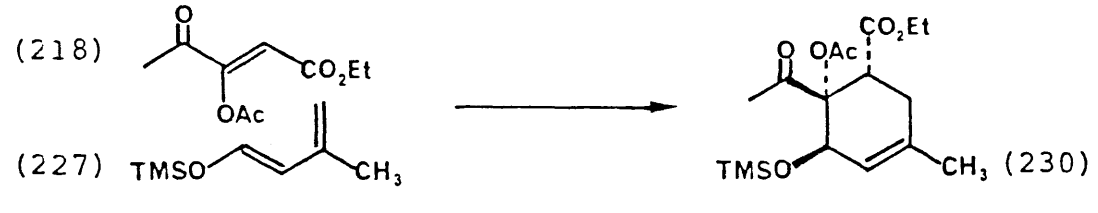
(227)



(229) (227)

Anhydrous $ZnCl_2$ (0.22g 1.61mmol) was suspended in dry triethylamine (12.65g, 125.00mmol) and stirred vigorously under argon at rt for 1h. A solution of enal (229) (4.67g, 55.60mmol) in dry C_6H_6 (10ml) was added, followed by trimethylsilylchloride (12.08g, 111.00mmol) and after stirring at rt for 1h the reaction was warmed to 40°C and stirred at this temperature for 12h. The crude reaction mixture was poured into Et_2O (400ml) and the resulting suspension filtered through celite. The filtrate was concentrated, diluted with Et_2O (100ml) and filtered through celite. The process was repeated until no more triethylamine hydrochloride precipitated out. The resulting crude brown oil was distilled to give *E-3-methyl-1-(trimethylsilyoxy) butadiene* (227) (4.29, 50%) as a colourless oil, b.p. 40-50°C (5mmHg), $\nu_{max.}$ (film) 3083, 3034, 2962, 1642, 1606, 1453, 1342, 1172, 924, 881 and 845cm^{-1}; δ_H (60MHz;$CDCl_3$) 0.25(9H,s,Si *Me*$_3$), 1.85(3H,s,*Me*), 4.75(2H,brS, *H-4*), 5.80 (1H,d,J=12.0Hz, *H-2*), 6.50(1H,d,J=12.0Hz, *H-1*); *M/Z*=156(M^+).

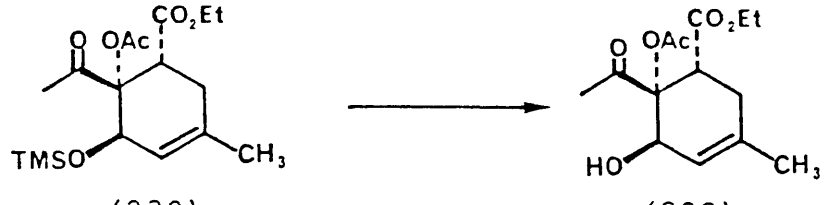
Preparation of (±) Ethyl (7α-acetoxy-7β-acetyl-4-methyl -6β-trimethylsilyoxy) cyclohex-4-en-*2a-Carboxylate* (230)



(230)

To a solution of Z-ethyl-3-acetoxy-4-oxo-pent-2-enoate (218) (0.200g,1.00mmol) in dry toluene (2ml) was added 3-methylsiloxybutadiene (227) (0.234g,1.50mmol). The solution was heated to 115°C under argon for 72h. After cooling to rt, solvent was evaporated under reduced pressure and the residue chromatographed (15%Et_2O-40-60°petrol) to give (±) ethyl *(7α-acetoxy-7β-acetyl-4-methyl-6β-trimethylsilyoxy) cyclohex-4-en-2α-carboxylate* (230) (0.167g,47%) as an oil, $\nu_{max.}$(film) 2961, 1743, 1443, 1370, 1347, 1248, 1202, 1165, 1076, 1040, 921 and 845 cm^{-1}; δ_H(250MHz;$CDCl_3$) 0.12(9H,s,Si *Me*$_3$), 1.23(3H,t,J=7.4Hz, CH_2CH_3), 1.69(3H,s, *Me*), 2.07(3H,s,OCO*Me*), 2.12(3H,s,CO*Me*), 2.20(1H,dd,J=19.6, 4.3 Hz, *H-3*), 2.67(1H,dd,J=19.6, 7.5Hz, *H-3*), 3.67(1H,dd, J=7.5,4.3Hz, *H-2*), 4.10(2H,m,CH_2 CH_3), 4.62(1H,m, *H-6*), 5.15(1H,m, *H-5*); *M/Z*=296(M^+-HOAc) (Found:C,57.07;H,7.90. $C_{17}H_{28}O_6Si$ requires C,57.28; H,7.92%).

Preparation of (±) Ethyl (7α-acetoxy-7β-acetyl-6β-hydroxy-4-methyl)cyclohex-4-en-2α-carboxylate (232)

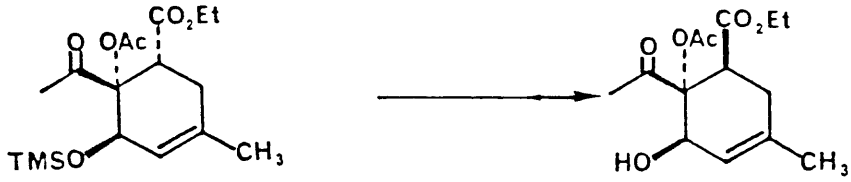


(230) (232)

To a stirred solution of trimethylsilyl ether (230) (0.402g, 1.13mmol) inTHF(5ml) was added HF(1.80ml of a 0.70M solution of 40% HF in acetonitrile, 1.24mmol). After 10 min the reaction was complete by TLC and the solution was poured into saturated $NaHCO_3$solution (10ml). The product was extracted into $CHCl_3$(3x20ml), the combined organic extracts were dried and the solvent evaporated under reduced pressure. The residue was chromatographed (60%Et_2O-40-60°

petrol) to give (±) *ethyl (7α-acetoxy-7β-acetyl-6β-hydroxy-4-methyl) cyclohex-4-en-2α*-carboxylate (232) (0.295g 92%) as a colourless oil, $\nu_{max.}$ (film) 3496, 2989, 2914, 1735, 1431, 1370, 1245, 1199, 1097, 1032, 933, 909, and 869cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.22(3H,t,J=7.6Hz, CH_2CH_3), 1.72 (3H,s,*Me*), 2.04(3H,s,OCO*Me*), 2.13 (3H,s,CO*Me*), 2.31(1H,dd,J=18.0, 6.0Hz, *H-3*), 2.45(1H,dd,J=18.0, 9.0Hz, *H-3*), 3.47(1H,dd,J=9.0, 6.0Hz, *H-2*), 4.09(2H,m,CH_2CH_3), 4.66(1H,m, *H-6*), 5.41(1H, m,*H-5*); *M/z*=284(M^+) (Found: C,58.97;H,7.40%. $C_{14}H_{20}O_6$ requires C,59.14;H,7.09%).

Preparation of (±) Ethyl (7α-acetoxy-7β-acetyl-6β-hydroxy-4-methyl)cyclohex-4-en-*2b-Carboxylate* (233)

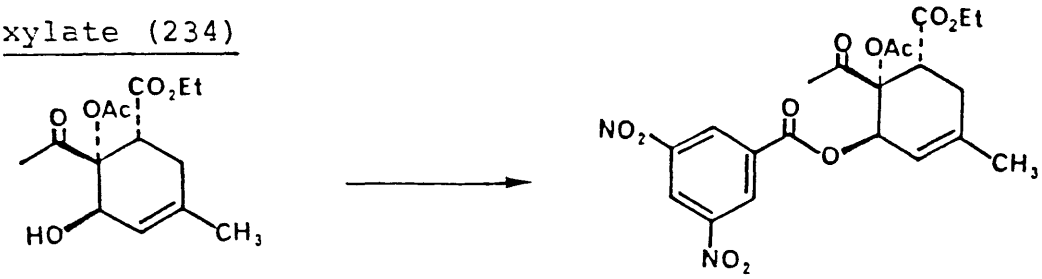


(230) (233)

To a stirred solution of trimethylsilyl ether (230) (0.681g,1.91mmol) in THF (6ml) at rt was added TBAF (2.10ml of a 1.0M solution in THF, 2.10mmol). The resulting solution was stirred rt for 2h, poured into water (10ml) and extracted with Et_2O (3x15ml). The combined organic extracts were washed with brine (15ml), dried and the solvent evaporated under reduced pressure to give a crude dark red oil which was chromatographed to give (±) *ethyl (7α-acetoxy-7β-acetyl-6β-hydroxy-4-methyl) cyclohex-4-en-2β-carboxylate* (233) (0.103g,19%) as a colourless oil, $\nu_{max.}$ (film) 3678, 3477, 2976, 2930, 1718, 1465, 1398, 1373, 1339, 1296, 1239, 1021, 972, and 950cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.24(3H,t,J=8.0Hz, CH_2CH_3), 1.79(3H,s,*Me*), 2.05(3H,s,OCO*Me*), 2.37(3H,s,CO*Me*), 2.30-2.62(2H,m,*H-3*), 3.30(1H,dd,J=11.0, 6.8Hz,*H-2*), 4.13

(2H,q,J=8.0Hz, CH_2CH_3), 5.22(1H,s,*H-6*), 5.62(1H,m,*H-5*); *M/z*=284 (M^+).

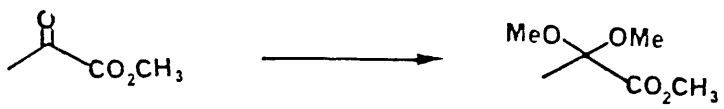
Preparation of (±) Ethyl (7α-acetoxy-7β-acetyl-6β-(3',5'-dinitrophenylcarboxy)-4-methyl) cyclohex-4-en-2α-carboxylate (234)



To a stirred solution of alcohol (232) (0.362g,1.27mmol) in dry pyridine (3.0ml) at 0°C under argon was added 3,5-dinitrobenzoyl chloride (0.439g, 1.90mmol). The resulting solution was allowed to warm to rt then stirred for 10h. The crude reaction mixture was poured into 0.5 M HCl (20ml) and the product extracted into Et_2O (4x20ml). The combined organic extracts were washed with brine (20ml) and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (Et_2O) to give (±) *ethyl (7α-acetoxy-7β-acetyl-6β-(3', 5'-dinitrophenylcarboxy)-4-methyl) cyclohex-4-en-2α-carboxylate* (234) (0.353g,58%) as pale yellow crystals, m.p. 142-143°C (from Et_2O), $\nu_{max.}$ (nujol) 1746, 1718, 1630, 1547, 1344, 1267, 1245, 1204, 1150, 1038 and 731cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.32(3H,t,J=7.0Hz, CH_2*Me*), 1.87(3H,s,*Me*), 2.13(3H,s,OCO*Me*), 2.27(3H,s,CO*Me*), 2.46(1H,dd,J=18.0, 9.0Hz, *H-3*), 2.65(1H,dd,J=18.0,6.5Hz, *H-3*), 3.71(1H,t,J=7.0Hz, *H-2*), 4.19(2H,t,J=7.0Hz, CH_2Me), 5.48(1H,m,*H-6*), 6.28(1H,m,*H-5*), 9.10(2H,d,J=2.0Hz, *H-2'*, *H-6'*), 9.24(1H,d,J=2.0Hz, *H-4'*); *M/z*=293 (Found:C,52.79; H,4.62; N,5.82%. $C_{21}H_{22}N_2O_{11}$ requires C,52.72;H,4.63;N, 5.85%).

X-Ray Crystallographic Data for (234): Crystals of (234), $C_{21}H_{21}O_{11}N_2$ M_R=478., are monoloclinic, a=11.134(2), b= 13.202(2) c=15.821(3) Å, β=95.84 (2)° , v=2313 Å^3, space group p2$_1$/n, z=4,M=477.4,D_c=1.38g cm^{-3}, μ(Cu-K_α)=9cm^{-1}, F(000)=996. 1914 independent observed reflections($|F_o|>3\theta(|F_c|)$,$\theta<\beta$) were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) and using ω scans. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The positions of all the hydrogen atoms were idealized(C-H=0.96Å) assigned isotropic thermal parameters, U(H)= 12 veq(c) and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement converged to give R=0.048, R_w= 0.051 [$w^3=\theta^2(F)$ +0.00029 F^2]·Maximum residual electron density was 0.19 eÅ^{-3} and the mean and maximum shift/error in the final refinement were 0.007 and 0.028 respectively.

Preparation of Methyl 2,2-(dimethoxy) propanoate (237)

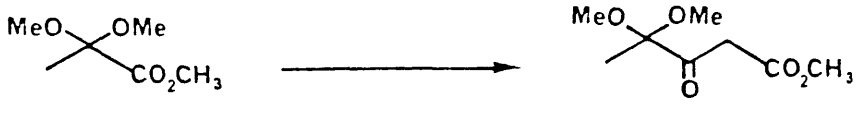


(236) (237)

Methyl pyruvate (10.21g,10.00mmol)was dissolved in analar MeOH (20ml). Trimethyl orthoformate (12.73g,120.00ml) was added followed by *p*TSA (0.25g, 1.31mmol). The resulting solution was heated to 85°C and the methyl formate distilled off the reaction *via* a Vigreaux column. The solution was allowed to cool to rt, then NEt_3(0.13g, 1.31mmol) was added. The solvent was evaporated under reduced pressure and the residue distilled to give methyl 2,2-(dimethoxy)

propanoate (237) (12.5g, 82%) as a colourless oil, b.p. 60-65°C (6mmHg), $\nu_{max.}$(film) 2949, 2837, 1749, 1452, 1290, 1143, 1047, 1020 and 893cm^{-1}. δ_H(60MHz;$CDCl_3$) 1.50 (3H,s, *Me*), 3.28(6H,s,O*Me*), 3.85(3H,s,CO_2*Me*); *M/Z*=116(M^+-MeOH).

Preparation of Methyl 4-oxo(dimethylacetal)-3-oxopentanoate (238)



(237) (238)

To a stirred boiling mixture of methyl ester (237) (74.00g, 500mmol) and methyl acetate (55.50g, 750mmol) at 80°C was added sodium metal (11.50g,500mmol) freshly cut into small pieces. The temperature was maintained at 80°C for 12h then more methyl acetate (7.00g, 500mmol) was added followed by sodium metal (11.50g, 500mmol) cut into small pieces. After heating for a further 3h at 80°C the solution was cooled to rt and carefully poured over crushed ice (600ml). The resulting solution was extracted with Et_2O (3x500ml), acidified to pH4 with 3.0M hydrochloric acid and further extracted with Et_2O (2x500ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue distilled to give *methyl 4-oxo(dimethylacetal)-3-oxo pentanoate*(238) (65.55g, 69%) as a pale yellow oil, b.p. 84-88°C / 0.3mmHg, $\nu_{max.}$(film) 2966, 2837, 1754, 1729, 1633, 1437, 1396, 1370, 1325, 1265, 1192, 1150, and 1046 cm^{-1}; δ_H(60MHz;$CDCl_3$) 1.40 (2.2H,s,*Me*), 1.50 (0.8,s,*Me enol*), 3.20(1.5H,s,O*Me enol*), 3.25(4.5H,s,O*Me*), 3.55(1.5H,s,*H-2*), 3.75(3H,s,CO_2*Me*), 5.55(0.5H,s,*H-2 enol*); *M/Z*=159(M^+-O*Me*) (Found:C:50.40;

H:7.62%.$C_8H_{14}O_5$ requires C:50.52; H:7.42%).

Preparation of Methyl 3,4-dioxopentanoate (239)



(238) (239)

To the dimethylacetal(239)(14.50g,76.24mmol), cooled in an ice/water bath,was added concentrated hydrochloric acid (37.5ml) dropwise. The resulting suspension was stirred for 20 min then warmed to rt and poured into distilled water (150ml). The solution was saturated with sodium chloride and extracted with Et_2O(5x150ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure to give methyl 3,4-dioxopentanoate(239) (10.30g,95%) as a yellow semi-crystalline solid, $\nu_{max.}$ (CH_2Cl_2) 3422, 3113, 2959, 1718, 1654, 1625, 1449, 1414, 1388, 1359, 1229, 1081, 1018, 940 and 842cm^{-1}; δ_H(60MHz; $CDCl_3$) 2.40(3H,s,*Me*), 3.70(1H,s,*H-2*), 3.80(3H,s,CO_2*Me*), 5.85(1H,s,*H-2* enol); *M/Z*=144(M^+) (Found:M^+144.0420. $C_6H_8O_4$ requires 144.0422).

Preparation of *Z*-Methyl 3-acetoxy-4-oxo-pent-2-enoate (235)

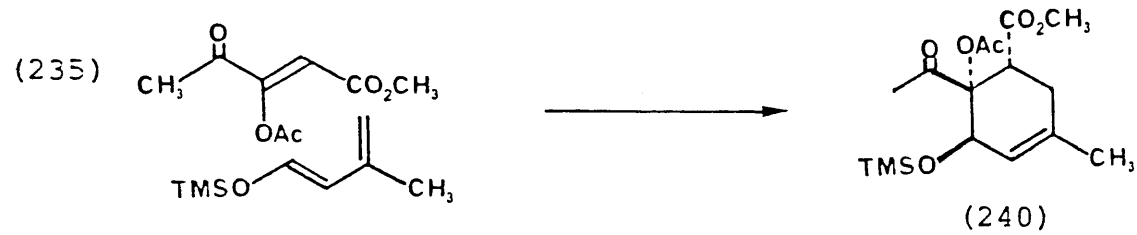


(239) (235)

A solution of diketone (239)(3.85g,26.71mmol) in isopropenyl acetate (20ml) and CSA (0.30g, 1.29mmol) was heated to 85°C. The acetone was allowed to distil off over 6h. The solvent was evaporated under reduced pressure and the residue chromatographed (30%Et_2O-40-60°petrol)to give

Z-methyl 3-acetoxy-4-oxo-pent-2-enoate (235) (3.19g,72%) as a pale yellow oil, $\nu_{max.}$(film) 3087, 3007, 2957, 2850, 1774, 1707, 1655, 1436, 1373, 1249, 1168, 1089, and 970cm^{-1}; δ_H(90MHz;$CDCl_3$) 2.32(3H,s,OCO *Me*), 2.37(3H,s,CO*Me*), 3.78 (3H,s,CO_2*Me*), 6.52(1H,s,*H-2*); *M/Z*=186 (M^+186.0.522. $C_8H_{10}O_5$ requires 186.0528).

Preparation of (±) Methyl (7α-acetoxy-7β-acetyl-4-methyl-6β-trimethylsilyoxy) cyclohex-4-en-2α-carboxylate (240)

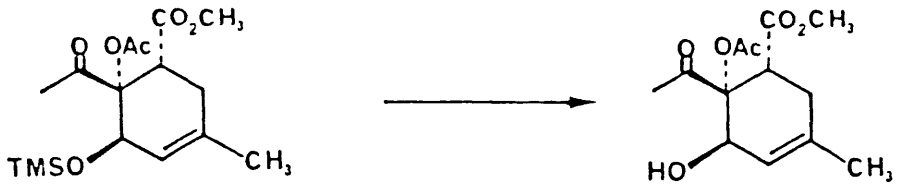


(227) (240)

To a stirred solution of Z-methyl-3-acetoxy-4-oxo-pent-2-enoate (235) (10.15g, 54.55mmol) in dry toluene (30ml), in a 100ml pressure bottle which had been soaked in hexamethyldisilazane, was added 3-methyltrimethylsiloxy-butadiene (227) (12.77g,81.85 mmol). The pressure bottle was purged with argon, sealed and heated to 115°C for 72h. The bottle was allowed to cool to rt, the solvent evaporated under reduced pressure and the residue chromatographed (15%Et_2O-40-60° petrol) to give (±) *methyl(7α-acetoxy-7β-acetyl-4-methyl-6β-trimethylsilyoxy)cyclohex-4-en-2α-carboxylate* (240) (11.69g, 63%) as a colourless oil, $\nu_{max.}$(film) 2955, 1743, 1434, 1368, 1250, 1204, 1164, 1077, 921, 867 and 844 cm^{-1}; δ_H(250MHz;$CDCl_3$) 0.12(9H,s, Si*Me*$_3$), 1.70(3H,s,*Me*), 2.06(3H,s,OCO *Me*), 2.12(3H,s,CO*Me*), 2.12(1H,dd,J=20.0,4.0Hz, *H-3*), 2.64(1H,dd,J=20.0,7.5Hz, *H-3*), 3.76(4H,m, *H-4*, CO_2*Me*), 4.59(1H,m,*H-6*), 5.18(1H,m, *H-5*); *M/Z*=282(M^+-H*OAc*) (Found:C,56.08; H,7.89%. $C_{16}H_{26}O_6Si$

requires C,56.12;H,7.65%).

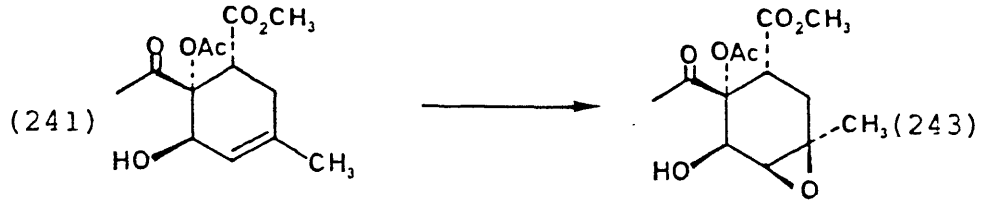
Preparation of (±) Methyl(7α-acetoxy-7β-acetyl-6β-hydroxy-4-methyl)cyclohex-4-en-2α-carboxylate(241)



(240) (241)

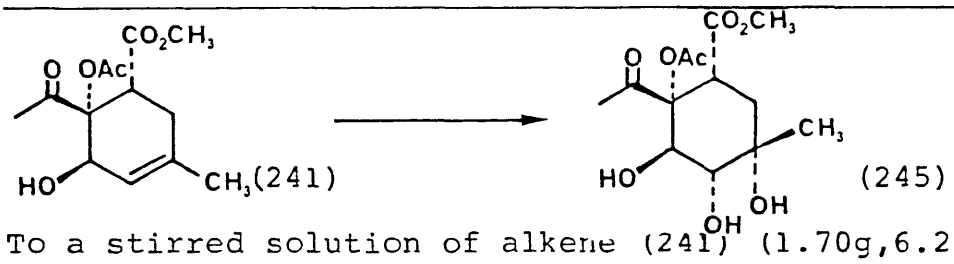
To a stirred solution of the trimethylsilyl derivative (240) (3.29g,9.61mmol) in THF (30ml) was added HF (14.28 ml of 0.70M solution of 40% HF in acetonitrile, 10.00mmol). After 20 min the reaction was complete by TLC and the solution was poured into saturated $NaHCO_3$ solution (30ml). The product was extracted into $CHCl_3$(4x50ml) and the combined organic extracts dried. The solvent was evaporated under reduced pressure and the residue chromatographed (60% Et_2O-40-60°petrol) to give *(±) methyl(7α-acetoxy-7β-acetyl-6β-hydroxy-4-methyl)cyclohex-4-en-2α-carboxylate* (241) as white crystals, m.p.86-87°C(from Et_2O-40-60°petrol), $\nu_{max.}$(CH_2Cl_2) 3467, 2953, 1741, 1434, 1370, 1244, 1166, 1098, 1031 and 828 cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.78(3H,s,*Me*), 2.10(3H,s,OCOC*H*$_3$), 2.18(3H,s, COC*H*$_3$), 2.46(1H,dd,J=18.7, 7.5Hz, *H-3*), 2.53(1H,dd,J=18.7,8.7Hz, *H-3*), 3.39(1H,d,J=3.7Hz, O*H*), 3.56(1H,dd,J=8.7, 7.5Hz,*H-2*), 3.69(3H,s,CO_2CH_3), 4.72(1H,m,*H-6*), 5.47(1H,m,*H-5*); *M/z*=270(M^+) (Found:C,57.77%; H,6.71% $C_{13}H_{18}O_6$ requires C,57.77;H,6.71%).

Preparation of (±) Methyl(7α-acetoxy-7β-acetyl-4β,5β-epoxy-6β-hydroxy-4α-methyl) cyclohexane-2α-carboxylate(243)



To a stirred solution of alkene(241) (0.168g, 0.62mmol) in dry CH_2Cl_2(5ml) under argon was added a solution of *m*CPBA(0.138g,0.68mmol) in dry CH_2CL_2(5ml). The resulting solution was warmed to rt, stirred for 12h, then washed thoroughly with saturated $NaHCO_3$ solution. The organic phase was dried, the solvent evaporated under reduced pressure and the residue chromatographed (70%Et_2O-40-60° petrol) to give (±) *methyl(7α-acetoxy-7β-acetyl-4β,5β-epoxy-6β-hydroxy-4α-methyl) cyclohexane-2α-carboxylate(243)* (0.149,84%) as a white solid, m.p.84-86° C, $\nu_{max.}$ (CH_2Cl_2) 3536, 3047, 2950, 1740, 1369, 1233, 1202, 1174, 1059, 1030 and 973cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.40(3H,s,*Me*), 2.07 (3H,s,OCO*Me*), 2.18(2H,m,*H-3*), 2.22(3H,s,CO*Me*), 3.18(1H, dd, J=6.9, 6.9Hz, *H-2*), 3.28(1H,d,J=4.4Hz, *H-5*), 3.58 (3H,s, CO_2*Me*), 4.31(1H,d,J=4.4Hz,*H-6*); *M/Z*=287(MH^+), 269 (MH^+-H_2O) (Found:C,54.65;H,6.37%. $C_{13}H_{18}O_7$ requires C,54.54; H,6.34%).

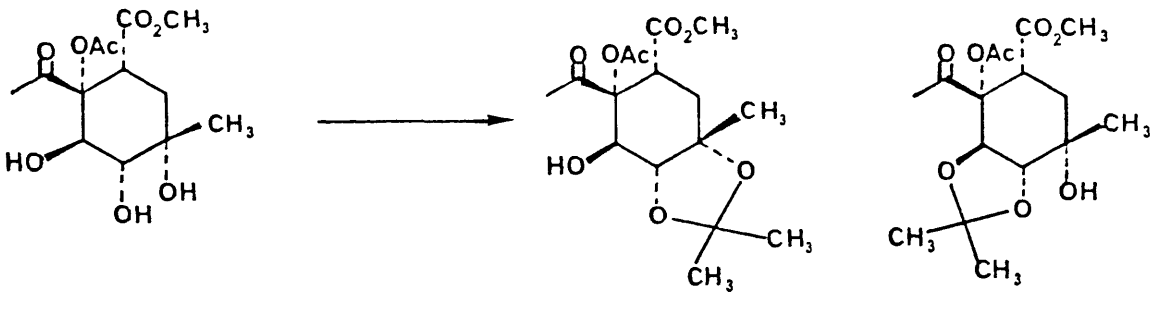
Preparation of (±) Methyl(7α-acetoxy-7β-acetyl-4β-methyl-4α,5α,6β-trihydroxy) cyclohexane-2α-carboxylate(245)



To a stirred solution of alkene (241) (1.70g,6.23mmol) in *tert*-butanol/THF/H_2O (10:3:1, 20ml) was added NMO (0.883g, 7.55mmol) followed by OsO_4(0.010g,0.04mmol). The resulting solution was stirred at rt for 36h. Aqueous $NaHSO_3$(5ml of 1.0 M solution) was added and stirring continued for a further 6h. Talc (3.0g) was added and the resulting suspension filtered. The solvent was evaporated under reduced pressure and the residue chromatographed(EtOAc)

to give (±) *methyl(7α-acetoxy-7β-acetyl-4β-methyl-4α, 5α, 6β-trihydroxy) cyclohexane-2α-carboxylate* (245)(1.49g,78%) as a white solid, m.p. 145-148°C, $\nu_{max.}(CH_2Cl_2)$ 3522, 3400, 3053, 2975, 2871, 1706, 1424, 1366, 1275, 1113,1022, 949 and 893 cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.28(3H,s,*Me*), 2.04 (1H,dd,J=17.4, 1.6Hz, *H-3*),2.14(3H,s,OCO*Me*), 2.21(3H,s, CO*Me*), 2.61(1H,dd,J=17.4, 7.3Hz,*H-3*), 2.68(1H,d,J=10.9Hz, *H-6*), 2.96(1H,s,C-4 O*H*), 3.15(1H,t,J=10.9Hz,*H-5*), 3.73 (3H,s,CO_2*Me*), 3.85(1H,dd,J=7.3, 1.6Hz,*H-2*), 4.13(1H,d, J=10.9Hz, C-5 O-*H*), 5.30(1H,s, C-6O*H*); *M/z*=305(MH^+), 286 (MH^+-H_2O) (F nd:C,51.32;H,6.64%. $C_{13}H_{20}O_8$requires C,51.31; H,6.62%).

Preparation of (±) Methyl(7α-acetoxy-7β-acetyl-4β-methyl-4α-5α-6β-trihydroxy-4α-5α-di-O-isopropylidene) cyclohexane-2α-carboxylate (250) and (±) methyl(7α-acetoxy-7β-acetyl-4β-methyl-4α-5α-6β-trihydroxy-5α,6β-di-O-isopropylidene) cyclohexane-2 -carboxylate (251).



(245) (250) (251)

To a stirred solution of triol (245) (1.03g,3.38mmol) in 2,2-dimethoxypropane(10ml) was added CSA (0.12g). The resulting solution was stirred at rt for 48h, poured into Et_2O (100ml) and washed with saturated $NaHCO_3$. The organic phase was dried, the solvent evaporated under reduced pressure and the residue chromatographed (30% Et_2O - 40-60° petrol) to give firstly *(±) methyl (7α-acetoxy-7β-acetyl-4β-methyl-4α,5α,6β-trihydroxy-4α,5α-di-O-isopropylidene) cyclohexane-2α-carboxylate (250)* (0.606g, 52%) as a white crystalline solid, m.p. 111-113°C (from Et_2O - 40-60° petrol), $\nu_{max.}$ (CH_2Cl_2) 3459, 2965, 2872, 1741, 1702, 1435, 1377, 1212, 1113, 1074, 1044, 985, and 865 cm^{-1}; δ_H (250MHz ; $CDCl_3$) 1.34 (3H,s,*Me*), 1.45 (3H,s,C*Me*), 1.51 (3H,s,C*Me*), 1.88 (1H,dd,J=14.1,3.1 Hz, *H-3*), 2.12 (3H,s,OCO*Me*), 2.16 (3H,s,CO*Me*), 2.51 (1H,t,J=14.1 Hz,*H-3*), 3.33 (1H,dd,J=14.1,3.1 Hz,*H-2*), 3.68 (3H,s,CO_2*Me*), 3.83 (1H,d,J=3.4 Hz,*H-5*), 4.78 (1H,d, J=1.7 Hz,C-6 O*H*), 5.09 (1H,dd,J=3.4,1.7 Hz,*H-6*) ; *m/z* = 344 (M^+) (Found : C, 55.70 ; H, 7.07 %. $C_{16}H_{24}O_8$ requires C, 55.81 ; H, 7.02 %), further elution gave *(±) methyl (7α-acetoxy-7β-acetyl-4β-methyl-4α,5α,6β-trihydroxy-5α,6β-di-O-isopropylidene) cyclohexane-2α-carboxylate (251)* (0.210g, 18%) as a white crystalline solid, m.p.159-161° C (from Et_2O - 40-60° petrol), $\nu_{max.}$ (CH_2Cl_2) 3682, 3433, 2964, 2930, 1747, 1711, 1379, 1226, 1141, 1113, 1045, and 873 cm^{-1} ; δ_H (250MHz; $CDCl_3$) 1.34 (3H,s,C*Me*), 1.38 (3H,s,C*Me*), 1.51 (3H,s,*Me*), 2.06 (1H,d,J=15.3 Hz,*H-3*), 2.14 (3H,s,OCO*Me*), 2.21 (3H,s,CO*Me*), 2.33 (1H,dd,J=15.3, 6.6 Hz,*H-3*), 3.32 (1H,d,J=10.9 Hz,*H-5/6*), 3.73 (1H,s,CO_2*Me*), 3.90 (1H,d,J=6.6 Hz, *H-2*), 4.40 (1H,d, J=10.9 Hz,*H-5/6*), 4.93 (1H,s,C-4 O*H*); *m/z* 345 (MH^+) (Found : C, 55.73; H,6.94 %. $C_{16}H_{24}O_8$ requires C, 55.81; H, 7.02 %).

X-Ray crystal data for (250) and (251).

(250)and (251) $C_{16}H_{24}O_8$ M=344.3, (250) monoclinic, a= 8.748 (1), b=21.685(3), c=10.228(2) Å, β=113.88(1)° , u= 1774 Å^3, space group $P2$, 1a, Z=4, D_c=1.29gcm^{-3},μ(Cu-K_α)= 8cm^{-1}, F(000)=736. (251) are monoclinic, a=1.111(5), b= 8.441 (2), c=16.370(5) Å,β=114.27(3)° ,u=1778 Å^3, space group $P2$, 1c, Z=4, D_c=1.29gcm^{-3}, μ(Cu-K_α)=8cm^{-1}, F(000) =736. 1666 and 1480 independant observed reflections for (250) and (251) respectively were measured on a Nicolet R3m diffractometer withCu-K_α radiation (graphite monochromator) and using ω-scans. Both structures were solved by direct methods, and the non-hydrogen atoms refined anisotropically. In both structures the position of the hydroxy hydrogen atom was determined from a ΔF map, and refined isotropically. The positions of all the other hydrogen atoms were idealized (C-H=0.96Å, assigned isotropic thermal parameters, U(H)=1.2 Ueq(c), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement converged to give R=0.051, R_w= 0.060 ($w^{-1}=\sigma(F) + 0.00066F^2$) for (250), R=0.063, R_w=0.065, ($w^{-1}=^2(F)$ +0.00068 F^2). Maximum residual electron density was 0.23 and 0.26 eÅ^{-3} for structures (250) and (251) respectively and the mean and maximum shift/error in the final refinement were 0.026 and 0.163 for (250) and 0.013 and 0.050 for (251).

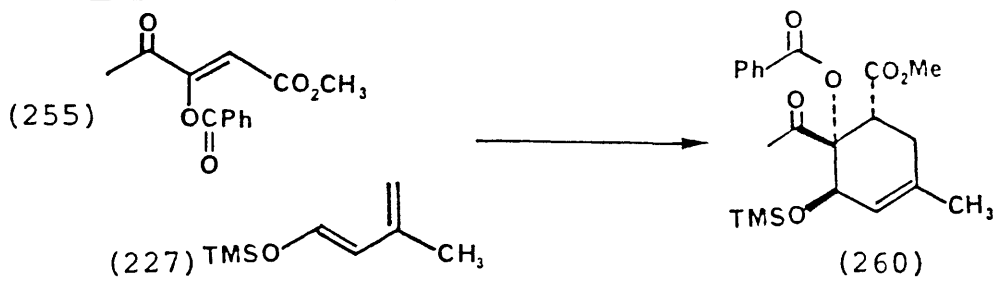
Preparation of Z-Methyl-3-phenylcarboxy-4-oxo-pent-2-enoate (255)



(239) (255)

To a stirred solution of diketone (239) (3.08g, 21.40mmol) in dry pyridine (15ml) under argon at 0° C was added benzoyl chloride (3.61g, 25.68mmol). The solution was stirred at 0° C for 1h then at rt for 5h. The solution was poured into 3M hydrochloric acid (100ml) and extracted with Et_2O (2x200ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (30% Et_2O-40-60° petrol) to give *z-methyl-3-phenylcarboxy-4-oxo-pent-2-enoate* (255) (2.02g,35%) as a pale yellow oil, $\nu_{max.}$ (film) 3075, 3007, 2953, 1733, 1653, 1600, 1450, 1243, 1173, 1093, 1023 and 856cm^{-1}; δ_H(60MHz;$CDCl_3$) 2.38(3H,s,*Me*), 3.67(3H,s,CO_2*Me*), 6.60 (1H,s,*H-2*), 7.60(3H,m,aromatic), 8.22(2H,m, aromatic); *M/z*=353 (M^++PhCO) (Found: C,63.20; H,4.89%. $C_{13}H_{12}O_5$ requires C, 62.90;H,4.87%).

Preparation of (±) Methyl (7β-acetyl-4-methyl-7α-phenyl-carboxy-6β-trimethylsilyoxy)cyclohex-4-en-2α-carboxylate(260).

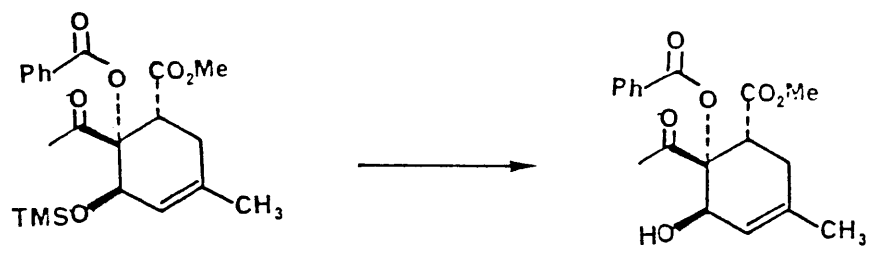


(255) (227) (260)

To a solution of siloxydiene(227) (0.156g, 10.00mmol) in dry toluene (10ml) in a 100ml pressure bottle which had been washed with hexamethyldisilizane was added z-methyl

-3-phenylcarboxy-4-oxo-pent-2-enoate (255) (1.65g,6.67 mmol). The vessel was flushed out with dry argon, sealed and heated to 115°C for 48h. The solution was allowed to cool to rt, the solvent evaporated under reduced pressure and the residue chromatographed (10%Et_2O-40-60° petrol) to give (±) *methyl (7α-phenylcarboxy-7β-acetyl-4-methyl-6β-trimethylsilyoxy)cyclohex-4-en-2α-carboxylate* (260) (0.860g 32%) as a white crystalline solid, m.p.83-85°C, $\nu_{max.}$ (CH_2Cl_2) 2954, 1723, 1678, 1449, 1379, 1351, 1275, 1252,1164, 1076, 912, and 843cm^{-1}; δ_H(250MHz;$CDCl_3$) 0.18(9H,s,Si*Me*$_3$), 1.86 (3H,s,*Me*), 2.20(3H,s,Co*Me*), 2.28(1H,dd,J=19.0,4.1Hz, *H-3*), 2.84(1H,dd,J=19.0, 7.4Hz, *H-3*), 3.44(3H,s,CO_2*Me*), 3.82 (1H,dd,J=7.4, 4.1Hz,*H-2*), 4.89(1H,m,*H-6*), 5.28(1H,m,*H-5*), 7.47(2H,dt, J=8.0,2.0Hz, *H-2';H-3'*), 7.60(1H,dt,J=8.0,2.0Hz, *H-4'*), 8.01(2H,dd,J=8.0,2.0Hz, *H-3'*, H-5'); *M/z*=373(M^+-OMe) (Found:C,62.37;H,6.97%. $C_{21}H_{28}O_6Si$ requires C,62.35; H,6.98%).

Preparation of (±) Methyl(7β-acetyl-6β-hydroxy-4-methyl-7α-phenylcarboxy) cyclohex-4-en-2α-carboxylate(261)

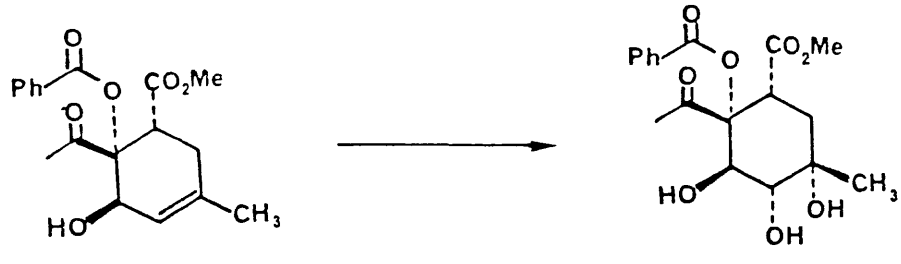


(260) (261)

To a stirred solution of trimethylsilyl ether derivative (260) (0.404g,1.00mmol) in CH_3CN (5ml) was added HF (2.09ml of a 0.70M solution of 40% HF in CH_{3CN}, 1.05mmol). After stirring at rt for 15 min the solution was poured into saturated $NaHCo_3$ solution (5ml). The aqueous phase was

extracted with $CHCl_3$(3x20ml) the combined organic phase dried and the solvent evaporated under reduced pressure. The residue was chromatographed (35%Et_2O-40-60° petrol) to give (±) *methyl(7β-acetyl-6β-hydroxy-4-methyl-7α-phenylcarboxy) cyclohex-4-en-2α-carboxylate* (261)(0.309g, 93%), as a white solid, m.p.126-130°C, $\nu_{max.}$(CH_2Cl_2) 3687, 3590, 3476, 3043, 2974, 1718, 1433, 1314, 1248, 1213, 1111, 1027 and 994cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.77(3H,s,*Me*), 2.20(3H,s,Co*Me*), 2.42(1H,dd,J=17.8, 5.9Hz,*H-3*), 2.72(1H,dd, J=17.8, 9.1Hz, *H-3*), 3.68(3H,s,CO_2*Me*), 3.70(1H,dd,J=9.1, 5.9Hz, *H-2*), 4.98(1H,m,*H-6*), 5.51(1H,m,*H-4*), 7.48(2H,m,*Ph*), 7.62(1H,m,*Ph*), 8.01(2H,m,*Ph*); *M/Z*=332 (M^+) (Found:C,64.77; H,6.00%. $C_{18}H_{20}O_6$ requires C,65.05%; H, 6.07%).

Preparation of (±) Methyl (7β-acetyl-4-methyl-7α-phenyl-carboxy-4α, 5α, 6β-trihydroxy) cyclohexane-2α-carboxylate(262)

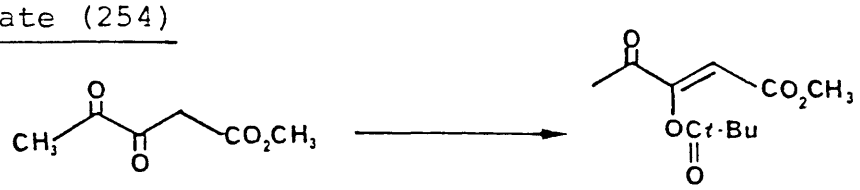


(261) (262)

To a stirred solution of alkene (261) (0.194g, 0.58mmol) in *tert* butanol/THF/H_2O 10/3/1 (5ml) was added NMO (0.095g, 0.70mmol) followed by osmium tetroxide (0.01g). The resulting solution was stirred at rt for 36h then saturated sodium bisulphate solution (3ml) was added and stirring continued for a further 6h. The suspension was filtered, the solvent evaporated under reduced pressure and the residue chromatographed (Et_2O) to give *(±)methyl (7β-acetyl-4-methyl-7α-phenylcarboxy-4α, 5α, 6β-trihydroxy) cyclohexane-2α-carboxylate* (262) (0.145g,68%) as a white solid, m.p.176°C

(decomp), $\nu_{max.}$ (CH_2Cl_2) 3687, 3521, 3398, 3043, 2972, 1717, 1436, 1282, 1213, 1090, 1070, and 960cm^{-1}: δ_H(250MHz; $CDCl_3$) 1.30(3H,s,*Me*), 2.08(1H,dd,J=15.9,2.0Hz), 2.26(3H,s, CO*Me*), 2.66(1H,dd,J=15.9, 7.9Hz,*H-3*), 2.73(1H,d,J=9.9Hz, *H-6*), 3.03(1H,s,C-4 O*H*), 3.22(1H,t,J=9.9Hz,*H-5*), 3.29 (3H,s,CO_2*Me*), 3.98(1H,dd,J=7.9, 2.0Hz,*H-2*), 4.32(1H,d, J=9.9Hz,C-5 *H*), 5.42(1H,s,C-6 O*H*), 7.48(2H,m,*aromatic*), 7.63(IH,m,*aromatic*), 8.06(2H,m,*aromatic*); *M/z*= 367(MH^+) (Found C,58.99; H,6.15%. $C_{18}H_{22}O_8$ requires c,59.01;H,6.05%).

Preparation of Z-Methyl 3-*tert*-butylcarboxy-4-oxo-pent-2-enoate (254)

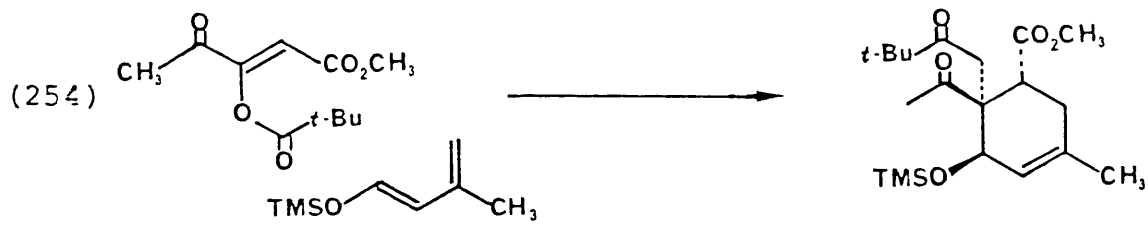


(239) (254)

To a stirred solution of diketone (239) (10.05g, 69.73mmol) in dry pyridine (50ml) at 0°C under argon was added pivaloyl chloride (9.26g, 76.70mmol)dropwise. The resulting solution was warmed to rt and stirred for 20h, then poured into Et_2O (200ml). The resulting etheral suspension was washed with 3.0M hydrochloric acid (2x150ml), brine (100ml) and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (15% Et_2O-40-60° petrol) to give firstly, E-methyl 3-*tert*-butylcarboxy-4-oxo-pent-2-enoate (256) (1.11g, 7%) as a pale yellow oil. $\nu_{max.}$ (film) 2978, 2875, 1757, 1716, 1645, 1481, 1436, 1344, 1274, 1155, 1031, 894 and 759 cm^{-1}; δ_H(90MHz;$CDCl_3$) 1.32 (9H,s,^{t}*Bu*), 2.50(3H,s,CO*Me*), 3.81(3H,s,CO_2*Me*), 5.94(1H,s,*H*);

M/z=227(M^+-H), 185 (M^+-*Me*CO) (Found:M^+-*Me*CO 185.0807. $C_9H_{13}O_4$ requires 185.0814), followed by *z-methyl-3-tert-butylcarboxy-4-oxo-pent-2-enoate*(254) (8.75g 55%) as a pale yellow oil, $\nu_{max.}$(film) 2977, 2875, 1757, 1733, 1707, 1653, 1431, 1363, 1340, 1275, 1244, 1178, 1106, 1031 and 864cm^{-1}; δ_H(90MHz;$CDCl_3$) 1.41(9H,s,^tBu), 2.36(3H,s, CO*Me*), 3.80(3H,s,CO_2*Me*), 6.52(1H,s,*H-2*); *M/z*=228(M^+) (Found:C, 57.80; H,7.21%. $C_{11}H_{16}O_5$ requires C,57.88; H,7.07%).

Preparation of (±) Methyl (7α-*tert*-butylcarboxy-7β-acetyl-4-methyl-6β-trimethylsilyoxy)cyclohex-4-en-2α-carboxylate(258)

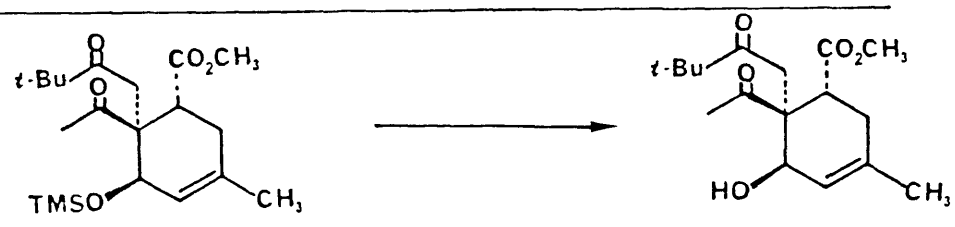


(227) (258)

To a solution of siloxydiene (227) (2.34g,15.00mmol) in dry toluene (15ml) in a 100ml pressure bottle,which had been washed with hexamethyldisilazane,was added *z*-methyl-3-*tert*-butylcarboxy-4-oxo-pent-2-enoate(254) (2.28g,10.00mmol). The vessel was flushed with dry argon gas, sealed and heated to 115°C for 72h. The contents were allowed to cool to rt, the solvent evaporated under reduced pressure and the residue chromatographed (15%-Et_2O-40-60° petrol) to give *(±)methyl (7α^{t}butylcarboxy-7β-acetyl-4-methyl-6β-trimethylsilyoxy) cyclohex-4-en-2α-carboxylate* (258) (1.84g, 48%) as a white solid, m.p. 88-90°C, $\nu_{max.}$(CH_2Cl_2) 2955, 1736, 1477, 1429, 1396, 1353, 1282, 1202, 1154, 1078 and 845 cm^{-1}; δ_H(250MHz;$CDCl_3$) 0.16(9H,s,Si*Me*$_3$), 1.20(9H,s,^tBu), 1.71(3H,s,*Me*), 2.11(3H,s,CO*Me*), 2.22(1H, dd, J=23.6,5.9Hz,*H-3*), 2.67(1H,dd,J=23.6, 10.1Hz, *H-3*),

3.64(3H,s,CO_2Me), 3.72(1H,dd,J=10.1,5.9Hz,*H-2*), 4.73 (1H,m,*H-6*), 5.22(1H,m,*H-5*); *M/z*=384(M^+) (Found:C,59.29; H,8.31%. $C_{19}H_{32}O_6Si$ requires C,59.34; H,8.39%).

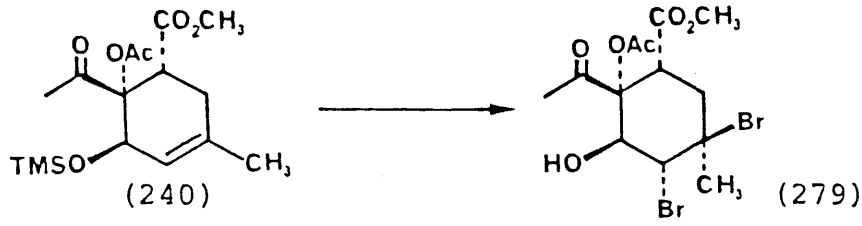
Preparation of (±) Methyl (7β-acetyl-7α-^{t}butylcarboxy-6β-hydroxy-4-methyl) cyclohexane-2α-carboxylate (259)



(258) (259)

To a stirred solution of silyloxy alcohol (259) (0.130g, 0.34mmol) in CH_3CN (5ml) was added HF (0.71ml of a 0.70M solution of 40% HF in CH_3CN, 0.50 mmol). After stirring at rt for 30 min the solution was poured into saturated $NaHCO_3$ solution (5ml). The aqueous phase was extracted with $CHCl_3$(4x20ml), the combined organic extracts dried and the solvent evaporated under reduced pressure. The residue was chromatographed (50%Et_2O-40-60°petrol) to give (±) *methyl (7β-acetyl-7α-tert-butylcarboxy-6β-hydroxy-4-methyl) cyclohexane-2α-carboxylate*(259) (0.094g, 91%) as a white solid, m.p. 85-86°C (from Et_2O-40-60°petrol), $\nu_{max.}$(CH_2Cl_2) 3590, 3475, 2935, 2873, 1718, 1477, 1432, 1353, 1161, 1059, 998 and 935cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.15 (9H,s,^tBu), 1.72(3H,s,*Me*), 2.08(3H,s,CO*Me*), 2.28(1H,dd, J=17.9, 6.6Hz,*H-3*), 2.58(1H,dd,J=17.9, 8.9Hz*H-3*), 3.57 (1H,dd,J=8.9,6.6Hz, *H-2*), 3.76(3H,s,CO_2Me), 3.95(1H,d, J=3.8Hz, O*H*), 4.75(1H,m,*H-6*), 5.44(1H,m,*H-5*);*M/z*=312 (M^+), 294 (M^+-H_2O) (Found:C,61.44; H,7.81%. $C_{16}H_{24}O_6$ requires C,61.52; H7.84%).

Preparation of (±) Methyl(7α-acetoxy-7β-acetyl-4β,5α-dibromo-6β-hydroxy-4α-methyl) cyclohexane-2α-carboxylate(279)



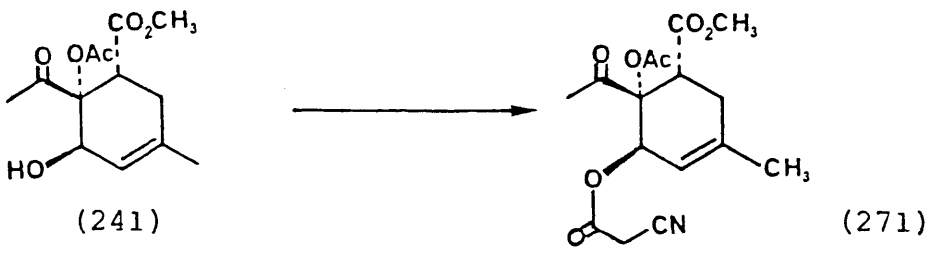
To a stirred solution of alkene (240) (0.210g, 0.61mmol) in THF(10ml) was added PHT (0.334g, 0.67mmol). The resulting solution was stirred at rt for 14h, the solvent was evaporated under reduced pressure , the residue dissolved in Et_2O(30ml) and washed with saturated $Na_2S_2O_3$ solution (10ml). The organic phase was dried, the solvent evaporated under reduced pressure and the residue chromatographed (50% Et_2O-40-60° petrol) to give (±) *methyl(7α-acetoxy-7β-acetyl-4β,5α-dibromo-6β-hydroxy-4α-methyl) cyclohexane-2α-carboxylate* (279) (0.200g, 77%) as a white solid, m.p. 145-147°C (from Et_2O-40-60°petrol), $\nu_{max.}$(CH_2Cl_2) 3579, 2962, 2870, 1744, 1436, 1370, 1231, 1113, 1069, 920 and 842 cm^{-1}; δ_H(250MHz;$CDCl_3$) 2.02(3H,s,*Me*), 2.17(3H,s,CO*Me*), 2.77(1H,dd,J=15.6,6.9Hz,*H-3*), 3.00 (1H,dd,J=15.6, 4.2Hz), 3.47(1H,d,J=4.2Hz,*H-5*), 3.69(3H,s,CO_2*Me*), 3.87(1H,dd,J=6.9, 4.2Hz, *H-2*), 4.66(2H,m,*H-6,OH*); *M/z*=431,429 (M^+) (Found: C,36.56;H,4.23%. $C_{13}H_{18}Br_2O_6$ requires C,36.30;H,4.22%).

X-Ray crystal data for (279)

$C_{13}H_{18}O_6Br_2$, (279) is monoclinic *a*=19.328(3), *b*=8.308(2), *c*=22.823(4)Å, β=119.46(1)° ,*u*=3191Å^3, space group $C_{2,c}$, Z=8, *M*=430.1, D_C=1.80g cm^{-3},μ(Cu-K_α)=67cm^{-1}. *F*(000)=1712. 1591 independant observed reflections ($|F_o|>3\sigma(|F_o|)$, $\theta \leq 50$) were measured on a Nicolet R3m diffractometer with Cu-K_α radiation, (graphite monochromator) and using ω-

scans. An empirical absorption correction based upon 306 azimuthal measurements was applied. The structure was solved by the heavy atom method and the non-hydrogen atoms refined anisotropically. The position of the hydroxyl hydrogen atom was obtained from a ΔF map and refined isotropically. The positions of all the other hydrogen atoms were idealized (C-H=0.96Å) assigned isotropic thermal parameters, $U(H)=1.2U$ eq (c), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Two of the methyl groups (C-9) and (C-4) displayed two orientations for the methyl protons which were refined with occupancies of 50% each. Refinement converged to give $R=0.032$, $R_w=0.038$ ($w^{-1}=\sigma^2(F)+0.00023F^2$). Maximum residual electron density was 0.35 eÅ^{-3} and the mean and maximum shift/error in the final refinement were 0.003 and 0.018 respectively.

Preparation of (±) Methyl (7α-acetoxy-7β-acetyl-6β-cyanoacetoxy-4-methyl) cyclohex-4-en-2α-carboxylate (271).

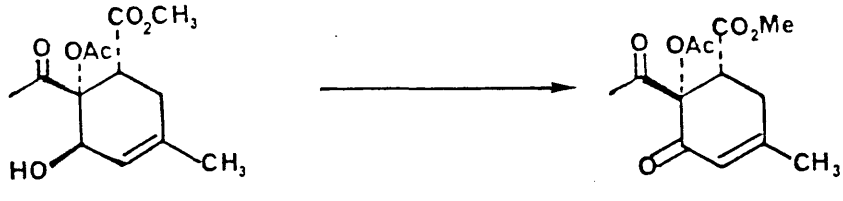


(241) (271)

To a stirred solution of cyano acetic acid under argon (0.311g, 3.66mmol), TsCl(0.622g, 3.26mmol) and dry pyridine (0.516g, 6.50mmol) in dry CH_2Cl_2 (5ml) was added a solution of alcohol (241)(0.353g, 1.30mmol) in dry CH_2Cl_2(5ml). The resulting solution was stirred at rt for 12h. The resulting suspension was poured into dilute hydrochloric acid (10ml of a 1.0M solution).The organic phase was separated and the aqueous phase extracted with CH_2Cl_2(2x20ml).

The combined organic phase was dried, the solvent evaporated under reduced pressure and the residue chromatographed (60%Et_2O-40-60° petrol) to give *(±) methyl (7α-acetoxy-7β-acetyl-6β-cyanoacetoxy-4-methyl) cyclohex-4-en-2α-carboxylate* (271) (0.314g, 81%) as a pale yellow solid, m.p. 106-107°C(from Et_2O-40-60° petrol), $\nu_{max.}$ (CH_2Cl_2) 3462, 2953, 2258, 1736, 1434, 1356, 1236, 1068, 1035, and 913 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.78 (3H,s,*Me*), 2.11 (3H,s,OCO*Me*), 2.23 (3H,s,CO*Me*), 2.36 (1H,dd,J=18.6, 6.6 Hz,*H-3*), 2.60 (1H,dd, J=18.6, 6.6 Hz,*H-3*), 3.48 (2H,s,OCOCH_2CN), 3.64 (1H,t,J=6.6 Hz, *H-2*),3.70 (3H,s,CO_2*Me*), 5.33 (1H,m,*H-6*), 5.92 (1H,m,*H-5*); *m/z*= 338 (MH^+) (Found : C, 56.90 ; H, 5.68 ; N, 4.05%·$C_{16}H_{19}NO_7$ requires C, 56.97 ; H, 5.68 ; N, 4.15 %).

Preparation of (±) Methyl (7α-acetoxy-7β-acetyl-4-methyl-6-oxo)cyclohex-4-en-2α-carboxylate (283).

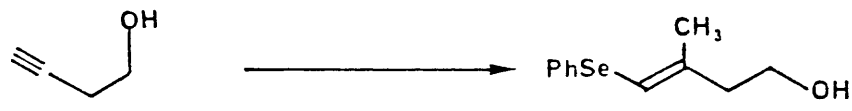


(241) (283)

A solution of alcohol (241) (0.248g, 0.92mmol) and freshly prepared N-iodosuccinimide (0.207g,0.92mmol) in dry C_6H_6 (5ml) was irradiated for 2.5 h with a 350 Watt lamp. The resulting solution was poured into Et_2O (20ml), washed with 10% sodium thiosulphate solution (10ml), brine (10ml) and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (60% Et_2O - 40-60° petrol) to give (±) methyl (7α-acetoxy-7β-acetyl-4-methyl-6-oxo)cyclohex-4-en-2α-carboxylate (283) (0.165g, 67%) as a colourless oil,

$\nu_{max.}$(film) 2954, 2849, 1733, 1684, 1636, 1435, 1369, 1317, 1284, 1239, 1076, 1028, and 964cm^{-1}; δ_H (250MHz;$CDCl_3$) 1.98(3H,d,J=0.5H ,*Me*), 2.15(3H,s,OCO*Me*), 2.20(3H,s,CO*Me*), 2.65(1H,dd,J=18.7,4.7Hz,*H-3*), 2.94 (1H,dd,J=18.7,6.2Hz, *H-3*), 3.67(3H,s,CO_2*Me*), 4.00(1H,t, J=5.3Hz, *H-2*), 5.95(1H,q,J=0.5Hz,*H-5*); *M/Z*=269(MH^+), 237 (M^+-O*Me*) (Found:M^+-OMe 237.0753. $C_{13}H_{16}O_6$ requires 237. 0763).

Preparation of E-3-Methyl-4-(selenophenyl) but-3-en-1-01 (308)

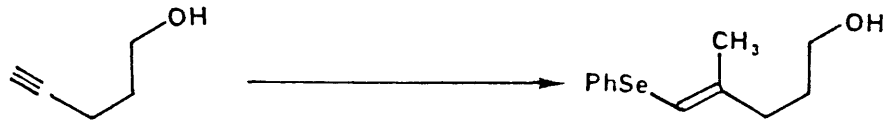


(305) (308)

To a stirred solution of bis (cyclopentadienyl) zirconium dichloride (0.730g, 2.50mmol) in dry 1,2-dichloroethane under argon at 0°C was added Me_3Al (11.54ml of a 2.60M solution in hexane, 30.00mmol) dropwise. A solution of 3-butyn-1-ol (0.70g, 10.00mmol) in dry 1,2-dichloroethane (5ml) was added and the resulting solution allowed to warm to rt and stirred overnight. After cooling to -30°C a solution of PhSeCl (2.87g, 15.00mmol) in dry 1,2-dichloroethane (30ml) was added. The resulting solution was stirred at -30°C for 20 min then warmed to rt. Saturated K_2CO_3 solution (10ml) was added dropwise (CARE). The resulting granular suspension was filtered and the residue washed with CH_2Cl_2(4x30ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (30%Et_2O-40-60° petrol) to give *E-3-methyl-4-(selenophenyl)but-3-en-1-ol* (308) (1.32g, 55%) as a pale yellow oil, $\nu_{max.}$(film) 3358, 3056, 2935, 1618,

1577, 1475, 1436, 1376, 1046, 1023, 737 and 690 cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.83(3H,d,J=1.1Hz,*Me*), 2.42(2H,dt,J=7.6, 0.9Hz, *H-2*), 3.72(2H,t,J=7.6Hz,*H-1*), 6.24(1H,q,J=1.1Hz, *H-4*), 7.24(3H,m,*aromatic*), 7.45(2H,m,*aromatic*); *M/Z*=241 (M^+) (Found: C,54.63;H,6.10%. $C_{11}H_{14}OSe$ requires C,54.55; H,5.84%).

Preparation of 4-Methyl-5-(selenophenyl)-pent-4-en-1-ol(311)



(309) (311)

To a stirred solution of bis(cyclopentadienyl) zirconium chloride (0.730g, 2.5mmol) in dry 1,2-dichloroethane (20ml) under argon at 0°C was added Me_3Al (11.54ml of a 2.6M solution in hexane, 30.00mmol). To the pale yellow solution was added a solution of 4-pentyn-1-ol(0.84g, 10.00mmol) in dry 1,2-dichloroethane (5ml). The resulting solution was stirred at rt overnight then cooled to -30°C. A solution of PhSeCl (2.87g,15.00mmol) in 1,2-dichloroethane (30ml) was added. After stirring at -30°C for 20 min the solution was warmed to rt and quenched with saturated K_2CO_3 solution (10ml) (CARE). The resulting granular suspension was filtered and the residue washed with CH_2Cl_2(4x25ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (25% Et_2O-40-60°petrol) to give *4-methyl-5-(selenophenyl) pent-4-en-1-ol* (311) as a pale yellow oil, $\nu_{max.}$(film) 3340, 2938, 1475, 1065, 736 and 690cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.76(2H,dt,J=7.0, 7.0Hz,*H-2*), 1.85(3H,d,J=0.9Hz,*Me*), 2.27 (2H,t,J=7.0Hz,*H-3*), 3.67(2H,t,J=7.0Hz,*H-2*), 6.19(1H,q, J=0.9Hz,*H-5*), 7.25(3H,m,*aromatic*), 7.45(2H,m,aromatic);

M/z=255 (M^+) (Found: C,56.63;H,6.47%. $C_{12}H_{16}OSe$ requires C,56.47;H, 6.32%).

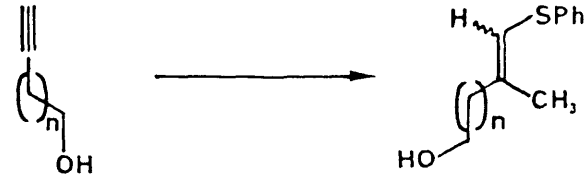
Preparation of *E*-2-Methyl-3-(selenophenyl) prop-2-en-1-ol (312)



(310) (312)

To a stirred solution of bis (cyclopentadienyl) zirconium dichloride (0.730g, 2.50mmol) in dry 1,2- dichloroethane (20ml) under argon at 0°C was added Me_3Al (11.54ml of a 2.6M solution in hexane, 30.00mmol). To the pale yellow solution was added a solution of propargyl alcohol (0.56g, 10.00mmol) in dry 1,2 dichloroethane (5ml). The resulting solution was stirred at rt for 16h then cooled to -30°C. A solution of PhSeCl (2.87g,15.00mmol) in dry 1,2-dichloroethane (30ml) was added. After stirring at -30°C for 20 min the solution was warmed to rt. Saturated K_2CO_3 solution (10ml) was added dropwise (CARE). The resulting granular suspension was filtered and the residue washed with CH_2Cl_2 (4x30ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (40% Et_2O-40-60° Petrol) to give *E-2-methyl-3-(selenophenyl)prop-2-en-1-ol* (312) (0.73g,32%) as a pale yellow oil, $\nu_{max.}$ (film) 3345, 1577, 1476, 1437, 1022, 735 and 690cm^{-1}; δ_H (250MHz;$CDCl_3$) 1.75 (3H,d,J=1.1Hz,*Me*), 3.93(2H,d,J=1.0Hz, *H-2*), 6.30(1H,d, J=1.0Hz,*H-3*), 7.12(5H,m,*aromatic*); *M/z*=227(M^+) (Found: C,53.16; H,5.25%. $C_{10}H_{12}OSe$ requires C,52.87; H,5.32%).

General procedure for the preparation of vinyl sulphides.



To a stirred solution of bis (cyclopentadienyl) zirconium dicloride (0.730g, 2.50 mmol) in 1,2-dichloromethane (20ml) under argon at 0°C was added Me_3Al (11.54ml of a 2.6M solution in hexane, 30.00mmol). To the pale yellow solution was added a solution of the alkyne (10.00mmol) in dry 1,2-dichloroethane (5ml). The resulting solution was stirred at rt for 12h then cooled to -30°C. A solution of PhSeCl (2.17g, 15.00mmol) in 1,2-dichloroethane (30ml) was added. After stirring at -30°C for 20 min the solution was warmed to rt and carefully quenched with saturated K_2CO_3 solution (10ml). The resulting granular suspension was filtered and the residue washed with CH_2Cl_2 (100ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (30% Et_2O-40-60°petrol)

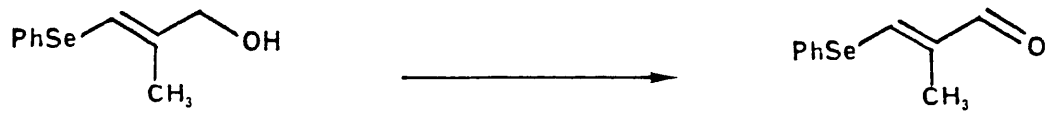
Propargyl alcohol (310) gave *2-methyl-3-(thiophenyl) prop-2-en-1-ol* (315c) (0.594g,33%) as a 1:1 mixture of E:Z isomers, $\nu_{max.}$ (film) 3402, 3056, 2916, 1663, 1582, 1478, 1437, 1312, 1088, 1024 and 739cm^{-1}; δ_H(90MHz;$CDCl_3$) 1.80(1.5H,s,*Me*), 1.85(1.5H,s,*Me*), 3.65(2H,s,*H-2*), 5.70 (1H,s,*H-3*), 7.20-7.35(5H,m, *aromatic*); *M/Z*=180 (M^+) (Found: C,66.40; H,6.60%. $C_{10}H_{12}OS$ requires C,66.63; H,6.71%).

3-butyn-1-ol (305) gave firstly *-3-methyl-4-(thiophenyl) but-3-en-1-ol* (315a)

(0.339g, 17%) as a pale yellow oil, $\nu_{max.}$(film) 3346, 3058, 2934, 1583, 1478, 1377, 1088, 1048, 862 and 739cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.86(3H,s,*Me*), 2.53(2H,t,J=6.6Hz,*H-2*) 3.69(2H,t,J=6.6Hz,*H-1*), 6.00(1H,s,*H-4*), 7.05-7.32(5H,m, *aromatic*); *M/Z*=194 (M^+) (Found:c,67.83; H,7.37%. $C_{11}H_{14}OS$ requires C,68.00; H,7.26%), followed by *E-3-methyl-4-(thiophenyl) but-3-en-1-ol* (315b) (0.680g, 35%) as a pale yellow oil, $\nu_{max.}$(film) 3362, 3058, 2935, 1583, 1478, 1438, 1376, 1048, 1026 and 739cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.88 (3H,d,J=1.0Hz,*Me*), 2.42(2H,t,J=7.5Hz,*H-2*), 3.74(2H,t,J= 7.5Hz,*H-1*), 6.04(1H,q,J=1.0Hz, *H-4*), 7.12-7.38(5H,m, *aromatic*); *M/Z*=194 (M^+) (Found: C,67.84;H,7.34;S,16.67%. $C_{11}H_{14}O$ requires C,68.00;H,7.26;S16.50%).

4-pentyn-1-ol(309) gave 4-methyl-5-(thiophenyl) pent-4-en-1-ol(315d) (1.50g,72%) as an inseparable 1:1 mixture of E:Z isomers, $\nu_{max.}$(film) 3340, 3060, 2940, 1570, 1460, 1420, 1370, 1050, and 739cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.64-1.83 (2H,m,*H-2*),1.88(1.5H,s,*Me*),1.91(1.5H,s,*Me*), 2.26(1H,t,J=8.2 Hz,*H-3*), 2.38(1H,t,J=8.2Hz,*H-3*), 3.68(2H,m,*H-1*), 6.97 (1H,m,*H-5*), 7.12-7.33(5H,m, *aromatic*);*M/Z*=208(M^+) (Found: C,68.90;H,8.04%. $C_{12}H_{16}OS$ requires C,69.19; H,7.74%).

Preparation of 2-Methyl-3-selenophenyl-prop-2-en-1-al(318)



(310) (318)

To a stirred solution of alcohol (310) (0.225g, 1.00mmol) in CH_2Cl_2 (20ml) was added MnO_2(1.74g,20.00mmol). The mixture was stirred at rt for 48h, filtered, and the solvent evaporated under reduced pressure. The residue was

chromatographed (10%Et_2O-40-60° petrol) to give 2-methyl-3-selenophenyl-prop-2-en-1-al(318) (.212g, 95%) as a pale yellow oil, $\nu_{max.}$ (film) 3317, 1663, 1588, 1313, 1018 and 749 cm^{-1}; δ_H(60MHz;$CDCl_3$) 1.80(3H,s,*Me*), 7.30(5H,m, *aromatic*), 9.24(1H,s,*H-1*); *M/z*=226(MH^+) (Found:M^+225.9892. $C_{10}H_{10}OSe$ requires 225.9896).

Preparation of E,E-2-methyl-1-(selenophenyl)-4-(thiophenyl)-1,3-butadiene(320)

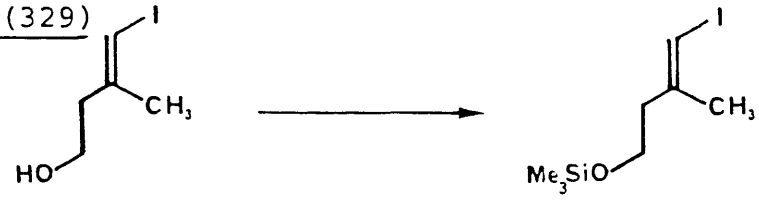


(318) (320)

To a stirred solution of phosphonate (319) (0.268g,1.23 mmol) in dry THF (5ml) at -78°C under argo was added nBuli (0.927ml of a 1.33 M solution, 1.36mmol). The resulting solution was stirred at -78° C for 1h, warmed to -40°C and stirred for a further 1h. A solution of enal (318) (0.252g, 1.11mmol) in THF (2ml) was added. Stirring was continued at -40° C for 1h then the solution was warmed to rt and stirred overnight. The THF was evaporated under reduced pressure and the residue taken up in Et_2O (20ml) and washed with brine (15ml). The organic phase was dried and the solvent evaporated under reduced pressure. The residue was chromatographed(1%Et_2O-40-60° petrol) to give E,E-2-methyl-1-(selenophenyl)-4-(thiophenyl)-1,3-butadiene (320) (0.238g,64%) as a pale yellow oil,$\nu_{max.}$ (film)3055, 1682, 1579, 1474, 1437, 1091, 1023, 738 and 689cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.93(3H,d,J=1.1Hz,*Me*), 6.28(1H,d,J=14.8 Hz,*H-3*), 6.43(1H,d,J=14.8Hz,*H-4*), 6.49(1H,d,J=1.1Hz,*H-1*),

7.19-7.50(10H,m,*aromatic*); *M/z*=332(M^+) (Found:M^+ 332.0125. $C_{17}H_{16}SSe$ requires 332.0138).

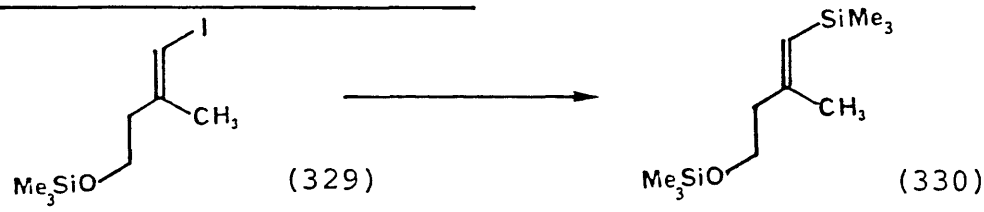
Preparation of E-1-iodo-2-methyl-4-(trimethylsilyoxy) but-1-ene (329)



(307) (329)

To a stirred solution of alcohol (307) (3.19g,15.05mmol) in CH_2Cl_2(70ml) under argon was added triethylamine (1.83g, 18.06mmol), trimethylsilylchloride (1.96g, 18.06mmol) and DMAP (0.15g). The resulting solution was stirred overnight at rt, then washed with water (50ml) and brine (50ml). The organic phase was dried and the solvent evaporated under reduced pressure. The residue was chromatographed (5%Et_2O-40-60°petrol to give *E-1-iodo-2-methyl-4-trimethylsilyoxy-but-1-ene* (329) (3.67g,86%) as a colourless oil, $\nu_{max.}$(film) 3058, 2954, 2864, 1616, 1431, 1250, 1143, 1100, 917, 841 and 748cm^{-1}; δ_H (60MHz;$CDCl_3$) 0.5(9H,s, Si*Me*$_3$), 1.95(3H,s,*Me*),2.35(2H,t,J=8.0Hz,*H-3*), 3.75(2H,t, J=8.0Hz, *H-4*), 5.90(1H,s,*H-1*); *M/z*=266(M^+-H_2O) (Found:C, 33.86;H,6.09%. $C_8H_{17}IOSi$ requires C,33.81; H, 6.03%).

Preparation of E-2-methyl-1-(trimethylsilyl)-4-(trimethylsilyloxy) but-1-ene. (330)

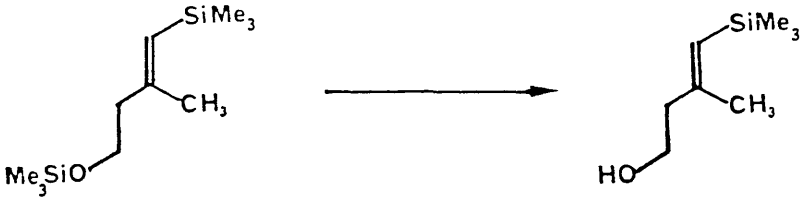


(329) (330)

Vinyl iodide (329) (1.14g,4.01mmol) was dissolved in dry Et_2O (15ml) and cooled under argon with stirring to -78°C. nBuli(3.70ml of a 1.30M solution, 4.80 mmol was added

dropwise. After the addition was complete the solution was warmed to -60°C and stirred at this temperature for 20 min. A solution of trimethylsilylchloride(0.52g,4.78 mmol) in dry Et_2O was added dropwise, the solution was stirred at -60°C for 1h then allowed to warm to rt. The crude reaction mixture was washed with water (30ml) and brine(20ml). The organic phase was dried and the solvent evaporated under reduced pressure. The residue was chromatographed (3%Et_2O - 40-60°petrol) to give *E-2-methyl-1-(trimethylsilyloxy)but-1-ene (330)* (0.56g, 61%) as a colourless oil, $\nu_{max.}$ (film) 2955, 2899, 2863, 1618, 1436, 1379, 1249, 1097, and 841 cm^{-1} ; δ_H (60MHz ; $CDCl_3$) 0.13 (9H, s,Si*Me*$_3$), 1.85 (3H,s,*Me*),2.30 (2H,t,J=8.0Hz,*H-3*), 3.80 (2H,t, J= 8.0 Hz,*H-4*), 5.30 (1H,s,*H-1*) ; *m/z* = 230 (M^+) (Found : C, 57.41 ; H, 11.41 %. $C_{11}H_{26}OSi_2$ requires C, 57.32 ; H, 11.37 %).

Preparation of E-4-hydroxy-2-methyl-1-(trimethylsilyl)but-1-ene (323).

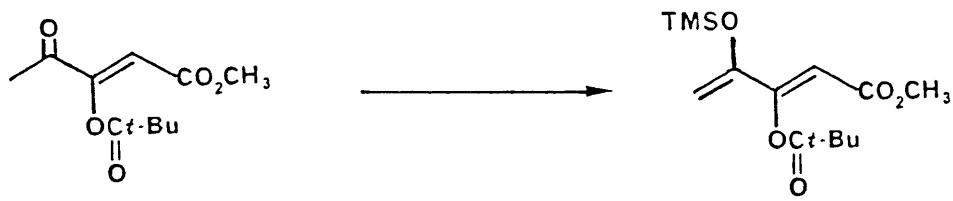


(330) (323)

To a stirred solution of trimethylsilyl ether (330) (0.230g, 1.00mmol) in THF (5ml) was added TBAF (0.25ml of 1.0M solution in THF, 1.09mmol). After stirring at rt for 1h the solution was poured into water (5ml) and the resulting aqueous phase was extracted with Et_2O (3x10ml). The organic

phase was dried, the solvent evaporated under reduced pressure and the residue chromatographed (30% Et_2O - 40-60° petrol) to give E-4-hydroxy-2-methyl-1-(trimethylsilyl)but-1-ene (323) (0.115g, 73 %) as a colourless oil, $\nu_{max.}$ 3460, 2980, 1618, 1430, 1379, 1250, 1164, 1020, adn 840 cm^{-1} ; δ_H (60MHz ; $CDCl_3$) 0.15 (9H,s,Si*Me*$_3$), 1.95 (3H,s,*Me*), 2.30 (2H,t,J=8.0 Hz, *H-3*),3.65 (2H,t,J=8.0 Hz,*H-4*), 5.30 (1H,s,*H-1*),*m/z* = 143 (M^+-Me) (Found : M^+ 143.0898 $C_7H_{12}OSi$ requires 143.0892).

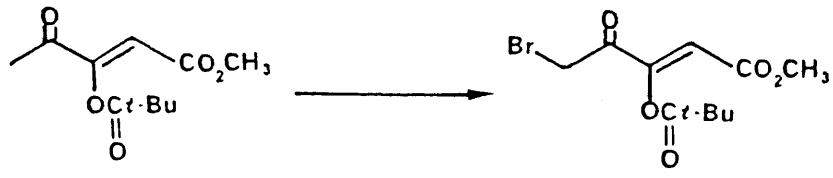
Preparation of E-Methyl-3-*tert*-butylcarboxy-4-(trimethylsilyoxy)pent-2,4 dien-oate (292)



(234) (292)

To a stirred solution of triethylamine (0.612g,6.00mmol) in dry DME (40ml) at -30°C was added trimethylsilyl triflate (1.332g, 6.00mmol) followed by enone (254) (1.14g,5.00mmol). The resulting solution was warmed to rt and stirred for 48h. Dry 40-60° petrol (100ml) was added to the reaction mixture which was cooled to 0°C for 12h. The solution was separated from the brown oil and the solvent evaporated under reduced pressure to give diene (292) (1.17g, 89%) as a pale yellow oil, $\nu_{max.}$ (film) 2962, 1761, 1640, 1603, 1480, 1433, 1301, 1256, 1197, 1180, 1102, 1011, 942, 914 and 853 cm^{-1}; δ_H(250MHz;$CDCl_3$) 0.28(9H,s,Si*Me*$_3$), 1.36 (9H,s,^{t}*Bu*), 3.69(3H,s,CO_2*Me*), 4.39(1H,dd,J=2.1,1.0Hz,*H-3*), 4.86(1H,dd,J=2.1,0.5Hz,*H-5*), 6.15(1H,s,*H-2*).

Preparation of 2-methyl-5-bromo-3-*tert* butylcarboxy-4-oxo-pent-2-enoate (284)



(254) (284)

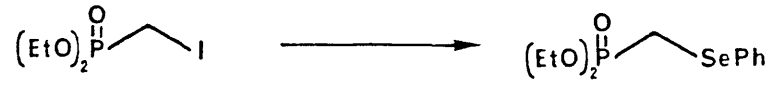
To a stirred solution of enone (254) (2.28g, 10.00mmol) in dry THF (100ml was added PHT (5.00g, 10.08mmol). The resulting suspension was stirred at rt for 72h, the solvent was evaporated under reduced pressure, the resulting residue was dissolved in Et_2O (100ml) and washed with water (100ml). The organic phase was dried and the solvent evaporated under reduced pressure to give α-bromoketone (284) (3.01g, 97%) as a yellow waxy solid, δ_H(60MHz;$CDCl_3$) 1.30(9H,s, ^tBu), 3.80(3H,s,CO_2Me), 4.20(2H,s,*H-5*), 6.65(1H,s,*H-2*); *M/z*=307(M^+).

General procedure for the preparation of phenyl sodium phenylselenide (359).

Diphenyldiselenide (3.12g, 10.00mmol) was dissolved in THF (50ml) and placed under argon. Sodium metal (0.49g, 21.30 mmol) freshly cut into approximately 20 pieces was added and the resulting suspension agitated in an ultrasonic bath at 30-35°C for 72h. The resulting off white suspension was transferred directly from the reaction vessel *via* syringe or canular. The concentration of phenyl selenide was calculated to be approximately 0.4M. Loss of solvent was not found to be a major problem, however any THF lost through evaporation was readily replaced by using precalibrated glassware.

In all cases 1.2 equivalents of sodium phenylselenide (359) was added to a stirred solution of the substrate (1.00mmol) in dry THF (10ml) and the reaction followed by TLC. When the reaction had reached completion, the solution was poured into water (20ml) and extracted with Et_2O (3x20ml). The ethereal layer was dried, the solvent evaporated under reduced pressure and the residue chromatographed.

Preparation of Diethyl phenylselenomethylphosphonate (359)

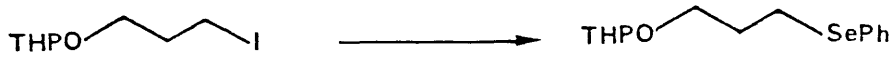


(358) (357)

Treatment of iodide (358) (0.280g, 1.00mmol) with sodium phenylselenide (359) (1.20mmol) gave diethyl phenylselenomethylphosphonate (359) (0.283g, 92%) as a pale yellow

oil, $\nu_{max.}$(film) 3467, 2982, 2938, 1635, 1477, 1440,1389, 1249, 1163, 1097, 1024 and 968 cm^{-1}; δ_H(60MHz;$CDCl_3$ 1.26 (6H,t,J=7.0Hz,*Me*), 2.90(2H,d,J=13.0Hz, CH_2), 4.03(4H,dq, J=8.0,7.0Hz CH_3CH_2), 7.10-7.30(3H,m,*aromatic*), 7.40-7.70 (2H,m,*aromatic*); *m/z*=308(M^+)

Preparation of 3-(Selenophenyl)-1-((tetrahedro-2H-pyran-2'-yl)oxy) propane (361)



(360) (361)

Treatment of iodide (360) (0.270g,1.00mmol) with sodium phenylselenide (359)(1.20mmol) gave *3-(selenophenyl),1-((tetrahydro-2H-pyran-2yl)oxy) propane* (361) (0.258g,86%) as a pale yellow oil, $\nu_{max.}$(film) 3055, 2939, 2867, 1576, 1476, 1352, 1259, 1200, 1134, 1075 and 870cm^{-1}; δ_H(250MHz; $CDCl_3$) 1.45-1.90(6H,m,*H-3',H-4', H-5',*), 1.98(2H,quintet J=7.9Hz,*H-2*), 3.00(2H,t,J=7.9Hz,*H-3*), 3.49(2H,m,*H-1*), 3.82(2H,m,*H-6*), 4.54(1H,t,J=3.6Hz,*H-2*); *M/z*=300(MH^+) (Found:C,55.98; H,6.76%. $C_{14}H_{20}O_2Se$ requires C,56.19; H, 6.74%).

Preparation of Methyl-3-(selenophenyl)propanoate(363)



(362) (363)

Treatment of iodide (362) (0.214g,1.00mmol) with sodium phenylselenide (359)(1.20mmol) gave methyl-3-(selenophenyl) propanoate (363) (0.214g,88%) as a pale yellow oil, $\nu_{max.}$ (film) 2949, 1736, 1476, 1434, 1347, 1223, 1165, 1022 and 738cm^{-1}; δ_H(250MHz;$CDCl_3$) 2.72(2H,t,J=7.9Hz,*H-2*),

3.10(2H,t,J=7.9Hz,*H-3*), 3.68(3H,s,CO_2*Me*), 7.27(3H,m,*aromatic*), 7.52(2H,m,*aromatic*); *M/z*=243(M^+)

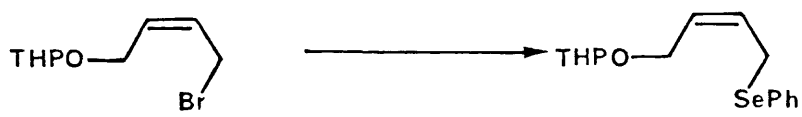
Preparation of (±) 4-(selenophenylmethyl)-2-phenyl-1,3-dioxane(365)



(364) (365)

Treatment of iodide (364) (0.304g, 1.00mmol) with sodium phenylselenide (359) (1.20mmol) gave *4-(selenophenylmethyl)-2-phenyl-1,3-dioxane* (365) (0.280g,84%) as a pale yellow oil, $\nu_{max.}$(film) 3062, 2954, 2925, 2853, 1576, 1476, 1450, 1395, 1359, 1248, 1175, 1127, 1022, 983 and 738cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.80(2H,m,*H-5*), 3.00(1H,dd, J=14.3,7.2Hz, PhSeCH_2), 3.23(1H,dd,J=14.3,7.2HzPhSeCH_2), 3.86-4.10(2H, m,*H-6*), 4.38(1H,ddd,J=14.6,7.2,2.7Hz,*H-4*), 5.49(1H,s,*H-2*), 7.20-7.58(10H,m,*aromatic*); *M/z*=334(MH^+) (Found:C,61.14; H,5.60%.$C_{17}H_{18}O_2Se$ requires C,61.26;H,5.44%)

Preparation of z-4-(selenophenyl)-1-((tetrahydro-2H-pyran-2-yl) oxy)but-2-ene (367)

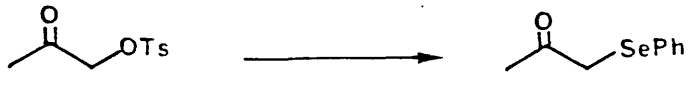


(366) (367)

Treatment of allylic bromide (366) (0.234g, 1.00mmol) with sodium phenylselenide (359) (1.20mmol) gave *z-4-(selenophenyl)-1-((tetrahydro-2H-pyran-2-yl)oxy)but-2-ene* (367) (0.292g,94%) as a pale yellow oil, $\nu_{max.}$(film) 3022, 2940, 2868, 1576, 1474, 1436, 1321, 1201, 1118, 1075, 1024 and 739cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.40-1.92(6H,m,*H-3'*,

H-4', *H-5'*,), 3.40-3.55(2H,m,*H-6*), 3.58(1H,d,J=8.2Hz, *H-1*), 3.73-3.93(2H,m, *H-4*,*H-2*), 4.04(1H,ddd,J= 16.1Hz,5.4, 1.0Hz,*H-4*), 4.62(1H,m,*H-2*), 5.57(1H,m,*H-3*), 5.78(1H,m, *H-2*, 7.24(3H,m,*aromatic*), 7.51(2H,m, *aromatic*); *M/Z*=312 (M^+) (Found:C,58.07;H,6.58%. $C_{15}H_{20}O_2Se$ requires C,57.88; H,6.48%).

Preparation of 1-(selenophenyl)propan-2-one (369)



(368) (369)

Treatment of tosylate (368)(0.228g, 1.00mmol) with sodium phenylselenide (359)(1.20mmol) gave *1-(selenophenyl)propan-2-one* (369)(0.198g,93%) as a pale yellow oil, $\nu_{max.}$(film) 3055, 2998, 2923, 1699, 1576, 1477, 1436, 1356, 1229, 1139, 1022 and 738cm^{-1}; δ_H(60MHz;$CDCl_3$) 2.30(3H,s,CO*Me*), 3.65(2H,s,CH_2), 7.20-7.75(5H,m,*aromatic*); *M/Z*=214(MH^+) (Found: C,50.67;H,4.94%. $C_9H_{10}OSe$ requires C,50.72; H,4.73%).

Preparation of (±) 3α-Methyl-4β(selenophenylmethyl)-γ-butyrolactone (371)

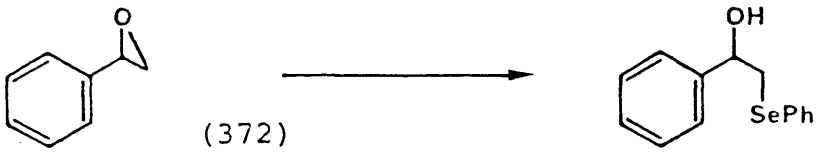


(370) (371)

Treatment of tosylate(370)(0.256g,1.00mmol) with sodium phenyl selenide (359)(1.20mmol) gave (±) *3α-methyl-4β (selenophenylmethyl)-γ-butyrolactone* (371)(0.223g,83%) as a pale yellow oil, $\nu_{max.}$(film) 3055, 2961, 1930, 2871, 1774, 1476, 1418, 1293, 1192, 1150, 1022, 939 and 739cm^{-1}; δ_H(250MHz;$CDCl_3$)1.15(3H,d,J=7.1Hz,*Me*), 2.19(1H,dd,J=17.8,

8.5Hz,*H-2α*), 2.42(1H,m,*H-3*), 2.74(1H,dd,J=17.8,8.2Hz, *H-2β*), 3.10(1H,dd,J=12.8,5.7Hz, CH_2SePh), 3.28(1H,dd, J=12.8,5.7Hz,CH_2SePh), 4.23(1H,dd,J=12.8,5.7Hz,*H-4*), 7.24-7.31(3H,m,*aromatic*), 7.50-7.60(2H,m,*aromatic*); *M/Z*= 270 (MH^+)(Found:C,53.65;H,5.44%.$C_{12}H_{14}O_2Se$ requires C,53.54; H,5.34%).

Preparation of 1-Phenyl-2-(selenophenyl)ethan-1-ol(373)



(372) (373)

Treatment of styrene oxide (372)(0.120g,1.00mmol) with sodium phenylselenide (359)(1.20mmol) gave *1-phenyl-2-(selenophenyl)ethan-1-ol*(373)(0.216g,78%) as a pale yellow oil, $\nu_{max.}$(film) 3403, 3058, 2929, 1576, 1475, 1435, 1300, 1054, 1022, 973 and 737cm^{-1}; δ_H(250MHz;$CDCl_3$) 2.83(1H, br,O*H*), 3.12(1H,dd,J=12.5,9.0Hz,*H-2*), 3.30(1H,dd, J=12.5, 3.7Hz,*H-2*), 4.73(1H,dd,J=9.0,3.7Hz,*H-1*), 7.20-7.35(8H,m, *aromatic*), 7.50-7.60(2H,m,*aromatic*); *M/Z*=278(MH^+)(Found: C,60.39;H,5.12%. $C_{14}H_{14}$)Se requires C,60.65;H,5.09%).

Preparation of 1-(prop-2'-eneoxy)-3-(selenophenyl) propan-2-ol(375)

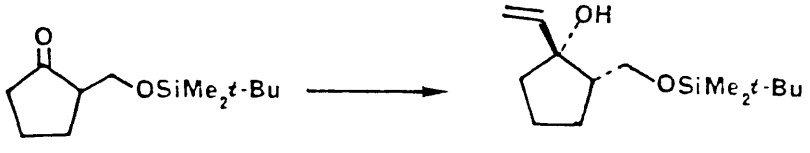


(374) (375)

Treatment of epoxide (374)(0.113g,1.00mmol) with PhSeNa (359) gave 1-(prop-2'-eneoxy)-3-(selenophenyl) propan-2-ol (375)(0.233g,86%) as a pale yellow oil, $\nu_{max.}$(film) 3429, 3068, 2857, 1642, 1475, 1266, 1108, 1020, 929 and 737cm^{-1}; δ_H(250MHz;$CDCl_3$) 2.79(1H,d,J=4.6Hz,O*H*),

3.03(1H,dd,J=14.3,6.4Hz*H-3*), 3.12(1H,dd,J=14.3,6.4Hz,*H-3*), 3.52(2H,m,*H-1*), 3.86-4.01(3H,m,*H-2,H-1'*), 5.20(1H,dd,J=11.4, 2.0Hz,*H-3' anti*), 5.27(1H,dd,J=17.8,2.0Hz, *H-3'syn*) 5.88(1H,m,*H-1'*), 7.20-7.32(3H,m,*aromatic*), 7.50-7.61(2H, m,*aromatic*); *M/Z*=272(MH^+) (Found:C,53.34;H,6.03%.$C_{12}H_{16}O_2Se$ requires C,53.14;H,5.95%).

Preparation of 2α-*tert*Butyldimethylsilyloxymethyl-1β-vinylcyclopentan-1α-ol(338)



(337) (338)

Vinyl bromide (0.230g,2.15mmol) was dissolved in dry Et_2O (3ml) and cooled to -120°C *tert* butyllithium (1.21ml, 1.78M, 2.15mmol) was added dropwise and the resulting solution stirred at this temperature for 3h. Ketone (337) (0.456g,2.00mmol) in Et_2O(3ml) was added dropwise and the solution allowed to warm to rt over 2h. The reaction mixture was poured into water (5ml), the organic phase was separated and the aqueous phase extracted with Et_2O (3x10ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure and the residue chromatographed (10%Et_2)-40-60°petrol) to give *2α-tert butyldimethylsilyloxymethyl-1β-vinylcyclopentan-1α-ol* (338)(0.236, 87%) as a colourless oil, $\nu_{max.}$(film) 3483, 2955, 2862, 1639, 1468, 1387, 1256, 1109, 1034 and 836cm^{-1}; δ_H(250MHz;$CDCl_3$) 0.10(6H,s,*Me*), 0.90(9H,s,^{t}*Bu*),1.64-2.06 (7H,m,*H-2, H-3, H-4, H-5*), 3.61(1H,dd,J=9.5,4.1Hz,C*H*O), 3.77(1H,dd,J=9.5,2.7Hz,C*H*O),4.03(1H,s,O*H*), 5.08(1H,dd, J=10.9,2.0Hz,*H-2'syn*), 5.31(1H,dd,J=17.2,2.0Hz,*H-2'anti*), 4.86(1H,dd,J=17.2,10.9Hz,*H-1'*); *M/Z* =256(M^+)(Found:C,65.45;

H,11.07%. $C_{14}H_{28}O_2Si$ requires C,65.57;H,11.01%).

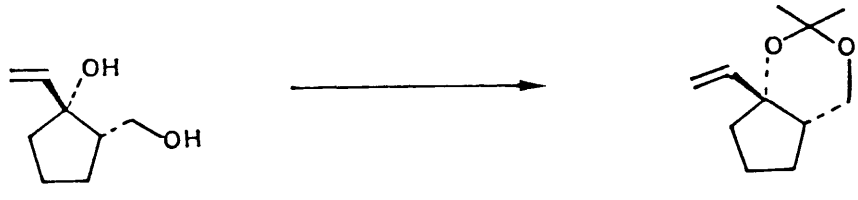
Preparation of 2α-hydroxymethyl-1β-vinylcyclopentan-1α-ol (339)



(338) (339)

To a stirred solution of silyl ether (338)(2.56g, 10.00 mmol) in THF(50ml) was added TBAF(11.00ml of a 1.0M solution in THF, 11.00mmol). The resulting solution was stirred at rt for 1h when tlc indicated the reaction had gone to completion. The reaction mixture was poured into brine (40ml) then extracted with $CHCl_3$(4x40ml). The combined organic extracts were dried,the solvent evaporated under reduced pressure and the residue chromatographed (70%Et_2O-40-60°petrol to give 2α-hydromethyl-1β-vinylcyclopentan-1α-ol(339)(1.33g,84%) as a colourless oil, $\nu_{max.}$(film) 3357, 2955, 2860, 1640, 1466, 1362, 1254, 1057, 996, 917, and 872cm^{-1};δ_H(60MHz;$CDCl_3$) 1.60-1.95(7H,m,*H-2,H-3,H-4,H-5,*), 3.60(2H,m,C*H*O), 5.10(1H,dd,J=11.0,2.0Hz,*H-2'syn*), 5.25 (1H,dd,J=18.0,2.0Hz,*H-2'anti*), 5.90(1H,dd,J=18.0,11.0Hz, *H-1'*); *M/z*=142(M^+)

Preparation of 2α-hydroxymethyl-di-O-isopropylidene-1β-vinylcyclopentan-1α-ol (340)

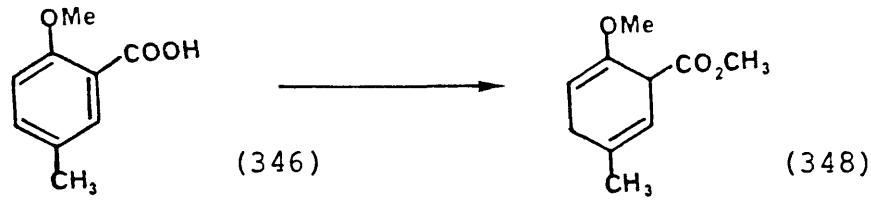


(339) (340)

To a stirred solution of diol(339)(0.142g,1.00mmol) in

2,2-dimethoxypropane(5ml) was added CSA(0.015g). The resulting solution was stirred at rt for 72h then poured into saturated $NaHCO_3$ solution (15ml). The aqueous layer was extracted with Et_2O(4x15ml), the combined organic layer dried and the solvent carefully dried under reduced pressure. The residue was chromatographed(5%Et_2O-40-60^0 petrol) to give 2α-hydroxy-methyl-di-O-isopropylidene-1β-vinylcyclopentan-1α-ol (340) (0.103g,64%0 as a colourless oil, $\nu_{max.}$(film) 3082, 2960, 2871, 1634, 1379, 1368, 1250, 1228, 1193, 1149, 1072,1043, 1000, 967 and 914cm^{-1}; δ_H (60MHz;$CDCl_3$) 1.40(3H,s,C*Me*), 1.45(3H,s,C*Me*), 1.50-2.15 (7H,m,*H-2,H-3.H-4,H-5*), 3.65(1H,dd,J=12.0,2.0HzC*H*O), 3.95 (1H,dd,J=12.0,5.5Hz, C*H*O), 5.05(1H,dd,J=18.0,2.0Hz,*H-2'anti*), 5.10(1H,dd,J=12.0,2.0Hz,*H-2'syn*), 6.15(1H,dd,J=18.0,12.0Hz, *H-1'*); *M/Z*=155(M^+-OMe).

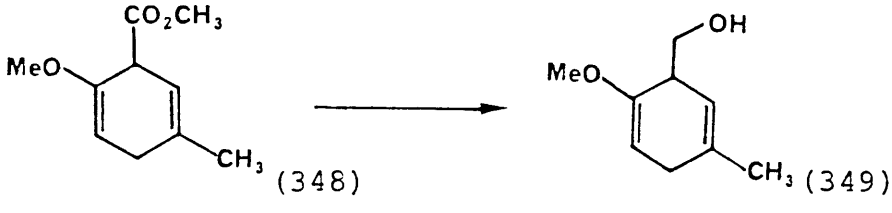
Preparation of 2-methoxycarbonyl-1-methoxy-4-methyl-3,6-cyclohexadiene (348)



Acid(346)(1.66g,10.00mmol) was dissolved in dry THF(15ml) and added to anhydrous ammonia(50ml) with stirring. Sodium metal(0.72g, 31.30mmol) cut into approximately 20 pieces was added and the resulting blue solution stirred for 5 min. Methanol (15ml) was cautiously added and the ammonia then allowed to evaporate. The residue was taken up in distilled water (50ml) and carefully acidified with 1.0M hydrochloric acid to pH4. The aqueous phase was extracted with $CHCl_3$(6x40ml) and the combined organic phase dried. Removal of the solvent gave a brown oil which was

redissolved in Et_2O (100ml). Diazomethane was bubbled through the ethereal solution until TLC indicated that the reaction had gone to completion. The solvent was evaporated under reduced pressure and the residue chromatographed(10%Et_2O-40-60^{0}petrol) to give 2-methoxycarbonyl-1-methoxy-4-methyl-3,6-cyclohexadiene (348)(0.430g,36%) as a colourless oil, $\nu_{max.}$(film)3000, 2953, 2911, 1741, 1697, 1434, 1306, 1262, 1217, 1161 and 1020cm^{-1}; δ_H (250MHz;$CDCl_3$) 1.73(3H,s,*Me*), 2.66(1H,td,J=21.1,4.6Hz, *H-5*), 2.85(1H,brd,J=21.1Hz,*H-5*), 3.56(3H,s,O*Me*), 3.70(3H, s,CO_2*Me*), 3.88(1H,d,J=1.0Hz,*H-2*), 4.82(1H,t,J=4.6Hz,*H-6*) 5.35(1H,m,*H-4*); *M/Z*=182 (M^+).

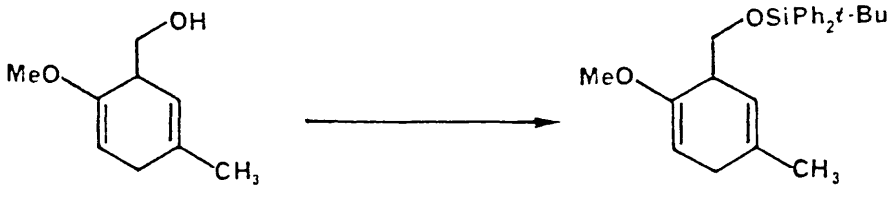
Preparation of 2-Hydroxymethyl-1-methoxy-4-methyl-3,6-cyclohexadiene (349)



To a stirred solution of the methyl ester (348)(0.380g, 2.08mmol) in Et_2O (15ml) was added $LiAlH_4$(0.040g,1.04mmol). The solution was stirred under argon until tlc indicated the complete consumtion of the starting methyl ester. EtOAc (5ml) was added dropwise followed by saturated Na_2SO_4 solution (10ml). After stirring for a further 20min the granular suspension was filtered and the remaining residue washed with Et_2O (4x30ml). The combined organic extracts were washed with brine and dried. The solvent was evaporated under reduced pressure and the residue chromatographed (40% Et_2O -- 40-60^{0}petrol) to give *2-hydroxy-methyl-1-methoxy-4-methyl-3,6-cyclohexadiene (349)* (0.316g,98%) as a colourless oil, $\nu_{max.}$ 3394, 2934, 2879, 1664, 1500, 1449, 1247, 1213, 1174, 1045,

and 790 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.69 (3H,s,*Me*),2.70 (2H,br m,*H-5*), 2.92 (1H,br s,O*H*), 3.56 (2H,m,C*H*O),3.59 (3H,s,O*Me*), 4.72 (1H,t,J=3.7 Hz),*H-6*), 5.22 (1H,m,*H-3*) ;*m/z* = 154 (M^+) (Found : C, 70.20 ; H, 9.20 %. $C_9H_{14}O_2$ requires C, 70.10 ; H, 9.15 %).

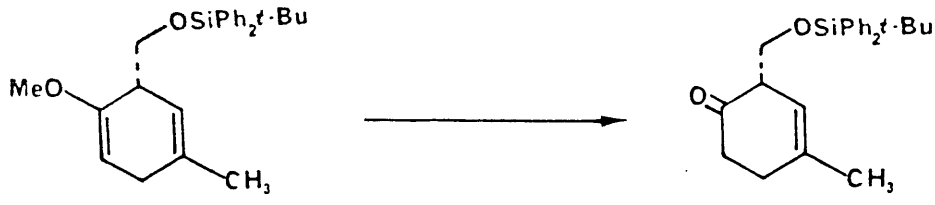
Preparation of 2-*tert*-Butyldiphenylsilyloxymethyl-1-methoxy-4-methyl-3,6-cyclohexadiene (350).



(349) (350)

TO a stirred solution of the alcohol (349) (1.40g,9.08mmol) in CH_2Cl_2 (40ml) under argon at 0°C was added TBDPS-Cl (2.74 g, 10mmol) and DMAP (0.061g, 0.5mmol). The solution was warmed to rt and stirred for 12h. The mixture was poured into Et_2O (100ml) and washed with water (2 x 50ml) followed by brine (60ml). THe organic phase was dried, the solvent evaporated under reduced pressure and the residue chromatographed (5% Et_2O - 40-60°petrol) to give *2-tert-butyldiphenylsilyloxymethyl-1-methoxy-4-methyl-3,6-cyclohexadiene (350)* (3.28g, 92%) as a colourless oil, $\nu_{max.}$ (film) 3070, 2931, 2857, 1663, 1589, 1468, 1427, 1213, 1174, 1112, 1011, 910, 823, and 738 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.06 (9H,s,^tBu), 1.78 (3H,s,*Me*), 2.72 (2H,br m,*H-5*),2.96 (1H,br s,*H-2*), 3.52 (3H,s,O*Me*), 3.82 (2H,m,C*H*O), 4.73 (1H,m,*H-6*),5.22 (1H,br s,*H-3*), 7.40 - 7.69 (10H,m,*Ph*) ; *m/z* = 335 ($M^+-{}^tBu$) (Found : C,76.26 ; H, 8.47 %. $C_{25}H_{32}O_2Si$ requires C, 76.48 ; H, 8.21%).

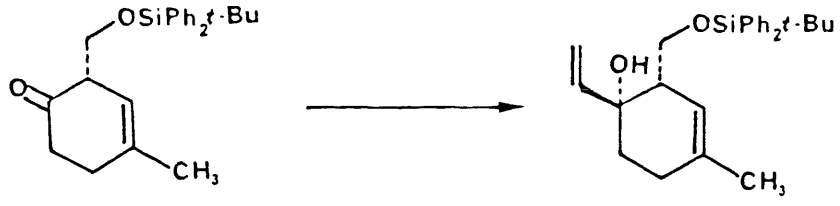
Preparation fo 2-*tert*-Butyldiphenylsilyloxymethyl-4-methyl-cyclohex-3-enone (345).



(350) (345)

To a slurry of silica gel (5.0 g) in CH_2Cl_2 (10ml) was added 5% H_2SO_4 solution (270mg). THe mixture was stirred for 20min during which time the acid solution became absorbed onto the surface of the silica. A solution of the enol ether (350) (0.392g, 1.00 mmol) in CH_2Cl_2 (3ml) was added and the slurry stirred at rt overnight. The mixture was filtered, the filtrate evaporated under reduced pressure and the residue chromatographed (15% Et_2O - 40-60^0 petrol) to give *2-tert-butyldiphenylsilyloxymethyl-4-methylcyclohex-3-en-1-one (345)* (0.362g, 96%) as a white solid, m.p. 41.5-43.0^{o}C, $\nu_{max.}$ (CH_2Cl_2) 3070, 2930, 2860, 1713, 1589, 1427, 1190, 1112, 823, and 740 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.06 (9H,s,^tBu), 1.84 (3h, s,*Me*), 2.42 (2H,m,*H-5*), 2.56 (2H,m,*H-6*),2.88 (1H,br s,*H-2*), 3.79 (1H,dd,J= 10.8, 4.3 Hz, C*H*O), 3.99 (1H,dd,J=10.8,5.2 Hz, C*H*O), 5.46 (1H,m,*H-3*), 7.40 - 7.66 (10H,m,*Ph*) ; *m/z* = 378 (M^+) (Found :C, 76.12 ; H, 8.06 %. $C_{24}H_{30}O_2Si$ requires C, 76.14 ; H, 8.06 %).

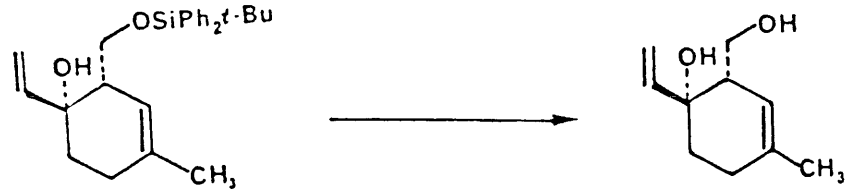
Preparation of 2α-*tert*-Butyldiphenylsilyloxymethyl-4-methyl-1β-vinylcyclohex-3-en-1α-ol (351)



(345) (351)

To a stirred solution of ketone (345) (0.250g, 0.66mmol) in Et_2O (5ml) under argon at -30°C was added vinyl magnesium bromide (3.44ml of a 1.0 M solution in Et_2O, 3.30mmol). The resulting solution was stirred at -30°C for 20min, warmed to 0°C and poured into saturated NH_4Cl solution (15ml). The aqueous phase was extracted with Et_2O (5 x 30ml), the combined organic extracts were then washed with brine (20ml), dried, and the solvent evaporated under reduced pressure. The residue was chromatographed (20% Et_2O - 40-60°petrol) to give *2α-tert-butyldiphenylsilyloxy-4-methyl-1β-vinylcyclohex-3-en-1α-ol (351)* (0.242g, 90%) as a colourless oil, $\nu_{max.}$ (film) 3353, 2927, 1638, 1428, 1377, 1113, 1070, 1026, 967, and 922 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.03 (9H,s,^tBu), 1.67 - 1.89 (2H,m,*H-6*), 1.70 (3H,s,*Me*),2.22 (2H,m,*H-5*), 3.68 (1H,dd, J= 11.0,5.0 Hz, C*H*O), 3.92 (1H,dd,J= 11.0,4.0 Hz,C*H*O),5.11 (1H,dd,J= 11.0, 1.8 Hz,*H-2'syn*), 5.14 (1H,m,*H-3*), 5.45 (1H,dd, J= 19.0, 1.8 Hz,*H-2'anti*), 5.86 (1H,dd, J=19.0, 11.0 Hz,*H-1'*), 7.32 - 7.50 (6H,m,*aromatic*), 8.60-8.72 (4H,m,*aromatic*) ; *m/z* = 396 (M^+-^tBu) (Found : C, 76.69 ; H, 8.69 % $C_{26}H_{34}O_2Si$ requires C, 76.80 ;H, 8.43 %).

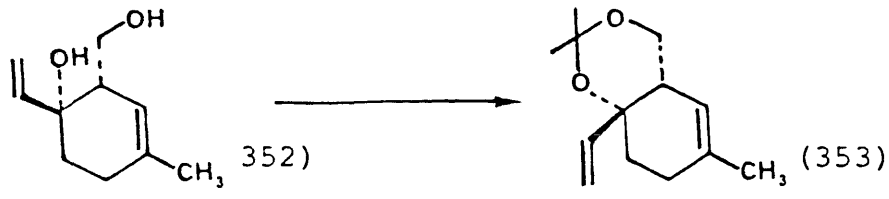
Preparation of 2 -Hydroxymethyl-4-methyl-1 -vinylcyclohex-3-en-1 -ol (352).



(351) (352)

To a stirred solution of the *tert*-butyldiphenylsilyloxy-derivative (351) (0.077g, 0.19mmol) in THF (3ml) under argon at 0°C was added TBAF (0.284ml of 1.0M solution in THF, 0.30 mmol). THe resulting solution was stirred at this temperature for 1h, poured into saturated NH_4Cl solution (5ml) and extracted with Et_2O (5 x 20ml). THe combined organic extracts were dried, evaporated under reduced pressure and the residue chromatographed (35% Et_2O - 40-60°petrol) to give *2α-hydroxymethyl-4-methyl-1β-vinylcyclohex-3-en-1α-ol (352)* as a colourless oil, $\nu_{max.}$ (film) 3353, 2927, 1638, 1428, 1377, 1113, 1070, 1026, 967, 922, and 850 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.71 (3H,s,*Me*), 1.84-2.00 (2H,m,*H-6*), 2.11-2.28 (2H,m,*H-5*), 2.56 (1H, br t,*H-2*), 3.68 (1H,m, C*H*O), 3.81 (1H,m,C*H*O), 5.13 (1H,dd, J= 11.2,2.0 Hz,*h-2'syn*), 5.25 (1H,m,*H-3*) 5.38 (1H,dd, J=17.5, 2.0 Hz,*H-2'anti*), 5.92 (1H,dd, J=17.5, 11.2Hz,*H-1'*), *m/z* = 150 (M^+-H_2O) (Found : C, 71.40 ; H, 9.73%. $C_{10}H_{16}O_2$ requires C, 71.39 ; H, 9.59 %).

Preparation of 2α-Hydroxymethyl-di-O-isopropylidene-4-methyl-1β-vinylcyclohex-3-en-1α-ol (353)



To a stirred solution of diol (352) (0.312g,1.50mmol) in 2,2-dimethoxypropane (5ml) was added CSA (0.035). The resulting solution was added CSA (0.035g). The resulting solution was stirred at rt for 72h and then poured into saturated $NaHCO_3$ solution (5ml). The solution was extracted with Et_2O (3x10ml) and the combined organic phase dried. The solvent was evaporated under reduced pressure and the residue chromatographed (5%Et_2O-40-60°petrol) to give *2α-hydroxymethyl-di-O-isopropylidine-4-methyl-1β-vinyl-cyclohex-3-en-1α-ol (353)* 0.263g, 74%) as a colourless oil, $\nu_{max.}$ (film) 3079, 2990, 2934, 1633, 1378, 1262, 1193, 1149, 1087, 998 and 872cm^{-1}; δ_H(250MHz;$CDCl_3$) 1.31 (3H,s,C*Me*), 1.30-1.40(1H,m,), 1.41(3H,s,C*Me*), 1.71(3H,s, *Me*), 1.72-1.86(2H,m), 2.02-2.20(1H,m), 2.36(1H,brS), 3.57 (1H,dd,J=12.5,4.7Hz, C*H*O), 4.04(1H,dd,J=12.5,3.1Hz,C*H*O), 5.06(1H,dd,J=18.7,1.0Hz,*H-2'anti*), 5.08(1H,dd,J=10.9,1.0Hz, *H-2'syn*), 5.21(1H,q,J=0.5Hz,H-3), 6.02(1H,dd,J=18.7,10.9Hz, *H-1'*); *M/z*=208(M^+) (Found:C,74.76; H,9.84%. $C_{13}H_{20}O_8$ requires C,74.96;H,9.68%).

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