UNIVERSITY OF SOUTHAMPTON

SYNTHETIC APPROACHES TOWARDS THE SYNTHESIS OF THE MILBEMYCIN AND AVERMECTIN FAMILY OF ANTIBIOTICS

A Thesis submitted for the degree of

Master of Philosophy

by

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Department of Chemistry

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With love to my family

"They (the pioneers who travelled from the east coast to the west coast of America) set off with great expectations, high hopes and such determination and optimism and in the end they were just pleased to get there."

(N. Rees, Quote, Unquote,
Radio 4, 1985)

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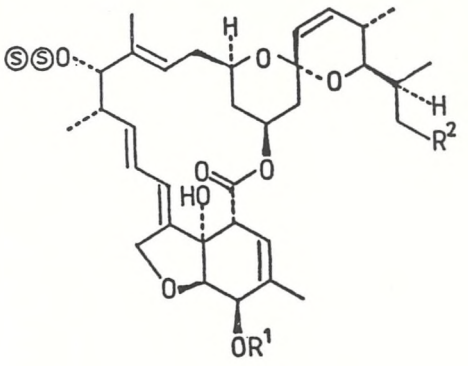
Note to the reader

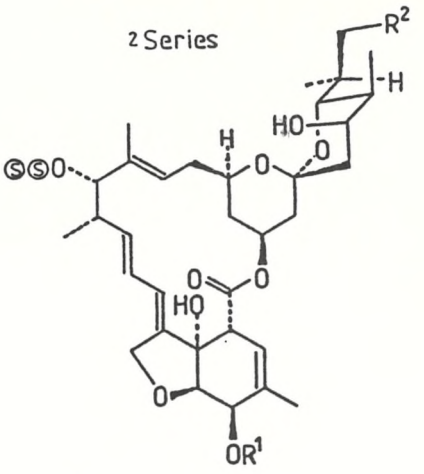
A pullout page is provided at the front of this thesis to enable the reader to refer to the main milbemycin/avermectin structures.

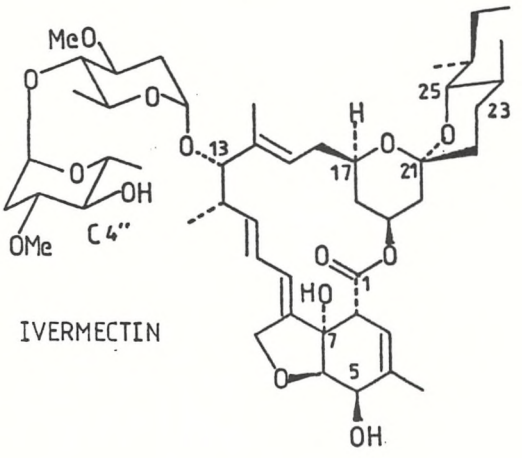
AVERMECTINS

1 Series



2 Series



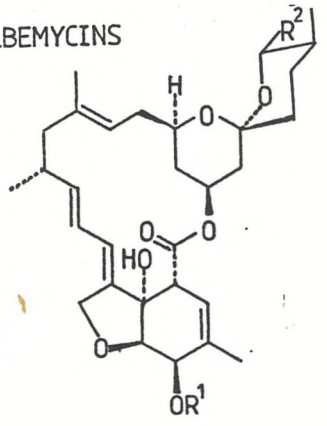


IVERMECTIN

Ⓢ Ⓢ = oleandrosyl – oleandrosyl

A Series	R^1 = Me
B Series	R^1 = H
a component	R^2 = Me
b component	R^2 = H

MILBEMYCINS

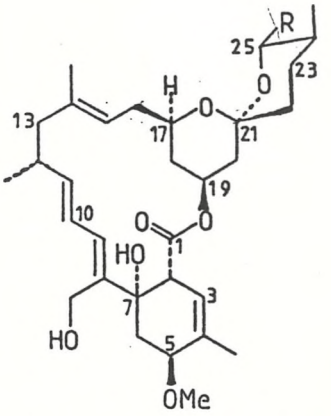


EXOCYCLIC ACETAL RING

ENDOCYCLIC ACETAL RING

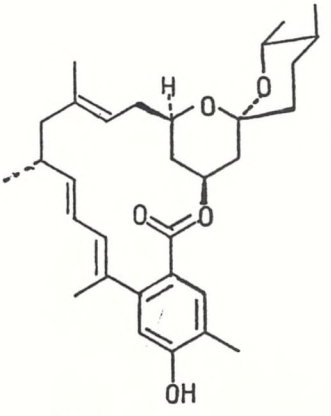
SOUTHERN HEMISPHERE

		R^1	R^2
Milbemycin	α1	H	Me
	α4	Me	Et
	D	H	^{i}Pr



Milbemycin β1 (1) R=Me

Milbemycin β2 R=Et



Milbemycin β3

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

SYNTHETIC APPROACHES TOWARDS THE SYNTHESIS OF THE MILBEMYCIN AND AVERMECTIN FAMILY OF ANTIBIOTICS

by David Mark Perryman Broom

A study directed towards the total synthesis of the simplest member of the milbemycin/avermectin family of antibiotics, milbemycin β_3 is described. The approach to the spiroacetal fragment of milbemycin β_3 involved the coupling of a lithium anion of 2R,3S-20-tetrahydropyranyl-3-methyl-pent-4-yn-2-ol with a protected form of 4S,6S-4-hydroxy-6-methanol-tetrahydropyran-2-one.

The synthesis of two such lactones, 4S,6S-4-hydroxy-40-(1'tert butyl-1',1'-diphenyl-silyl)-6-(1'0-phenyl methyl)methanol-tetrahydropyran-2-one and 4S,6S-4-hydroxy-40-(phenyl methyl)-6-(1'0-phenyl methyl)-methanol-tetrahydropyran-2-one from 1,6-anhydro-β,D-gluco pyranose(levoglucosan) is described. The application of the dibenzyl lactone to the construction of the milbemycin/avermectin family of antibiotics is shown by the synthesis of 2S,4S,6S,8S,9R-2-methanol-4-hydroxy-8,9-dimethyl-1,7 dioxaspiro-(5,5)-undecane,a key intermediate required for a proposed synthesis of milbemycin β_3.

The reaction of two organometallic reagents derived from ethyl-2-bromomethyl-prop-2-enoic acid with phenyl oxirane to form α-methylene-δ-lactones was attempted. It was found that the treatment of phenyl oxirane with π-2-carboethoxy-allyl zinc bromide afforded ±-3-methylene-5-(phenyl methyl)dihydrofuran-2-one and not the isomeric α-methylene-δ-lactone.

CONTENTS

Synthetic approaches towards the synthesis of the Milbemycin and Avermectin antibiotics

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ABBREVIATIONS

Ac = Acetate

AIBN = Azobis *iso* butyro nitrile

Al_2O_3 = Alumina

All = Allyl (1-prop-2-enyl)

aq = aqueous

atm = atmosphere

9-BBN = 9-Borabicyclo(3.3.1)nonane

B_n = Benzyl

B_u = Butyl

B_z = Benzoyl

cat = Catalytic

ci = Chemical ionization

COD = Cyclo-octa-1,5-diene

Cp = Cyclo pentadiene

CSA = Camphorsulphonic acid

DBU = 1,8-Diazabicyclo (5.4.0)undec-7-ene

DCM = Dichloromethane

DET = Diethyltartrate

DHP = 2,3-Dihydropyran

DIBAL = Di *iso* butyl aluminium hydride

DMAP = N,N-Dimethyl-4-aminopyridine

DME = 1,2-Dimethoxyethane

DMF = N,N-Dimethylformamide

DMS = Dimethyl sulphide

DMSO = Dimethyl sulphoxide

ei = electron ionization

Et = Ethyl

gc = gas chromatography

glycol = ethylene glycol

HMPA = Hexamethylphosphoramide

HPLC = High performance liquid chromatography

hrs = hours

i = *iso*

LDA = Lithium di *iso* propyl amide

mCPBA = *meta*-Chloroperoxybenzoic acid

Me = Methyl

Mes = Methanesulphonate

mins = minutes

MOM = Methoxymethyl

OVNT - overnight

PCC = Pyridinium chlorochromate

PL = Phenyl

PPTS = Pyridinium *para* toluene sulphonic acid

Pn = Propyl

Pth = Phthalide

PTSA = *para* Toluene sulphonic acid

py = pyridine

RT = Room temperature

s = *sec*

t = *tert*

TBDMS = *tert* Butyl dimethyl silyl

TBDPS = *tert* Butyl diphenyl silyl

TCE = Trichloroethyl

Tf = Trifluoro methane sulphonate

TFA = Trifluoro acetic acid

THF = Tetrahydro furan

THP = Tetrahydropyranyl

TLC = Thin layer chromatography

TMS = Trimethylsilyl

Tris = 2,4,6-Tri *iso* propyl benzene sulphonate

Ts = 4-ethyl benzene sulphonate

VFP = Vaccum flash pyrolysis

Δ = reflux

Synthetic approaches towards the synthesis of the Milbemycin and Avermectin family of antibiotics

INTRODUCTION

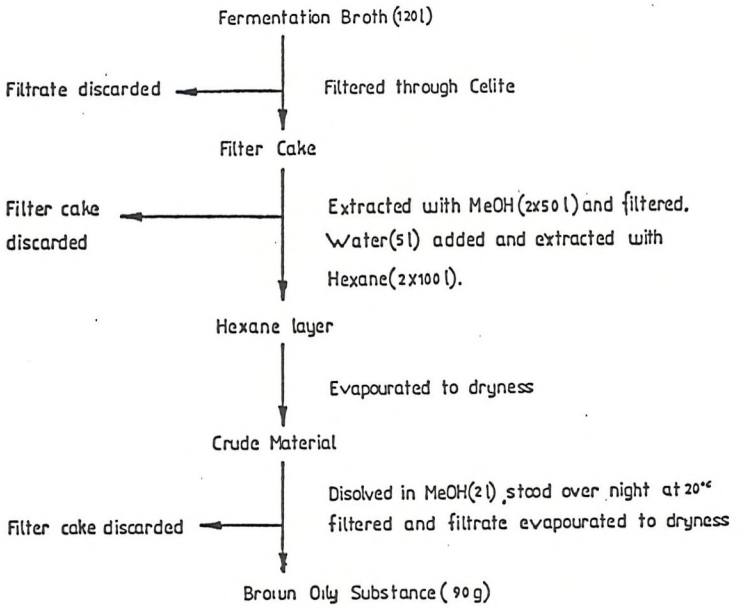
A definition of the word parasite is one frequenting the tables of the rich and repaying with flattery. This could be construed to include all the known infectious diseases. The human health aspect of parasitology has been a major problem in the Third World; causing malnutriton, blindness, debility, disfiguration and eventually death. However parasites in these cases do not exactly flatter the host nor do they frequent the tables of the rich.

Many thousands of natural products of diverse chemical structure and exhibiting a wide spectrum of biological properties have been isolated from fermentation broths. Anthelmintic activity however is only shown by a few, namely, aspiculemycin[1], aureothin[2], orthosomycin[3], tetranactin[4] and the milbemycins[5] and avermectins[6]. It is this type of activity, which if exploited, offers a potential solution to the problems associated with parasites.

Isolation and Structure Determination of the milbemycin/avermectin family

In 1974 a screening program at Sankyo Co, Japan highlighted the insecticidal and acaricidal properties of a crude extract from a *Streptomyces* species[7]. From this culture broth, thirteen compounds were isolated and purified as shown in Figure 1. Further investigation[8] indicated the presence of a class of complex 16 membered macrocyclic lactones. These compounds were called the milbemycins and could be divided into two groups, the members of the α series (1 to 10) contained a tetrahydrofuran ring, whilst the remaining three compounds, classified as the β group [5], did not.

From the latter group, the spectral evidence indicated the presence of a common skeleton incorporating a spiroacetal moiety, a diene unit and a cyclohexenediol or phenol. X-ray analysis of the crystalline p-bromophenyl urethane derivative of milbemycin β_1 revealed the structure 1[5]. Members of the α and β series are shown (Figures 2 and 3) and it can be seen that there are two main areas of structural variance in the milbemycins. The first arises in the Southern Hemisphere and the other appears in the exocyclic acetal ring.



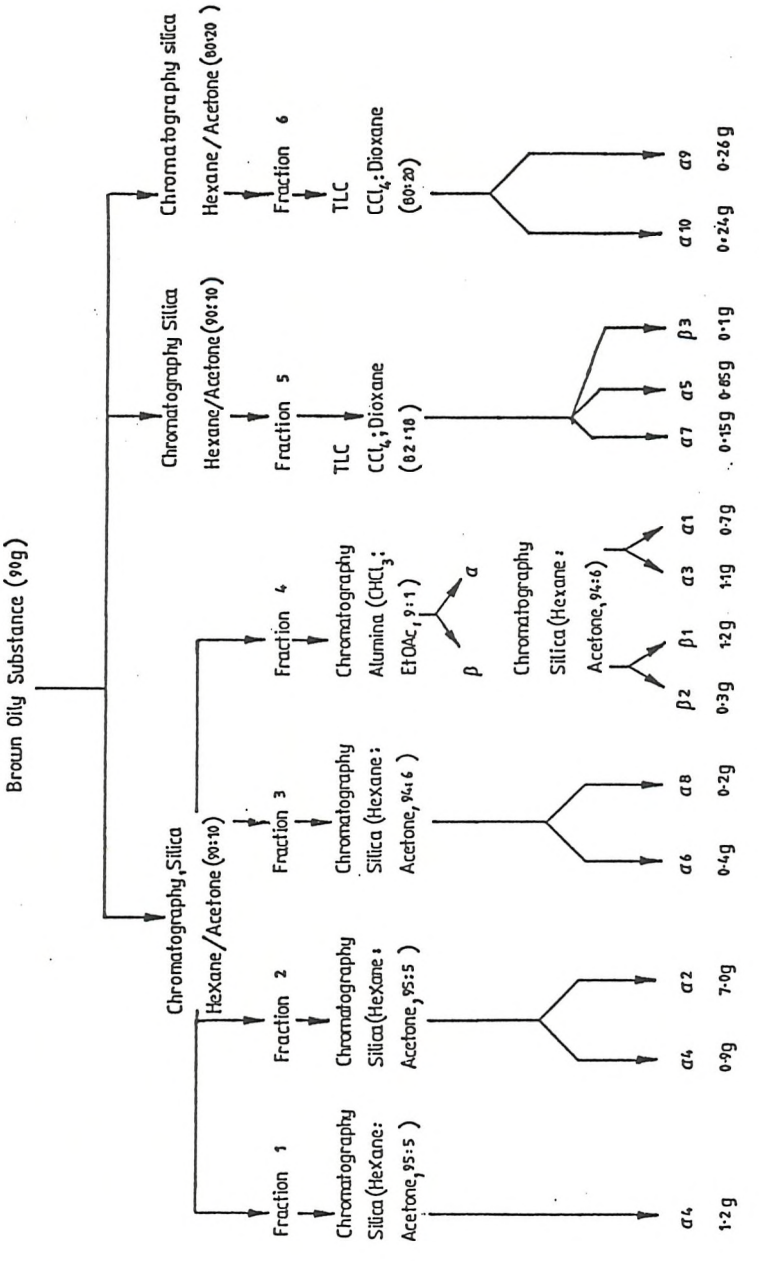
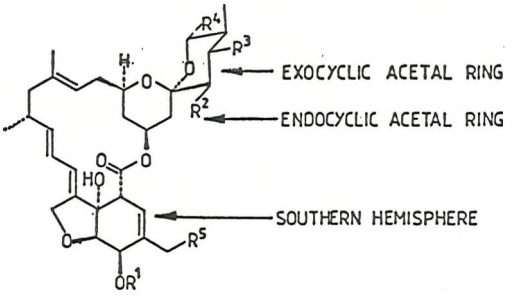


Figure 1. The isolation of the milbemycin family

Figure 2. The structure of the milbemycin α series



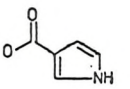
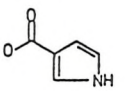
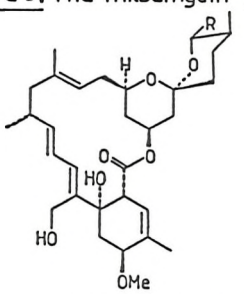
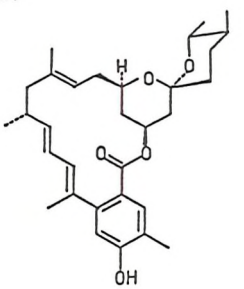
Substituent	R^1	R^2	R^3	R^4	R^5
Milbemycin					
α 1	H	H	H	Me	H
α 2	Me	H	H	Me	H
α 3	H	H	H	Et	H
α 4	Me	H	H	Et	H
α 5	H	OH	OCO(CHMe)Bu	Me	H
α 6	Me	OH	OCO(CHMe)Bu	Me	H
α 7	H	OH	OCO(CHMe)Bu	Et	H
α 8	Me	OH	OCO(CHMe)Bu	Et	H
α 9	H	H	H	Me	
α 10	H	H	H	Et	

Figure 3. The milbemycin β series.



β 1 (1) R=Me

β 2 R=Et



β 3

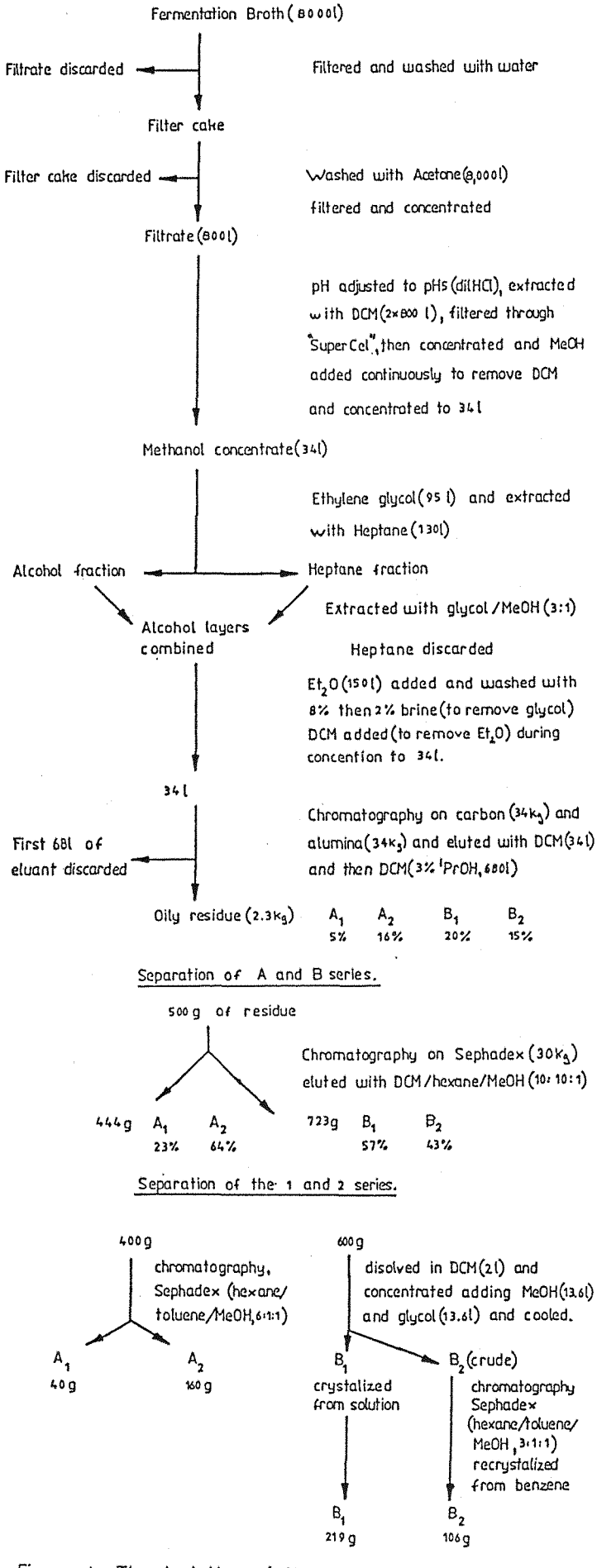
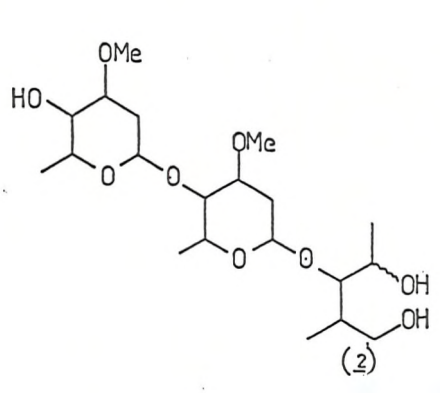
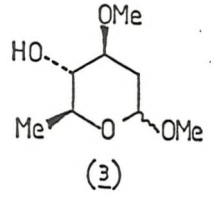


Figure 4. The isolation of the avermectin family

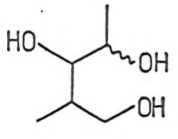
From a similar screening program at Merck, Sharpe and Dohme, the fermentation broth of an actinomycete obtained from a soil sample at Kawana, Ito City, also showed anthelmintic properties. Isolation of this bacterium[9] at the Kitsato Institute, Japan, showed that it was morphologically distinct and not a subspecies. The actinomyete was later named *Streptomyces avermitilis*. Further analysis of the fermentation broth led to the discovery of eight compounds which were named the avermectins. The isolation of the avermectins is outlined in Figure 4 and is similar to that of the milbemycins[10]. Degradation studies of these lactones showed a disaccharide residue attached to two epimeric pentane triol (2). Methanolysis of this disaccharide (2) afforded a mixture of ∝ and β - methyl oleandroside (3) and the respective triols (4). It was proposed that the glycoside residue was attached to a C13 hydroxyl groups of a milbemycin.



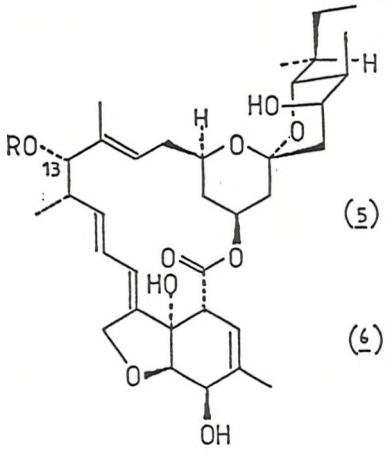
(2)



(3)

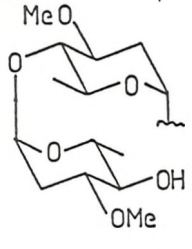


(4)



(5) R = H

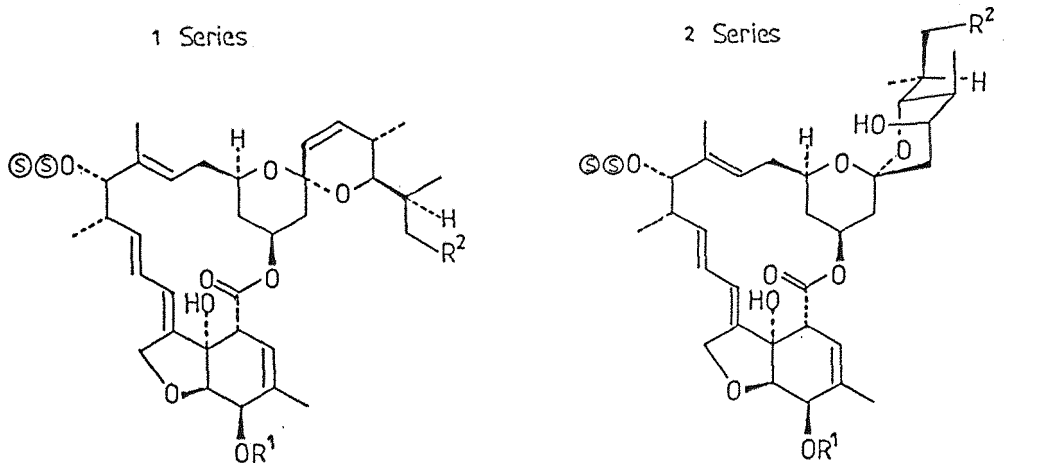
(6) R =



The rest of the gross structure was determined by high resolution mass spectrometry and NMR spectroscopy. The information that was obtained could be related to the milbemycins provided that two further structural changes were made. These were: the introduction of a C22-C23 double bond or a C23 hydroxyl substituent and secondly a *sec*-butyl or *iso*-propyl group at C25, rather than an ethyl or methyl group. The absolute stereochemistry was proved unambiguously using X-ray crystallography[12]. This was performed on the aglycon (4) and revealed the structure of avermectin B_{2a} as (6).

All eight avermectins are shown in Figure 5 and are named in the following manner:-

Capital letter	refers to the C5 substituent
	A C5 methoxy group
	B C5 hydroxyl group
Subscript number	shows the substitution in the C22-C23 region
	1 C22-C23 double bond
	2 axial C23 hydroxyl group
Subscript letter	indicates the C25 substituent
	a *sec*-butyl group
	b *iso*-propyl substituent



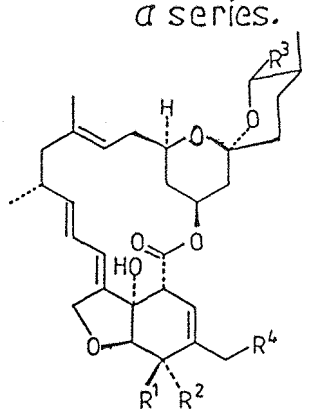
A Series R^1 = Me
B Series R^1 = H
a component R^2 = Me
b component R^2 = H

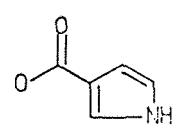
Ⓢ Ⓢ = oleandrosyl - oleandrosyl

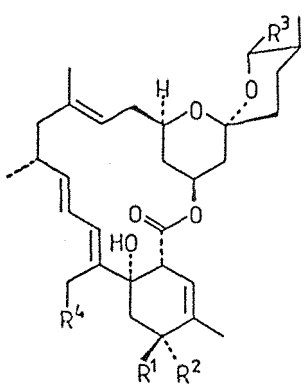
Figure 5, The structure of the avermectin family

From the fermentation broth four major components were isolated and were found to possess a *sec*-butyl group at C25 whilst the four minor homologues, which were produced in up to 20% of the broth, were shown to contain a C25 *iso*-propyl group. The development of a more efficient strain of milbemycin producing bacteria was achieved by mutation of the latter named *Streptomyces hygroscopicous* subsp. *aureolaccrimosaus* using UV irradiation[13]. To date, these mutants have produced seven new milbemycins[14], of which five possess an *iso*-propyl group at C25 and not the customary ethyl or methyl substituent. Three of the milbemycins (H, J and K) contain a ketone group at C5 instead of the normal hydroxy or methoxy moiety of the α or β series. The relationship between the new milbemycins and the α and β series are shown (Figures 6 and 7).

Figure 6. Comparison of the new milbemycins with the α series.



Milbemycin	R^1	R^2	R^3	R^4
α 1	OH	H	Me	H
D	OH	H	^{i}Pr	H
F	OH	H	^{i}Pr	
G	OMe	H	^{i}Pr	H
J	=O		^{i}Pr	H
K	=O		Et	H



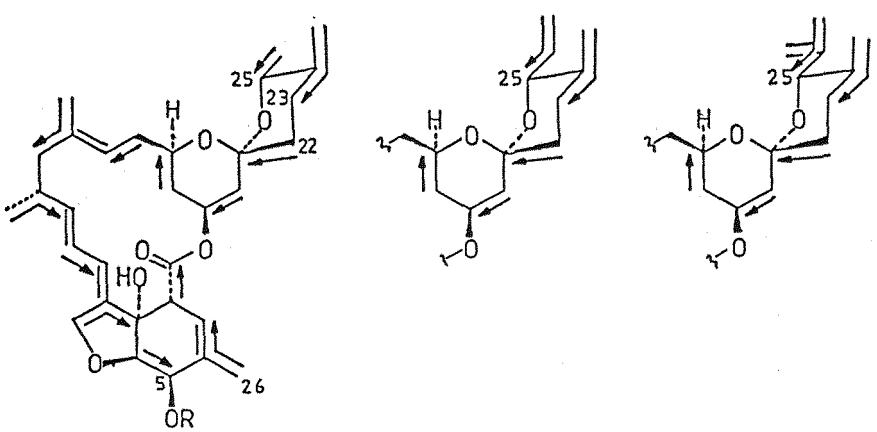
Milbemycin	R^1	R^2	R^3	R^4
β 1	OMe	H	Me	OH
E	OMe	H	^{i}Pr	OH
H	=O		^{i}Pr	H

Figure 7. Comparison of the new milbemycins with the β series.

Biosynthesis of milbemycins and avermectins

The biosynthetic origins of the carbon atoms of the milbemycin skeleton have been determined by the use of ^{13}C labelled precursors and ^{13}C NMR spectroscopy[15]. With the exception of the C25 substituent, seven acetates and five propionate units are incorporated as shown in Figure 8.

Polyketide biosynthesis starts at C25 and in milbemycin α_2(7) and α_4(8) this carbon is supplied by acetate and propionate respectively. However, in milbemycin D (9), carbon 25 showed significant incorporation with both labelled (1-^{13}C)-*iso*-butyrate and DL-(2-^{13}C)-valine(10). It has been suggested that DL-valine is first metabolized into *iso*-butyryl-CoA which is then incorporated into the C25 position. It was shown that the methyl group of the C5 methoxy moiety of milbemycin α_2(7) was derived from L-(methyl-^{13}C)-methionine.



(7) α2 R=Me (8) α4 R=Me (9) D R=H

⟶ ≡ H_3C-CO_2H ⟿ ≡ $H_2C(CH_3)-CO_2H$

Figure 8 ,The biosynthesis of milbemycin α2, α4 and D

In another study, Albers-Schönberg and co-workers[16] investigated the biosynthetic origins of the carbon atoms of the avermectins using the same techniques. The labelled carbon skeleton revealed the same pattern of incorporation as the milbemycins (Figure 9). The authors suggested in a footnote that the C25 substituents were derived from the amino acids L-isoleucine (11) and L-valine (12) but no evidence was given to substantiate this supposition. In later work[17] they proposed that the C25 *sec*-butyl group originated from L-methylbutyric acid which in turn was obtained from L-isoleucine. Similarly the C25

iso-propyl group could have originated from L-valine (12), however there was no indication whether (1-^{13}C)labelled *iso*-butyrate was incorporated.

In the same report[16], the origins of the oxygen atoms were probed using specifically labelled precursors and the results obtained were shown in Figure 9, of particular note is the retention of the C17-oxygen bond and the cleavage of the C21 oxygen bond. This implies that the formation of the spiroacetal occurs by attack of the C17 and C25 hydroxyl groups on the C21 carbonyl with the subsequent loss of the C21 oxygen label. This simple process is not generally applicable to the biosynthetic formation of spiroacetals[18]. Also of note is the retention of the C23 bond which indicates that avermectin 2 series is not obtained from the 1 series *via* hydration of the C22-C23 double bond of the 2 series (Figure 9).

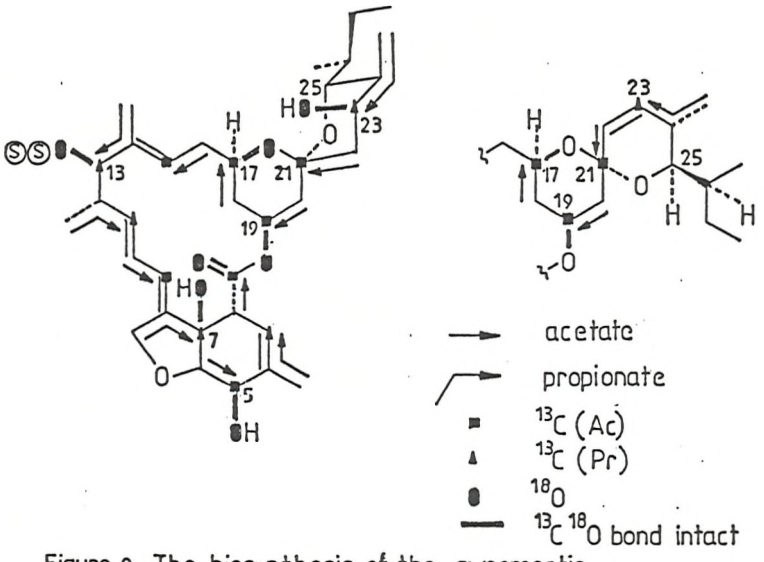


Figure 9, The biosynthesis of the avermectin 1 and 2 series.

There are two further points of interest, firstly the C13 hydroxyl bond is intact. This rules out the possibility that the avermectins are derived from the milbemycins by oxidation at an advanced stage in the biosynthetic sequence. It does not eliminate the possibility of a common precursor. Secondly, the fact that the C7 hydroxyl bond has remained intact, eliminates a complex mechanism of formation. It does not leave the possibility that a simple aldol process may be responsible for the formation of the complex cyclohexene ring of the southern hemisphere.

Within the milbemycin/avermectin family, the formation of the tetrahydrofuran ring poses an interesting biosynthetic problem. Perhaps this formation is a two step process, with milbemycin β_1 or β_2 as biosynthetic intermediates on the pathway to the α series. To test this naive hypothesis, the origin of the ring oxygen needs to be determined in both the α series and the corresponding member of the β series. Also of interest are the origins of the oxygen atoms of the highly functionalized milbemycins such as α_5 and α_9 which are oxygenated at the C22-C23 and C26 positions respectively.

Semisynthetic Analogues of avermectins

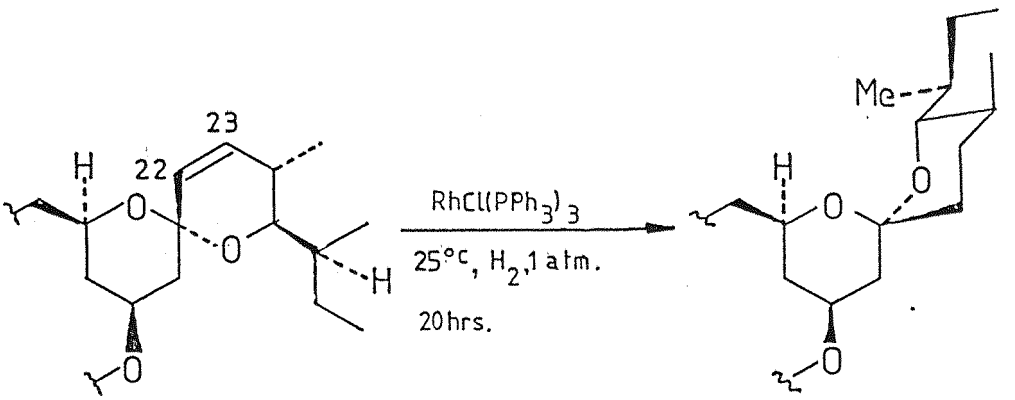
Before discussion the activity of the avermectins and related compounds, the chemistry which has been developed to produce these analogues must first be mentioned. The avermectins have been altered in three distinct ways; by the modification of the spiroacetal ring, the derivatization of the alcohol groups and the removal of the disaccharide moiety.

1. Modification of the spiroacetal ring

The difference between the avermectin 1 and 2 series is found in the different substitution of the *exo* spiroacetal ring; therefore changes in the conformation of the spiroacetal moiety can cause subtle changes in activity. One way in which the conformation can be altered is by the removal of the *cis* C22-C23 double bond. In order to perform this transformation, the catalyst must be able to differentiate between the other four centres of unsaturation in the molecule. Wilkinson's catalyst, known to be very sensitive to both the environment and degree of substitution of the olefin, was the reagent chosen[19]. As a general rule, in the reactions shown below, the starting avermectin is contaminated with up to 20% of the minor C25 isopropyl analogue but for convenience this material is not shown.

The reduction of the avermectins A, was carried out in benzene under one atmosphere of hydrogen to provide C22-C23 saturated derivative (19) in excellent yield. Similarly, reduction of avermectin B_1 afforded 22,23-dihydro-avermectin B_1 (20) (later named Ivermectin), though this material was contaminated with 3% of 3,4,22,23-tetrahydro-avermectin B_1 (Scheme 1).

There has been limited evidence[20] for the acid catalysed addition of hydrogen chloride and butanethiol to the C22-C23 double bond of avermectin B_1. The acid catalysed methanolysis of avermectin B_1 will be discussed later.

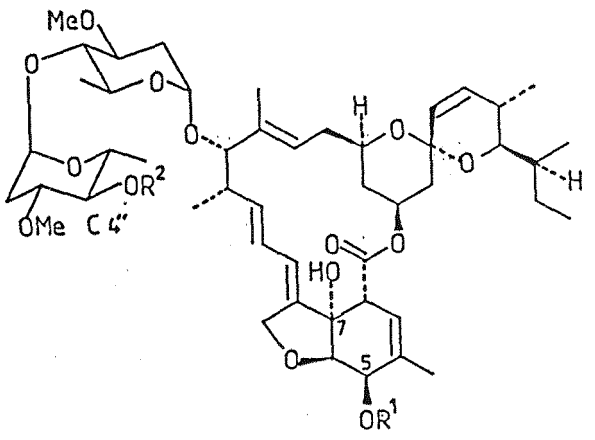


Avermectin	Solvent	Product	Yield/%
A_1	benzene	22,23dihydro-A_1(19)	92
B_1	toluene	22,23dihydro-B_1 [Ivermectin,(20)]	85

Scheme 1

2. Derivatization of the alcohol groups

The avermectins possess four hydroxyl groups which could be derivatized and the order of reactivity which may be deduced is 5 ⩾ 4" ⩾ 23 >> 7 depending on the number of alcohol groups available for protection and the steric demands of the protecting group. The tertiary C7 alcohol group appears to be inert towards mild acetylation procedures and if more severe conditions are employed, aromatization of the highly oxygenated C2-C7 cyclohexene ring is observed[21]. In the case of avermectin B_{1a}, which has three alcohol groups, Mrozik *et al* [22] have shown that the use of the bulky protecting group 1-*tert*butyl-1, 1-dimethyl-1-chlorosilane (TBDMS chloride), afforded the C5 silylether (21) as the major product in 70% yield. Acylation of this intermediate (21) and subsequent deprotection afforded a range of C4"-acyl-compounds e.g. (22) (Scheme 2).



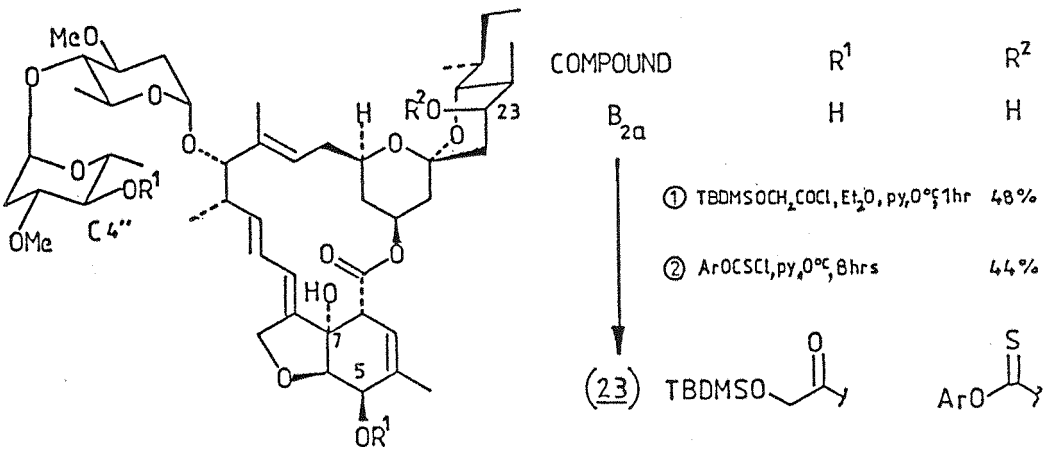
COMPOUND	R^1	R^2	
B_{1a}	H	H	
	TBDMSCl, DMF, imadazole.		70%
(21)	TBDMS	H	
	① DMAP, DCM, ^tBuCOCl, $^iPrNEt_3$ ② 1% PTSA, MeOH		
(22)	H	^tBuCO	

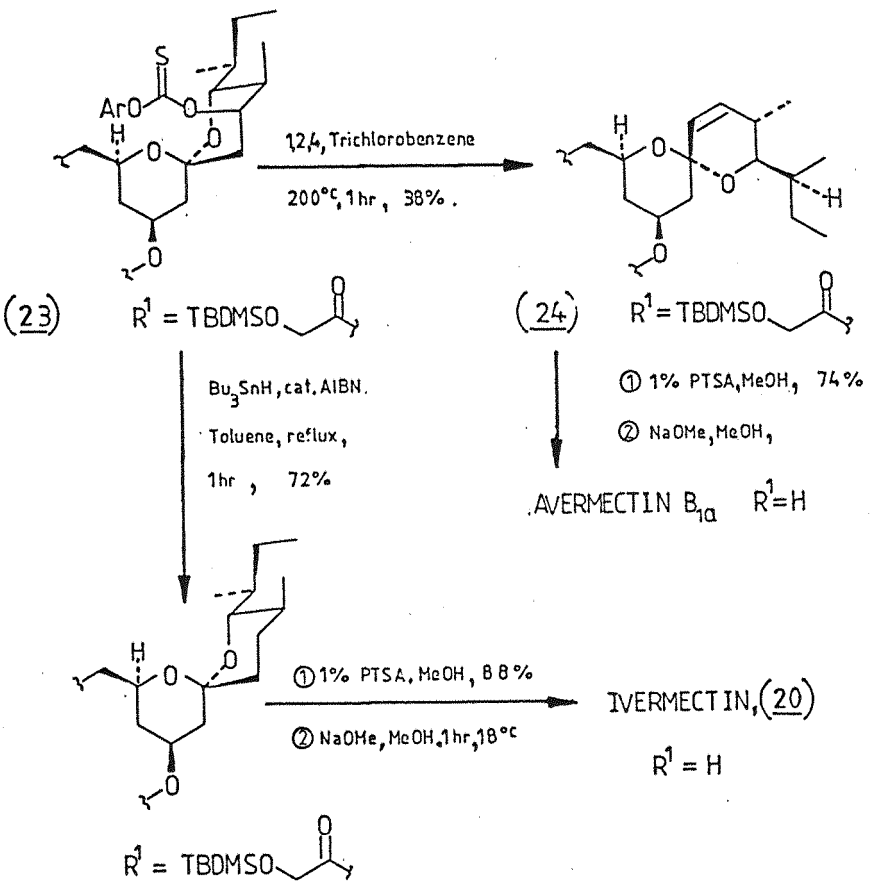
Scheme 2

This order of reactivity has been exploited to protect the more reactive C5 and C4" functions of avermectin B_{2a}. Sequential treatment of avermectin B_{2a} with 2-(butyl-dimethyl, silyloxy)-acetyl chloride and tolyl thiochloroformate gave the thiocarbonate(23).

This intermediate has been used[23] in the synthesis of avermectin B_{1a} and Ivermectin.

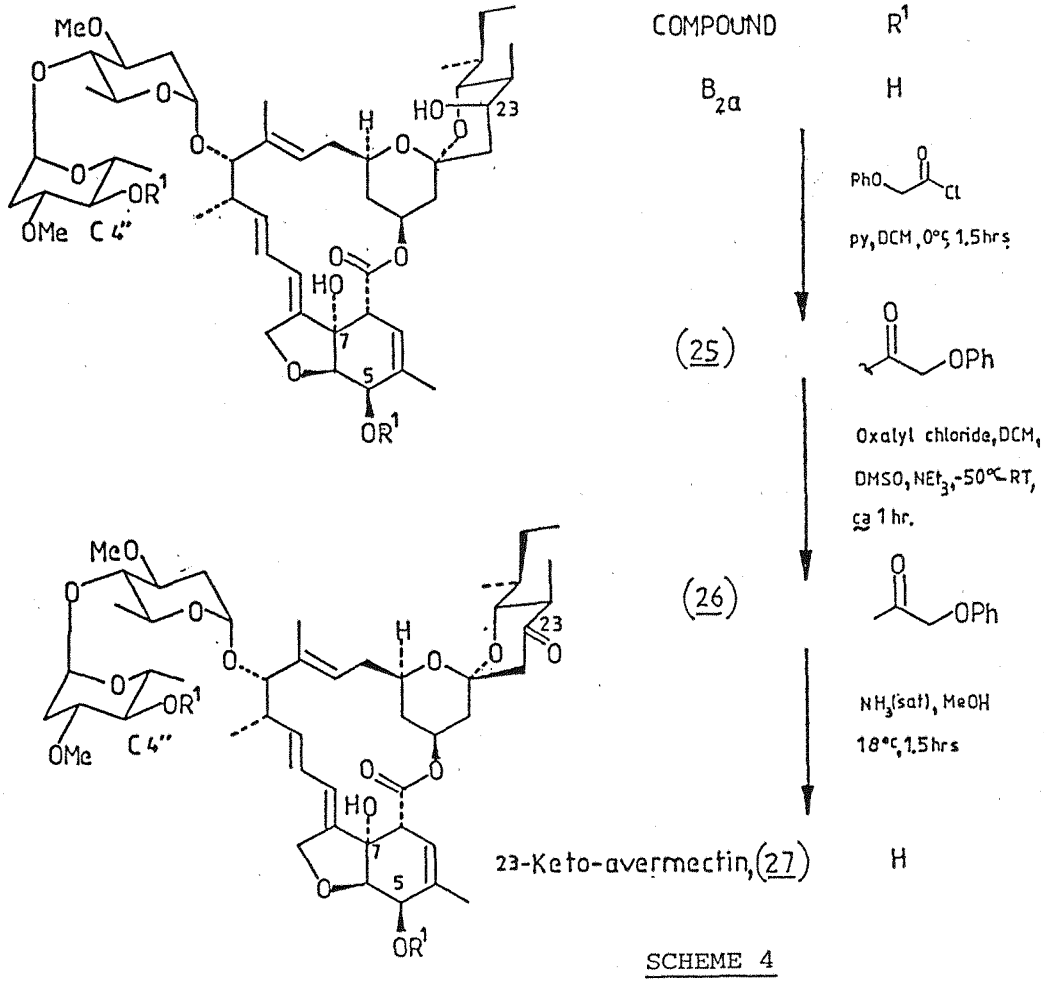
Pyrolysis of the thiocarbonate (23) gave the olefin (24) in 38% yield and deprotection gave avermectin B_{1a}. Reduction of the intermediate (23) with tributyltin hydride in 72% yield and after the two step removal of the protecting group completed the conversion of avermectin B_{2a} into Ivermectin (20) (Scheme 3).


MeO
OMe
C 4"
OR¹
R²O
H
HO
23
7
5
OR¹
COMPOUND
R¹
R²
B2a
H
H
① TBDMSOCH2COCl, Et2O, py, 0°C, 1hr 48%
② ArOCSCl, py, 0°C, 8hrs 44%
(23) TBDMSO
ArO


ArO
H
1,2,4, Trichlorobenzene
200°C, 1hr, 38%.
(23) R¹ = TBDMSO
(24) R¹ = TBDMSO
Bu3SnH, cat. AIBN.
Toluene, reflux,
1hr, 72%
① 1% PTSA, MeOH, 74%
② NaOMe, MeOH,
AVERMECTIN B1a R¹=H
① 1% PTSA, MeOH, 88%
② NaOMe, MeOH, 1hr, 18°C
IVERMECTIN, (20)
R¹ = H
R¹ = TBDMSO
Ar = 4 (Methyl) phenyl

Scheme 3

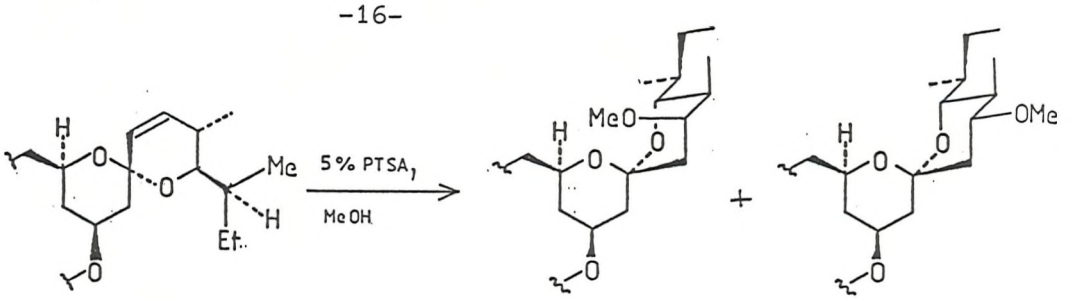
A similar protection sequence has been used[24] in the synthesis of 23 keto avermectin B_2. Thus avermectin B_2 was converted to the alcohol (25) which was then oxidized under Swern conditions to provide the C23 ketone (26). Removal of the phenoxyacetyl protecting group of (26) using a saturated solution of ammonia in methanol gave the 23-keto avermectin B_2 (27) in an unspecified yield (Scheme 4).



SCHEME 4

3. Removal of the disaccharide moiety

In degradation studies[11] directed towards the structure elucidation of the avermectin A series[12], the disaccharide linkages were cleaved under acidic conditions (Table 1). Using methanol as solvent[11,20], the aglycon (28) was obtained[11,20], however with isopropanol[20] only the monosaccharide (29) was obtained[20]. Treatment of avermectin B_1[20] with similar methanolysis conditions led to addition of methanol to the spiroacetal double bond as well as the removal of the sugar linkages. This process was not stereoselective and afforded an epimeric mixture of ethers (30) and (31). The use of aqueous acidic conditions on avermectin B_1 afforded a mixture of the aglycon (32) and the monosaccharide (33).



(30) (31)

Avermectin	Conditions	Products	Yield or Ratio
A_{2a}	1 % H_2SO_4, MeOH, 10hrs.	AG A_{2a} (28)	57 %
A_{2a}	1% H_2SO_4, ^{i}PrOH, 24hrs, 18°c	MS A_{2a} (29)	89 %
B_{1a}	5% PTSA, MeOH, 24hrs, 18°c	AG B_{1a}	1
		AG (30)	5
		AG (31)	4
B_{1a}	10% H_2SO_4, 50% aq. THF.	AG B_{1a} (32)	50%
		MS B_{1a} (33)	25%

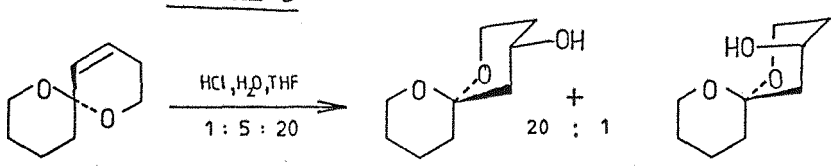
AG is the avermectin with both oleandrosyl sugar units removed

MS is the avermectin with one oleandrosyl unit still attached at carbon 13

Table 1, The treatment of various avermectins under acidic conditions.

Surprisingly no addition of water was observed to the 22-23 double bond, since the addition of water to ∝, β unsaturated spiroacetals has been reported[25] and used in the synthesis of Talaromycin B[26] (Scheme 5). Recently two synthesis of the disaccharide oleandrosyl-oleandrosyl have appeared[27,28] and the crucial coupling of this unit to an avermectin aglycon has also been developed[28].

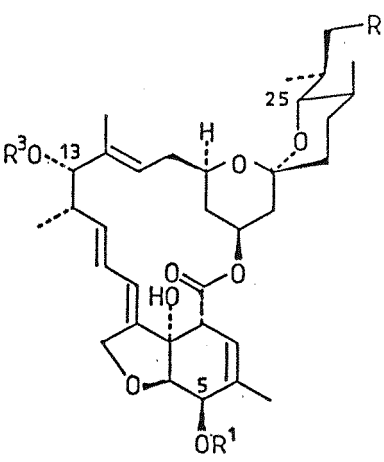
SCHEME 5



Scheme 5

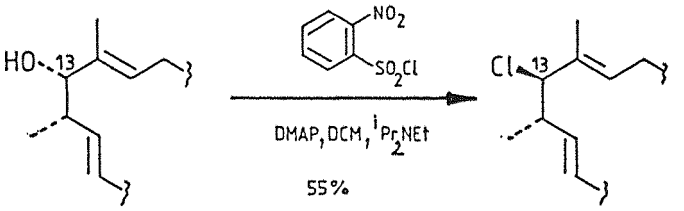
Interest in the insecticidal properties of the avermectin/ milbemycin family has prompted workers at Merck to study the conversion of avermectin B_1 into the less accessible milbemycin ∝ series. This synthesis[29] incorporated all three main structural modifications previously mentioned. The disaccharide moiety of Ivermectin *(20) was removed by methanolysis and afforded a 76% yield of the aglycon (34) which formally required deoxygenation at C13 to complete the synthesis of a milbemycin. Selective protection of the C5 alcohol group with TBDMS chloride afforded the readily separable analogues (35) and (36) in 75% yield. It was found that the mesyl or tosyl derivatives of the C13 alcohol group of (35) could not be used in the preparation of the chloride (37). However the use of excess O-nitro-benzene sulphonyl chloride and diisopropylethylamine the chloride (37) was obtained directly (55%) *via* the O-nitro benzene sulphonate. Reduction of the allylic chloride (37) with tributyltin hydride afforded an 88% yield of an isomeric mixture of olefins (38) and (39). After removal of the silyl protecting group, a 9:1 mixture of the C25 *sec*-butyl analogue of milbemycin $∝_1$ (40) and the C13-C14 double bond isomer (41) was isolated. This mixture was separated by reverse phase HPLC (Scheme 6). In an analogous manner, the silyl ether (36) was converted into the then recently isolated milbemycin D(9).

*contains up to 20% of the C25 minor isoproyl analogue, 22,23-dihydro-avermectin B_{1b}.



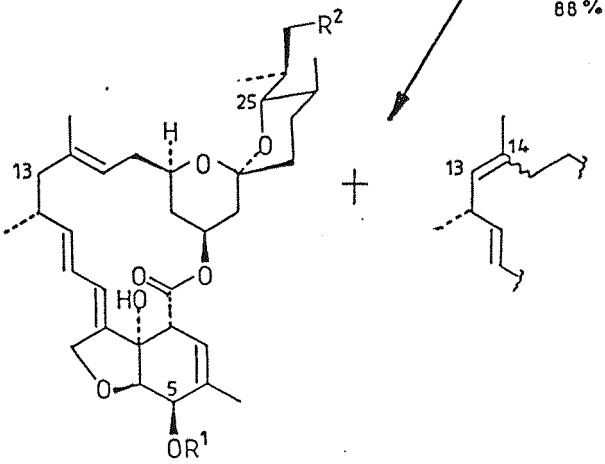
COMPOUND	R^1	R^2	R^3
IVERMECTIN (20)	H	Me(20%H)	Ⓢ Ⓢ
	1% H_2SO_4, MeOH, 25°C, 18 hrs — 76%		
(34)	H	Me(20%H)	H
	TBDMSCl, DMF, imadazole. — 75%		
(35)	TBDMS	Me	H
(36)	TBDMS	H	H

ⓈⓈ= oleandrosyl – oleandrosyl



(35) R^1=TBDMS R^2=Me — (37) R^1=TBDMS R^2=Me

Bu_3SnH, cat. AIBN, Toluene, 85°C, 2 hrs, 88%



(38) R^1=TBDMS, R^2=Me — (39) R^1=TBDMS, R^2=Me

77% — 1% PTSA, MeOH

(40) R^1= H R^2= Me — (41) R^1= H R^2= Me

(9), Milbemycin D R^1= H R^2= H

SCHEME 6

The Biological Activity of the milbemycin and avermectin family

The development of antiparasitic agents for the Third World has remained neglected for economic and political reasons. However, parasites cause enormous economic losses in agriculture by decreasing crop yields and lowering growth rates in livestock. The anthelmintic properties exhibited by milbemycins and avermectins offer a potential solution to the numerous problems associated with parasites.

The assay for antiparasitic properties was the first obstacle to overcome. Milbemycins were isolated during a screening program designed to detect pesticidal antibiotics. In these assays[30], the two spotted spider mite was used as a test insect. Since then the Sankyo Company of Japan has claimed a wide range of insecticidal activity for milbemycins in the patent literature and recently a report of the acaricidal activity has appeared in print[31].

The screening procedure employed at Merck, Sharpe and Dohme in the discovery of the avermectins was slightly different. When compared with an *in vitro* test, a direct test in animals was expensive but it did provide direct information about both efficacy and toxicity. The crude culture broth was fed to mice which has been previously infected with a nematode[32,33]. It was found that not only did this crude broth remove all traces of worm eggs from the mouse faeces but it also killed all the intestinal worms. It was from this crude fermentation broth that the avermectins were isolated and a general brief view of the biological activity of the avermectins is presented below.

Essentially no difference in activity was found between the corresponding members of the a and b series. This conveniently eliminated the need for difficult separations in order to test the biological activity. In the results[32] shown on table 2, the compounds tested were mixtures of the a and b series containing up to 20% of the minor isopropyl (b) analogues.

In general, members of the B series (C5 hydroxyl) were found to be more potent agents than members of the A series (C5 methoxy). Comparison between the respective members of 1 and 2 series is less straightforward. This may be due to the change in the conformation

Avermectin	A_1	A_2	B_1	B_2
Nematode	% reduction in worm burden			
Harmondus contortus				
L_4	73	>96	96	90
Adults	59	>99	98	0
Ostertagia circumcinta				
L_4	17	9	95	99
Adults	69	99	98	>99
Trichostronglus axei				
Adults	4	98	>99	>99
Trichostronglus columbriformis				
Adults	8	97	>99	99
Cooperia oncophoria				
L_4	0	36	97	>98
Adults	72	13	94	98
Oesophagostronium columbrianium				
Adults	18	100	100	100

L_4 = 4th instar larvae

Table 2. The efficacy of the avermectins against infections in sheep at a dose of 0.2 mg/kg.

of the spiro acetal ring which causes subtle changes in the activity. The most potent natural avermectin appears to be avermectin B_1.

Avermectins have been modified by the removal of the disaccharide moiety[19] and by the derivatization of the C5 and C4" hydroxyl groups[22]. In general, this produced a significant decrease in activity. By far the most successful alteration to avermectin B_1 was the reduction of the double bond in the spiro acetal ring to produce Ivermectin[19,20]. This analogue possessed superior toxicological properties and a better all round efficacy than the parent avermectin B_{1a}.

Initially, the avermectins and analogues were found to be active against a variety of nematodes in animals hosts such as cattle[6,34], horses[34], sheep[6], pigs[35], dogs[6,36] and poultry[6]. Ivermectin (20) is at present undergoing preliminary trials as a nematocide in man[37]. Initial results suggest that Ivermectin (20) possesses less side effects than the conventional cures for the debilitating disease of river blindness. The anthelmintic activity of avermectin B_2 has been used as a method of control of the nematode which caused root knot in cucumbers[38], tobacco[39] and tomatoes[38].

In general Ivermectin (20) and avermectin B_1 are the most active compounds in animal hosts, while in the case of plant hosts, the most active agents are avermectin B_2 and the 23-keto analogue (27). It has recently been demonstrated[24] that micro organisms in the soil metabolize avermectin B_2 into the 23-keto analogue (27) and this is probably the reason for the prolonged activity of avermectin B_2 in the soil.

Avermectins and their derivatives were also shown to be active against ecto-parasites. These include lice[40], ticks[41] and blow fly larvae[42] in pigs, cattle and sheep respectively. Just as before, this insecticidal activity has been extended to plant hosts. A range of insects affected by avermectin B_2 is shown in table 3.

The activity of the foliar residues is persistant and can continue for as long as one month after application[38]. In the case of mites, avermectin B_1 has been shown to be lethal by both contact and ingestion. The mites become moribund soon after contact and die three to four days later. Therefore it would appear that avermectin

B_1 has a different mode of action to organophosphorus and pyrethroid insecticides. Furthermore it possesses about 100 times the activity when compared with conventional acaricides.

Parasitic infections generally cause well defined and easily identifiable diseases and so, in theory, should be easy to treat. One of the methods of rational parasite chemotherapy is to achieve selectivity by using the differences between the host and the parasite, eg inhibition of an enzyme unique to the parasite.

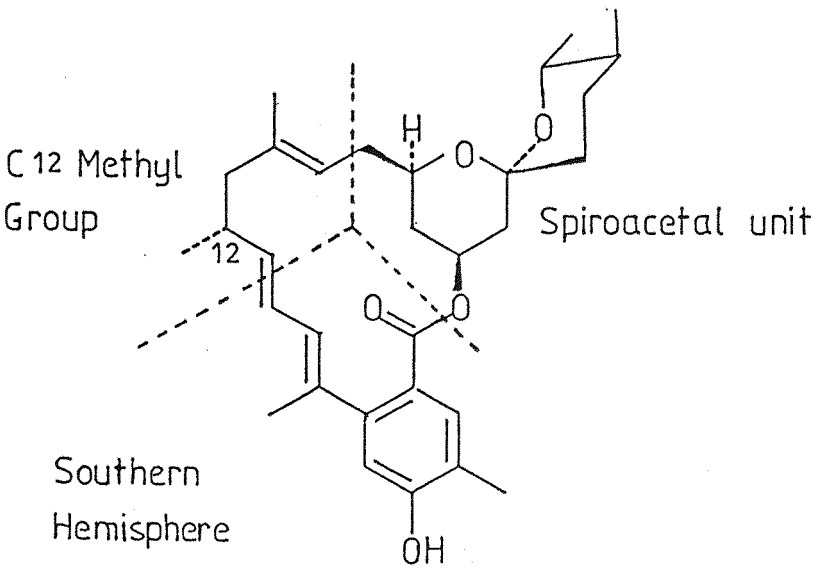
In higher animals, both γ-aminobutyric acid (GABA) and acetyl choline are common neurotransmitters, but the GABA system is confined to the central nervous system which is protected by the blood brain barrier. In mammals, avermectins cannot pass this blood brain barrier but if it is artifically introduced into the brain, inhibition of neurotransmittion is observed[46]. Insects and nematodes do not possess a brain and the GABA system is distributed throughout the body. Avermectins have been shown to inhibit the action of GABA[47] and consequently avermectins selectively inhibit neurotransmittion in insects and nematodes but not in the mammalian host.

Insect	General class	Lc_{90} (ppm)	Ref
Citrus red mite	Acari	0.02	33
Two spotted spider mite	Acari	0.03	33
Colorado potatoe beetle	Coleoptera	0.03	38
Confused flour beetle	Coleoptera	—	43
Tomato hornworm	Lepidoptera	0.02	38
Southern armyworm	Lepidoptera	6.0	38
Pea aphid	Homoptera	0.4	38
Robust bot fly (larvae)	Diptera	—	43
Stable fly (larvae)	Diptera	—	44
Red imorted fire ant	Hymenoptera	Surpresses reproduction	45

Table 3. The efficacy of avermectin B_1 against several classes of insect

Synthetic Approaches towards milbemycins and avermectins

The simplest member of the avermectin and milbemycin family is milbemycin β_3 (42). In the analysis of the synthetic approaches towards this class of compounds, the molecule (42) will be treated in three distinct parts. The spiroacetal unit will be considered first, then the origin of the lone methyl group at C12 and finally the synthesis of the aromatic southern hemisphere (Figure 10). To date the assembly of these three fragments has been achieved by two groups[48,49].



Milbemycin β3 (42)

Figure 10

1. Spiroacetals

Many reports are concerned with the synthesis of milbemycin β_3 (42) and few are directed towards the synthesis of the more complex avermectin series . The synthetic approaches towards the spiroacetal unit may be divided into groups A and B. The first approach to be considered (type A) involves the derivation of the Ring A from the corresponding lactone (eg (43)). The alternative strategy (Type B), in which Ring B provides the basis for the synthesis of the spiroacetal unit will be discussed later.

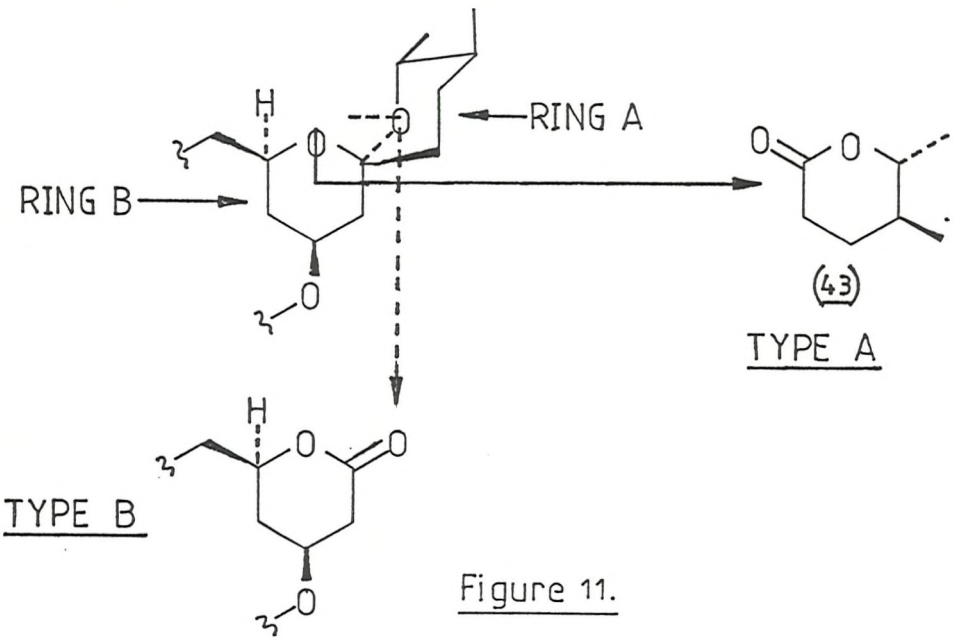
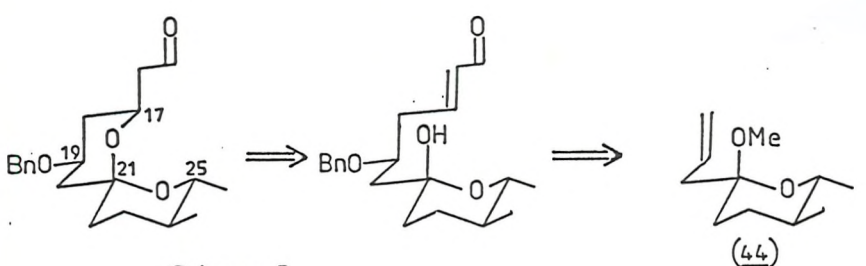


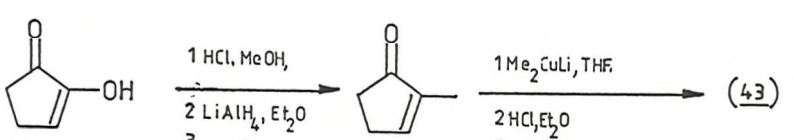
Figure 11.

Type A

Smith *et al* [48], in the first reported total synthesis, used the strategy outlined (Scheme 7). The racemic starting lactone (43) was prepared as shown (Scheme 8). Reaction of the lactone (43) with allyl



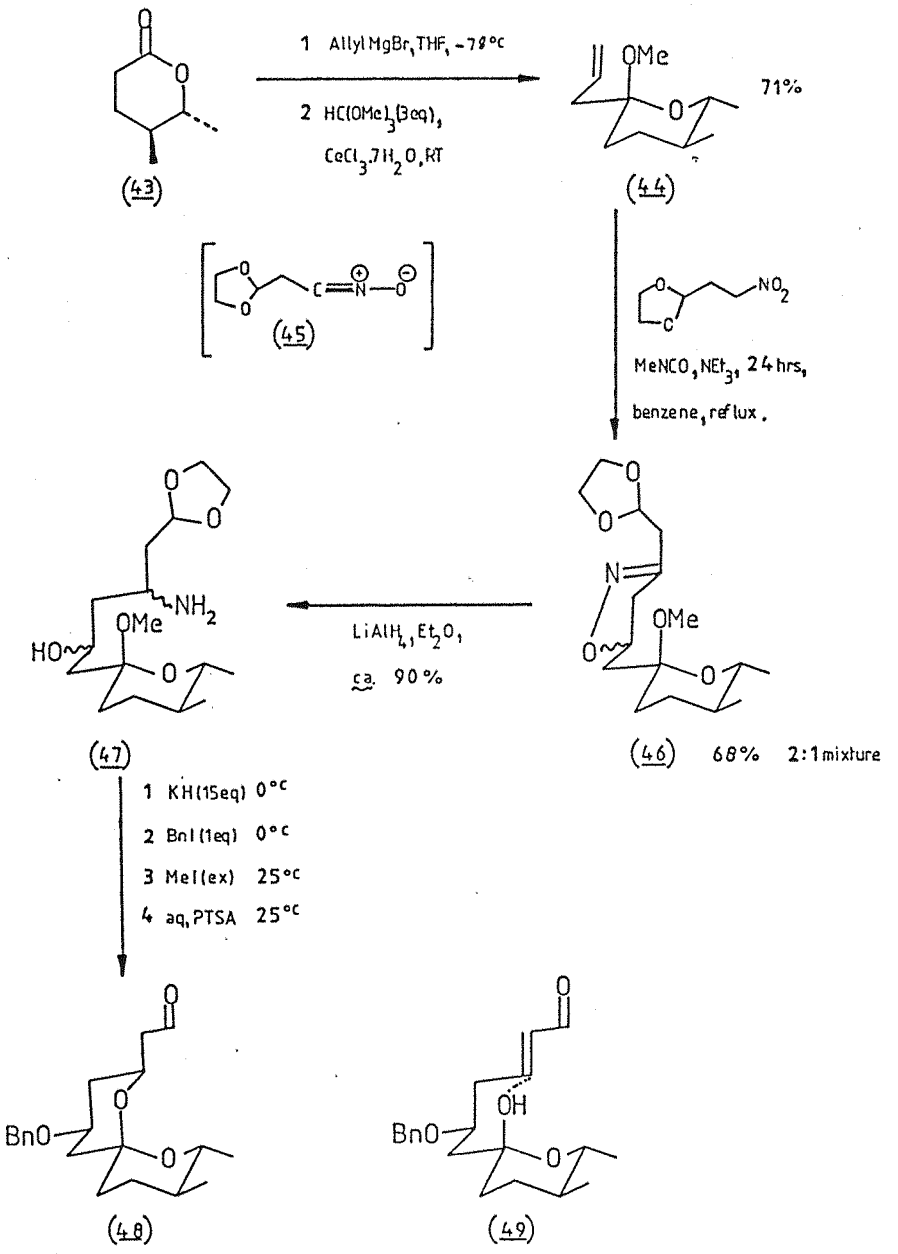
Scheme 7



Scheme 8

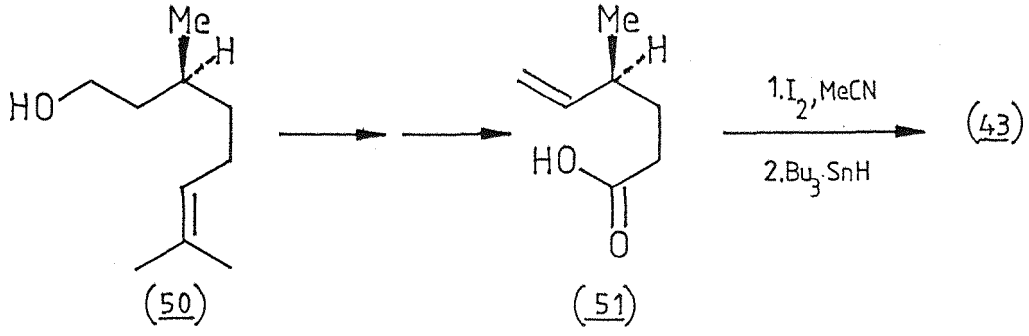
magnesium bromide, followed by ketalization afforded the ketal (44) in 71% yield. Treatment of this ketal with the nitrile oxide (45) in refluxing benzene gave a 68% yield of a 2:1 mixture of the isoxazaline (46). This 1,3 dipole addition introduced the C19 oxygen substituent and also the C17 amine functionality which was later used to form the α, β unsaturated aldehyde moiety required for cyclization. Thus after reduction, the resulting amino alcohols (47) (4 isomers)were presumably converted to a mixture of α, β unsaturated aldehydes. These materials could not be isolated, since under the reaction conditions, acid catalysed cyclization was observed. A 20-25% yield of a single spiroacetal (48) was obtained. The structure of (48) was confirmed by a direct spectral comparison with an authentic sample obtained by the degradation of milbemycin β_1 (1) (Scheme 9).

This material must have been derived from the aldehyde (49) where the substituents have adopted the preferred pseudo equatorial conformation. In other conformers, unfavourable 1,3 diaxial interactions inhibit cyclisation. It was unfortunate that the cyclo addition was not specific and that the isoxazolines (46) were not separated and then carried through the sequence.


1 AllylMgBr, THF, -78°c
2 HC(OMe)3(3eq), CeCl3.7H2O, RT
71%
(43)
(44)
(45)
MeNCO, NEt3, 24 hrs, benzene, reflux.
LiAlH4, Et2O, ca. 90%
(46) 68% 2:1 mixture
(47)
1 KH(15eq) 0°c
2 BnI(1eq) 0°c
3 MeI(ex) 25°c
4 aq. PTSA 25°c
(48)
(49)

Scheme 9.

Using a completely different strategy, Williams and co-workers[49] have reported the conversion of a chiral lactone (43) into a milbemycin spiroacetal. The chiral lactone (43) was derived from (-)-citronellol (50), *via* an iodolactonization of the carboxylic acid (51) in an overall yield of about 40% (Scheme 10).

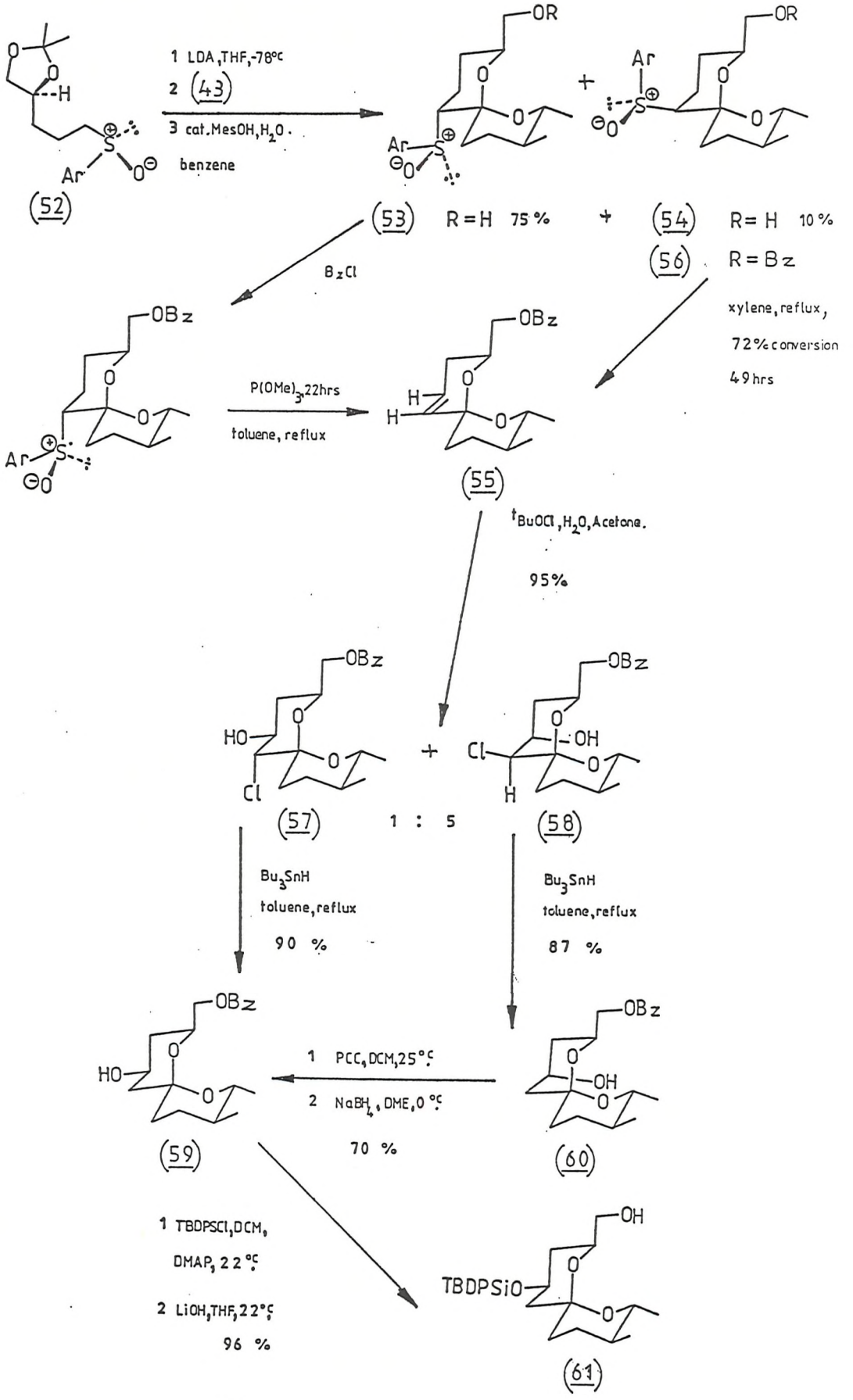


Scheme 10.

The chiral lactone (43) was reacted with the anion of the sulphoxide (52) (available from D-mannitol) and subsequently cyclisation in wet benzene afforded the spiroacetals (53) and (54) in 75% and 10% yields respectively. It was envisaged that the equatorial C19 oxygen moiety could be introduced using the alkene (55). Protection of the primary alcohol group followed by thermolysis in toluene gave the required olefin (55) in excellent yield. The elimination of the axial sulphoxide (56) required more forcing conditions.

Treatment of this unsaturated spiroacetal (55) with ^{t} butylhypochlorite in wet acetone gave a separable mixture of chlorohydrins (57) and (58) in excellent yield. Unfortunately the major product was the undesired *trans* diaxial chlorohydrin (58). Removal of the chlorine was effected with tributyl tin hydride in refluxing toluene and gave the spiroacetals (59) (from 57) and (60)(from (58)). The axial alcohol (60) was inverted in 70% yield using an oxidation/reduction sequence. Protection of the C19 alcohol groups as the silyl ether followed by saponifacation of the C17 benzoate ester afforded the required spiroacetal (61) in excellent yield (Scheme 11).

The construction of the spiroacetal 10 was achieved with excellent regio and stereochemical control but the introduction of the equatorial C19 oxygen functionality proved lengthy.

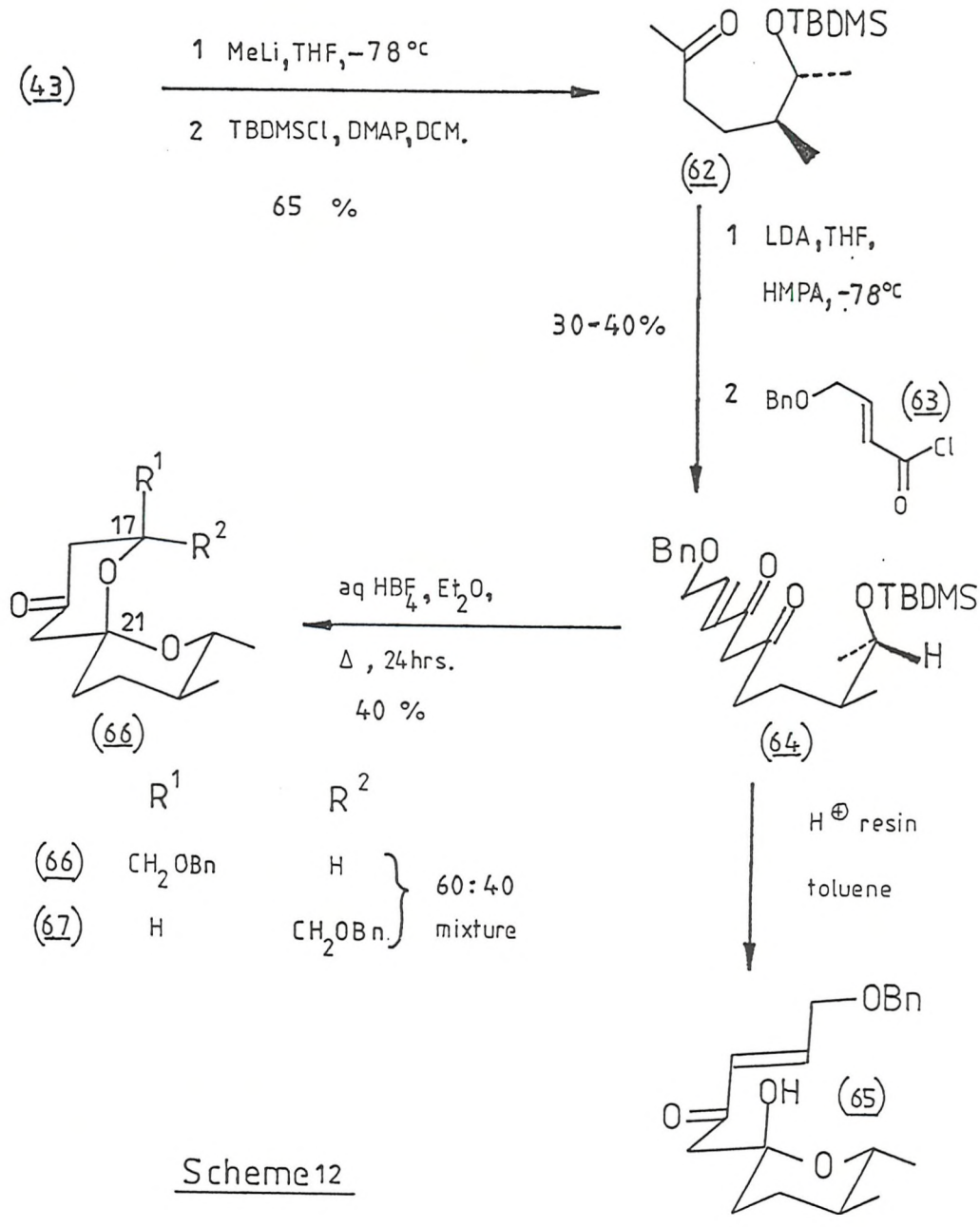


Scheme 11.

Ar = 4-methyl-benzene

In an alternative approach, Williams and Barner[50] later investigated the acylation of the methyl ketone (62) which was available from the lactone (43). Lithiation of this material and acylation with the acid chloride (63) afforded the diketone (64) (40%) together with up to 60% of the starting ketone (62).

Attempted cyclisation with fluoride ion in THF led to decomposition. Acid catalysed cyclisation conditions led to the formation of the A ring only (65) but using a two phase system of 20% aqueous fluoroboric acid in refluxing ether, a 60:40 mixture of spiroacetals (66) and (67) was obtained in 40% yields (Scheme 12).



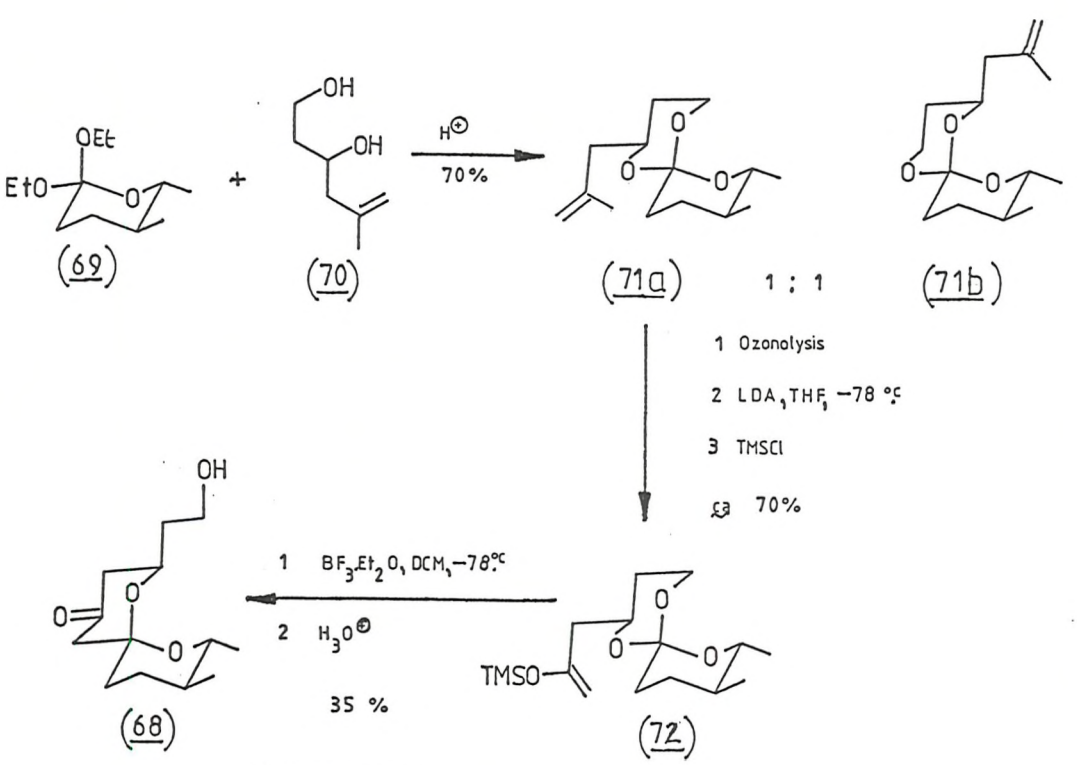
Scheme 12

The second approach[50] developed by the Williams group did not improve on the original route[49] but suffered from the low yields and poor selectivity in the cyclisation to the spiroacetal (66).

The reaction of silyl enolethers with acetals under Lewis-acid catalysis has been termed the Mukaiyama reaction. The spiro-acetal (68) has been prepared[51] using an orthoester in an intra-molecular Mukaiyama reaction.

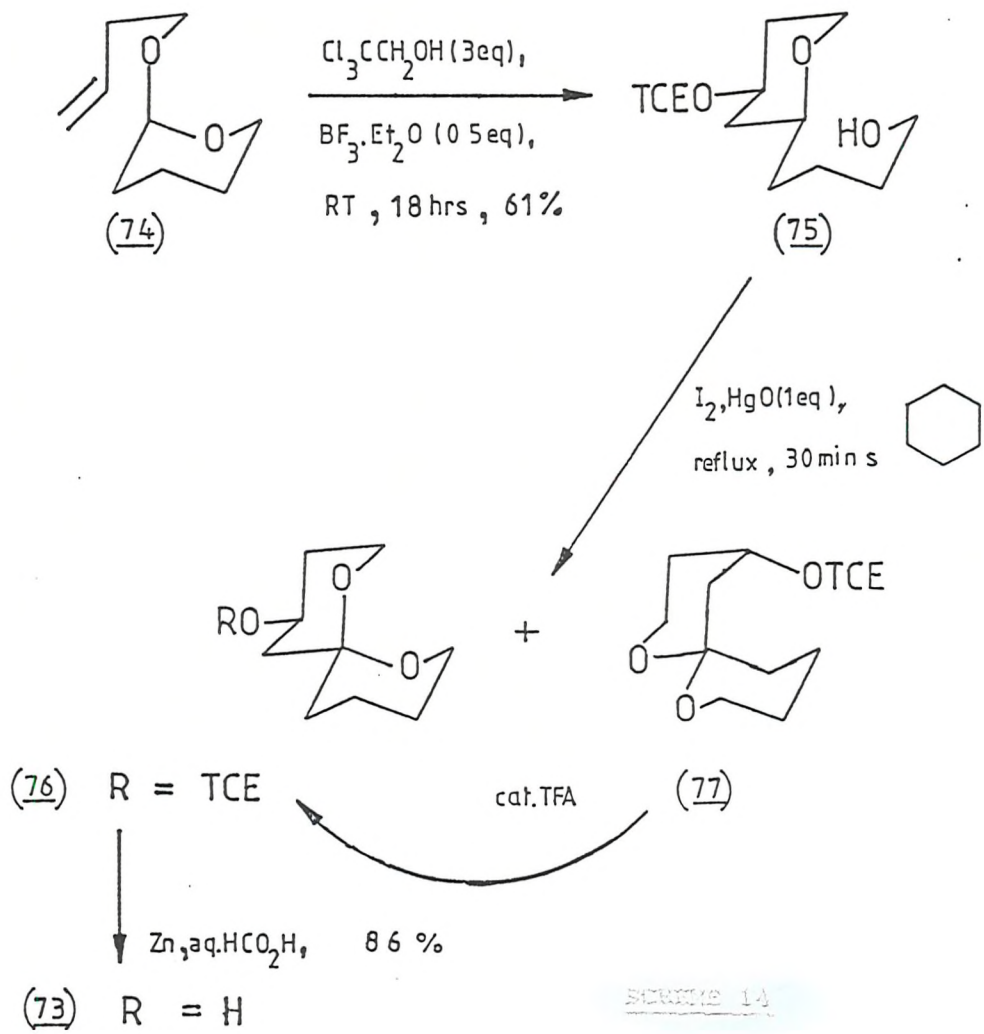
Treatment of the orthoester (69) with the diol (70) using acid catalysis led to the spiro cyclic compounds (71a) and (71b) in 70% yield. These isomeric compounds were separated by chromatography to afford a 1:1 mixture of pure (71a) and (71b). Conversion of the olefin (71a) into the required precursor (72) was achieved in about 70% yield. Treatment of this orthoester (72) with boron trifluoride etherate in methylene chloride at -78 °C for 15 minutes, followed by aqueous workup and chromatography led to the spiroacetal (68) in 35% yield (Scheme 13).

The use of chiral starting materials in this approach would eliminate the formation of the spiro-orthoester (71b) and hence provide (68) as the only spiroacetal formed.



Scheme 13.

A short synthesis of the 4-hydroxy spiroacetal (73) has been achieved by an elegant cationic olefin cyclisation[52]. Treatment of the tetrahydropyranyl ether (74) with boron trifluoride etherate in 1,1,1-trichloro-ethanol induced the closure of Ring B to afford the alcohol (75) in 61% yield. Oxidation of compound (75) with iodine and mercuric oxide in refluxing cyclohexane afforded a mixture of isomers (76) and (77). Treatment of this mixture with a catalytic amount of trifluoroacetic acid provided only the more stable derivative (76), which on deprotection gave the required spiroacetal (73) in 86% yield and 50% overall (Scheme 14).



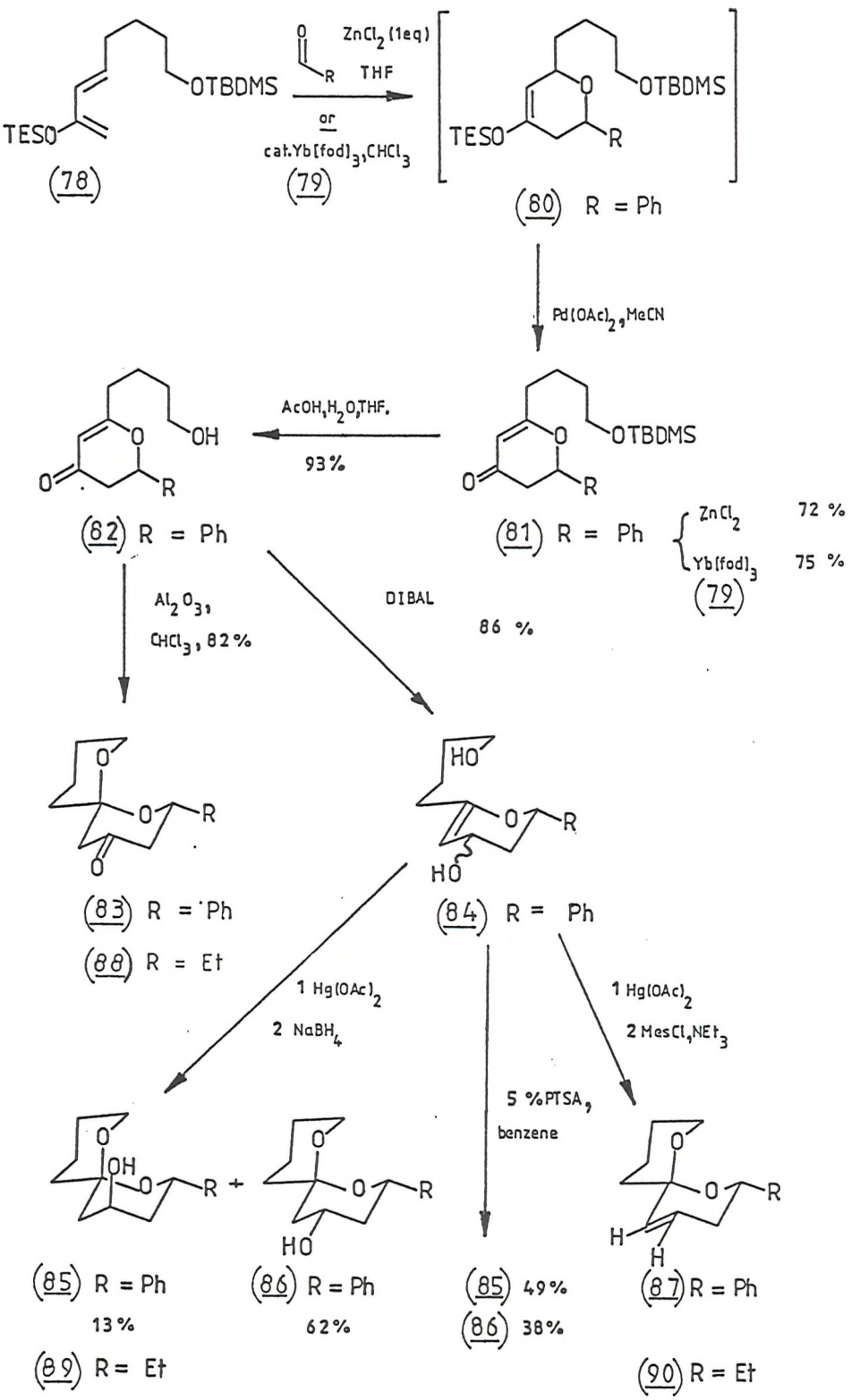
Scheme 14

Danishefsky and co-workers have recently developed the reaction of aldehydes with electron rich dienes[53]. This type of methodology has been applied to the synthesis of spiroacetals[54]. Treatment of the silyl enol ether (78) with benzaldehyde and either zinc chloride or a catalytic quantity of the ytterbium complex (79) gave the crude adduct (80). Oxidation of (80) with palladium acetate afforded the vinylogous ester (81) in *ca* 75% yield from (78).

It was surprising that no spirocyclic compounds were obtained when the silicon protecting group was removed under acidic conditions. The required transformation was effected by treatment of a solution of the alcohol (82) with neutral alumina. This gave the single diastereomer (83) in 82% yield.

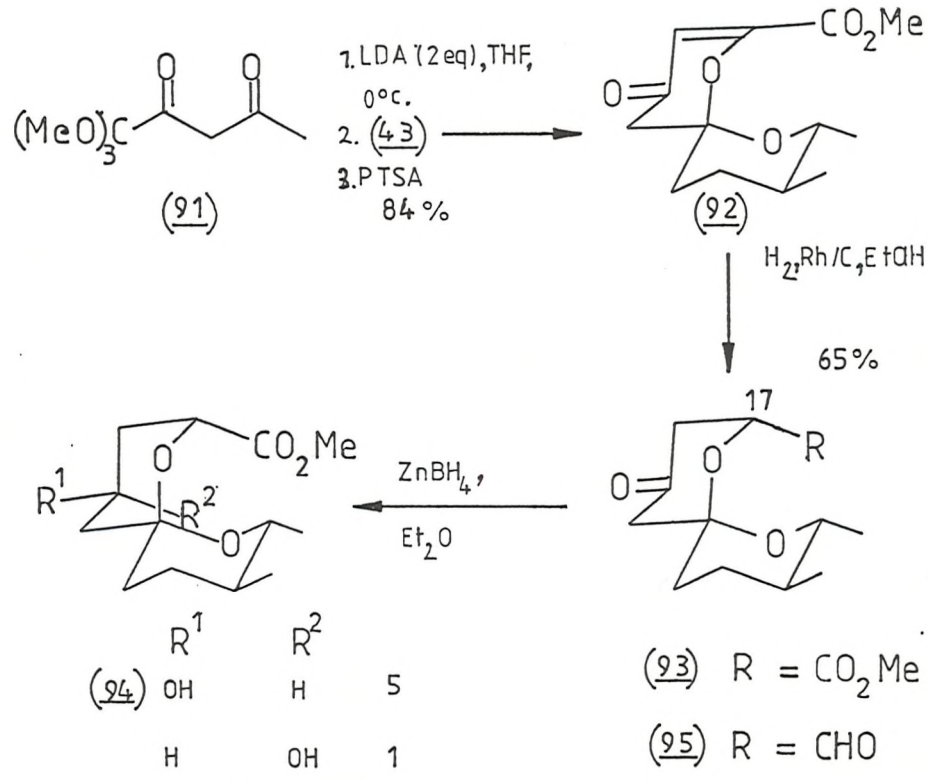
Reduction of the vinylogous ester (82) with DIBAL afforded a mixture of diols (84) in 80% yield. These alcohols have been used to investigate the conditions required for the synthesis of the different spiroacetals of the avermectin family. Cyclization using mercuric acetate followed by reduction of the organometallic species gave the epimeric alcohols (85) and (86) in 62% and 13% yield respectively. The extension of this approach to the synthesis of the avermectin B_{2a} spiroacetal might prove cumbersome because the required axial C23 alcohol (85) was formed as the minor isomer. Treatment of the intermediate mercurial with mesyl chloride and triethylamine caused elimination to the olefin (87) and this route appears to be the most promising of the two approaches into the avermectin spiroacetal skeleton. Rearrangement of the diols (84) using acid conditions gave a mixture of (85) and (86) in 49% and 38% yield respectively. This sequence has been repeated with propionaldehyde to give the spirocyclic compound (88) in good overall yield. This intermediate has still be be converted into the Ring A variants such as (89) and (90). (Scheme 15).

Barrett and co-workers[55] have presented a preliminary account of their efforts in the synthesis of the milbemycin/avermectin area. The first approach involved the condensation of the dianion of (91) with the lactone (43) and afforded the spiroacetal (92) in 84% yield after acid catalysed cyclisation. Hydrogenation of this system with rhodium on carbon gave the ester (93) which had the undesired


TESO
OTBDMS
(78)
ZnCl2 (1eq)
THF
or
cat.Yb[fod]3,CHCl3
(79)
(80) R = Ph
Pd(OAc)2, MeCN
AcOH, H2O, THF.
93%
(82) R = Ph
(81) R = Ph
ZnCl2 72 %
Yb[fod]3 75 %
(79)
Al2O3,
CHCl3, 82%
DIBAL
86 %
(83) R = Ph
(88) R = Et
(84) R = Ph
1 Hg(OAc)2
2 NaBH4
1 Hg(OAc)2
2 MesCl, NEt3
5 %PTSA,
benzene
(85) R = Ph
13%
(89) R = Et
(86) R = Ph
62%
(85) 49%
(86) 38%
(87) R = Ph
(90) R = Et

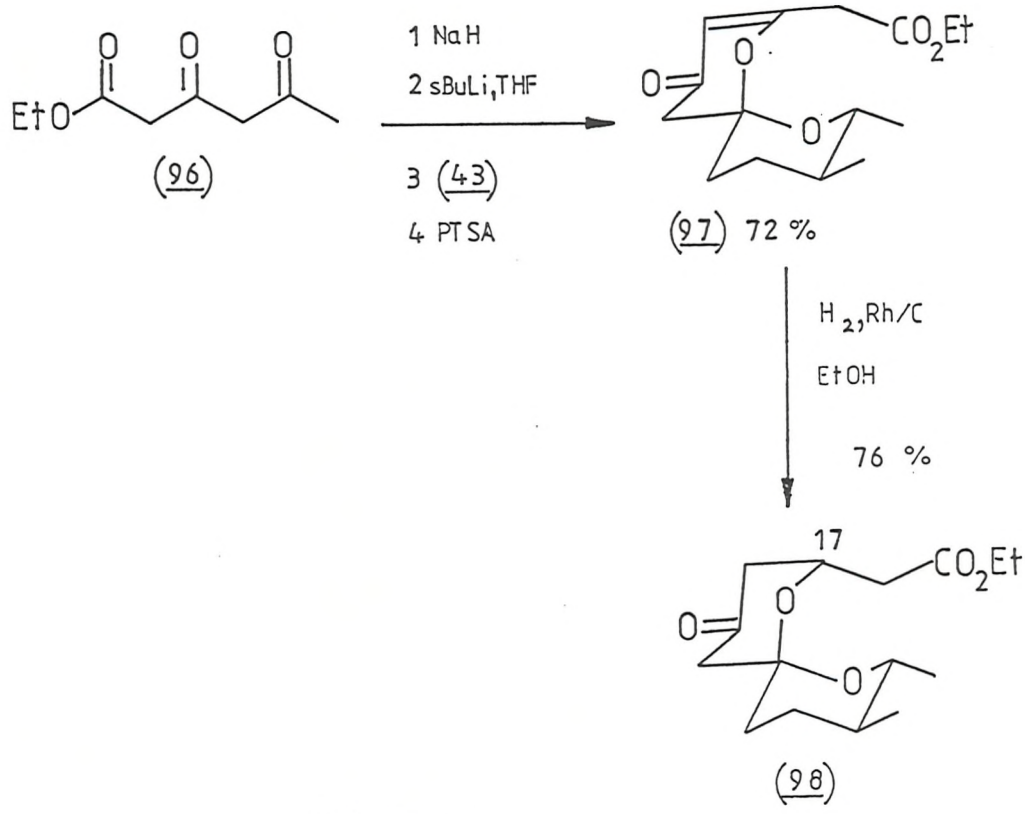
Scheme 15 .

stereochemistry at C17. The ketone moiety was then reduced with zinc borohydride to afford the alcohol (94) as the major product. Williams *et al*[49] have previously shown that the aldehyde (95) could be epimerized with DBU (Scheme 16).



Scheme 16

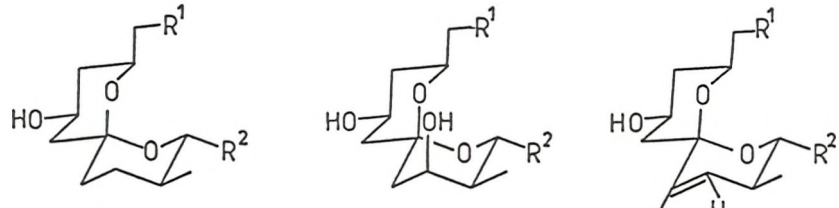
A biomimetic approach[55], used the condensation of the trianion of (96) with the lactone (43) and afforded the spiro compound (97) in 72% yield. However, catalytic hydrogenation once again gave the undesired keto-ester (98). In principle this compound (98) could be epimerized, but as yet all attempts to do so have been unsuccessful. Although these approaches are at an early stage, the problem of epimerization has to be overcome before these routes become feasible. (Scheme 17).



(96) (97) (98)

Scheme 17.

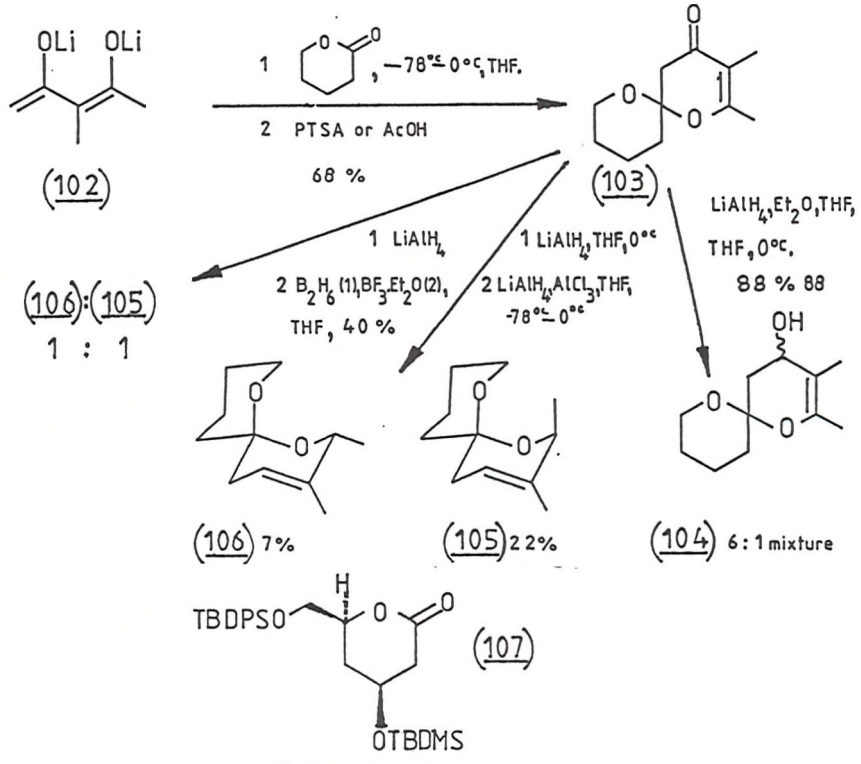
The Ring A strategy generally produces the spiroacetal skeleton required for the milbemycins (eg (99)) with good control of the stereochemistry of the spiroacetal substituents. However the extension of this approach to the more complex avermectins has proved difficult and these additional complications can be seen in the synthesis of spiroacetals by Danishefsky *et al*[54]. (Scheme 15). This is the only attempt to produce Ring A analogues (eg (100) and (101)) using the Ring A approach.



(99) (100) (101)

Type B Approach

Model studies aimed at the total synthesis of the milbemycin/avermectin antibiotics employing the type B strategy have been reported[56]. Condensation of the dianion (102) with δ-valerolactone afforded the spirocyclic compound (103) in 68% yield after acidic workup. Reduction of this pyrone(103) gave either the alcohols (104) or varying ratios of the spiroacetals (105) and (106) depending on the reagents used (Scheme 18).



Scheme 18

Attwood and Barrett[57] have recently reported the multistep preparation of the lactone (107) from the sugar ribose. However, to date there have been no further reports by this group of the condensation of the dianion (102) and the lactone (107) to form a spiroacetal.

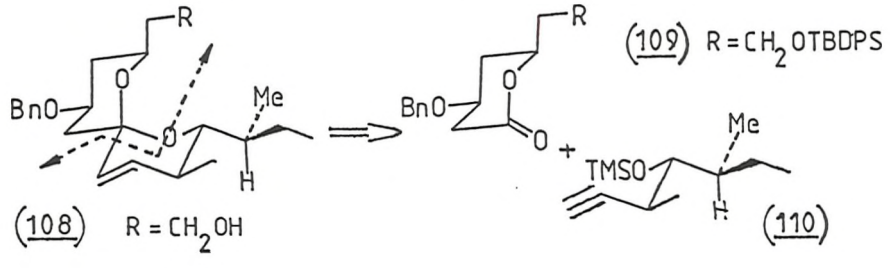
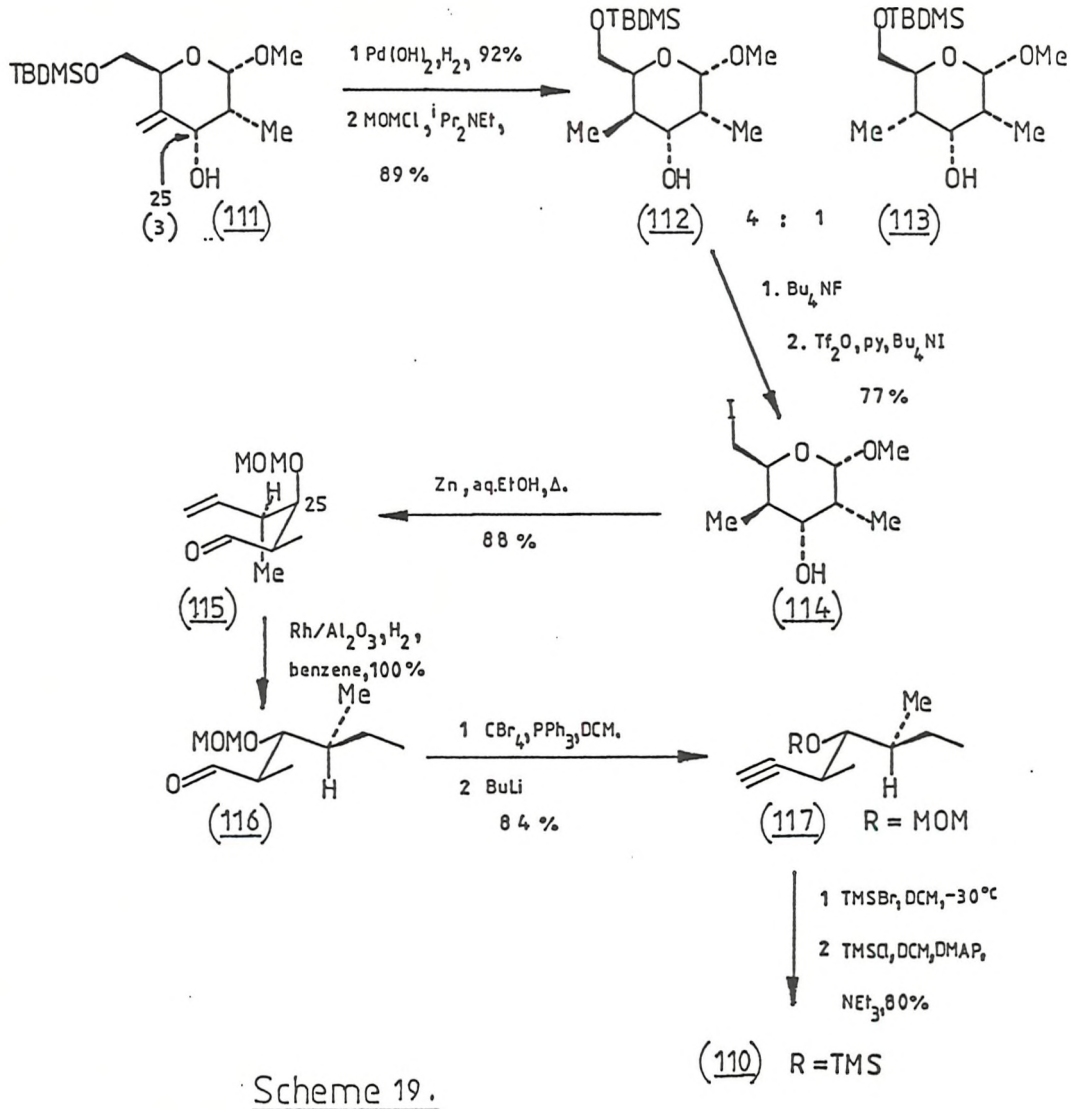


Figure 12.

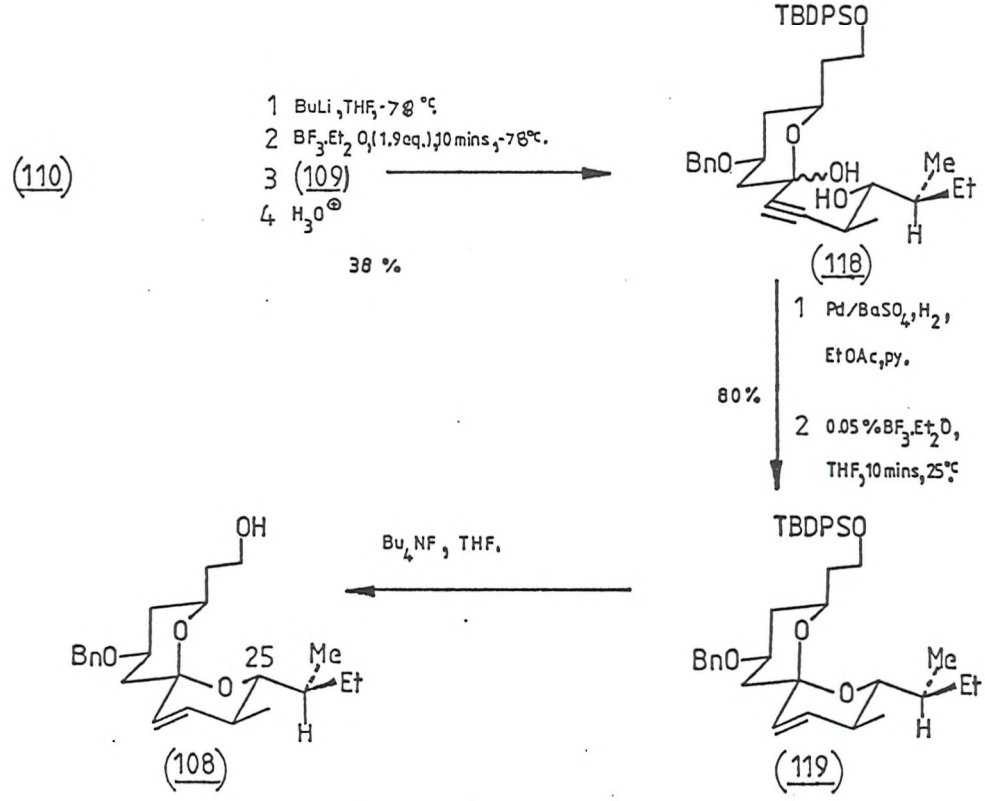
Most of the synthetic approaches have been limited to the synthesis of the simpler milbemycin spiroacetal system, but one approach to the more complex spirocyclic system of avermectin B_{1a} (108) has been reported[58]. The retrosynthetic analysis of (108) is shown on Figure 12 and involves the coupling of a chiral lactone eg (109) with the chiral acetylene (110).

The chiral precursors (111), "readily available" from D-glucose[59], was first hydrogenated and the secondary hydroxyl functionality protected on the methoxymethyl ether. This afforded a high yield of a 4:1 mixture of ethers (112) and (113) epimeric about the latent C26 (C3 in the sugar) position, which were readily separable by chromatography. Deprotection of the major isomer (112) with fluoride and the subsequent conversion to the iodide 14 proceeded in good yield. Elimination of the iodo acetal (114) with zinc dust in ethanol afforded the olefin (115), which after the subsequent hydrogenation unveiled the latent chiral C25 *sec*-butyl substituent of (116) in excellent yield. Homologation of this aldehyde (116) with carbon tetrabromide and triphenylphosphine gave the intermediate vinyl bromide which was converted into the acetylene (117) in 84% yield by treatment with butyl lithium. Deprotection of the ether (117) with trimethyl silyl bromide at -30 °C and subsequent silylation afforded the required chiral acetylene (110) in 80% yield (Scheme 19).

It was found that the coupling of the two chiral fragments was best achieved by formation of the lithium acetylide with butyl lithium and sequential addition of boron trifluoride etherate and the chiral lactone (109). After acidic work up, this afforded a 38% yield of the adduct (118) (90% based on recovered lactone (109)). Partial reduction of the acetylene moiety of the adduct (118) with Lindlar catalyst in an aprotic solvent system afforded the *cis* unsaturated spiroacetal (119) in 80% yield after Lewis acid induced cyclisation. The removal of the silyl protecting group gave the alcohol which is analogous to an intermediate used by Smith *et al*[48] in the total synthesis. of a milbemycin (β_3). (Scheme 20)



Scheme 19.



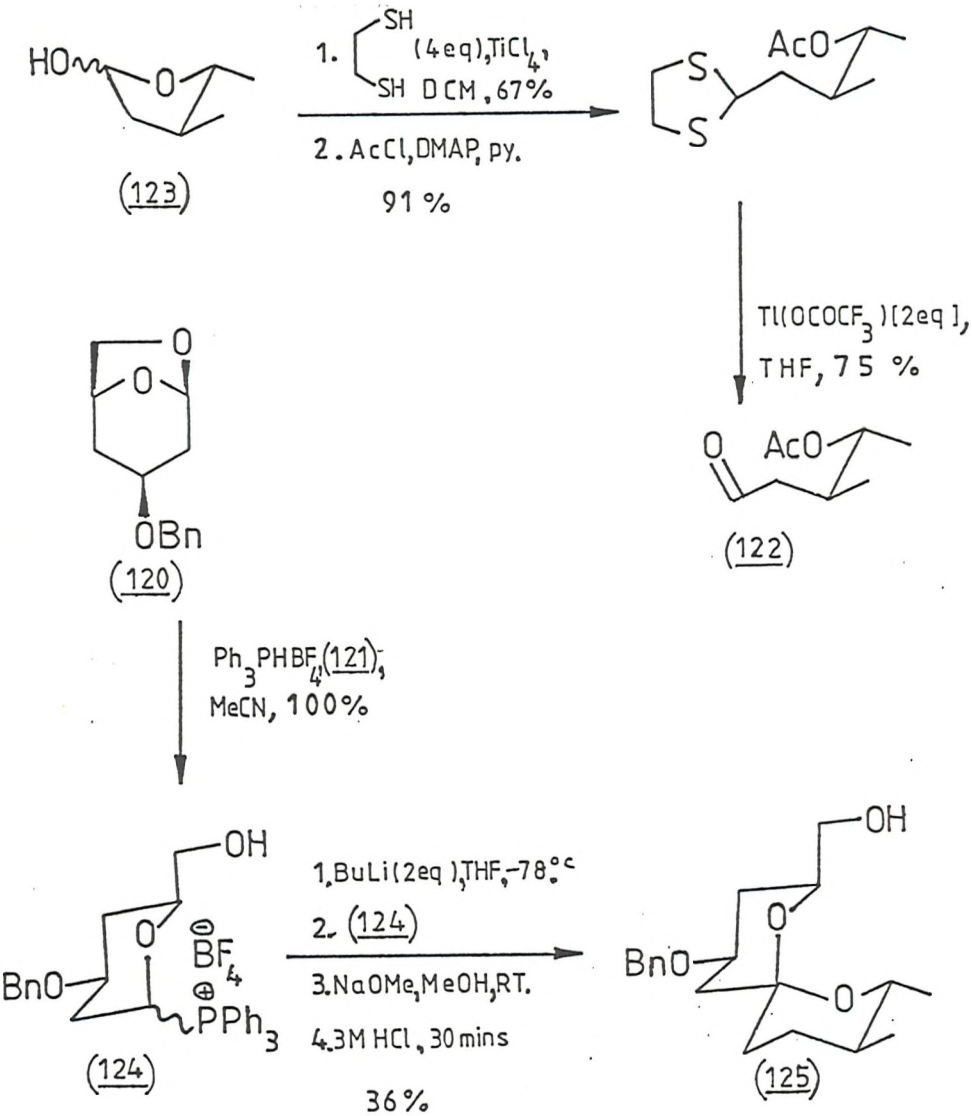
Scheme 20

The use of the glycoside (114) to introduce the chiral C25 *sec* butyl group *via* the olefin (115) was not obvious. However the starting material does not appear to be available from glucose in a short concise manner.

Ley *et al* have extended their synthesis of spiroacetals[60] to the synthesis of the milbemycin skeleton[61] and have exploited the opening of the strained 1, 6 anhydro bridge of the ether (120) by the phosphorus salt (121) (Scheme 21). The aldehyde (122) required for the condensation was available from the chiral lactol (123). In the initial study[60], the reaction of lactol anions cleanly gave spirocyclic products, but in this case the use of lactol (123) or its anion was successful.

Formation of the dianion of (124) with butyl lithium followed by addition of the chiral aldehyde (122) gave an adduct which was treated with base to remove the acetate protecting group. Acid induced cyclisation led to the hydroxy spiroacetal (125) in 36% overall yield from the phosphorus salt (124) (Scheme 21).

Generally, the Ring B approach is convergent and offers the flexibility required to synthesise a range of spiroacetals containing different Ring A substitution. Both partners for the condensation are normally available in a chiral form with the lactone B usually derived from a carbohydrate source.



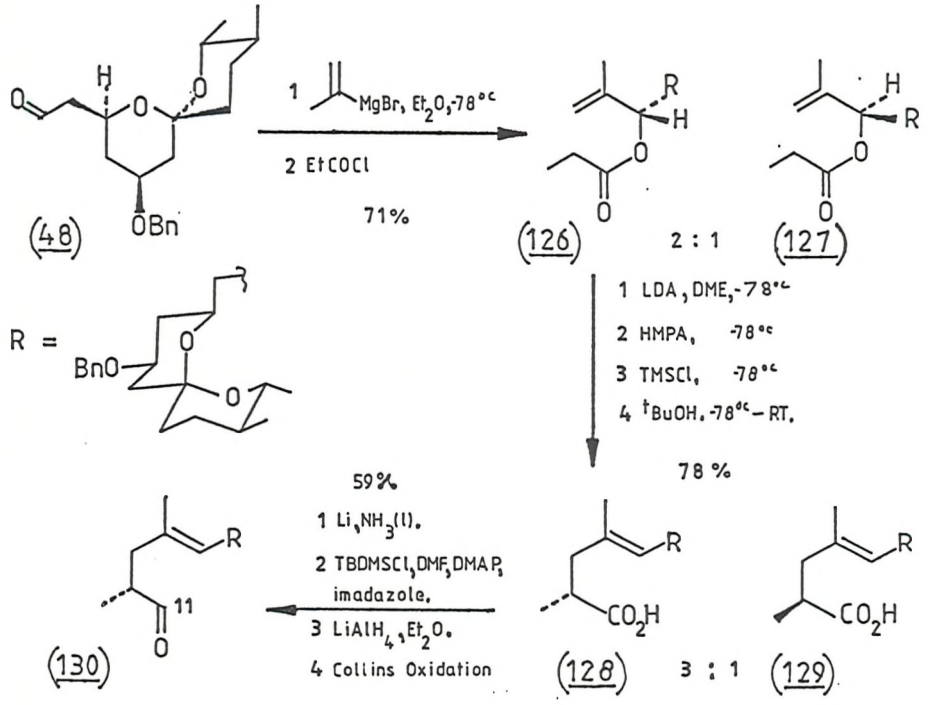
Scheme 21

2. The Origin of C12 lone methyl group

The C12 methyl group is isolated from the spiroacetal moiety by the *trans* trisubstituted double bond. Smith *et al*[48] introduced this stereochemical centre by the use of the Claisen rearrangement of the allylic proprionate (126). Reaction of the aldehyde (48) with isopropenyl Grignard and acylation of the resulting alkoxide with propionyl chloride afforded a 71% yield of a separable 2:1 mixture of propionates (126) and (127). Using the modified Ireland/Claisen conditions, the major propionate (126) was converted into a 78% yield of a 3:1 mixture of acids (128) and (129). The major component (128) contained the required C12 stereochemistry. The stereoselectivity for this rearrangement could be increased by the use of potassium amide bases but a

lower yield resulted.

The change of the C19 protecting group was achieved using standard conditions and the resultant acid converted to the aldehyde (130) in 59% overall yield *via* a reduction oxidation sequence. The Claisen rearrangement cleverly introduced the C12 methyl group by the use of the *trans* C14-C15 double bond and it also provided the C11 oxygen functionality required for the coupling to the aromatic portion. (Scheme 22).

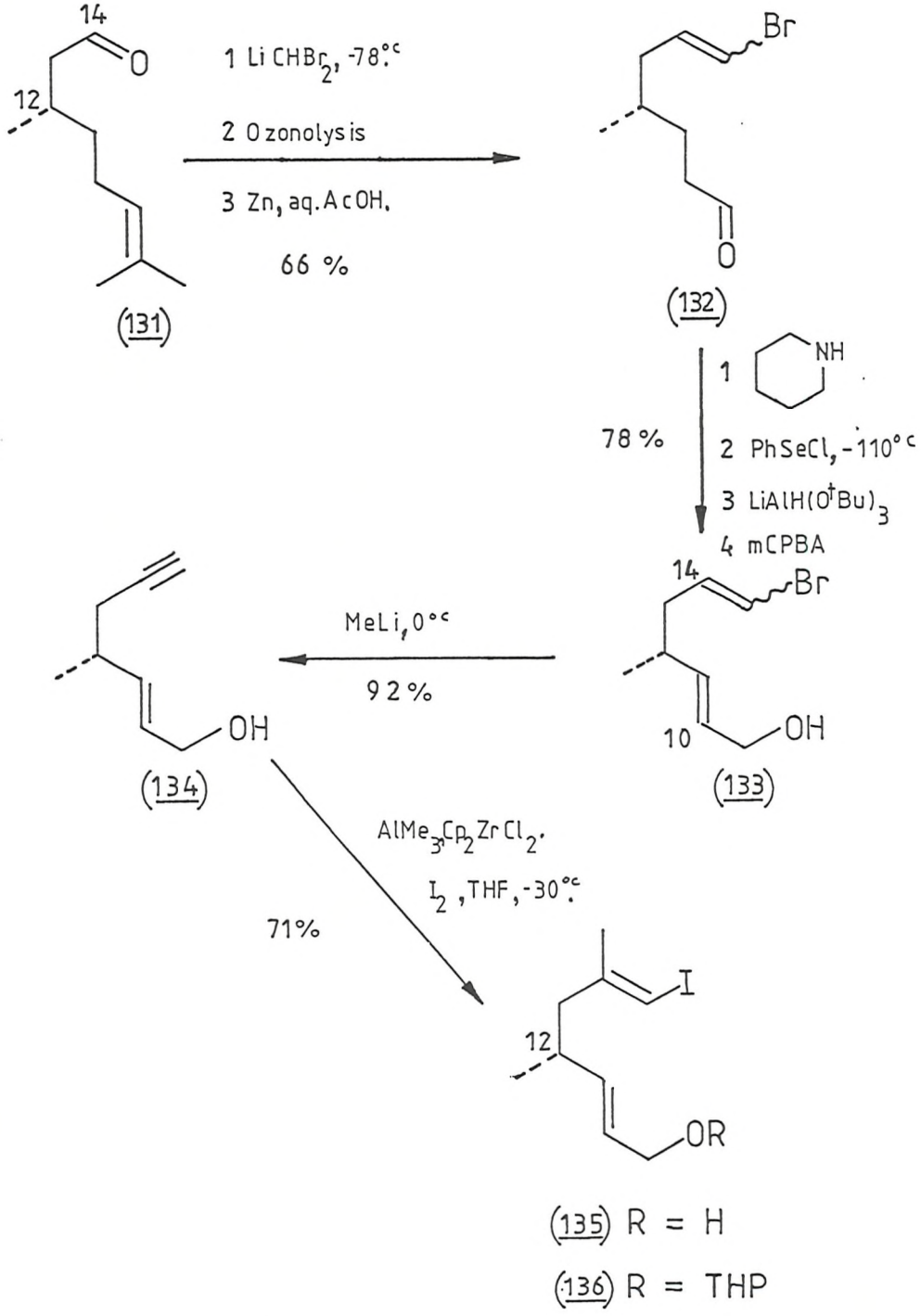


Scheme 22.

Williams and co workers[49] once again used S-citronellol (50) as a chiral building block for the introduction of the C12 stereochemical centre. Treatment of the chiral aldehyde (131) with lithiodibromomethane achieved the required homologation. The subsequent ozonolysis revealed the C9 aldehyde group and finally elimination using zinc in acetic acid afforded the vinyl bromide (132) in 66% overall yield. Introduction of the [E]-C10,C11 double bond was effected using organoselenium chemistry. Selenation of the inter-

mediate enamine, then reduction of the resultant aldehyde and finally oxidative elimination of the selenoxide gave the required disubstituted olefin (133) in 78% yield. This procedure was employed to avoid the possibility of epimerization at C12.

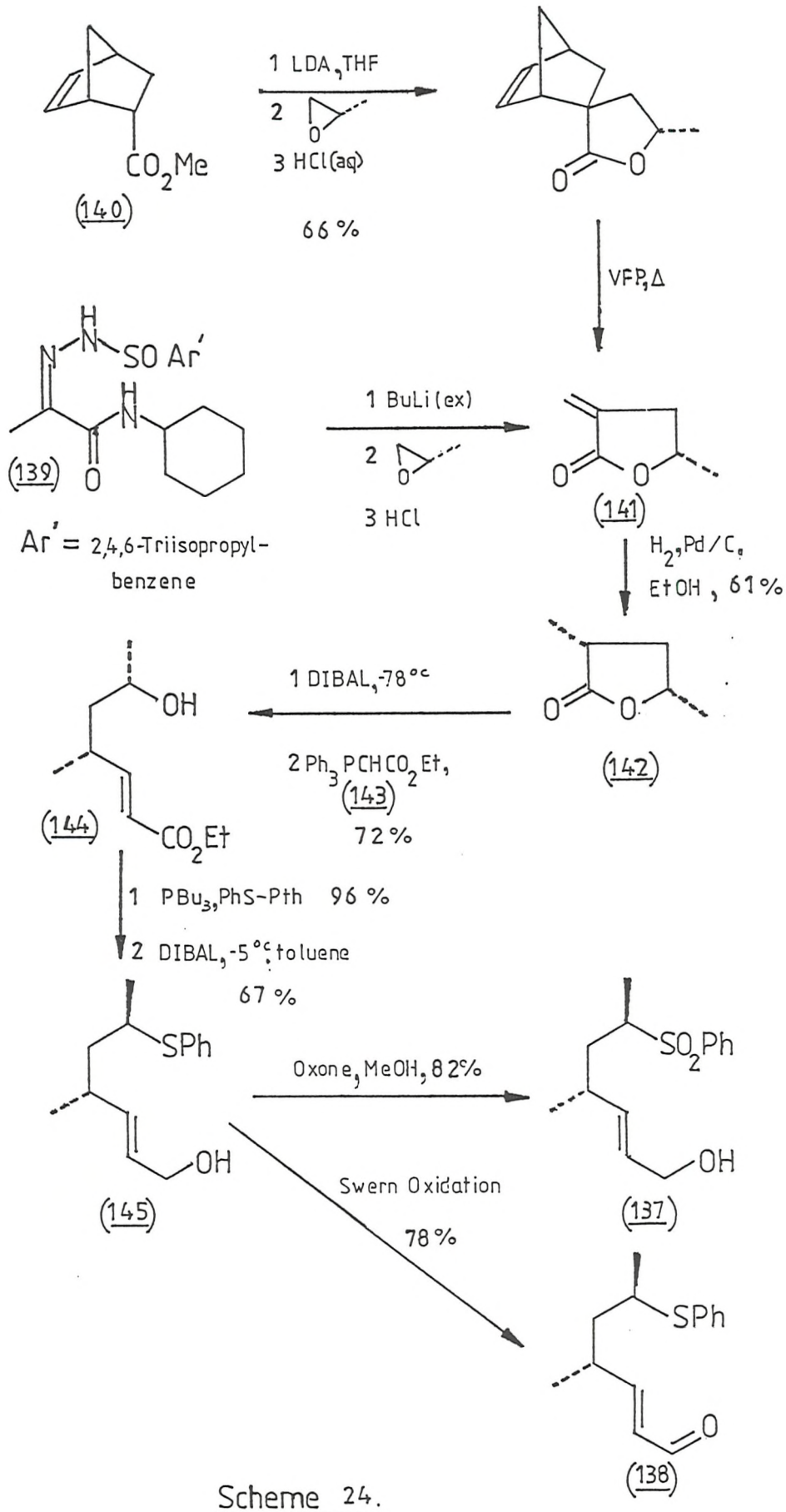
Treatment of the vinyl bromide (133) with methyl lithium provided the acetylene (134) in excellent yield. Conversion of this intermediate acetylene into an [E]-trisubstituted olefin (135) was achieved by the use of Negishi carbometallation reaction. This afforded the required diene system (136) in good overall yield and with excellent stereochemical control (Scheme 23).



Scheme 23.

Barrett and co-workers[55] planned to introduce the C12 methyl group by the use of the compounds (137) and (138). Alkylation of the dianion (139) or its equivalent (140) with chiral propylene oxide afforded the α-methylene-γ-lactone (141). Hydrogenation of the olefin moiety led to the chiral *cis* dimethyl-γ-lactone (142) which after reduction to the lactol and homologation using the stablized phosphorane (143) afforded a reasonable yield of the unsaturated ester (144). Treatment of this system with N-(phenylsulphenyl)pthalimide and tributyl phosphine introduced the C14 sulphur group in 91% yield and the subsequent reduction of the ester functionality with DIBAL afforded the allylic alcohol(145) in good yield. Oxidation of the alcohol (145) in good yield. Oxidation of the alcohol group (145) under Swern conditions led to the α,β-unsaturated aldehyde (138) in 82% yield. Alternatively treatment of (145) with Oxone converted the sulphide into the sulphone (137) in 78% yield (Scheme 24).

The two complementary intermediates (137) and (138) were synthesised from the common intermediate (145) with excellent control of the required C12 stereochemistry and in good overall yield. However to date there have been no reports of the incorporation of these intermediates into a synthesis of a milbemycin.

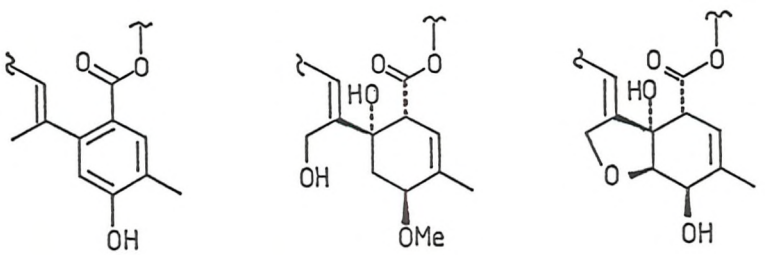

1 LDA, THF
2
3 HCl(aq)
66 %
CO2Me
(140)
VFP, Δ
SO Ar'
(139)
Ar' = 2,4,6-Triisopropyl-benzene
1 BuLi (ex)
2
3 HCl
(141)
H2, Pd/C, EtOH, 61%
(142)
1 DIBAL, -78 °C
2 Ph3PCHCO2Et, (143)
72 %
OH
CO2Et
(144)
1 PBu3, PhS-Pth 96 %
2 DIBAL, -5 °C; toluene
67 %
SPh
OH
(145)
Oxone, MeOH, 82%
SO2Ph
OH
(137)
Swern Oxidation
78 %
SPh
O
(138)

Scheme 24.

3. The synthesis of the Southern Hemisphere

In the milbemycin family there are three basic C1-C8 skeletons, of these, the aromatic segment of milbemycin β_3 is the simplest (Figure 13). The Diels-Alder reaction has emerged as the most common strategy in the synthesis of this aromatic segment (146).

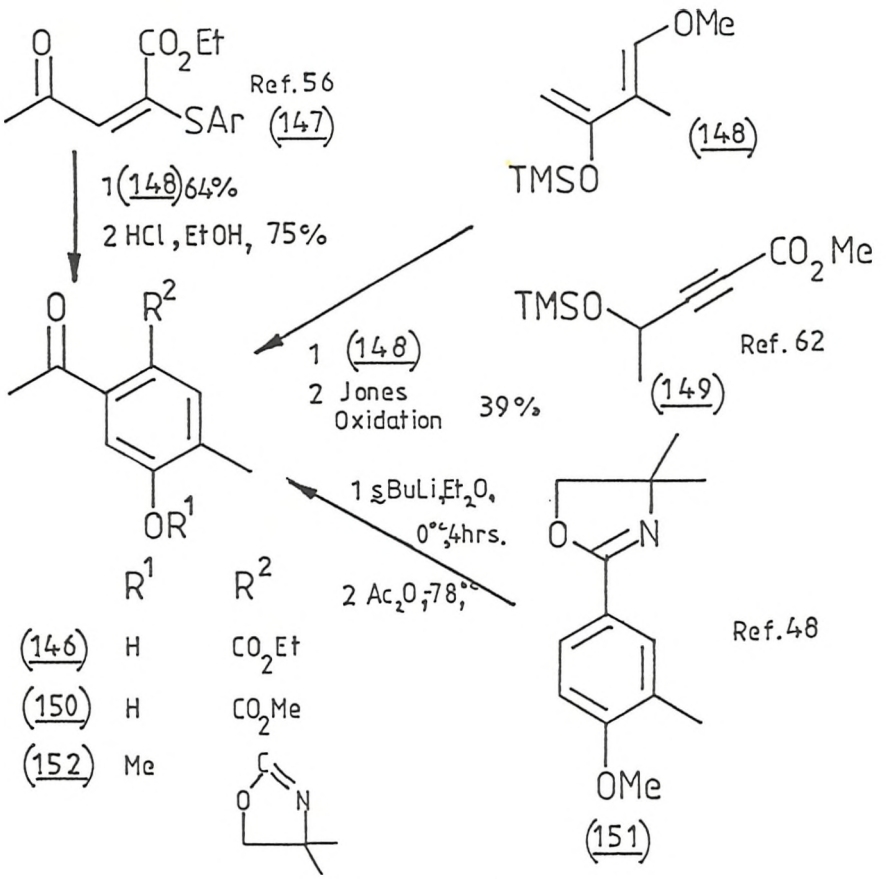
Figure 13.



Milbemycin : β_3 β_1 α_1

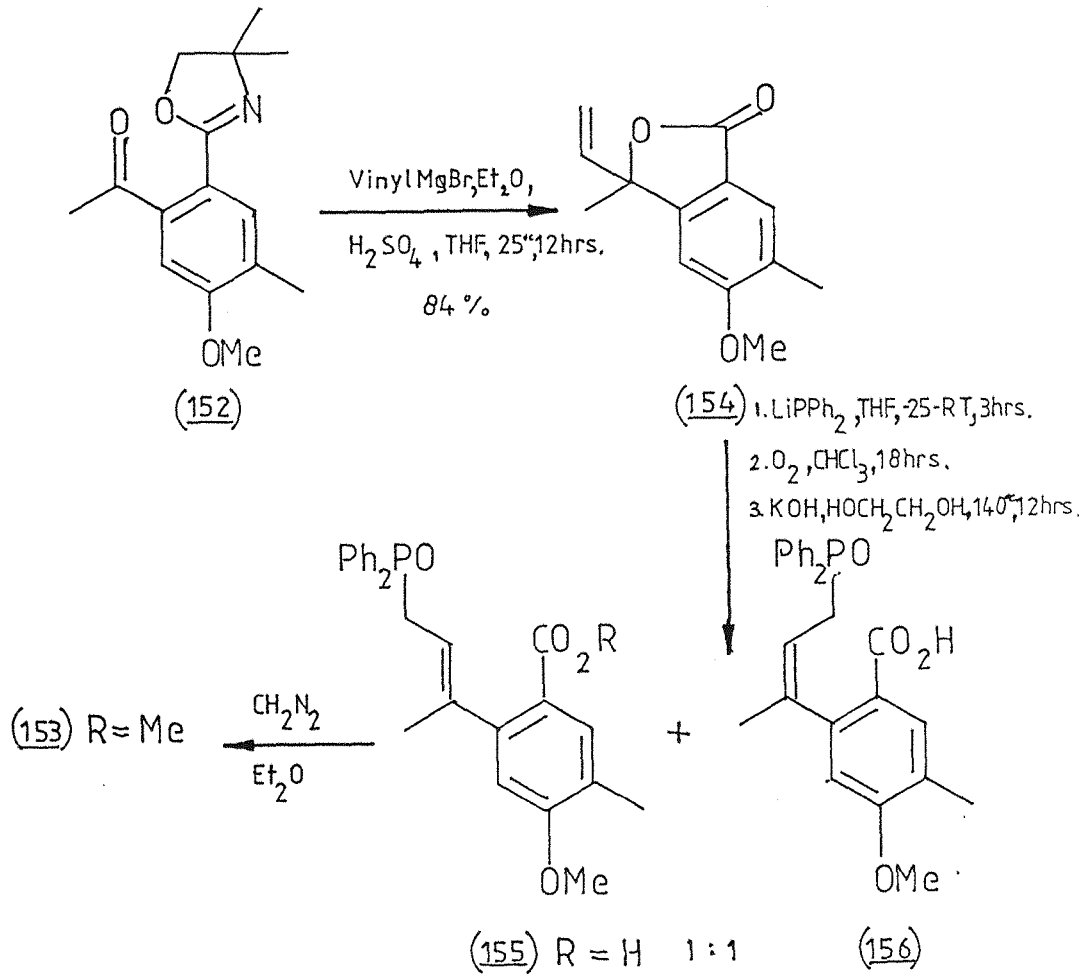
Avermectin: B series

The first published route[56] to the aromatic segment (146) involved the Diels-Alder reaction of the acetylene equivalent (147) with the highly reactive Danishefsky diene analogue (148). This afforded a 64% yield of an adduct which on treatment with ethanolic HCl effected aromatization to the methyl ketone (146) in 75% yield. The second Diels-Alder strategy[62] used the acetylene (149). Oxidation of the crude adduct to the methyl ketone with Jones reagent also caused aromatization to the analogous system (150) in 39% yield. Alternatively[48], sequential lithiation and acylation of the protected acid (151) afforded the substituted aromatic (152) as the sole product. In general, the yields for these processes are about 50% or less (Scheme 25).



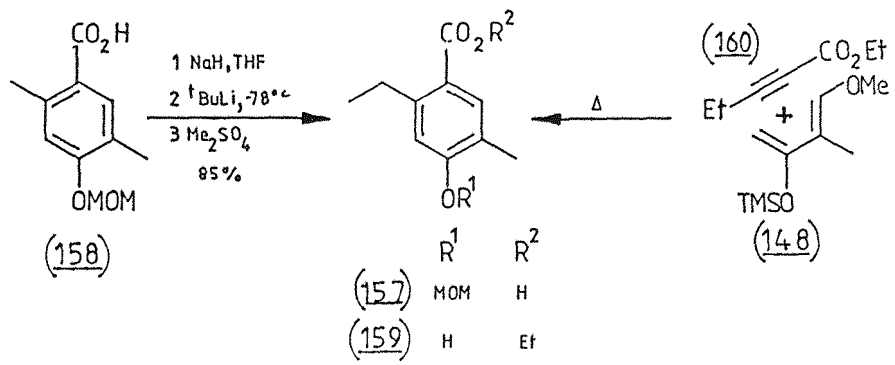
Scheme 25.

The last intermediate (152) has been used by Smith *et al*[48] to form the phosphine oxide (153). Reaction of (152) with vinyl Grignard afforded the lactone (154) in 84% yield after hydrolysis. Treatment of the lactone (154) first with lithium diphenyl phosphine and then exposure to air led to a separable mixture of the phosphine oxides (155) and (156). Treatment of this 3:1 mixture with potassium hydroxide in ethylene glycol led to a more favourable 1:1 ratio of (155) and (156). Finally, exposure of (155) to diazomethane in ether completed the synthesis of the aromatic phosphine oxide (153) required for use in coupling to the Northern Hemisphere (Scheme 26).



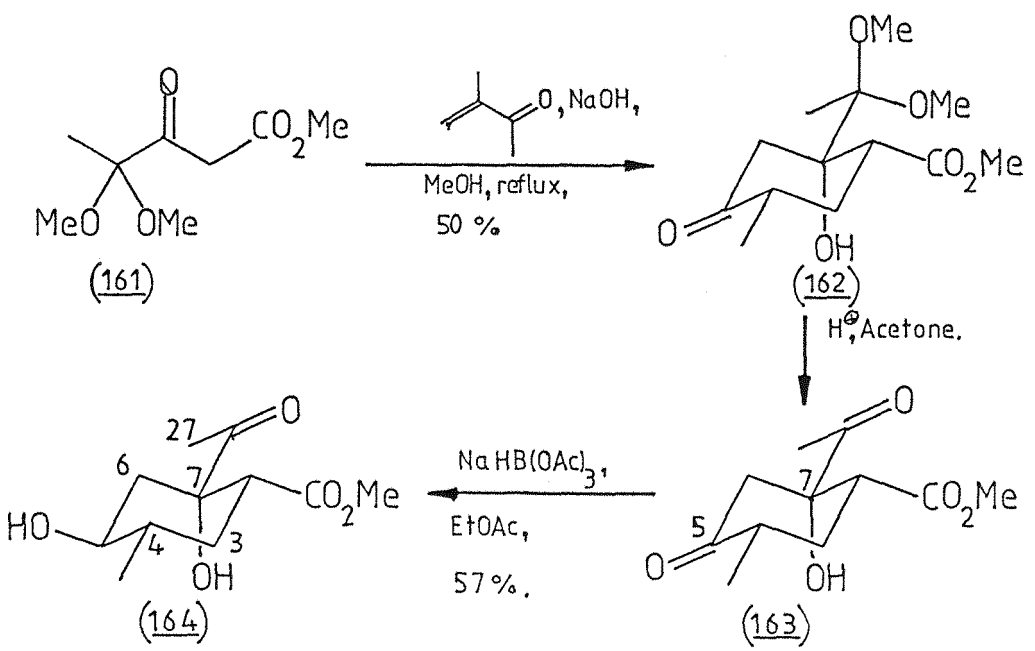
Scheme 26.

The benzoic acid (157) has been synthesised[49] in 85% yield by the methylation of the dianion of (158). Barrett *et al*[55] have yet again used a Diels-Alder strategy for the synthesis of an analogous system (159) using the acetylene (160) and the diene (148) (Scheme 27).



Scheme 27.

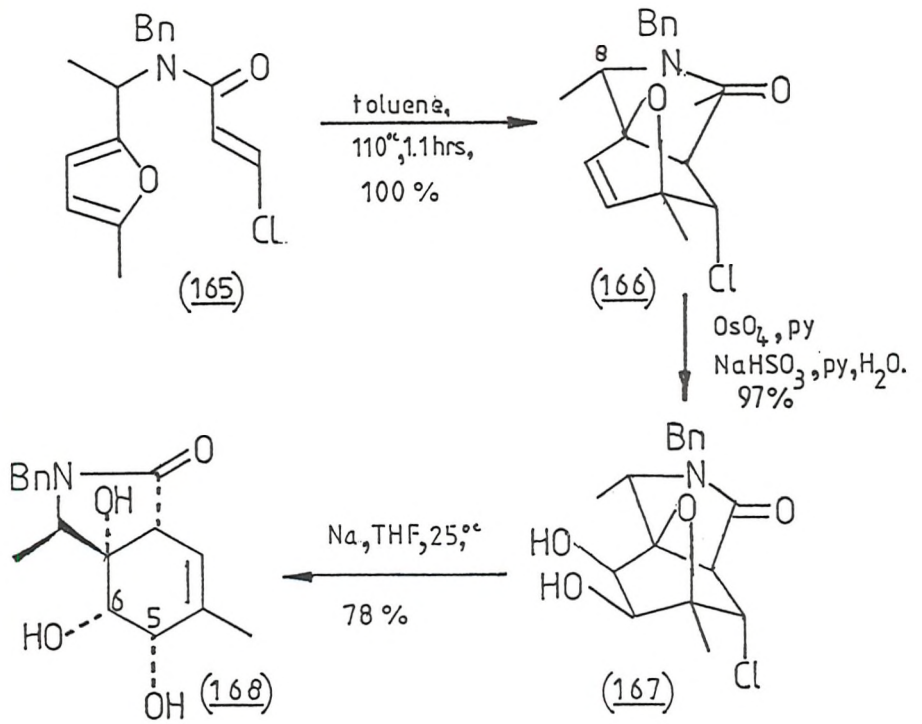
Recently a report[63] of model studies directed towards the synthesis of the more complex Southern Hemispheres based upon the Robinson annelation of a β-keto-ester with a Micheal acceptor has appeared. The reaction was found to be stereospecific if stopped prior to dehydration. Condensation of the β-keto-ester (161) with acrolein afforded the cyclic alcohol (162) in 50% yield which after deprotection of the acetal moiety using acid conditions led to the di ketone (163). Reduction of this system with sodium triacetoxy borohydride gave the diol (164) in 57% yield. Chelation of the reducing agent to the C7 tertiary alcohol directed the regio and stereo-specific delivery of hydride to the C5 carbonyl group (Scheme 28).



Scheme 28.

This approach provided a short and stereospecific entry into the highly oxygenated cyclohexane (164). Application of this promising strategy to the synthesis of the southern hemisphere of milbemycin β_1 requires the introduction of the C3-C4 double bond and allylic oxygenation at C27. The synthesis of the highly oxygenated southern hemisphere of avermectins and the ∝ series of milbemycins using this methodology would also require the construction of the C6-C27 tetrahydrofuran ring.

The intramolecular Diels-Alder reaction of the furan (165) to form the basic carbocyclic skeleton of the southern hemisphere of avermectin B_1 has been reported[64]. Hydroxylation of the Diels-Alder product (166) with osmium tetroxide afforded the diol (167) in 97% yield and reductive elimination of β-chloro-ether moiety of (167) with sodium in THF gave the β,γ-unsaturated ester in 78% yield (Scheme 29).



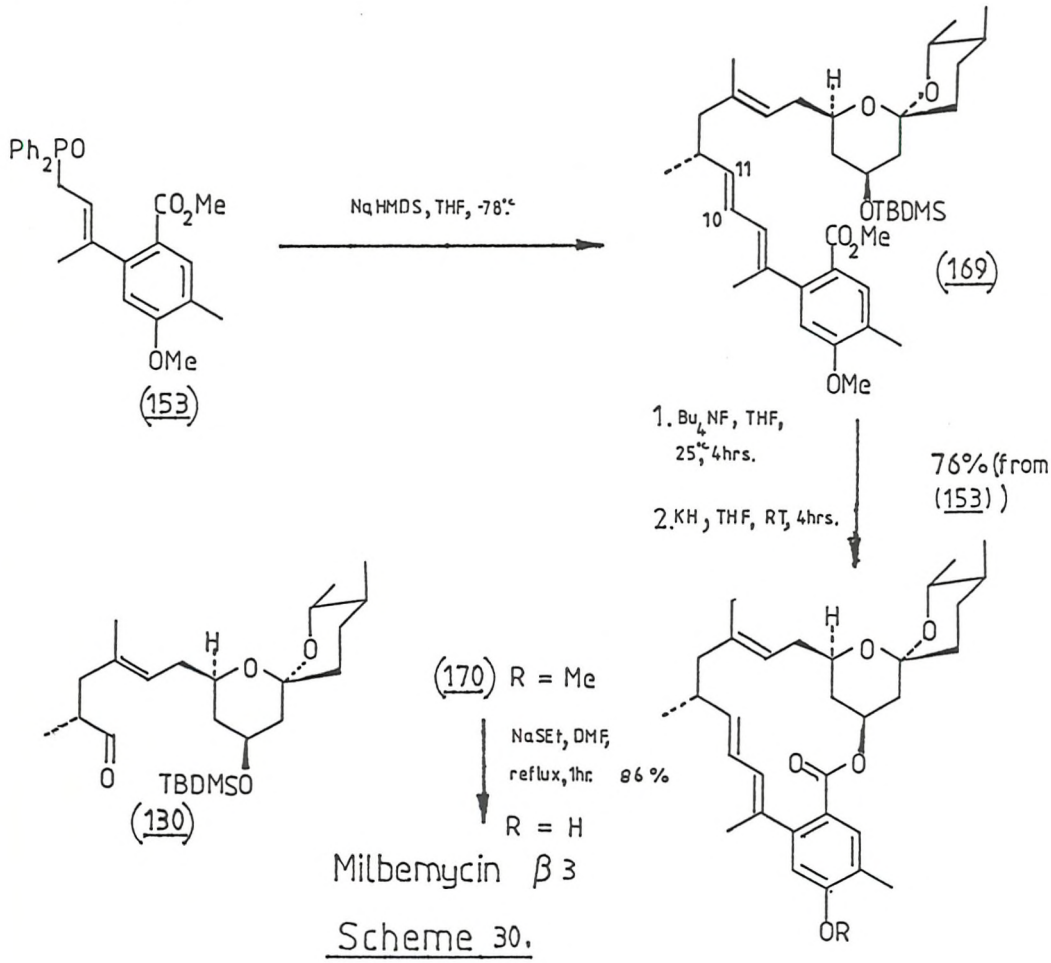
Scheme 29.

The correct relative configuration between the C2-C7 centres and the C3-C4 double bond were introduced in an elegant and high yielding manner. However the *cis* hydroxylation occurred unexpectedly from the *exo* face of (166) and was converted into the undesired C5-C6 epimeric compound (168).

4. The total synthesis of milbemycin β_3

To date only two groups[48,49] have reported the assembly of the two halves. The first successful synthesis was achieved by Smith *et al*[48] using a Wittig reaction between the phosphine oxide (153) and the aldehyde (130). Treatment of the anion of (153) with the aldehyde (130) at -78 °C afforded the diene (169) in 85-95% yield. No epimerization was seen at the C12 position but the material was shown

by NMR spectroscopy to be a 7:1 mixture of E/Z isomers about the C10-C11 double bond. Deprotection of the silyl ether moiety with fluoride ion and macrolide formation using potassium hydride gave (±)-milbemycin β_3 methyl ether (170) in 76% from (153). Removal of the aryl methyl ether group with sodium ethanethiolate in DMF was achieved in 86% yield and this completed the first total synthesis of milbemycin β_3 (Scheme 30).



Milbemycin β_3

Scheme 30.

The first synthesis of ± milbemycin employed a good strategy. Of particular note was the separation of all the stereochemical features into the northern hemisphere and the adventurous use of the Claisen rearrangement to transfer the stereochemical information from the spiroacetal moiety to the C12 position.

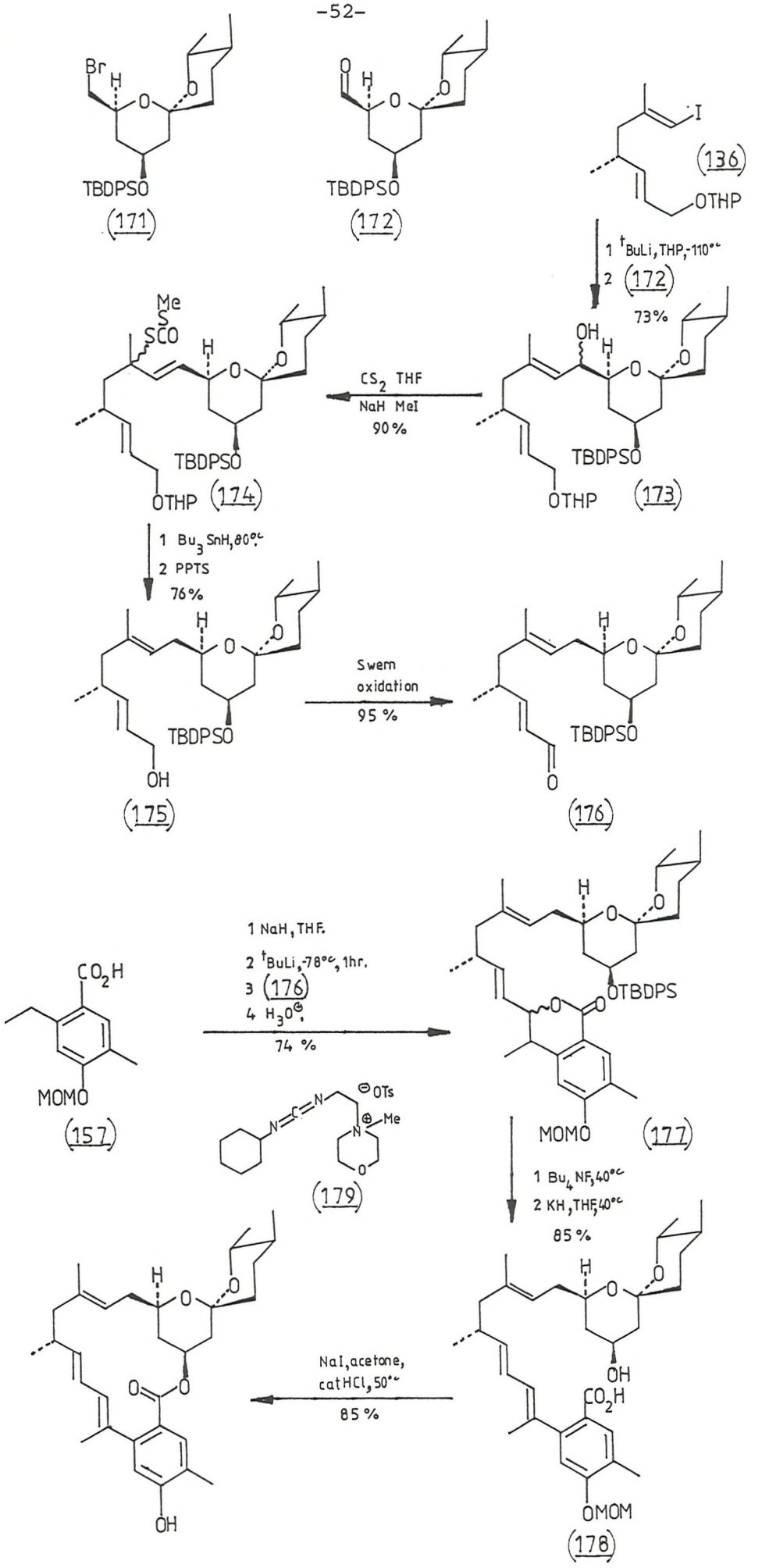
It was unfortunate that the construction of the spiroacetal was low yielding and that the route as a whole suffered from many isomeric mixtures.

The final coupling of the two halves was achieved in high yield and without the need for complex cyclization procedures.

Williams and co-workers[49] have attempted unsuccessfully to couple the vinyl lithium deviative of the vinyl iodide (136) to the bromide (171). The coupling of a vinyl lithium species with a bromide such as (171) has received considerable attention at Southampton[65], but to date only limited success with this reaction has been achieved.

Treatment of the vinyl iodide (136) with *tert*-butyllithium in THF at -110°C followed by addition of the aldehyde (172) clearly gave the allylic alcohol (173) in 73% yield. The spiroacetal bromide (171) and aldehyde (172) were available from the alcohol (61). Removal of the C15 allylic alcohol functionality proved difficult but formation of the rearranged xanthate (174) (90% yield) followed by reduction with tributyl tin hydride and deprotection afforded the E,E allylic alcohol (175) in 76% isolated yield. The authors claimed that the reduction was stereo-selective but chromatography gave a faster running fraction (ca 25%) which contained three olefin isomers which were neither separated nor fully characterized. Finally to complete the synthesis of the northern hemisphere, oxidation under Swern conditions led to the α,β-unsaturated aldehyde (176) in excellent yield (Scheme 31). Reaction of the dianion of the benzoic acid (157) with this aldehyde (176) afforded the lactone (177) in 74% yield after mild acid cyclisation. Removal of the silicon protecting group and base induced elimination gave the seco acid (178) in 85% yield. Cyclisation using the carbodiimide (179) and deprotection of the methoxymethyl ether group produced natural milbemycin β_3 in 85% yield from (177) (Scheme 31).

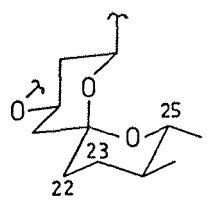
In the second total synthesis of milbemycin β_3, the coupling of the C15-C16 carbon bond proved difficult and the introduction of the C19 oxygen functionality seemed somewhat lengthy. The route employed was highly convergent and in general the first chiral synthesis of milbemycin β_3 was achieved with good control of the stereochemical features.

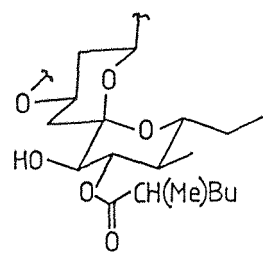

Br
TBDPSO
(171)
TBDPSO
(172)
I
(136)
OTHP
1 tBuLi, THP, -110°c
2 (172)
73%
Me
SCO
CS2 THF
NaH MeI
90%
OH
TBDPSO
OTHP (174)
TBDPSO
OTHP (173)
1 Bu3SnH, 80°c
2 PPTS
76%
Swern
oxidation
95 %
TBDPSO
OH
(175)
TBDPSO
O
(176)
1 NaH, THF.
2 tBuLi, -78°c, 1hr.
3 (176)
4 H3O⊕.
74 %
CO2H
MOMO
(157)
⊖OTs
N=C=N
⊕Me
(179)
OTBDPS
MOMO (177)
1 Bu4NF, 40°c
2 KH, THF, 40°c
85 %
Nal, acetone,
cat HCl, 50°c
85 %
OH
CO2H
OMOM
(178)
OH

Scheme 31.

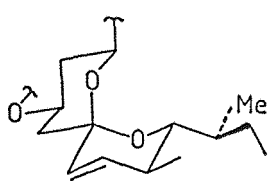
RESULTS AND DISCUSSION

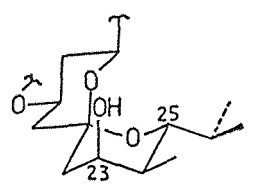
Within the spiroacetal moiety of the milbemycin/avermectin family, there are four basic ring A skeletons. The differences in substitution are confined to the alkyl groups at C25 and the increasing levels of oxidation at the C22-C23 positions. A general entry into this family of antibiotics would require the flexibility to synthesize the four analogues ideally from a common intermediate. The ring A approach would require four different lactones and a common linear methodology for the construction of the spiroacetal moiety.





Milbemycin $\alpha 1$ and $\alpha 2$ $\alpha 7$ and $\alpha 8$

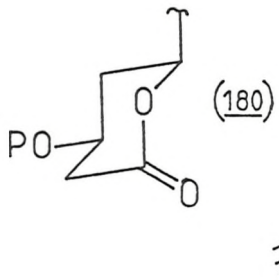




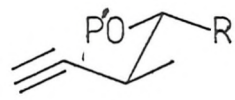
Avermectin 1a series 2b series

Figure 14. The four basic spiroacetal moieties of the milbemycin avermectin family

The chosen strategy was to couple an acetylene with a lactone[66]. The ring B of the spiroacetals (Figure 14) is a common feature of all the members of the milbemycin/avermectin family and this fact suggested that the lactone could be derived from a lactone of the type (180). It was also envisaged that the use of the acetylene (181) would provide the latent functionality to produce all four ring A skeletal analogues.



(180)



(181) R=Me, Et, ^{i}Pr or ^{s}Bu.

Figure 15.

The plan was to incorporate the spiroacetal unit into a synthesis of a milbemycin /avermectin skeleton by the displacement of a leaving group by a vinyl organometallic species eg (182). This required the lactone (180) to have the structure (183) and this in turn suggested a carbohydrate precursor. Levoglucosan (184) provided several of the features required for the synthesis of the lactone (183). In particular, the anhydrosugar (184) provided the required absolute stereochemistry of the lactone (183) at C19 and C17 positions and also the oxygenation at C21 and C16. The first apparent disadvantage is that the two remaining alcohol groups (C2 and C4 of (184)) must be removed (Figure 16).

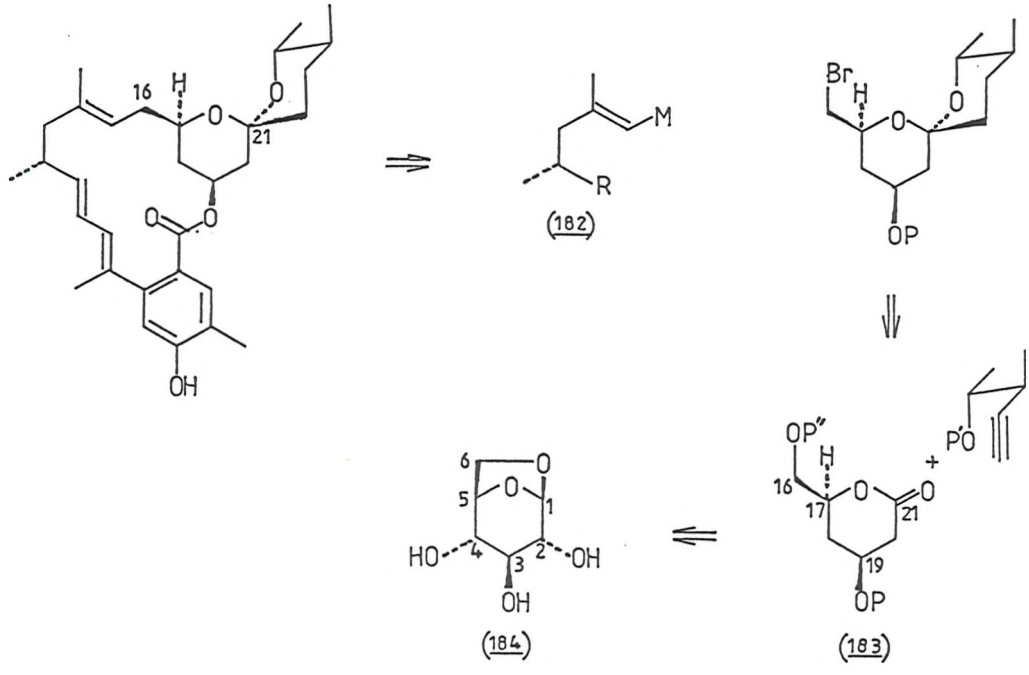
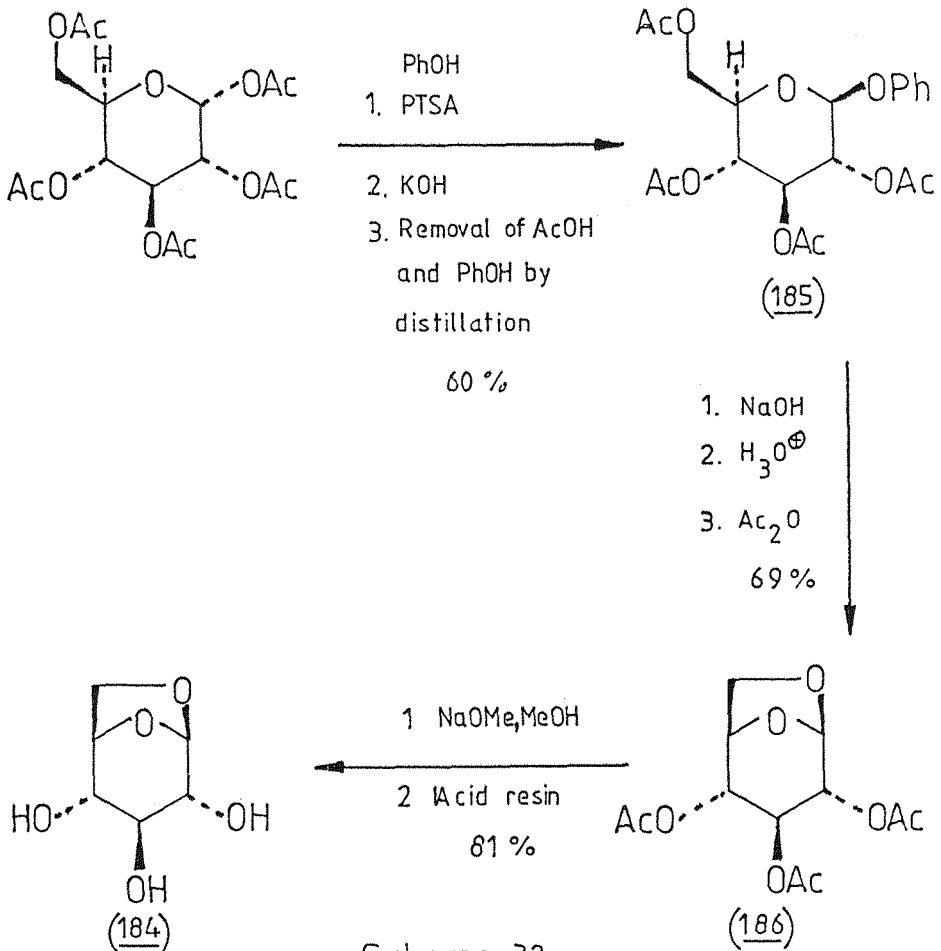


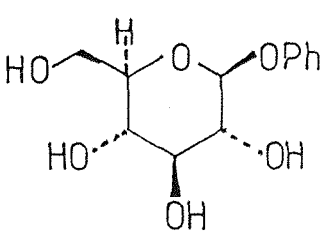
Figure 16.

Synthesis of levoglucosan

The synthesis of anhydro sugars has been comprehensively reviewed by Černý and Stanek[67]. The pyrolysis of starch[68,69] provides the shortest route to levoglucosan (184). However initial results suggested that this route was not a viable approach because of the difficulty in obtaining and purifying the crude levoglucosan. The alternative literature approach[70] which proved adequate is shown in Scheme 32. The major drawbacks in this route were firstly in the formation of phenyl tetra acetyl-β-D-*gluco* pyranoside (185)[69] and the subsequent treatment of this glycoside with aqueous base. Due to difficulties in purification, the crude levoglucosan was acetylated to afford the crystalline triacetate (186)[69] in 69% yield. Removal of the acetate groups[68] with 1% sodium methoxide in methanol afforded the crystalline levoglucosan (184) in 81% yield (Scheme 32). Recently the treatment of phenyl-β-D-*gluco* pyranoside (187) with aqueous potassium hydroxide has been reported[71] to afford levoglucosan (184) directly. This type of procedure has been reported elsewhere[72] but required the use of high dilution conditions and the subsequent difficulties in handling of the crude products have been overcome by the use of various acidic and basic conditions[73].



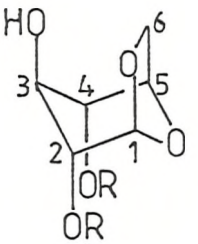
Scheme 32



(187)

Synthesis of 1,6-anhydro-2,4-dideoxy-β-D-*threo* hexopyranose

At this stage, the removal of the C2 and C4 alcohol groups was accomplished by reduction of the ditosylate (188). Treatment of levoglucosan (184) under the literature conditions[74] (tosyl-chloride in dry acetone and pyridine) afforded a virtually quantitative yield of the 2,4-ditosylate (188). The C2 and C4 alcohol groups were selectively derivatized in the presence of the C3 alcohol moiety because of the interaction of the C3 hydroxyl functionality with the 1,6-anhydro bridge.



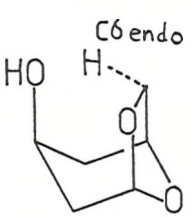
(184) R=H

TsCl, py,
Acetone, RT,
5 days.

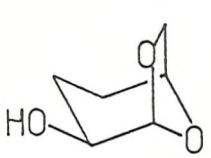
(188) R=Ts

Scheme 33.

Reduction of this ditosylate (188) was achieved according to the method of Kelly and Roberts[75]. Treatment of the crude ditosylate (188) in dry THF at 0°C with lithium triethylborohydride (5 eq) afforded a crude oil, after oxidative workup and continuous extraction of the aqueous reaction mixture with dichloromethane. Purification of the crude material, which contained up to 50% of the mixture of alcohols (189) and (190), was best achieved by chromatography on Florosil using ether as the eluant and not as previously described[75] by extraction of the crude material with hot ether. This afforded a 75% yield of the mixture of alcohols (189) and (190) (from levoglucosan (184)).

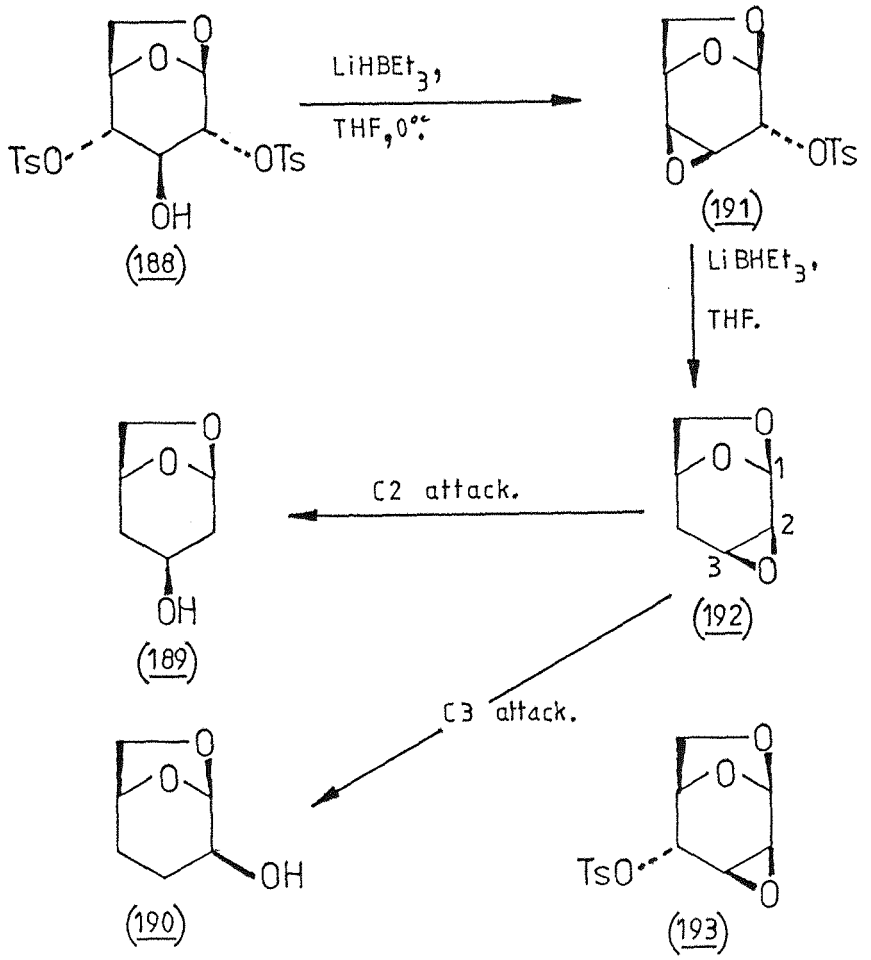


(189)



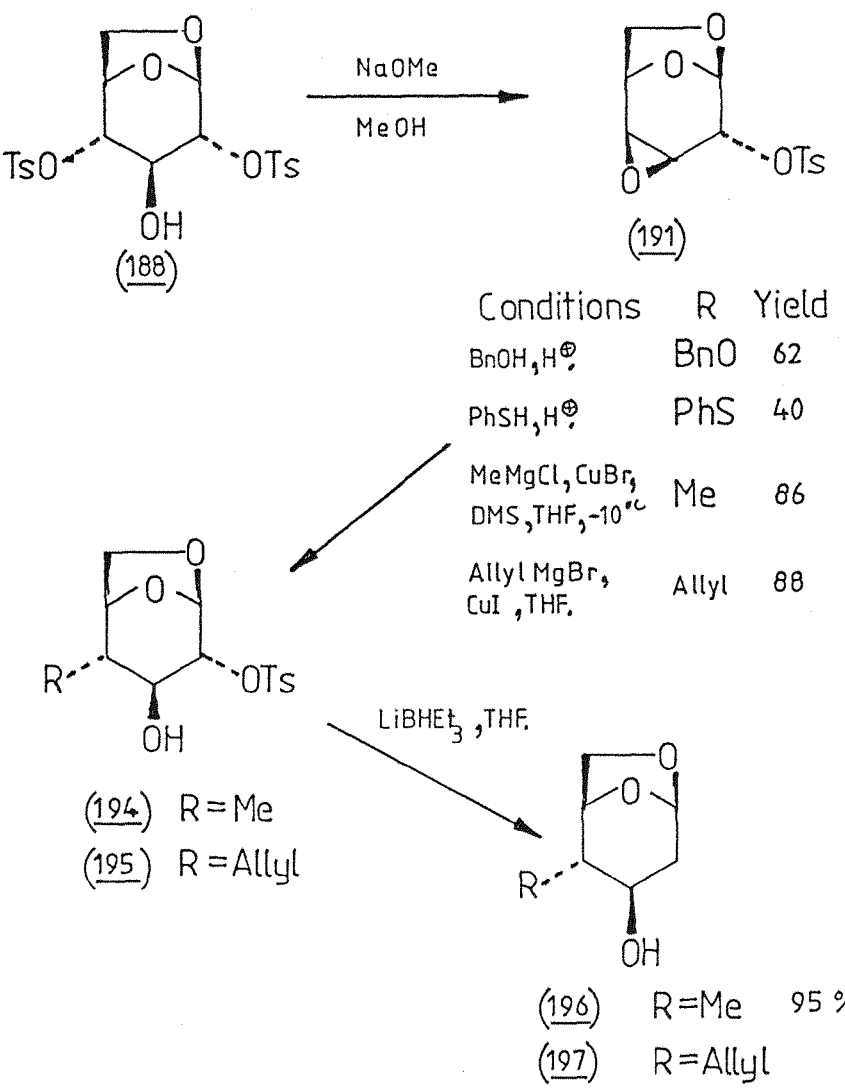
(190)

The anomeric proton (C1) of (189) at δ 5.6 was clearly separated from the isomer (190) at δ 5.2 and the 1,6-anhydro bridge was obviously intact as shown by the presence of the doublet at δ 4.4 (J = 7 H_z) of the C6 *endo* hydrogen. This reduction has been shown[75] to proceed *via* the 3,4 epoxytosylate (191) which is in turn converted into the 2,3 epoxy compound (192). These intermediates have been isolated[75] from the reaction mixture by preparative tlc and in the initial study[75], the effect of the reducing agent on the epoxide (192) was mentioned. If lithium triethylborohydride was used, the ratio of (189) to (190) was 4.5:1 but Černý *et al* [76] found that the use of lithium aluminium hydride changed this ratio to *ca* 2:1. The ratio of (189) to (190) is also dependant on the mode of attack of the reducing agent on the epoxide (192). If attack occurs at C2, it does so in a preferred *trans* diaxial ring opening of the epoxide moiety but displacement at C2 is disfavoured by the inductive effect of the β oxygen atoms of the internal acetal functionality at C1 (Scheme 34).



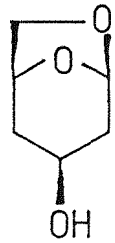
Scheme 34.

This inductive effect may account for the preferential formation of the 3,4 epoxytosylate (191) over the corresponding 2,3 epoxytosylate (193). In fact, treatment of the ditosylate (188) with sodium methoxide in methanol afforded the proposed intermediate (191) in 70% yield[77]. This system (191) has been treated with oxygen[74], sulphur[78] and carbon[71,79] nucleophiles and in the last case, analogous reduction of the products ((194) and (195)) gave the alcohols((196) and (197) respectively) as the sole products in excellent yield. This selectivity may be explained by the increased steric hinderance provided by the C4 alkyl group.

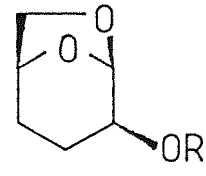


Scheme 35.

The isomeric ratio of (189) and (190) was determined in two ways, by glc analysis (FFAP) of the mixture of (189) and (190) and by nmr spectroscopy, by comparison of the integration of the anomeric protons of (189) and (190). This ratio was found to be 8:1 which was considerably higher than previously reported[75] although it was found on one occasion to be as low as 3:1. With this mixture (189) and (190) in hand, the literature procedure[75] of separation was attempted. This relied upon the selective silylation (trimethylsilyldiethylamine, ($TMSNEt_2$) in dry acetone) of the equatorial hydroxyl group of (190) in the presence of the hindered axial alcohol moiety of (189). As soon as it was indicated (glc analysis FFAP) that the alcohol (190) had disappeared, the reaction mixture was poured into water and the water extracted with pentane to remove the silyl ether (198). Back extraction of the aqueous layer with dichloromethane afforded the desired 1,6-anhydro alcohol (189) in 80% yield.

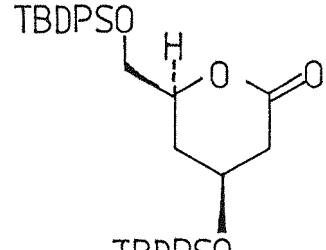


(189)



(190) R=H

(198) R=TMS

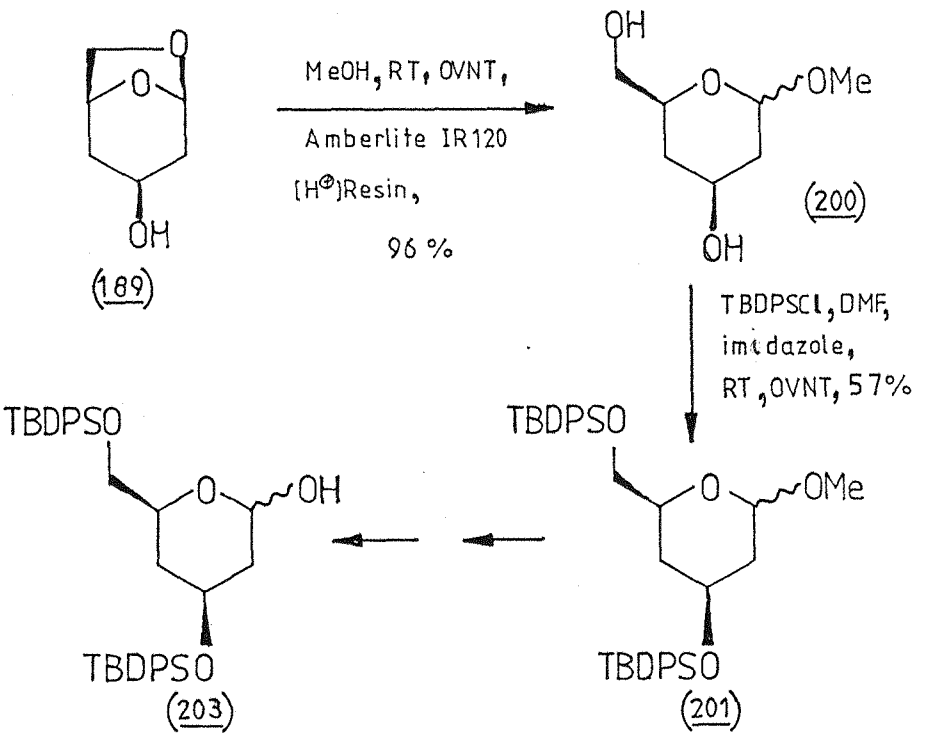


(199)

Attempted synthesis of the lactone (199)

The initial target lactone was the disilyl protected species (199). Treatment of the alcohol (189) with Amberlite IR120 (H^+) resin in dry methanol[79] afforded the methyl glycoside (200) as a mixture of anomers in 96% yield. The structure of this material was confirmed using nmr spectroscopy where the incorporation of methanol could easily be seen by a three proton singlet at δ3.3 and the loss of the strained 1,6-anhydro bridge was clearly evident by the shift in the anomeric proton from δ5.6 to δ4.9. Conversion of this diol (200) to the diprotected methyl glycoside (201) was achieved in 57% yield by the standard conditions[80] of

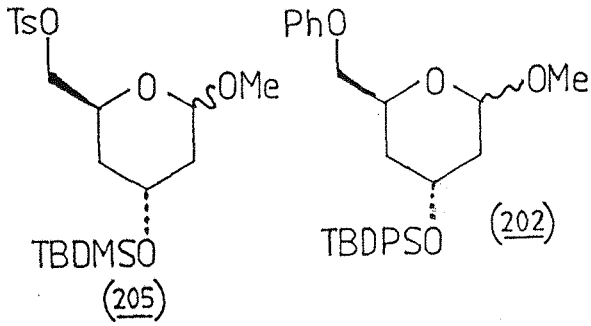
1-*tert* butyl-1-chloro-1,1-diphenylsilane (TBDPSCl) and imidazole in dry DMF. Mass spectral evidence showed the incorporation of the *tert* butyl diphenyl silyl moiety and the nmr spectrum clearly showed the *tert* butyl group at δ0.9(s) and the diphenyl moiety (δ7.6 m). Also evident was the anomeric proton (C1) at δ4.6 and the expected methyl group of the glycoside moiety (δ3.1)(Scheme 36).

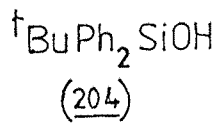


Scheme 36

Deprotection of the methyl glycoside (202), which also contained a secondary *tert* butyl diphenyl silyl ether group, was achieved using the conditions of acetic acid/THF/water (3:2:2) at 70 °C for 16 hours[81]. However the use of these conditions on the diprotected methyl glycoside (201) did not afford the lactol (203) but clearly produced the silyl alcohol (204) as the only isolated product. Later Heathcock *et al*[82] found that the TBDMS ether group of the methyl glycoside (205) was not stable to the conditions required for the hydrolysis of the methyl glycoside linkage. The deprotection of the methyl glycoside (201) was not

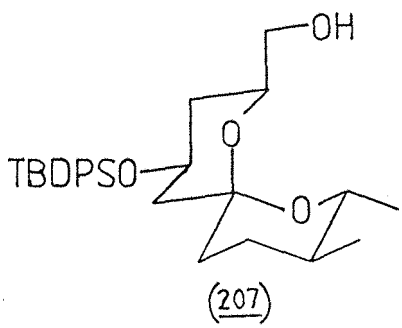
attempted again and this approach to the lactone (199) was abandoned due to a more attractive entry into a related system.

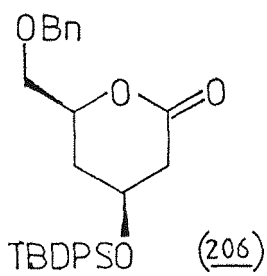


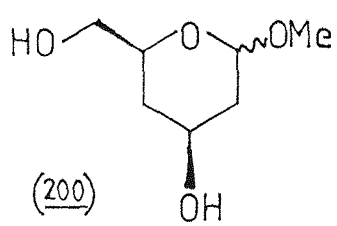


Synthesis of the differentially protected lactone (206)

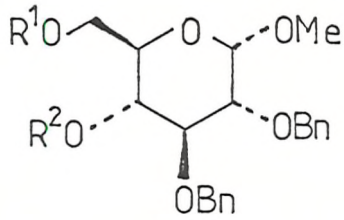
In the initial strategy towards a synthesis of milbemycin β_3, it was planned to protect the C19 oxygen functionality as a stable *tert* butyl diphenyl silyl ether eg(207). If the formation of this silyl ether moiety was incorporated at an early stage a protection/ deprotection sequence would be avoided. The benzyl group was chosen to protect the primary alcohol functionality because it can be removed using several mild methods[83] and is stable to both acidic and basic conditions. The target lactone then became the compound (206) but this required the selective benzylation of the C16 (6) alcohol group of the methyl glycoside (200).







The benzylation of a primary alcohol functionality in the presence of a secondary alcohol group is known to be plagued by formation of mixtures of mono and di-substituted products. In certain cases, a high degree of selectivity in the alkylation of the glycoside (208) has been achieved by the use of phase transfer catalysis[84] (Scheme 37).



(208)

R^1	R^2	Yield
H	H	

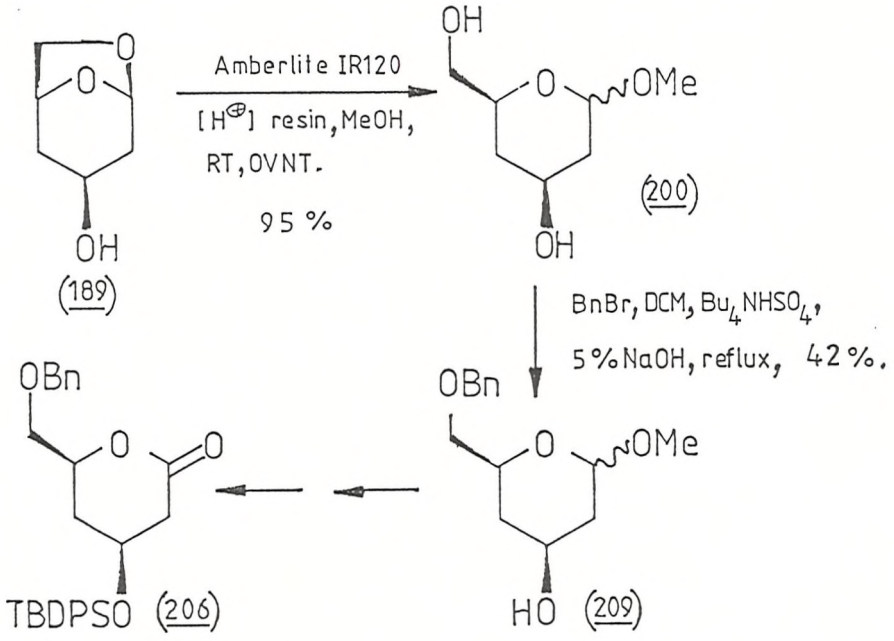
BnBr, Bu_4NHSO_4, DCM, 5% NaOH, reflux, 48hrs.

Bn	H	68 %
H	Bn	18 %

Scheme 37

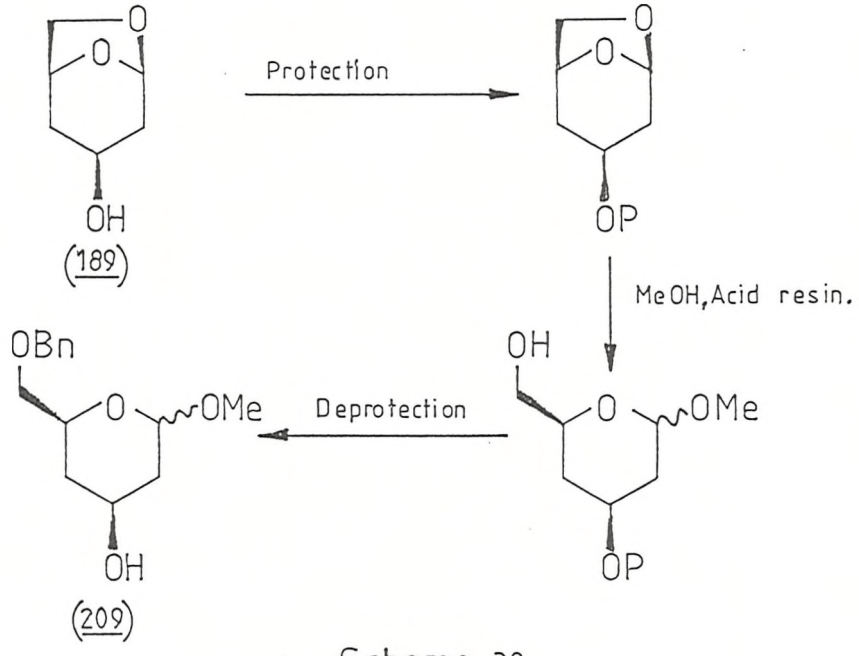
Selective monoprotection was attempted using similar phase transfer conditions and this afforded the presumed primary benzyl protected compound (209) in 42% yield. Mass spectral evidence suggested that the C6 benzyl protected species was obtained because of the ion at m/e 131 (5%, $M^+-C_7H_7-CH_2O$) which is due to the cleavage of the C5-C6 bond. Evidence for some contamination was obtained by the tlc which showed a fast fading light blue spot immediately below the product spot, but this could not be detected by glc or nmr. This route to the lactone (206), was not pursued further because of the length of reaction time, the high water solubility of the diol (200) and the low yield involved in the transformation {(200) to (209)} (Scheme 38).

An alternative strategy for the synthesis of the lactone (207) involves the protection of the secondary alcohol groups of 1,6-anhydro-2,4-dideoxy-βD-*threo*-hexopyranose (189) followed by acid catalysed ring opening to free the primary alcohol moeity. Conversion of this hydroxyl functionality into a benzyl ether and deprotection of the secondary alcohol group would afford



Scheme 38

the key intermediate (209). Such a protecting group, P, would have to survive both acidic and basic conditions and be easily introduced (Scheme 39).

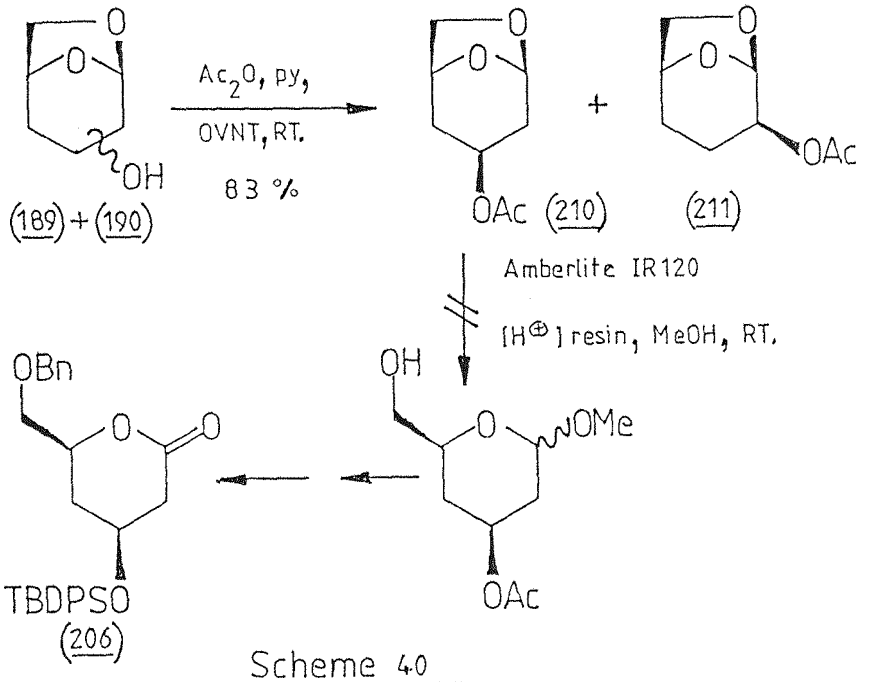


Scheme 39

At this stage, attempts to separate the mixture of alcohols (189) and (190) by the literature procedure[75] as described previously, or by a similar selective derivatization with the more hindered TBDMS chloride, failed to afford the alcohol (189) after back extraction with dichloromethane. Although glc analysis indicated the selective reaction of the minor isomer (190), the same isomeric ratio and glc trace was obtained on workup. Later it was found that this separation could be achieved if the reaction mixture was first poured into pentane and the alcohol (189) extracted into water. Saturation of the aqueous layer with potassium carbonate and the subsequent back extraction with dichloromethane afforded the alcohol (189).

Initially, the acetate group was chosen because it was known that the two acetate esters (210) and (211) could be separated by chromatography[85] and so avoid the need for a selective silylation which at the time proved troublesome. Acetylation of the mixture of alcohols (189) and (190) according to the literature conditions[85] afforded an 83% yield of the desired ester (210) after chromatography. The acetate (210) showed an expected shift in the C3 proton (from δ4.1 to δ5.1) and the doublet at δ4.2 (J = 7Hz) was indicative of the C6 *endo* proton showing that the 1,6 anhydro bridge was still intact. Acid catalysed methanolysis of the 1,6 anhydro bridge of (210), as described before, afforded a complex mixture of products as shown by nmr spectroscopy and chromatographic analysis (Scheme 40).

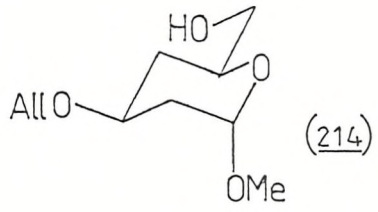
An alternative protecting group was sought and the allyl ether moiety[83,86] seemed to meet all the requirements of stability, steric bulk and ease of protection and deprotection. Treatment of the sodium alkoxide of the mixture of alcohols (189) and (190) with allyl bromide afforded the allyl ethers (212) and (213). Chromatographic separation gave the major allyl ether (212) in 57% yield. Once again the nmr spectrum showed the doublet at δ4.3 (J = 7Hz) indicated that the 1,6-anhydro bridge was present and the complex multiplets centred at δ4.15, δ4.25 and δ4.9 and the doublet at δ4.0 showed the expected incorporation of the allyl protecting group. Treatment of this cyclic anhydro compound (212) with the acid resin, Amberlite IR120, in methanol afforded the mixture of methyl



Scheme 40

glycoside (214) in 95% yield. Cleavage of the 1,6-anhydro bridge could be inferred by the shift in the anomeric (C1) proton from δ5.1 to δ4.85 and the incorporation methanol was shown by the singlet at δ3.3. The loss of methanol from the glycoside could be seen in the mass spectrum at m/e = 171 (M^+-OMe,19%) and the presence of the alcohol group was evident by the O-H stretch at ν = 3440 m^{-1} in the infra red spectrum.

The 100 MHz nmr spectrum of the methyl glycoside (214), shown in figure 17, was subjected to decoupling experiments. The allyl group was easily assigned and irradiation at C1 simplified the C2 and C3 splitting patterns into the expected AMX system of the vinyl moiety. The two converging sets of multiplets at δ1.8 - δ2.2 could not be separated but were simplified by irradiation at C1(δ4.9) to two sets of overlaping 4 and 5 line multiplets. This irradiation also simplified the down field signals at δ1.1 - δ1.7 but once again full assignment could not be obtained. Further irradiation at C3 diol simplify this region but it did not prove that informative. Further decoupling studies were not successful and did not simplify the spectral data.



(214)

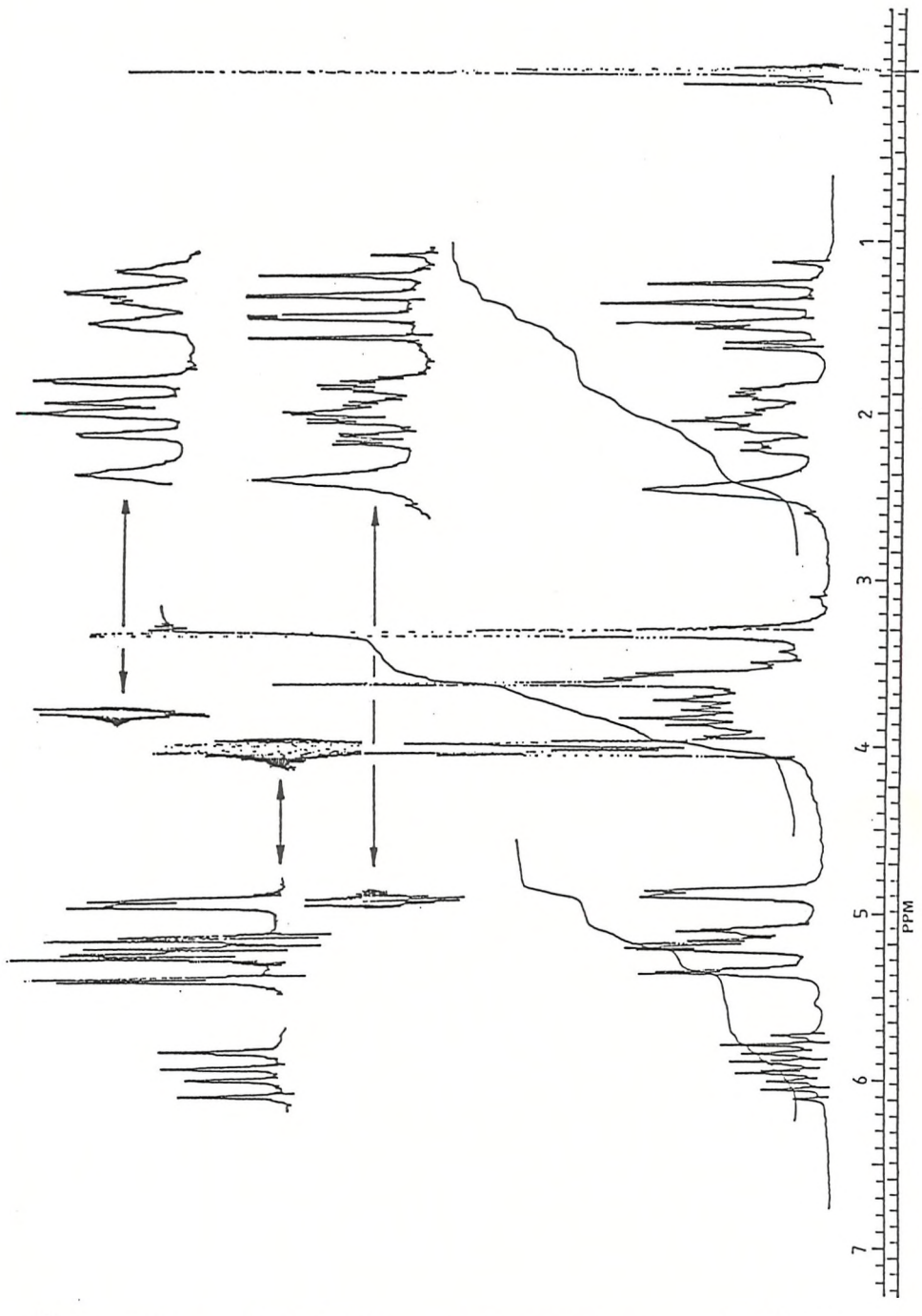
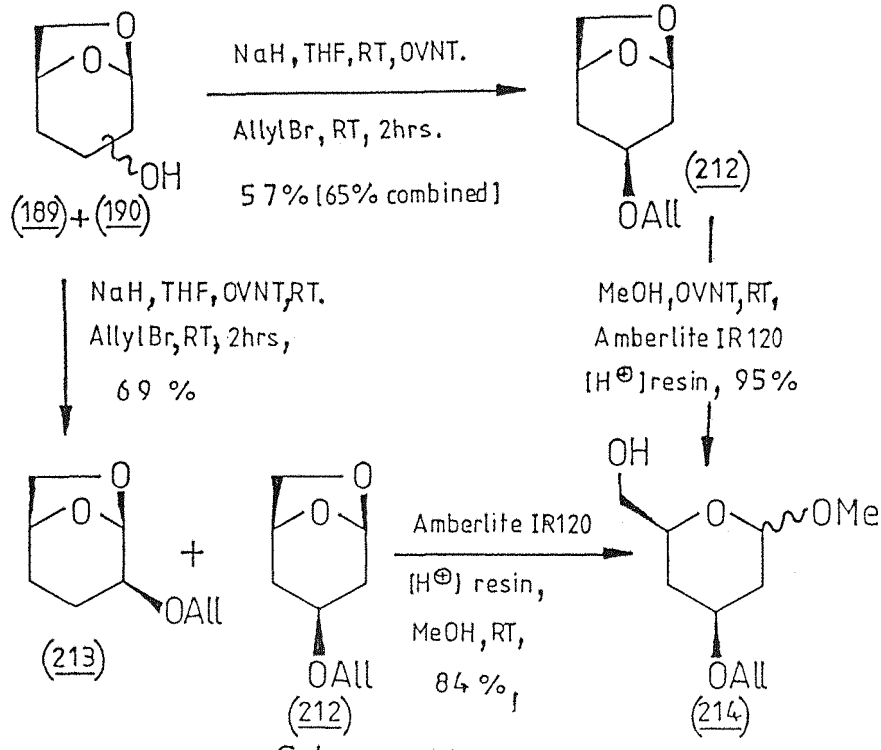


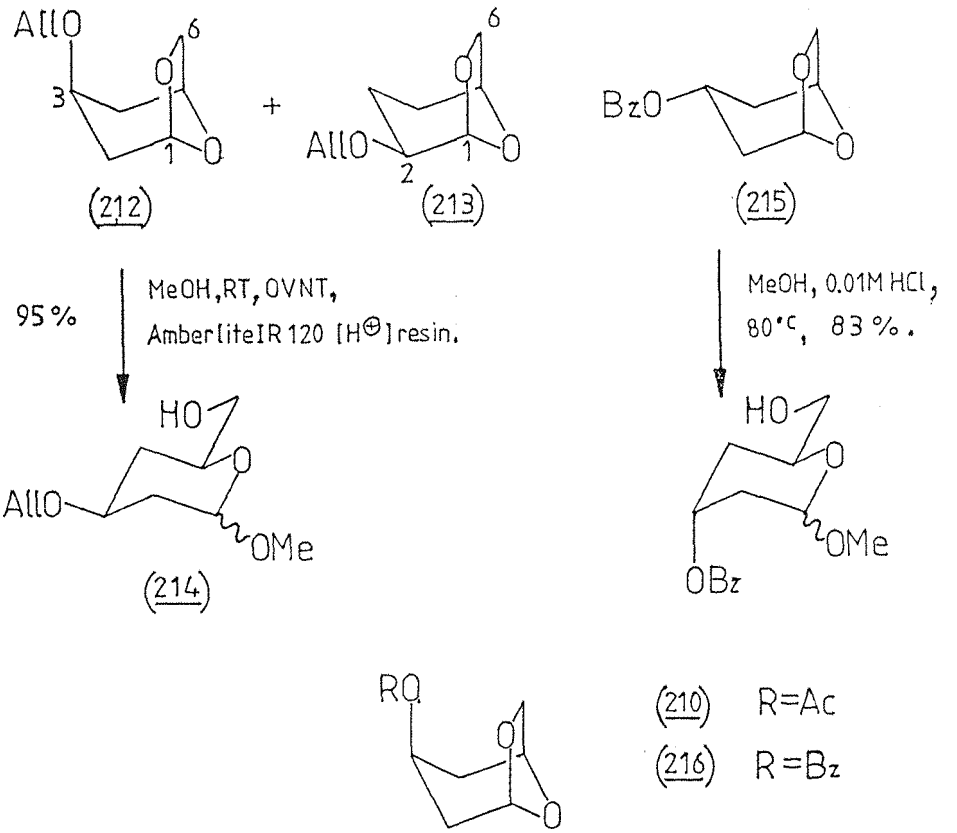
Figure 17. A 100 MHz NMR spectrum of (214).

In monitoring the reaction by glc (OV101), it was observed that an impurity peak (*ca* 1%), which was assumed to be the C2 allyl ether (213) remained inert towards these acidic conditions whereas the C3 allyl ether (213) was converted into the methyl glycoside (214). With this observation in mind, the mixture of ethers (212) and (213) was treated with Amberlite IR 120 (H^+) resin in dry methanol and, as expected from the earlier result, only the required ether (212) underwent reaction giving the mixture of methyl glycosides (214) in 84% yield (Scheme 41).



Scheme 41

The ease with which the internal acetal moiety of the 1,6 anhydro compound(212) was cleaved may be due to the release of the 1,3 diaxial interactions between the 1,6-anhydro bridge and the axial C3 substituent. In the case of the isomeric ether (213), the interactions between the 1,6 anhydro bridge and the C2 substituent are considerably reduced and so the ether (213) appears inert under the reaction conditions (Scheme 42).



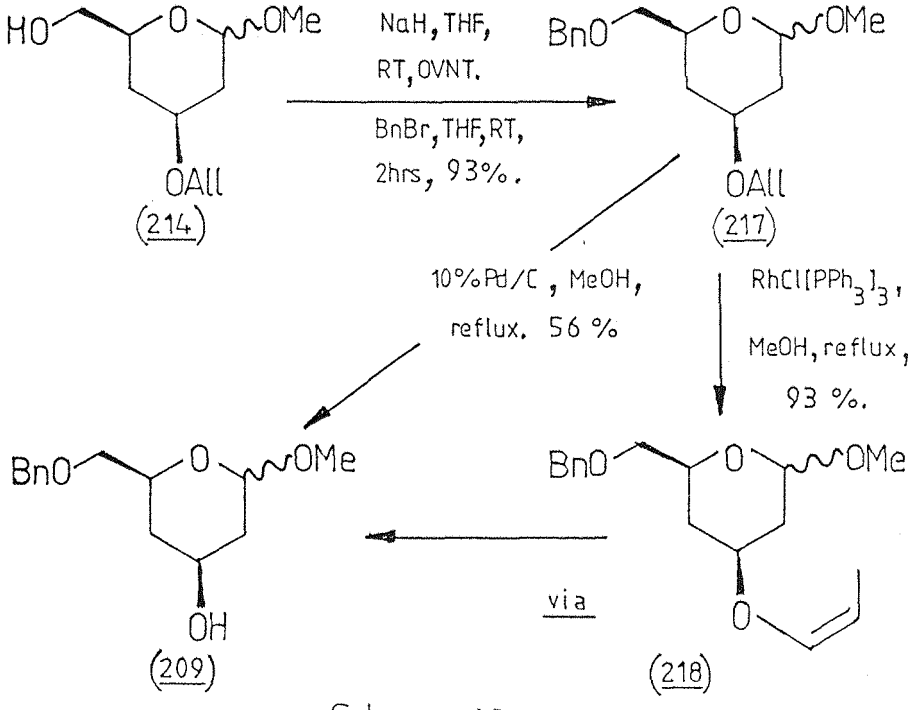
Scheme 42

A recent and related opening of the benzoate derivative (215)[87] required the use of more forcing conditions and in this case the equatorial C3 substituent suffers virtually no steric interactions with the 1,6-anhydro bridge. No discrete products were isolated when the acetate (210) was treated with an acid resin in methanol (Scheme 40) and, in retrospect, a more stable derivative, such as a benzoate ester (216), might have proved a better choice (Scheme 42).

Alkylation of the alcohol (214) was achieved by formation of the sodium alkoxide followed by the subsequent treatment with benzyl bromide afforded the methyl glycoside (217) in 93% yield. Having obtained the differentially protected compound (217), the selective removal of the allyl protection was required. Of the methods

available[88], the most appropriate appeared to be the use of 10% palladium on carbon in refluxing methanol[89]. The allyl ether moiety is initially rearranged by the transition metal catalyst into an intermediate enol ether which is then hydrolysed into its deprotected alcohol and propionaldehyde. Treatment of the allyl ether (217) with 10% palladium on carbon in refluxing methanol slowly formed a more polar species.

After 48 hours, a 56% yield of the deprotected alcohol (209) was obtained together with 30% of the parent allyl ether (217). A superior method of deprotection was sought because of the poor conversion of the palladium catalyst system and Wilkinson's catalyst ($RhCl(PPh_3)_3$) in refluxing ethanol has been used for the deprotection of an allyl ether[90]. In this application, methanol was used as solvent to avoid exchange at the anomeric centre and the allyl ether (217) and Wilkinson's catalyst (tris triphenyl rhodium(1)chloride) was heated to the point of reflux and after about 20 minutes a *less* polar spot appeared by chromatography analysis. After about 2 hours, all the reaction mixture appeared to have been converted into this less polar component which was assumed to be the enol ether (218)[91]. The reaction mixture was left at the point of reflux overnight and only a more polar spot, which was of identical Rf to the alcohol (209) could be seen by chromatographic analysis. One solution of this material by column chromatography showed it to be identical to the alcohol (209) (Scheme 43).



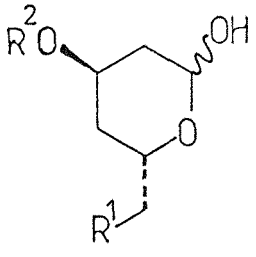
Scheme 43

Formation of the alkoxide anion by treatment of the alcohol (209) with sodium hydride in dry THF overnight and the subsequent additional-*tert* butyl-1,1-diphenyl silyl chloride (1.1 eq) afforded the silyl ether (219) in 80% yield. The loss of the alcohol group in the spectrum was clearly evident and the incorporation of the *tert* butyl diphenyl silyl moiety was seen both in the nmr {δ0.9,s,9H) and (δ7.4,m,15H)} and in the mass spectrum (m/e = 199,24%,($Ph_2SiO^{+}_{-1}$)). The use of the potassium bases in highly oxygenated substrates is known to be superiour to the sodium analogues. Although the use of potassium hydride, in this case did increase the yield slightly (80% to 84%) but increased difficulties in handling and workup of reaction did not justify the use of the potassium alkoxide.

With this material (219) in hand, the unveiling of the C1 lactol moiety was attempted. The first conditions employed were those used in the deprotection of an analogous intermediate (203) by Yang and Falck[81]. However treatment of the methyl glycoside (219) with a mixture of acetic acid/THF/water (3:2:2) at 70 °C for 8 hours resulted in the formation of an emulsion from which the lactol (220) could not be observed in the nmr spectrum or by the analysis of the reaction mixture. It was considered that the silyl ether (209) was not actually dissolved in the aqueous phase so alternative one phase conditions were sought. The silyl ether (219) was dissolved in THF and the 1M.HCl was added until an emulsion had just started to form and then THF was added so that a one phase system was formed. The reaction mixture was heated to the point of reflux until the analysis indicated than an unknown side product had started to form (*ca* 7 hours). This resulted in in a 52% yield of a more polar component which was presumed to be the lactol (220) and a 37% yield of recovered starting material. An nmr of this more polar material showed the loss of the methyl group at δ3.1, the expected shift in the anomeric proton from δ4.6 to δ5.3. Further spectral evidence substantiated the removal of the methyl glycoside moiety by the presence of an O-H stretch in the infrared spectrum at 3500 cm^{-1} and the appearance of the molecular ion 14 mass units lower than that obtained previously. With these high molecular weight silyl ethers, the molecular ion could only

be detected if chemical ionization conditions were used because the *tert*-butyl diphenyl silyl moiety as well as the benzyl group and the methyl glycoside functionality fragment quickly in the mass spectrometer.

Two methods which have recently been used for this transformation in the related *erythro* system are pyridinium chlorochromate (PCC)[81] and Fetizon's reagent (silver carbonate on Celite)[92]. Considering the nature and substitution of the intermediates (202) and (221) (Figure 18), the reagent chosen must not



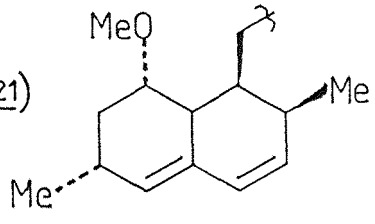
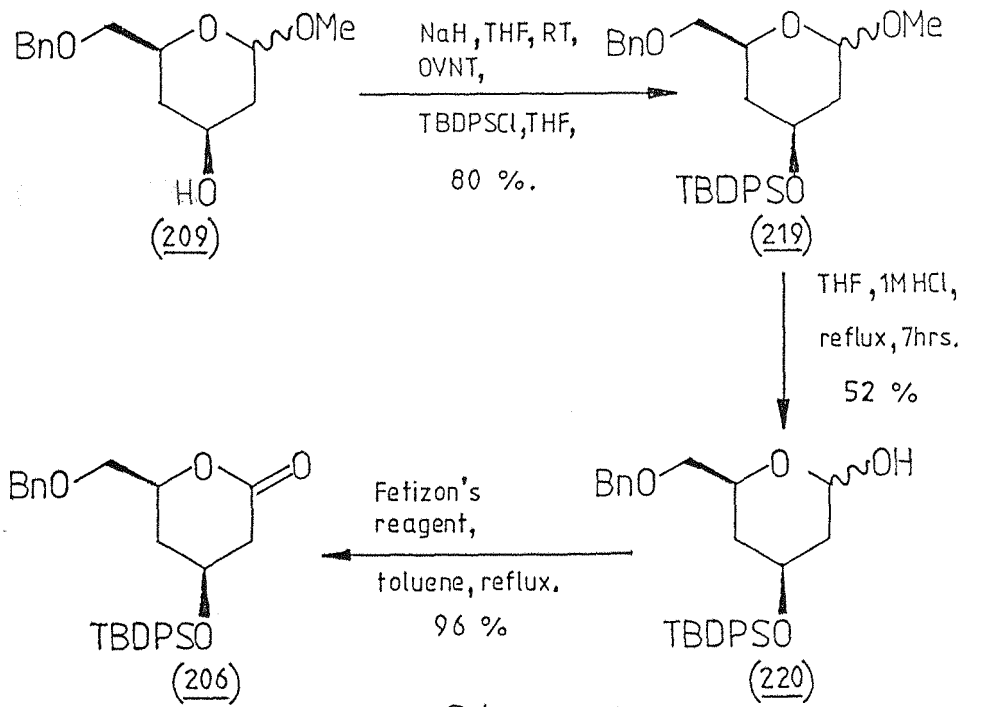
	R^1	R^2	Reagent	Yield	Ref.
(221)		TBDMS	Fetizon's reagent	100%	92
(202)	PhO	TBDPS	PCC		81

Figure 18

cause any enolization; otherwise, a β elimination of $^{t}BuPh_2SiOH$ may result. Consequently the essential neutral and mild Fetizons reagent was used. Treatment of the lactol (220) with freshly prepared Fetizons reagent[93] in dry benzene at reflux did not cause the characteristic change in colour of the reaction mixture

or any change in the tlc analysis. The solvent was changed to the higher boiling toluene and within 15 minutes the colour of the reaction mixture changed from creamy yellow to grey/black and tlc analysis indicated that the reaction was complete after about 2 hours. After isolation and column chromatography, a 96% yield of the lactone (206) was obtained.



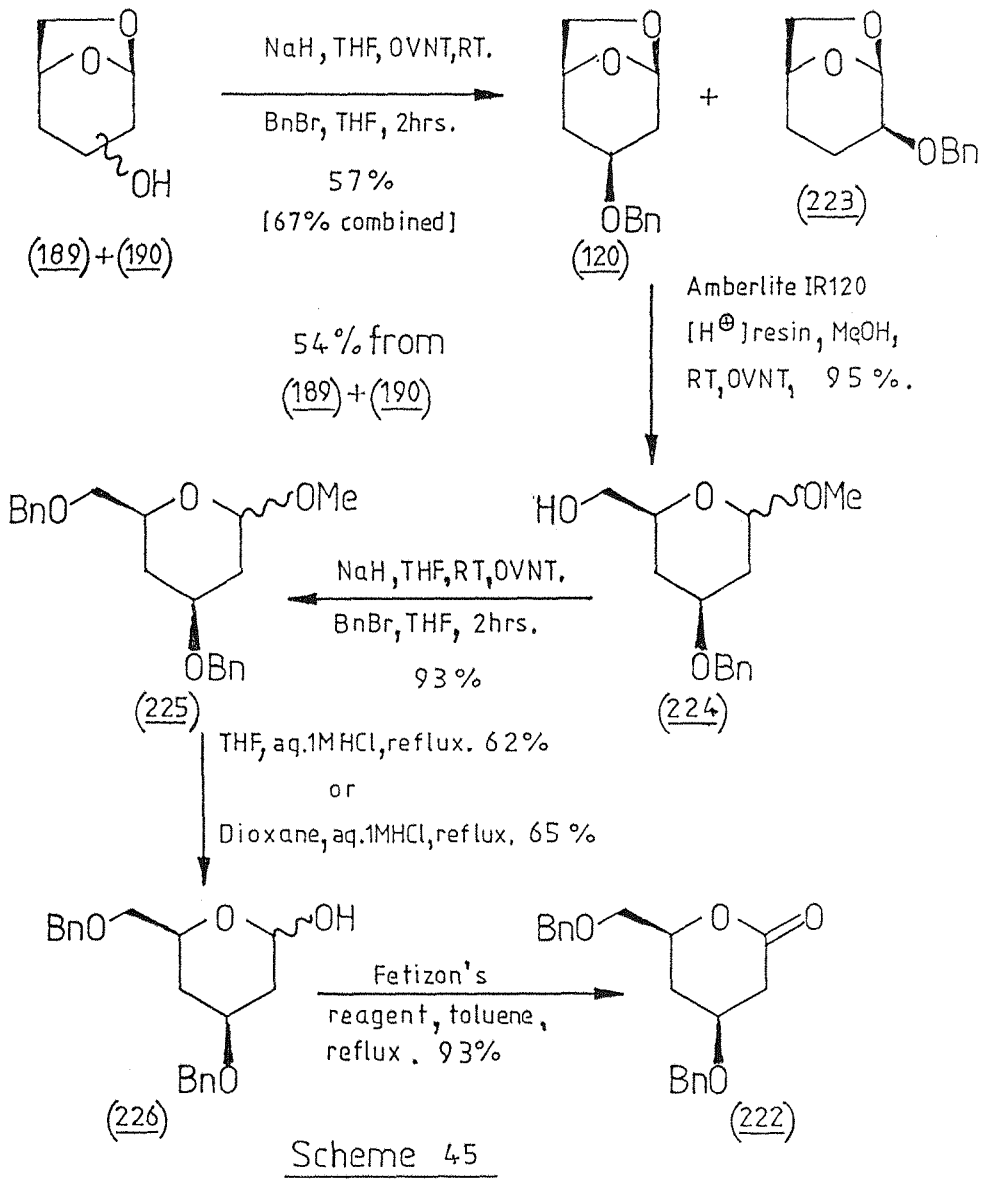
Scheme 44

The carbonyl moiety of the lactone (206) could be seen in the infrared spectrum at υ = 1740 cm^{-1} and the expected shift (δ1.0-1.9 to δ2.0-2.5) of the C2 protons β to the carbonyl group could be observed in the nmr spectrum. Once again the molecular ion could not be detected in the mass spectrum using e.i. techniques. With the use of chemical ionization conditions the molecular ion (M+1) could be seen at m/e = 475 as well as the adduct of the lactone with ammonia ($M+NH_4$) at m/e = 492.

Synthesis of the dibenzyl lactone (222)

The synthesis of an analogous dibenzyl lactone (222) was carried out in parallel with the production of the differentially protected lactone (206). The 1,6-anhydro-benzyl compounds (120) and (223) were available in a combined yield of 67% using the same methodology as described earlier for the allyl ethers (212) and (213). The benzyl ethers (120) and (223) could be separated by column chromatography and the incorporation of the benzyl group was obvious from the spectral data. The mass spectrum of the major component (120) showed the expected tropylium ion ($C_7H_7^{\oplus}$) at m/e = 91 (100%) and the nmr spectrum exhibited the doublet at δ4.3 (J=7Hz) of the C6 *endo* hydrogen as well as the aromatic and benzylic protons at δ7.4 and δ4.5. This compound (120) was later prepared by Ley *et al*[61] in 71% yield and used in a synthesis of the milbemycin spiroacetal (125). The 1,6-anhydro compound (120) was subjected to acid catalysed methanolysis and this afforded the mixture of methyl glycosides (224) in 95% yield. Alternatively, methanolysis of the mixture of ethers (120) and the 2 isomer (223) caused the selective reaction of only the 3 benzyl isomer (120) and the 2 isomer (223) was recovered unchanged. A mixture of methyl glycosides (224) was obtained in 54% yield from the anhydro-compound (120) and the methyl groups of the glycosides (224) could be seen in the nmr spectrum as singlets at δ3.1 and δ3.3 in a ratio of *ca* 2:1. This mixture was not separated but converted into the di-benzyl protected species (225). Formation of the alkoxide of (224) using sodium hydride in THF and the subsequent treatment with benzyl bromide afforded the methyl glycoside (225) in 93% yield and the incorporation of the benzyl group was evident from the spectral data.

Once again the problem of the hydrolysis of the methyl glycoside linkage was encountered. The conditions employed were those used for the hydrolysis of the glycoside (219) and this afforded the lactol (226) and starting material (225) in 62% yield and 31% yield respectively. The use of dioxane and aqueous HCl at reflux was comparable to the initial procedure (THF, 1MHCl, reflux) but both conditions proved superior to the use of acetic acid/THF/water (3:2:2) which once again suffered from the problem of emulsion formation. The lactol (226) showed a shift in the C1 proton from δ4.6 to δ5.4 and the appearance of an OH stretch in the infrared spectrum at υ = 3500 cm^{-1}.

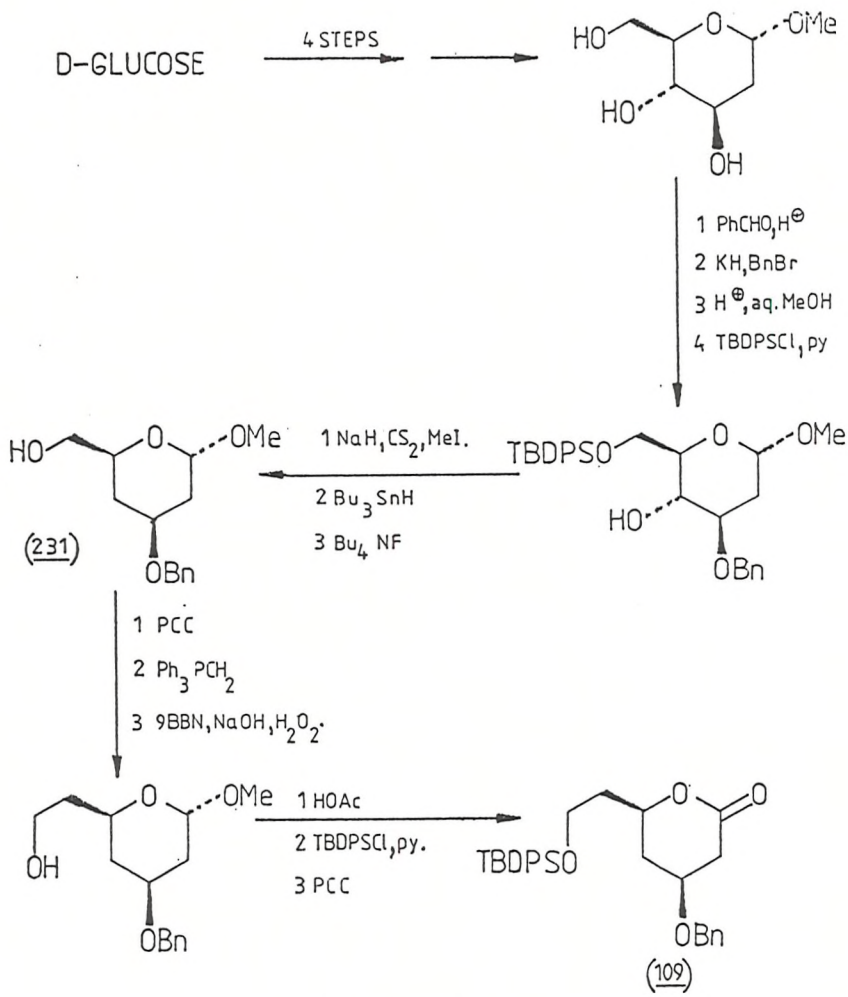


Scheme 45

Oxidation of the lactol (226) to the required lactone (222) was achieved in 93% yield by the use of Fetizon's reagent[93] in dry toluene at reflux. The nmr spectrum of the lactone (222) showed the loss of the anomeric proton and the shift in the C2 protons from (δ 1.0-1.9 to δ 2.0-2.5) and the infrared spectrum showed the lactone carbonyl absorbtion at υ = 1730 cm^{-1}. The molecular ion (M+1) could be observed at m/e = 327 in the c.i. mass spectrum of the lactone (222) (Scheme 45).

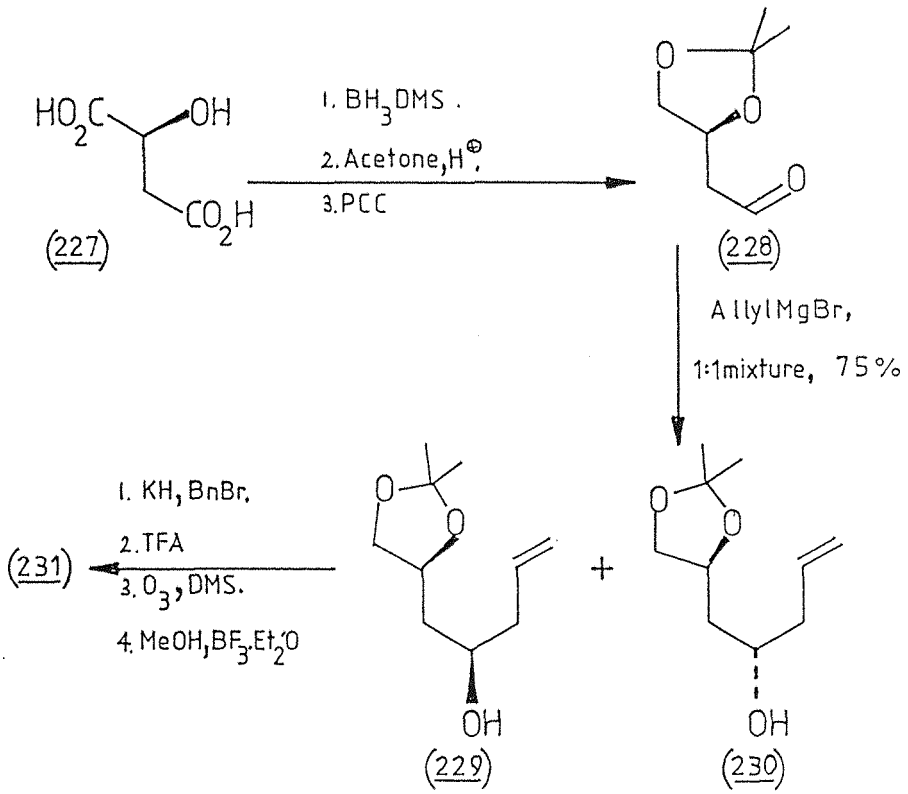
Synthesis of similar type B lactones

During the course of this work, the synthesis of two type B lactone (109) and (107) have been reported by Hanessian *et al*[58] and by Attwood and Barrett[57] respectively. The chiral lactone (109) was prepared from D-glucose using well established methodology in good overall yield (Scheme 46).



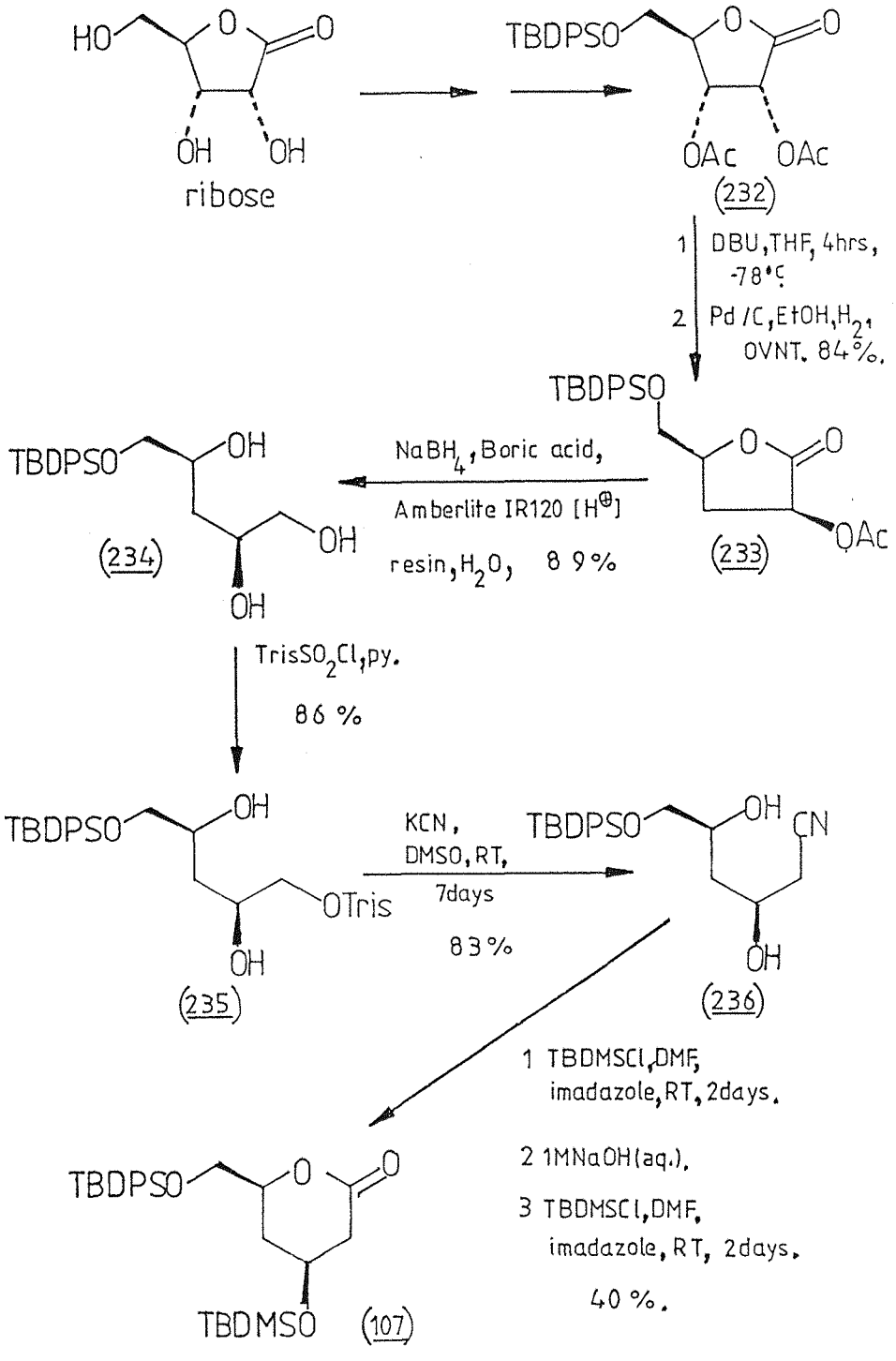
Scheme 46

Alternatively, the same lactone (109) could be synthesised from S-malic acid (227) (Scheme 47). Reduction of the diacid (227) with borane dimethyl-sulphide complex followed by acetylation afforded a 9:1 mixture of alcohols in 92% yield. Chromatographic separation and subsequent oxidation of the desired alcohol with PCC afforded the aldehyde (228). Reaction of the compound (228) with allyl magnesium bromide gave a *ca* 1:1 mixture of homoallylic alcohols (229) and (230) (75%) which was separable by chromatography. The more polar component (229) was then protected as the benzyl ether. The olefin moiety was oxidatively cleaved and converted into the mixture of glycosides (231). This was then elaborated, as shown earlier (Scheme 20), into a milbemycin spiroacetal (108).



Scheme 47

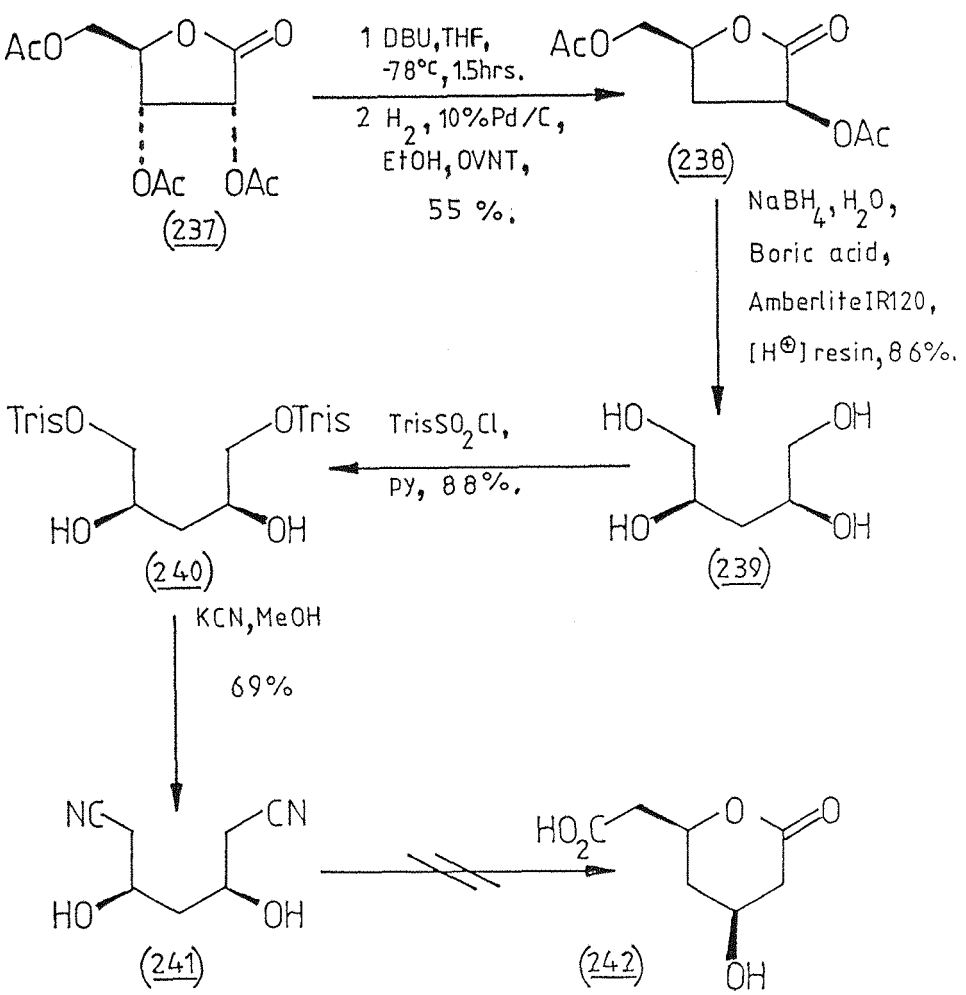
The analogous lactone (107) was later synthesised by Attwood and Barrett[57] from the ribose derivative (232). Inversion of the C19 oxygen functionality of the lactone (232) was achieved by an



Scheme 48

elimination/reduction sequence in 84% yield. Subsequent reduction of the lactone moiety of (233) afforded the intermediate triol (234) in 89% yield. This system (234) possessed the required configurations at C17 and C19. Homologation of the sulphate derivative (235) with potassium cyanide gave the nitrile (236) in 83% yield. This compound contained the required level of oxidation and substitution patterns for the lactone (107). Hydrolysis of the cyanide (236) to the lactone (107) with aqueous sodium hydroxide followed by protection of the C19 alcohol group gave a 40% yield (after distillation) of the required lactone (107). (Scheme 48).

Using a similar strategy[57], triacetyl-ribose-γ-lactone (237) was converted into the γ-lactone (238) in 55% yield. Reduction of the diacetate (238) afforded the symmetrical tetraol (239) in 86% yield. Displacement of the disulphonate derivative (240) with cyanide anion gave the dinitrile (241) 69% yield. However all attempts to hydrolyse this system (241) to the lactone (242) met with failure(Scheme 49).



Scheme 49

Application of the dibenzyl lactone (222) to the synthesis of the spiroacetal moiety of the milbemycin family of antibiotics

The initial strategy towards the synthesis of milbemycin β3 was to couple the vinyl organometallic species (182) with the spiroacetal bromide (171). Model studies on the coupling of a vinyl cuprate with alkyl bromide proved successful. However the application of this reaction to the formation of the C15 - C16 bond proved problematical[65]. This required the production of further quantities of the spiroacetal bromide (171) for more studies into this crucial coupling. The spiroacetal bromide (171) was available from the diol (243) using a standard protection/deprotection sequence. The diol (243) has been previously prepared[94] using the well established methodology[66,94] involving the coupling of an acetylene (244) with the dibenzyl lactone (222) (Figure 19).

The required acetylene (244) has a *threo* relationship between the C24 methyl group and the C25 alcohol group. The synthesis of the chiral *threo* system is far more complex than the *erythreo* analogues[95]. The synthesis of the simplest member of the milbemycin/avermectin family, milbemycin β3 required the use of the chiral acetylene (244). The strategy employed by Baker and Boyes[94,96] towards this compound (244) the resolution of the racemic alcohol (245). This was achieved by partial resolution of the phthlate half ester (246) as its α-methyl benzylamine salt (Scheme 50).

Synthesis of the spiroacetal (243) was attempted according to the method of Baker *et al*[94]. Formation of the lithium anion of the chiral acetylene (244) according to the method of Baker and Swain[96] afforded a crude adduct (247). This adduct (247) was treated with Amberlite IR120 ($H^{\oplus}$) resin in methanol overnight. These conditons removed the C25 protecting group and formed a mixed ketal (248) at C21 which protected the C21 ketone functionality. The acid resin was removed and the crude ketal (248) in methanol subjected to hydrogenation using 10% palladium on carbon.

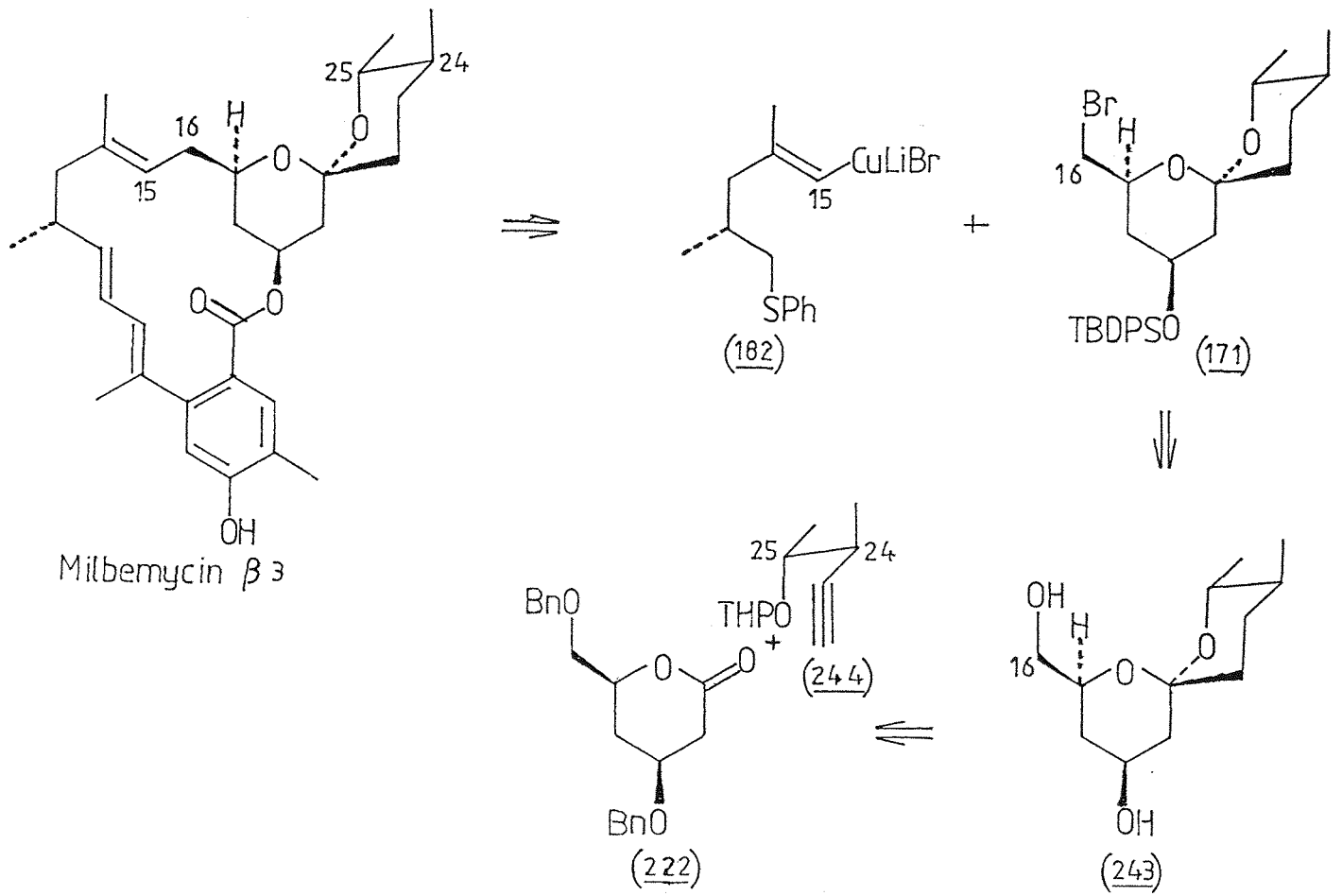
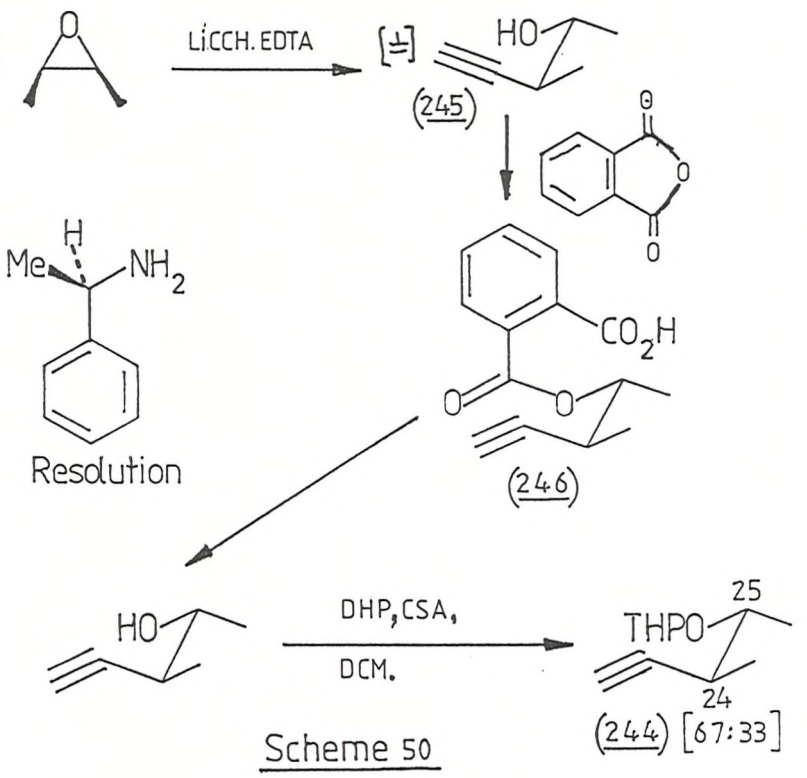

25
24
16
H
O
O
15
O
O
OH
Milbemycin β 3
CuLiBr
15
SPh
(182)
+
Br
H
16
O
O
TBDPSO
(171)
25
24
BnO
THPO
+
O
O
(244)
BnO
(222)
OH
H
16
O
O
OH
(243)

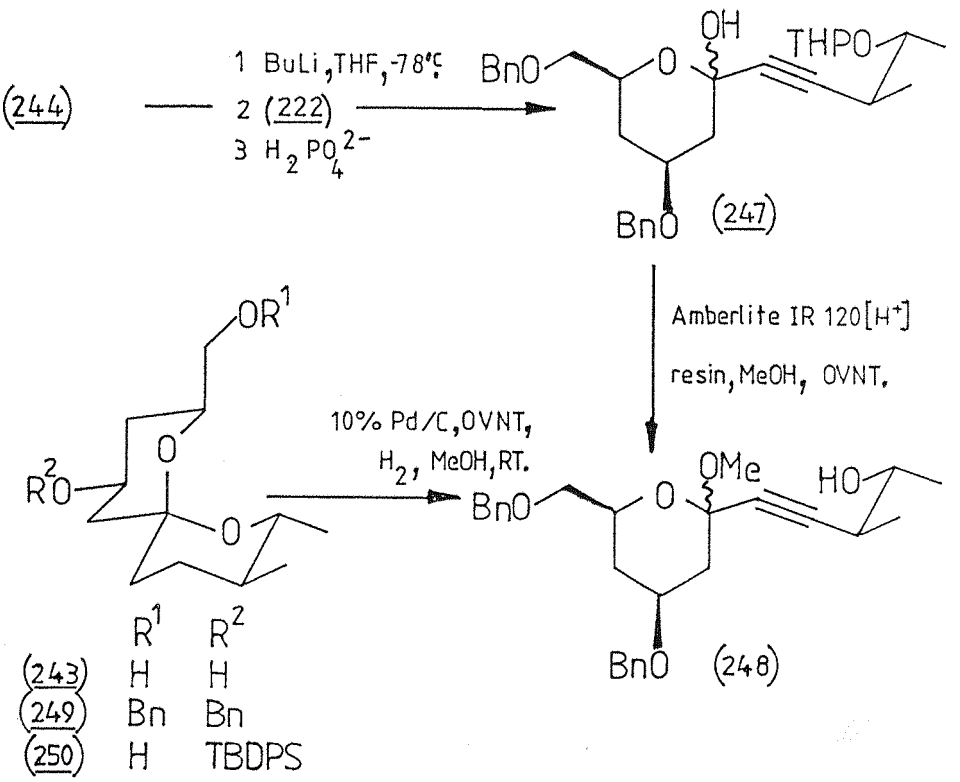
Figure 19.



Scheme 50

Chromatographic analysis showed a polar component (248) which during the reduction was quickly converted into a very non polar spot. This material was slowly converted to a highly polar component. Isolation of this component by column chromatography showed it to be the required spiroacetal (243) in 71% yield (lit[94] 80% yield) which was comparable with an authentic sample of the diol (243). It was assumed that the hydrogenation of the acetylene moiety of the mixed ketal (248) proceeded quickly and that the resultant intermediate cyclised under the reaction conditions into the non polar spiroacetal (249). The removal of both the benzyl protecting groups was much slower and the loss of one benzyl ether could be inferred from the analysis of the reaction mixture (Scheme 51).

A reaction sequence has been carried out with the same acetylene (244) and the differentially protected lactone (206) by Baker *et al*[94]. This gave the spiroacetal (250) in 30% yield.



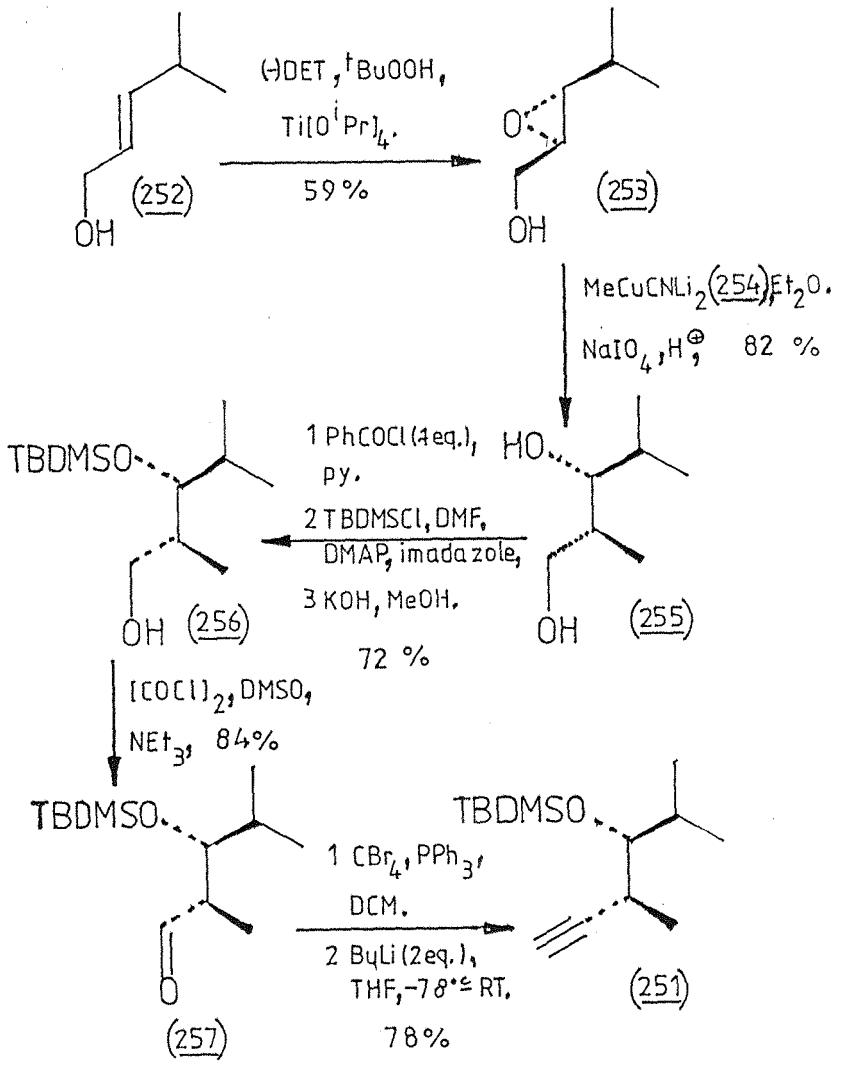
Scheme 51

Use of the dibenzyl lactone (222) in the synthesis of the spiroacetal moiety of the avermectin family of antibiotics

From the outset of this work it was envisaged that a lactone, such as (222), derived from the ring B could be applied to the synthesis of the more complex avermectin spiroacetal moieties. The use of the lactone (222) in avermectin synthesis has recently been reported by Baker, Swain and Head[97] and the well established methodology[66,94] required the synthesis of the chiral acetylene (251).

Asymmetric Sharpless epoxidation of the [E]-allylic alcohol (252) gave a 59% yield of the chiral epoxide (253). Treatment of

this epoxide (253) with the mixed cuprate (254) afforded an excellent yield of the 1,3 diol (255). The unrequired 1,2 isomer was conveniently removed by an oxidative workup with sodium meta-periodate. A standard protection sequence was employed to convert the diol (255) into the silyl ether (256) (72% yield) which after oxidation under Swern conditions led to the chiral aldehyde (257) in 84% yield. Sequential treatment of this aldehyde (257) with carbon tetrabromide/triphenyl phosphine and butyllithium afforded the required acetylene (251) in 78% yield (Scheme 52).

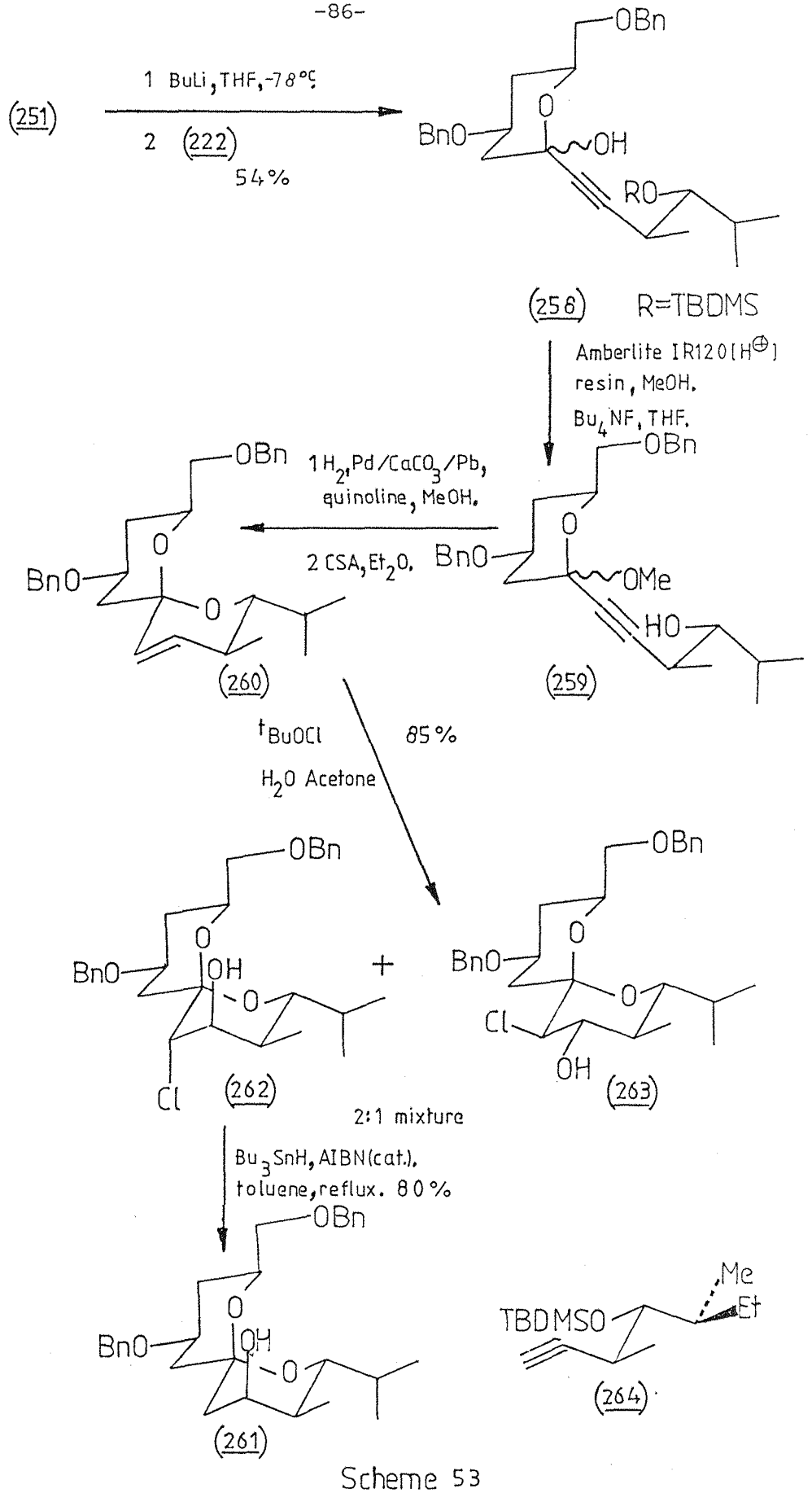


Scheme 52

Formation of the anion of the acetylene (251) with butyl lithium and addition of the lactone (222) led to the adduct (258) in 54% yield. Sequential treatment of this adduct (258) with an acid resin in methanol and tetrabutylammonium fluoride in THF gave the unsaturated alcohol (259). Partial reduction of the acetylene moiety with 5% Lindlar catalyst in a methanol/quinoline mixture and cyclisation with camphorsulphonic acid (CSA) in ether provided the avermectin B_{1b} spiroacetal group (260) in 83% yield (from (258)).

This unsaturated compound (260) was then further elaborated into the avermectin B_{2b} spiroacetal (261) by formation and reduction of the chlorohydrin (262). Treatment of the olefin (260) with ^{t}butyl-hypochlorite in aqueous acetone afforded an 85% yield of a 2:1 mixture of the chlorohydrins (262) and (263). The major chlorohydrin (262) was separated by chromatography and reduction of the chloride functionality with tributyltin hydride gave the spiroacetal (261) in 80% yield.

Extension of this approach to the synthesis of other avermectin and milbemycin analoges such as the avermectin a series by the use of (S)-2-methyl butyraldehyde in the synthesis of the analogous acetylene (264) is obvious. The synthesis of milbemycin β_3 spiroacetal derivative (243) as well as the more complex avermectin spiroacetals (260) and (261) illustrate the key role played by the lactone (222) in a strategy towards the total synthesis of the milbemycin/avermectin family of antibiotics.


(251)
1 BuLi, THF, -78°C
2 (222)
54%
OBn
BnO
O
OH
RO
(256) R=TBDMS
Amberlite IR120[H⊕] resin, MeOH.
Bu4NF, THF.
1 H2, Pd/CaCO3/Pb, quinoline, MeOH.
2 CSA, Et2O.
OMe
HO
(259)
(260)
tBuOCl
H2O Acetone
85%
Cl
(262)
(263)
2:1 mixture
Bu3SnH, AIBN(cat.), toluene, reflux. 80%
(261)
TBDMSO
Me
Et
(264)

Scheme 53

EXPERIMENTAL

Infra-red spectra (IR) were recorded on a Perkin Elmer 157G grating spectrometer with polystyrene used as reference and the absorption (v max) quoted in units of cm^{-1}. Such spectra were recorded either as thin films on sodium chloride plates or as 10% solutions in chloroform in sodium chloride solution cells (cell thickness = 0.1 mm). The following abbreviations were used to describe such IR spectra:- s = strong, m = medium, w = weak and b = broad. Proton nmr spectra were recorded on either a 60 MHz Hitachi Perkin Elmer R24B instrument or at 100 MHz using a Varian Associates XL-100-12 (deuterium lock) spectrometer. Tetramethyl silane was used as an internal standard and in general deuteriochloroform was employed as the solvent for such spectra. The following abbreviations were used to describe the peak shape:- s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad. Coupling constants, J, are expressed in Hertz.

Mass spectra were recorded on a Kratos MS30 spectrometer equipped with the DS 50S data system. All such spectra were recorded at 70 eV and the major ion fragments were reported as m/e values and as percentages of the base peaks. Chemical ionization (ci) mass spectra were obtained on the same spectometer in the ci mode with ammonia as the reagent gas. Optical rotations were measured on an AA-100 polarimeter in the solvent quoted in the text.

Removal of volatile solvents was carried out by evaporation at reduced pressure (*ca* 15 mm Hg) using a rotary evaporator. Flash column chromatography as described by W C Still *et al*[93] was performed on MN Keiselgel 60 (230-400 mesh). The solvents used were distilled before use and petroleum ether refers to the fraction which distilled between 40-60°C. Thin layer chromatography was performed on pre-coated silica gel plates (MN keiselgel 60) and visualized by a combination of iodine vapour, UV light and 1% vanalin in an acidic methanol solution. Gas liquid chromatography was carried out using a Pye 104 chromatograph on either 5% OV101 on diatomite CLQ(100-120 mesh) between 70°C-300°C or on 5% FFAP on diatomite AAW/DMcS(100-120

mesh) between 80°C-240°C.

All glassware for anion reactions was assembled hot and flame-dried before use under a positive pressure of dry nitrogen. Solvents such as methanol and ethanol were redistilled from magnesium/iodine before use. Dichloromethane was dried immediately before use by passing the solvent through a short column of basic Alumina (activity grade 1). Alkyl halides, DMF, dioxane and silica compounds were redistilled from calcium hydride under a dry nitrogen atmosphere and/or at reduced pressure. THF and ether were distilled from sodium/benzophezone under a dry nitrogen atmosphere. Penta acetyl-β,D-*gluco*-pyranose was used as supplied by the Fluka Chemical Company. The protected acetylene (244) was prepared by Boyes[96] and redistilled from calcium hydride before use.

Phenyl tetra-O-acetyl-β,D-*gluco*-pyranoside (185)

To a solution of 4 methylbenzenesulphonic acid (2g, 0.01 mls) in warm phenol (125 g) was added penta acetyl-β,D-*gluco* pyranose (150 g, 0.39 moles). The mixture was heated strongly on a steam bath at 20 mm/Hg for 30 minutes, after which time a liquid began to distill and the pressure was further reduced to 10 mm Hg by means of an air bleed. It was kept at this pressure for 15 minutes and the distillation was interrupted and a solution of sodium hydroxide (0.7 g, 0.017 moles) in warm phenol (40 g) was added. The distillation was continued at 10 mm Hg until the phenol ceased distilling. The pressure was then reduced to 1 mm Hg and the distillation again continued until the phenol stopped distilling.

The dark syrupy residue was then poured into hot water (1 l) and the mixture was allowed to cool with periodic stirring. The water was decanted and the remaining tan solid was recrystallized from hot ethanol (125 ml). After filtration, the crystals were washed with cold ethanol (*ca* 50 mls). This afforded phenyl tetra-O-acetyl-β,D-*gluco*-pyranoside (185) (983 g, 60%) after air during mp 118-120 °C.

lit[69] 120 °C, yield 60%, lit[69] 65-75%

1,6-anhydro-2,3,4-tri-O-acetyl-β,D-*gluco*-pyranose (186).

Phenyl tetra-O-acetyl-β,D-*gluco*-pyranoside (185), (80 g, 0.18 moles) was added to a solution of sodium hydroxide (62 g, 1.5 moles) in water (480 mls). This mixture was then maintained at a gentle reflux overnight. The cooled solution was then neutralised by the addition of concentrated sulphuric acid (66 mls), in ice (66 g) and treated with charcoal and filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was then extracted with boiling ethanol (40 mls). The undissolved salts were then thoroughly extracted with hot ethanol (2x70 mls). After removal of the ethanol *in vacuo*, the residue was carefully acetylated by the cautious addition of acetic anhydride (217 mls, 2.3 moles) and heated on a steam bath for 1 hour. Water (20 mls) was cautiously added to decompose the excess acetic anhydride and the acetic acid removed by distillation at reduced pressure. The residue was extracted with chloroform (300 mls) and the organic

extracts washed with water (2x50 mls) to remove the suspended salts. Removal of the chloroform *in vacuo* afforded a syrupy residue which was recrystallised from ethanol (20 mls). The crystals were filtered off and the filtrate was concentrated to an oil which was treated with ether (20 mls) and the solution placed in the refrigerator to crystallize The crystalline products were triturated with ether (80 mls) at 0 °C and filtered. This afforded a combined yield of 1,6 anhydro-2,3,4-tri-O-acetyl-β,D-*gluco*-pyranose (186) (38 g, 69%.

mp 110 °C	lit[69]	110 °C
yield 60%	lit[69]	73-80% yield

1,6-anhydro-β,D-*gluco*-pyranose (184)

1,6 anhydro-2,3,4-tri-O-acetyl-β,D-*gluco*-pyranose (184) (37 g, 0.13 moles) was dissolved in methanol (455 mls) and a 1% solution of sodium in methanol (45 mls) was then added and allowed to stand for 15 minutes at room temperature. The solution was then neutralized by the addition of Amberlite 1R-120 ($H^{\oplus}$ form) resin and the mixture was treated with charcoal (10 g) and stirred, filtered and finally evaporated to dryness. The crystalline residue was recrystallized from methanol and gave the title compound (184) (16.8 g, 81%)[68].

mp 182 °C	lit[68]	182 °C
yield 81%	lit[68]	100%

1,6 anhydro-2,4-di({4'-methylphenyl }sulphonate)-β,D-*gluco*-hexopyranose (188).

To the triol (184) (9 g, 55.5 moles) in dry pyridine (27 mls) and acetone (27 mls) was added, portionwise, 4'-methylphenyl-sulphonyl choride (22,5 g, 0.12 moles) over a period of four hours. The reaction mixture was left to stir in the dark for four days[74]. Water (20 mls) was then added dropwise and the reaction mixture left

to stir for a further six hours. The reaction mixture was then extracted with ether (4x50 mls) and washed with water (2x10 mls) and dried over anhydrous magnesium sulphate. Removal of the solvent at reduced pressure afforded a syrup (27 g, 103%) which was contaminated with pyridine. This was not purified further but used directly in the synthesis of 1,6 anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189).

1,6 anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189).

To a stirred solution of the 1,6 anhydro-2,4,di({4'-methyl phenyl} sulphonate)-β,D-*gluco*-hexopyranose (188) (27 g, 0.057 moles) in dry THF (400 mls) under a nitrogen atmosphere at 0 ^{o}C was added lithium triethyl borohydride (Super hydride) (0.34 moles, 6 eq) over a period of eight hours. The reaction mixture was left to stir for four days under a nitrogen atmosphere and this afforded a golden coloured solution. Water (40 mls) was then carefully added dropwise and was followed by a similar addition of aqueous 3M sodium hydroxide (130 mls). After the final and cautious addition of 30% aqueous hydrogen peroxide, (120 mls), the stirred reaction mixture was left to cool to room temperature. The aqueous layer was saturated with potassium carbonate and dichloromethane (300 mls) was then added to the two phase system and the organic layer separated off. The aqueous phase was continuously extracted overnight with dichloromethane (150 mls), the combined organic layers were dried over anhydrous magnesium sulphate and the organic solvents removed at reduced pressure. This afforded an oil (12 g) which was purified by column chromatography on Florosil using ether as eluant. This gave the title compound (189) together with the isomer 1,6 anhydro-3,4 - dideoxy-β,D-*glycero*-hexopyranose (5.6 g, 75%) in a ratio of *ca* 6:1 by nmr and glc analysis (on FFAP isothermal at 150 ^{o}C).

TLC Rf (silica, ether)

(189) 0.25 royal blue spot vanalin

(190) 0.23 light blue fast fading spot also in vanalin

Separation of 1,6 anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189) from 1,6 anhydro-3,4-dideoxy-β,D-*glycero*-hexopyranose (190).

To a solution of the above mixture (4.1 g, 32 m moles) in dry acetone (25 mls) at 0 °C was added N,N-diethyl trimethyl silylamine (0.48 g, 33 moles) and the solution was stirred at 0 °C until glc analysis (FFAP) indicated that the *glycero*-hexopyranose isomer (190) had reacted. Water (20 mls) was then added, the acetone solvent removed at reduced pressure and the aqueous solution extracted with pentane (2x20 mls). The aqueous solution was saturated with potassium carbonate and then extracted continuously overnight with dichloromethane (100 moles). The organic extract was dried over anhydrous magnesium sulphate and concentrated at reduced pressure to afford 1,6 anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189) (3.4 g, 83%).

1,6 anhydro-2,4-dideoxy-β,D-*threo* hexopyranose (189).

IR 3500 (br, OH), 2900 (s, CH) and 1250 (w, CO) cm^{-1}.

NMR 1.5-2.0 (m, 4H, H2 ∝ and β, H4 ∝ and β), 3.7 (m,1H,H6 *exo*) 4.0 (m,1H H3), 4.3 (d,1H, J = 7H_z, H6 *endo*), 4.5 (m,1H,H5) and 5.6 (brs,1H,H1).

Methyl 2,4-dideoxy-∝ and β,D-*threo*-hexopyranoside (200)

To a solution of 1,6 anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189) (1 g, 7.7 m moles) in dry methanol (20 mls) was added methanol washed Amberlite IR120 ($H^{\oplus}$ resin) (1 spatula). The solution was stirred overnight and the resin filtered off and the solvent removed at reduced pressure. This afforded the above glycoside (200) (1.2 g, 96%) as a low melting solid.

IR($CDCl_3$) 3500 (brs, OH), 3080 (s,CH) and 1250 (w,C-O) cm^{-1}.

NMR (60 MH_z) 1-2 (m,4H,H2 ∝ and β, H4 ∝ and β), 3.2 (s) and 3.3 (s) (combined 3H, *OMe*), 3.5-4.3 (m, 5H,H3,H5,H6 ∝ and β, and O*H* x2) and 4.9 (d,J=4H_z,1H,H1).

Methyl 2,4-dideoxy-3 ,6 -di(1'{1,1 dimethyleth ( )-1',1'-diphenylsilyl)-α and β,D-*threo*-hexopyranoside (201)

To a stirred mixture of methyl-2,4-dideoxy-α and β,D-*threo*-hexopyranoside (200) (410 mgs, 2.5 m moles), imidazole (850 mgs, 12.5 m moles) and dry DMF (20 mls) under a dry nitrogen atmosphere at room temperature was added 1-chloro-1,1-diphenyl-1-(1',1'-dimethylethyl)silane(1.5 mls, 5.8 m moles). The progress of the reaction was monitored by the tlc and left to stir for a total of 16 hours. After which time the reaction mixture was poured into water (30 mls) and extracted with ether (2x50 mls). The ethereal extract was washed with brine (20 mls) and water (20 mls) and dried over anhydrous potassium carbonate. Removal of the solvent at reduced pressure afforded an oil which was subjected to flash column chromatography with 10% ethyl acetate/petroleum ether as eluant. The major product obtained was the title compound (201) (900 mgs, 57%).

IR($CDCl_3$) 3080(s), 2950(w), 2860(w,CH), 1590(m,C=C) and 1250(w,C-O) cm^{-1}

NMR ($CDCl_3$ 60MH_z) 0.9(s,18H,^{t}Bu x 2), 1.0-2.0 (complex m, 4H, H2 *ax* and *eq* and H4 *ax* and *eq*). 3.1(s,3H, *OMe*),3.2 - 4.2(complex m, 4H, H3, H5 and H6 α and β), 4.6 (bs,1H,H1) and 7.2 - 7.6(m,20H, aromatic H)

MS(El) No $M^{\oplus}$ 274(0.8%) 241(8.6%), 219(27%), 218(13%), 217(76%), 214(20%), 213 (100%, $Ph_2SiO\,CH_2^{\oplus}$) 199(24%, $Ph_2SiOH^{\oplus}$), 183(20%, Ph_2Si), 181(14%) and 105(11%).

2,4-dideoxy-3 ,6 -di(1'{1,1 dimethylethyl}-1',1'-diphenylsilyl)-α and β,D-*threo*-hexopyranose (203)

The methyl glycoside (201) (500 mgs, 0.78 m moles) was dissolved in an acetic acid/THF/water (3:2:2)mixture (25 mls) and heated at 70 °C for 16 hours according to the conditions of Falck and Yang[81]. The mixture was allowed to cool and extracted with ether (2 x 50 mls). The organic extracts were washed with water and dried over anhydrous sodium sulphate. Removal of the solvent at reduced pressure afforded an oil which after chromatography on silica (50% ethyl acetate/ petroleum ether) gave the silyl alcohol (204) (240 mgs, 65%) as the only isolatable material.

IR($CDCl_3$) 3500(br,OH), 3010(s,CH), 2930(w,aromatic CH), 1640(C=C) and 1280(C-O) cm^{-1}.

NMR($CDCl_3$) 0.9(s,9H,^tBu), 3.2(brs,1H,OH)
7.2 - 7.6(brm, 20H, Ph x 2)

Methyl 2,4-dideoxy-6 -phenyl methyl-α and β,D-*threo*-hexopyranose (209)

Methyl-2,4-dideoxy-α and β,D-*threo*-hexopyranoside (200) (400 mgs, 2.47 m moles),tetra-n-butyl ammonium hydrogen sulphate (170 mgs, 0.49 m moles) and benzyl bromide (0.5 mls, 4.2 m moles) were dissolved in dichloromethane (40 mls). 5% aqueous sodium hydroxide (3 mls) was added and the stirred mixture heated under reflux for 48 hours. The mixture was then cooled and the two layers separated. The organic layer was shaken with water (5 mls), dried over anhydrous sodium sulphate and then concentrated at reduced pressure. Flash column chromatography of the resultant oil on silica using ethyl acetate as eluant afforded the title compound (209) (260 mgs, 42%) as the sole product. Extraction of the aqueous layer with dichloromethane failed to isolate the starting diol (200).

IR($CDCl_3$) 3350(brs,OH), 2950(s,CH), 2930(w, aromatic CH), 1650(C=C) and 1340(C-O) cm^{-1}.

NMR(60 MH_z,$CDCl_3$) 1-2.1(complex m,4H,H2 α and β,M4 α and β), 3.3(s,3H,O*Me*),3.4-4.3(complex m,5H,H3,H5,H6 x 2 and OH),4.6 (s,2H,Ph CH_2),4.8(bd,1H,J=4H_z,H1) and 7.4(s,5H,*Ph*).

MS(ei) No $M^{\oplus}$, 221(1.5%,$M^{\oplus}$ - O*ME*),202(18%,$M^{\oplus}$ - MeOH-H_2O), 131(5.6%),$M^{\oplus}$ - C_7H_7 -CH_2O), 113(30%, $C_6H_9O_2^{\oplus}$) 107(16%,$C_7H_7O^{\oplus}$), 92(12%,$C_7H_8^{\oplus}$), 91(100%,$C_7H_7^{\oplus}$),87(9%) and 59%(13%)

3 -acetyl-1,6-anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (210)

To a mixture of the alcohols (189) and (190) (*ca* 9:1) (500 mgs, 3.85 m moles) in dry pyridine (5 mls) was added acetic anhydride (1 ml, 10 m moles) and left to stir overnight. The reaction mixture was decomposed by the addition of water (2 mls) and the organic material extracted with chloroform (2 x 25 mls). The organic layer was washed with water until a 5% copper II sulphate solution indicated the pyridine was no longer present and dried over anhydrous magnesium sulphate. Removal of the solvent at reduced pressure afforded an oil (600 mgs). Flash column chromatography using 25% ethyl acetate/petroleum ether as eluant afforded the title compound (210) as the major product (550 mgs, 83%).

IR(neat) 2990(s,CH, 1750(s,C=O), 1380(C-O), 1270(C-O) and 1230(C-O) cm^{-1}

NRM($CDCl_3$ 60 MH_z) 1.6-2.5(m,7H,H2 α and β, H4 α and β, and *Me* CO), 3.75(bt,1H,J=7H_z,H_6 *exo*),4.2(d,1H,J=7H_z,H_6 *endo*), 4.5(m,1H,H5),5.1(brs,1H,H3) and 5.65(s,1H,H1).

Methyl 2,4-dideoxy-3 -acetyl-β,D-*threo*-hexopyranoside

To a solution of 1,6-anhydro-2,4-dideoxy-3 -acetyl-β,D-*threo*-hexopyrose (500 mgs, 2.9 m moles) in dry methanol (10 mls) was added methanol washed Amberlite IR120 ($H^{\oplus}$ form)(1 spatula). The reaction mixture was stirred at room temperature and monitored by tlc and glc, both of which indicated a complex mixture of products. The methanolic solution was filtered and the solvent removed at reduced pressure. Chromatography of the resultant oil on silica using 50% ether/ petroleum ether as eluant did not afford any discrete products.

1,6-anhydro-2,4-dideoxy-3 -(prop-2'enyl)-β,D-*threo*-hexopyranose(212)

To a slurry of pentane washed and dried sodium hydride(0.5 g, 21 mmoles) in dry THF(20 mls) under a nitrogen atmosphere was added a mixture of 1,6-anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189) and 1,6-anhydro-3,4-dideoxy-β,D *glycero*-hexopyranose (190) (2 g, 15 mmoles) in dry THF(20 mls). The resulting suspension was stirred overnight at room temperature. Allyl bromide (5 mls, 58 mmoles) was added dropwise and the reaction mixture stirred for a further two hours and wet ether (30 mls) was added to decompose any excess sodium hydride. Water (10 mls) was added to the off-white slurry and the two phase system stirred for a further 30 minutes and extracted with ether (2x30 mls). The combined organic phase was washed with brine (2x20 mls) and dried over anhydrous potassium carbonate. The solvent was removed at reduced pressure to afford a yellow oil which was purified by flash column chromatography on silica using 20% ethyl acetate/petroleum ether as the solvent system. This afforded the title compound (212) (1.5 g, 57%) and slower running fractions which contained a mixture of the 2 and 3 allyl ethers (213) and (212) (0.25 g). The combined yield for the allylation was 67%.

IR($CDCl_3$) 2960(s,CH), 2900(s,CH), 1640(w,C=C), 1330(C-O) 1130(C-O) and 1030(C-O) cm^{-1}.

NMR (60MH_z,$CDCl_3$) 1.6-2.2(complex m,4H,H2 *ax* and *eq*,H4 *ax* and *eq*), 3.5 - 3.8(brt,J=6H_z,2H,H3,H6 *exo*) 3.9(d,J=4H_z, 2H,OCH_2 allylic), 4.3(d,J=6H_z,1H,H6 *endo*), 4.4 - 4.5(m,1H,H5) and 5.1(brs,1H,H1).

MS(ei) No $M^{\oplus}$, 129(7.5%,$M^{\oplus} - C_3H_5$),125(14%),115(60%) 113(25%,$M^{\oplus} - C_3H_5O$),84%(21%), 83(39%), 82(14%), 71(27%), 69(100), 67(57%), 57(32%,$C_3H_5^{\oplus}$ O),55(41%) and 41(37%,$C_3H_5^{\oplus}$)

$\{\alpha\}_D^{25}$ -70.1°(c,0.95,CH_2Cl_2)

Methyl 2,4-dideoxy-3 -(prop-2'-enyl)-α and β,D-*threo*-hexopyranoside (214)

Methanol washed Amberlite IR 120($H^{\oplus}$ resin)(1 spatula) was added to a stirred solution of 1,6-anhydro-2,4-dideoxy-3 -(prop-2'-enyl)-β,D-*threo*-hexopyranose (212) (1.5 g, 8.8 m moles) in dry methanol (20 mls) and left overnight at room temperature. The acid resin was filtered off and washed with methanol (10 mls) and the solvent removed at reduced pressure. This afforded the mixture of pyranosides (214) (1.7 g, 95%).

IR($CDCl_3$) 3440(br,OH), 2920(s,CH), 1630(C=C), 1120(C-O) and 1080(C-O) cm^{-1}

NMR(100 MH_z,$CDCl_3$) 1H,1.35(m,1H,H4 *ax*), 1.6(m,1H,H2 *ax*),1.95(m, 1H,H4 *eq*),2.1(1H,H2 *eq*),2.45(brs,1H,O*H*), 3.3 (s,3H,O*Me*), 3.5-3.9(complex m,4H,H3,H5,H6 α and β), 4.6(d,$J_{1'2'}$= 6 H_z,$J_{1'3'}$=smaller,2H, Cl',OCH_2 allylic) 4.85(brd,$J_{1'2'}$ *ax* = 2H_z,1H,H1), 5.15(brdd,$J_{2',3'}$ syn = 9H_z, $J_{1'3'}$ syn = small, $J_{3'}$syn, 3' anti = 2H_z, $J_{1'3'}$ anti = small, 1H,H3' *anti*) 5.3(dd,$J_{2'3'syn}$= 9 Hz, $J_{3'syn,3'anti}$ = 2 Hz,1H, 3'*syn*), 5.5(dd,$J_{2'3'anti}$= 12 Hz,$J_{3'syn\ 3'anti}$ = 2Hz,1H,H3' *anti*) and 5.9 (ddt,$J_{2'3'anti}$ = 12Hz,$J_{2'3'syn}$ =9Hz,$J_{1'2'}$ = 6Hz,1H,H2')

MS(ei) No $M^{\oplus}$,171(19%,$H^{\oplus}$ - O*Me*),115(24%), 113(100%) 85(66%),84(28%), 71(39%),67(19%),58(18%) and 55(20%).

$\{\alpha\}_D^{25}$ +138°(C,1.05,CH_2Cl_2).

1,6-anhydro-2,4-dideoxy-3 -(prop-2'-enyl)-β,D-*threo*-hexopyranose (212) and 1,6-anhydro-3,4-dideoxy-2 -(prop-2'-enyl)-β,D-*glycero*-hexopyranose (213)

A mixture of 1,6-anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189) and 1,6-anhydro-3,4-dideoxy-β,D-*glycero*-hexopyranose (190)(1.1 g, 8.5 m moles) in dry THF (10 mls) was added to a stirred slurry of

pentane washed and dried sodium hydride (0.24 g, 10 m moles) in dry THF (10 mls). After being left overnight, allyl bromide (2 mls, 23 m moles) was added and the reaction mixture treated as described previously. This afforded a mixture of the title compounds (212) and (213) (1.0 g, 69%) which was used directly in the synthesis of Methyl 2,4-dideoxy-3 -(prop-2'-enyl)-α and β,D-*threo*-hexopyranoside (214).

Methyl 2,4-dideoxy-3 -(prop-2'-enyl)-α and β,D-*threo*-hexopyranoside (214)

A solution of the allyl ethers (212) and (213) (1.0 g, 5.9 m moles) in dry methanol (20 mls) was treated with methanol washed Amberlite IR 120 ($H^{\oplus}$ resin) (1 spatula) and the reaction monitored by tlc and glc (OV101). When the reaction was shown to be complete, the acid resin was removed by filtration and the solvent removed at reduced pressure and the resultant ail was subjected to chromatography on silica. Elution with 20% ethyl acetate/petroleum ether afforded the unrequired 1,6-anhydro-3,4-dideoxy-2 -(prop-2'-enyl)-β,D-*glycero*-hexopyranoside (213) (90 mgs) and elution with ethyl acetate gave the title compound (214) (1.0 g, 84%) which was identical by nmr, tlc and glc analysis to a sample prepared by the method described previously.

Methyl 2,4-dideoxy-6 -(phenylmethyl)-3 -(prop-2'-enyl)-α and β, D-*threo*-hexopyranose (217)

To a slurry of pentane washed and dried sodium hydride (0.5 g of 50% dispersion in oil, 10.4 m moles) in dry THF (20 mls) under a dry nitrogen atmopshere was added Methyl 2,4-dideoxy-3 -(prop-2'-enyl)-α- and β,D-*threo*-hexopyranoside (214) (1.6 g, 7.9 m moles) and the reaction mixture stirred overnight. Benzyl bromide (2 mls, 16.8 m moles) in dry THF (20 mls) was then added and stirred at room temperature for a further two hours. The reaction mixture was then carefully treated with wet ether (40 mls) in order to destroy the excess sodium hydride. Water (10 mls) was then added and the organic layer separated and washed with water (2 x 10 mls). The organic extract was then dried over anhydrous potassium carbonate and the solvent removed at reduced pressure. The resultant oil was subjected to flash column chromatography (20% ethyl acetate/petroleum ether) and gave Methyl 2,4-dideoxy-6 -(phenylmethyl) -3 -(prop-2'-enyl)-α and β,D-*threo*-hexopyranoside (217) (2.15 g, 93%).

IR($CDCl_3$) 3350(br,OH), 2940(s,CH), 2900(s,CH) 1650(w,C=C) 1110(s,CO) and 1060(s,C-O) cm^{-1}.

NMR,(60MH_z,$CDCl_3$) 1.0-2.3(complex m, 4H, H2 ∝ and β, H4 ∝ and β), 3.25(s,3H,O*Me*)3.3-3.8(complex m,4H,H3,H5,H6 ∝ and β),3.95(d,J=6H_z,2H,H1' ∝ and β), 45(s,2H,PhCH_2),4.75(brd,J=4H_z, 1H,H1),5.1(dd,$J_{2'3'syn}$=9H_z, $J_{3'syn,3'anti}$ =2H_z,1H,H3' *syn*),5.2(dd,$J_{2'3'anti}$=15H_z, $J_{3'syn,3'anti}$ = 2H_z,1H,H3' anti) and 5.9(ddt,$J_{2'3'anti}$ = 15H_z,$J_{2'3'syn}$ = 9H_z, $J_{1'2'}$ = 6H_z, 1H,H2')

Methyl 2,4-dideoxy-6 -(phenylmethyl)-∝ and β,D-*threo*-hexopyranoside (209) using Palladium-catalysed rearrangement of the allyl ether (217)

The allyl ether (217)(0.5 g,1.7 mmoles) was dissolved in dry methanol(30 mls) in a dry nitrogen atmosphere and 10% palladium on carbon (100 mgs) was then added. The stirred mixture was then heated to the point of reflux. The reaction was followed by tlc analysis which indicated the gradual appearance of a more polar spot. The reaction was left at reflux for 16 hours and after cooling the catalyst was removed by filtration and the catalyst washed with methanol(10 mls). The solvent was removed at reduced pressure and the starting material (127)(0.15 g,30%) was obtained after chromatography on silica (20% ethyl acetate/petroleum ether). Elution with ethyl acetate gave the title compound (209)(0.24 g,56%) which was identical to the material prepared by an alternative route.

Methyl 2,4-dideoxy-6 -(phenylmethyl)-∝ and β,D-*threo*-hexopyranoside (209), *via* rearrangement of the allyl ether (217) by Wilkinson's catalyst

Similarly tris(triphenyl phosphine)rhodium(I)chloride(100 mgs) was added to a solution of Methyl 2,4-dideoxy-6 -(phenylmethyl)-3 -(prop-2'-enyl)-∝ and β,D-*threo*-hexopyranoside(217)(2.15 g,7.4 mmoles) in dry methanol (30 mls) under a dry nitrogen atmosphere. The reaction mixture was heated to the point of reflux for two hours and tlc

analysis(20% ethyl acetate/petroleum ether) indicated a less polar spot (Rf 0.6). Continued heating overnight afforded a single more polar spot (Rf=0.5, ethyl acetate) and the reaction mixture was then allowed to cool. The solvent was removed at reduced pressure and the residue was subjected to flash column chromatography on silica using ethyl acetate as eluant. This gave the title methyl glycoside (209)(1.75 g,95%) as an oil and this proved to be identical to a sample prepared by a previous route.

Methyl 2,4-dideoxy-3-(1'(1,1-dimethylethyl)-1',1'-(diphenyl silyl)-6-(phenylmethyl)-α and β,D-*threo*-hexopyranoside (219) (using sodium hydride).

Methyl 2,4-dideoxy-6-(phenylmethyl)-α and β,D-*threo*-hexopyranoside (209)(1.75 g, 7 m moles) in dry THF(20 mls) was added to a slurry of pentane washed and dried sodium hydride (0.4 g, 8.3 m moles) in dry THF(20 mls) under a dry nitrogen atmosphere. This solution was stirred overnight and then 1-chloro-1-(1',1'-dimethylethyl)-1,1-diphenyl silane(2 mls, 7.7 m moles) was added. The reaction mixture was stirred for a further four hours and wet ether (40 mls) was added in order to decompose the excess sodium hydride. Water(10 mls) was then added and the inorganic salts were allowed to dissolve. The organic layer was separated and washed with brine (2x20 mls) and dried over anhydrous potassium carbonate. Removal of the volatile solvents at reduced pressure afforded an oil which was subjected to flash column chromatography on silica using 10% ethyl acetate/ petroleum ether as the eluant. This afforded the title compound (219) (2.65 g,80%) as an oil.

IR($CDCl_3$) 2950(s,CH), 2900(s,CH), 1640(w,C=C), 1620(w,C=C), 1130(s,C-O) and 1050(s,C-O) cm^{-1}

NMR(60MH_z,$CDCl_3$) 1.0(s,9H,^tBu) 1.1-2.2(complex m,4H,H2 α and β) H4 α and β 3.1-3.8(complex m,7H,H3,H5,H6 α and β and O*Me*), 4.5(s,2H,PhCH_2), 4.7(brs,1H,H1) and 7.2-7.9 (complex m,25H, aromatic protons).

MS(ci) ($M^{\oplus} + NH_4^{\oplus}$) calculated 508.2883 found 508.2809

MS(ci) 508(M + 11%,$NH_4^{\oplus}$), 265(24%), 234(11%), 233(23%), 217(11%),

216(19%), 207(53%), 203(40%), 199(24%), 187(11%), 157(49%), and 91(100%, $C_7H_7^{\oplus}$).

Methyl-2,4-dideoxy-3-(1'-{1,1-dimethylethyl}-1'1'-diphenylsilyl)-6-(phenylmethyl)-α and β,D-*threo*-hexopyranose (219) (by the use of potassium hydride as the base).

Methyl 2,4-dideoxy-6-(phenylmethyl)-α and β,D-*threo*-hexopyranoside (209) (1 g, 4 m moles) in dry THF (10 mls) was added to a slurry of pentane washed and dried potassium hydride (0.2 g, 5 m moles) in dry THF (10 mls) under a dry nitrogen atmosphere. The solution was stirred overnight and 1-chloro-1-({1',1'-dimethyl}-ethyl)-1,1-diphenyl silane (1.3 mls, 5 m moles) was added. Treatment of the reaction mixture as described previously afforded after column chromatography the methyl glycoside (219) as an oil (1.59 g, 84%) which was identical by tlc analysis to an authentic sample.

2,4-dideoxy-3-(1'-{1,1-dimethylethyl}-1',1'-diphenyl-silyl)-6-{phenylmethyl}α and β,D-*threo*-hexopyranose (220)

The methyl glycoside (219) (2.3 g, 4.8 m moles) was dissolved in redistilled THF (30 mls) and 1MHCl (2 mls) was added and a further amount of THF (*ca* 10 mls) was added. The stirred homogenous solution was heated at the point of reflux for five hours. After cooling, ether (50 mls) was added and the organic layer washed with water (20 mls) and brine (2x20 mls) and finally dried over anhydrous magnesium sulphate. The volatile solvent was removed at reduced pressure and the resultant oil was subjected to flash column chromatography (20% ethyl acetate/ petroleum ether). This afforded the starting glycoside (219) (0.85 g, 37%) and a more polar material which was assigned as the title compound (220) (1.15 g, 52%) (82% based on recovered starting material).

IR($CDCl_3$) 3420(brs,OH), 2930(s,CH), 2860(s,CH), 1740(w,C=O), 1110(s,C-O) and 700(s,C-O) cm^{-1}.

NMR(60MH_z,$CDCl_3$) 1.0(s,9H, ^tBu), 1.2-2(complex m,4H,H2 *ax* and *eq*)

2.6(brs,1H,O*H*), 3.3-4.3(complex m,4H,H3,H5,H6 α and β), 4.5(s,2H,PhCH_2), 5.4(brs,1H,H1) and 7.3-7.9(m,15H, aromatic).

MS(ci) $C_{29}\ H_{38}\ O_4\ Si\ (M^{\oplus})$ calculated 476.2382
found 476.2262

MS(ci) 494(2%,M + $NH_4^{\oplus}$), 477(1%,$M^{\oplus}$+1), 476(3%,$M^{\oplus}$), 233(23%), 207(30%),203(32%),199(15%), 157(47%) 105(14%) and 91(100%,$C_7H_7^{\oplus}$).

4*S*,6*S*-4-(1'-(1,1-dimethylethyl)-1',1'-diphenyl silyl)-6-(1'-{phenylmethyl}-methanol)-tetrahydropyran-2-one(206).

The lactol (220) (1.10 g,2.4 m moles) was dissolved in dry toluene (30 mls) and freshly prepared Fetizon's reagent[93] (7 g, 12 m moles) was added. The stirred off-yellow reaction mixture under a dry nitrogen atmosphere was heated to the point of reflux by means of an oil bath until tlc analysis indicated that the starting lactol (220) had disappeared. The black/grey precipitate was then removed by filtration and the precipitate was washed with ether (2x30 mls). The volatile solvents were removed at reduced pressure and the lactone (206) (1.05 g, 96%) was obtained after chromatography of the residue on silica (20% ethyl acetate/petroleum ether).

IR ($CDCl_3$) 2930(s,CH), 2860(s,CH), 1740(s,C=O),1115(s,C-O) and 730(s,C-O) cm^{-1}.

NMR(100 MH_z,$CDCl_3$) 1.07(s,9H,^tBu), 1.5-2.2(m,2H,H4 *ax* and *eq*), 2.3-2.9(m,2H,H2 *ax* and *eq*), 3.58(d,J=5 H_z,2H, CH_2O),3.8-4.4(m,2H,2 x CH), 4.55(s,2H,PhCH_2) and 7.0-7.8(m,15H, aromatic).

ms(ci) $C_{29}\ H_{35}\ O_4\ Si(M^{\oplus}+1)$ calculated 475.2305
found 475.2189

492(33%),M + $NH_4^{\oplus}$), 475(7%,{$M^{\oplus}$+1}), 274(10%), 249(14%), 236(13%), 216(21%), 199(15%), 196(13%), 105(30%) and 91(100%), $C_7H_7^{\oplus}$).

$\{\alpha\}_D^{25}$ + 10.4°(*c*,1.0,$CH_2\ Cl_2$).

1,6-anhydro-2,4-dideoxy-3 -(phenylmethyl)-β,D-*threo*-hexopyranose (120)

To a slurry of pentane washed and dried sodium hydride (1.5 g, 62.5 m moles) in dry THF (20 mls) under a dry nitrogen atmosphere was added dropwise a mixture of 1,6-anhydro-2,4-dideoxy-β,D-*threo*-hexopyranose (189) and 1,6-anhydro-3,4-dideoxy-β,D-*glycero*-hexopyranose (190) (4.5 g, 35 m moles) in dry THF (50 mls) and the reaction mixture left to stir overnight before the addition of benzyl bromide (12.5 mls, 51 m moles). The alkylation reaction was stirred for a further 3 hours before the wet ether (30 mls) was carefully added to destroy the excess sodium hydride. Water (40 mls) was then added and the two phase mixture left to stir and dissolve the sodium bromide produced in the reaction. The aqueous layer was extracted with ether (2x20 mls) and the combined organic layers were washed with brine (2x30 mls) and dried over anhydrous potassium carbonate. Evaporation of the volatile solvents at reduced pressure afforded a red oil which was subjected to flash column chromatography on silica (20% ethyl acetate/petroleum ether). This afforded the title compound (120) (4.3 g, 57%) as well as some slower running mixed fraction (0.8 g) containing the undesired 1,6-anhydro-3,4-dideoxy-2 -(phenylmethyl)-β,D-*glycero*-hexopyranose (223). The combined yield for the alkylation was 67%.

IR($CDCl_3$) 2950(s,CH), 2920(s,CH), 1640(w,C=C) and 1090(s,C-O)cm^{-1}.

NMR(60 mHz,$CDCl_3$) 1.1-2.0(complex m,4H,H2 *ax* and *eq*,H4 *ax* and *eq*), 3.5-3.8(m,2H,H3 and H6 *exo*), 4.3(d,J=7Hz,1H, H6 *endo*) 4.3-4.4(m,1H,H5),4.6(s,2H,PhCH_2) and 7.3(s,5h,*Ph*).

MS(ei) 221(1%,$M^{\oplus}$), 1141(5%,$M^{\oplus}$+1-C_7H_7O), 92(14%,$C_7H_8^{\oplus}$) and 91(100%,$C_7H_7^{\oplus}$).

$\{\alpha\}_D^{25} = {}^{o}$(C,1.0,$CH_2Cl_2$)

Methyl 2,4-dideoxy-3 -(phenylmethyl)-α and β,D-*threo*-hexopyranoside (224)

1,6-anhydro-2,4-dideoxy-3 -(phenylmethyl)-β,D-*threo*-hexopyranose (120) (4.3 g,20 m moles) was dissolved in dry methanol (100 mls) and Amberlite IR120 ($H^{\oplus}$ form) acid resin (1 spatula) was

added to the stirred solution which was then left to stir overnight. TLC analysis indicated that the reaction was complete and the acid resin removed by filtration and the unwanted resin washed with methanol (2x20 mls). The combined methanol solution was then concentrated at reduced pressure and the subsequent oil purified by flash column chromatography on silica (50% ethyl acetate/petroleum ether). This afforded methyl-2,4-dideoxy-3-(phenylmethyl)-α and β, D-*threo*-hexopyranoside (224) (4.75 g, 95%).

IR($CDCl_3$) 3430(br,OH), 2920(s,CH), 2890(s,CH), 1630(w,C=C) 1080(s,C-O) cm^{-1}.

NMR(60mHz,$CDCl_3$) 1.1-2.1(complex m,4H,H2 *ax* and *eq*, H4 *ax* and *eq*) 2.3(brs,1H,O*H*) 3.1(s) and 3.3(s), (3H combined O*Me*) 3.5-3.9(complex m,4H,H3,H5,H6 α and β), 4.5(s,2H,PhCH_2) 4.8(brs,1H,H1) and 7.3(s,5H,aromatic)

MS(ei) No $M^{\oplus}$, 221(1%,$M^{\oplus}$-MeO), 202(1%,$M^{\oplus}$-MeOH-H_2O), 120(8%), 114(11%), 113(10%), 92(7%,$C_7H_8^{\oplus}$), 91(100%,$C_7H_7^{\oplus}$) and 70(21%)

1,6-anhydro-2,4-dideoxy-3-(phenylmethyl)-β,D-*threo*-hexopyranose (120) and 1,6-anhydro-3,4-dideoxy-2-(phenylmethyl)-β,D-*glycero*-hexopyranose (223).

To pentane washed and dried sodium hydride (1.2 g,50 m moles) was added dry THF(10 mls) under a dry nitrogen atmosphere. To the resultant slurry was added the mixture of the alcohols (189) and (190) in dry THF(50 mls) and the reaction mixture stirred overnight. After which time, benzyl bromide (9.5 mls,80 m moles) was added and then left to stir for a further three hours. Wet ether (30 mls) was added followed by water (30 mls) to dissolve the suspended salts. The aqueous layer was removed and extracted with ether (2x20 mls) and the combined organic layers were washed with brine (2x30 mls) and dried over anhydrous potassium carbonate. Removal of the volatile solvents at reduced pressure afforded a red oil which was subjected to flash column chromatography on silica (20% ethyl acetate/petroleum ether) and this gave a mixture of the title compounds as an oil (4.7 g)

which was used directly in the synthesis of the methyl glycoside (224).

Methyl 2,4-dideoxy-3 -(phenylmethyl)-α and β,D-*threo*-hexopyranoside (224)

The mixture of alcohols (120) and (223) (4.7 g) was dissolved in dry methanol (100 mls) and the acid resin Amberlite IR120 ($H^{\oplus}$ form)(1 spatula) was added. After the reaction had been stirred overnight, tlc analysis indicated that the benzyl ether (120) had disappeared and a more polar was now present. The acid resin was then removed by filtration and washed with methanol (2x20 mls). Concentration of the combined organic solution at reduced pressure afforded an oil. Purification of the resultant oil by column chromatography on silica using 20% ethyl acetate/petroleum ether gave the undesired anhydro-benzyl ether (223). Elution with 50% ethyl acetate/petroleum ether afforded methyl-2,4-dideoxy-3 -(phenylmethyl)-α and β,D-*threo*-hexopyranoside (224)(4.19 g, 54%) from (189) and (190) which proved to be identical to a sample prepared by the previous method.

Methyl 2,4-dideoxy-3,6-di(phenylmethyl)-α and β,D-*threo*-hexopyranoside (225)

The pentane washed and dried sodium hydride (0.77, 32 m moles) under a dry nitrogen atmosphere in dry THF (50 mls) was added dropwise the alcohol (224) (4 g, 16 m moles) in dry THF (50 mls) and the reaction left to stir overnight. Benzyl bromide (4.5 mls, 0.038 m moles) was added dropwise and the reaction mixture left to stir for a further three hours. After such time, wet ether (50 mls) added to destroy the excess sodium hydride and then water (30 mls) added to dissolve the suspended salts. The aqueous layer was extracted with ether (2 x 40 mls) and the combined organic phase washed with brine (2 x 40 mls) and dried over anhydrous magnesium suplhate. Concentration of the organic phase at reduced pressure gave an orange oil which was subjected to flash column chromatography (20% ethyl acetate/petroleum ether) and this afforded methyl-2,4-dideoxy-3,6-di(phenyl methyl)-α and β,D-*threo*-hexopyranoside (225) as an oil (5.05 g, 93%).

IR($CDCl_3$) 2920(s,CH), 2870(s,CH), 1650(w,C=C) and 1120(s,C-O) cm^{-1}.

NMR(60MH_z,$CDCl_3$) 1.0-2.1(m,4H,H2 *ax* and *eq*, H4 *ax* and *eq*), 3.1-4.1(m,7H,H3,H5,H6 α and β, and O*Me*) 4.6(s,4H,PhCH_2), 4.8(brd,J=2H_z,1H,H1) and 7.3(s,10H,*Ph*).

2,4-dideoxy-3,6-di(phenyl methyl)-α and β,D-*threo*-hexopyranose (226) {using THF as solvent}

The methyl glycoside (225) (5 g, 146 m moles) was dissolved in redistilled THF (60 mls) and 1MHCl (5 mls) was added. To the resultant emulsion was added a further quantity of redistilled THF (20 mls) until the solution appeared turbid. The reaction mixture was then heated to the point of reflux under a nitrogen atmosphere for 7 hours. After such time, tlc analysis showed the appearance of a more polar material and ether (100 mls) was then added and the aqueous phase extracted with ether (2 x 50 mls). The combined organic phase was washed with brine (2 x 30 mls) and dried over anhydrous sodium sulphate.

Removal of the volatile organic solvents at reduced pressure afforded an oil which was then subjected to flash column chromatography on silica (10% ethyl acetate/petroleum ether). This gave the title lactol (226) as an oil (2.97 g,62%) together with the starting glycoside (225) (1.55 g,31%).

IR($CDCl_3$) 3500(brs,OH), 2930(s,CH), 2800(s,CH), 1720 (w,C=O), 1650(w,C=C),and 1120(s,C-O).

NMR(60MH_z,$CDCl_3$) 1.2-2.2(m,4H,H2 *ax* and *eq*, H4 *ax* and *eq*), 3.1-4.3(m,4H,H3,H5,H6 α and β), 4.5(s,4H, PhCH_2) 5.4(brs,1H,H1) and 7.3(s,10H,*Ph*).

2,4-dideoxy-3,6-di(phenylmethyl)-α and β,D-*threo*-hexopyranose (226) {using dioxane as solvent}

Methyl 2,4-dideoxy-3,6-di(phenylmethyl)-α and β,D-*threo*-hexopyranoside (225)(2 g,5.85 m moles) was added to redistilled dioxane (20 mls) and 1MHCl(2 mls) was then added. The reaction mixture was then heated to the point of reflux under a nitrogen atmosphere for 7 hours. Tlc analysis indicated, the presence of the more polar material and ether (50 mls) was then added and the aqueous phase extracted with ether (2 x 30 mls). The combined organic phase was washed with brine (2 x 20 mls) and dried over anhydrous sodium sulphate. After removal of the organic solvents at reduced pressure and chromatography of the resultant oil on silica, the 2,4-dideoxy-3,6-di(phenylmethyl)-α and β,D-*threo*-hexopyranose (226) was obtained (1.25 g,65%) which proved to be identical to a sample prepared by the previous method as well as the starting material (225)(0.5 g,25%).

4*S*,6*S*-4-(phenylmethyl)-6-(1'phenylmethyl)methanol-tetrahydropyran-2-one(222)

The lactol (226)(2.5 g, 7.6 m moles) was dissolved in dry toluene (70 mls) and freshly prepared Fetizon's reagent[93] (13 g,23 m moles) was added. The stirred off-yellow reaction mixture under a dry nitrogen atmosphere was heated to the point of reflux until tlc analysis indicated that the starting lactol (226) had disappeared (*ca* 3 hours).

The black/grey precipitate was then removed by filtration, the precipitate (washed with ether (2 x 30 mls) and the solvents) removed at reduced pressure. Chromatography of the residue on silica (10% ethyl acetate/petroleum ether) afforded 4*S*,6*S*-4-(phenylmethyl)-6-(1'-phenylmethyl)methanol-tetrahydropyran-2-one (222) as an oil (2.3 g,93%).

IR($CDCl_3$) 2920(s,CH), 2870(s,CH), 1730(s,C=O), 1640(w,C=C) and 1130(s,C-O) cm^{-1}

NMR(60MH_z,$CDCl_3$) 1.5-2.2(m,2H,H4 *ax* and *eq*),2.3-2.9(m,2H,H2 *ax* and *eq*), 3.6(d,J-5H_z,2H,CH_2O), 3.8-4.4 (m,2H,H3 and H5)4.5(d,J=small,4H,PhCH_2) and 7.2(s,10H,*Ph*)

ms(ci) $C_{20}\ H_{23}\ O_4$ ($M^{\oplus}$+1)

calculated 327.1596
found 327.1346

344(3%,M+$NH_4^{\oplus}$), 327(0.33%,$M^{\oplus}$+1), 235(1%,$M^{\oplus}-C_7H_7$), 136(3%), 129(4%), 114(1%), 113(3%), 109(2%,$C_7H_7O^{\oplus}$), 108(28%,$C_7H_8O^{\oplus}$), 107(32%,$C_7H_7^{\oplus}$), 92(17%,$C_7H_8^{\oplus}$), 91(100%,$C_7H_7^{\oplus}$) and 79(29%)

$\{\alpha\}_D^{25}$ =

{2*S*,4*S*,6*S*,8*S*,9*R*}-2-methanol-4-hydroxy-8,9-dimethy-1,7-dioxaspiro-(5,5)-undecane (243)[94]

To a solution of butyl lithium in hexane (1,6 M, 1.1 mls, 1.76 m moles), pre-cooled to -60°C, was added {2*R*,3*S*}-20-tetrahydropyranyl-3-methyl-pent-4-yn-2-ol (244)[94,96] (30 mgs, 1.69 m moles) in dry THF (10 mls) under a dry nitrogen atmosphere and left at -60°C for an hour. The reaction mixture was cooled from -60°C to -78°C and the dibenzyl lactone (222) (500 mgs, 1.5 m moles) in dry THF (10 mls) was added and the reaction mixture maintained at -78°C for a further three hours. After such time, 10% aqueous phosphate buffer solution (20 mls) was added and the reaction mixture allowed to warm to room temperature. Ether (2x30 mls) was then added and the combined organic phases washed with water (2x10 mls) and brine (2x10 mls) and dried over anhydrous magnesium sulphate. Removal of the volatile solvents at reduced pressure, gave an oil which was dissolved in ether (50 mls) and the solution re-dried over anhydrous magnesium sulphate. After removal of the solvent, the infra red spectra of the resultant oil indicated the incorporation of the acetylene moiety (2210 cm^{-1},m) and the presence of an OH group (3400 cm^{-1},bs) and a carbonyl moiety (1720 cm^{-1},w). This oil was dissolved in dry methanol (50 mls) and Amberlite IR120 ($H^{\oplus}$ form) acid resin (1 spatula) was added and the reaction mixture was then stirred overnight at room temperature. The acid resin was then removed by filtration and the resin was washed with methanol (2x10 mls). To the combined methanol solution was added 10% palladium on carbon (*ca* 50 mgs) and the suspension subjected to hydrogenation at atmospheric pressure. Tlc analysis of the reaction mixture indicated the presence of a polar starting material and after *ca* 2 hours a *less* polar material was produced which was assumed to be the dibenzyl protected spiroacetal (249). The reaction was allowed to continue overnight until the required spiroacetal (243). The hydrogenation catalyst was removed by filtration and the solvent was removed at reduced pressure. The resultant oil was subjected to column chromatography on silica and this afforded the title compound (243) (250 mgs, 71%) which proved indentical to an authentic sample supplied by Dr C J Swain.

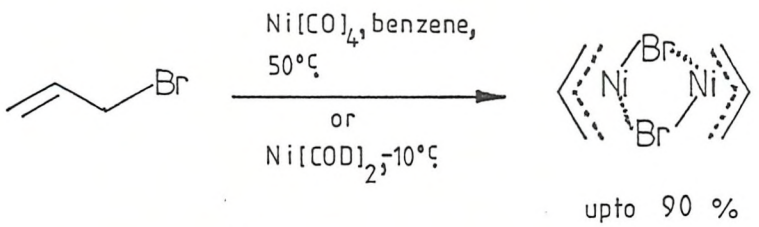
IR(thin film) 3400(OH,bs), 2980(CH,s), 2940(CH,s), 2890(CH,s), = 1380(m), 1100(C-O,s) and 1040(C-O,s) cm^{-1}.

NMR(60MHz,$CDCl_3$) 0.9(bs,3H,C10 *Me*), 1.15(d,$J_{Me,H9}$= 6Hz, 3H,C9 *Me*), 1.2-2.4(complex m,9H,H9,H8 α and β, H7 α and β, H5 α and β and H3 α and β) and 3.1-45 (complex m with brs at 3.5, 7H,2xOH, 10H,H4,H2 and H1' α and β)

THE USE OF π-ALLYL NICKEL HALIDE COMPLEXES TO FORM ∝ METHYLENE-δ-LACTONES

The synthetic utility of π-allyl nickel halide complexes

In the past few decades, considerable effort has been expended in the search for mild and selective carbon - carbon bond formation. Many of the methods use the organometallic proporties of copper[99], iron[100] or palladium[100,101] but π -allyl nickel complexes offer potential synthetic utility because of their unusual reactivity patterns. These dimeric π -allyl complexes[102] are readily available from the reaction of an allyl halide with a source of zero valent nickel usually nickel tetracarbonyl or bis (1,5-cyclocetadienyl) nickel ($Ni(COD)_2$) (Scheme 54).



upto 90 %

Scheme 54

The resultant complexes have been isolated from solution and crystallized as air sensitive solids. Alternatively, other leaving groups such as acetate, mesylate or tosylate have been used as precursors to π -allyl nickel complexes. The preparation and reactivity of these compounds has been reviewed[100,103,104] and some interesting examples involving a typical system, such as π (2-methallyl) nickel bromide (265) are illustrated in Table 4.

The yields for the reaction between the complex (265) and aryl and vinyl bromides were comparable to those obtained with simple alkyl halides[102]. Interestingly, the treatment of the complex (265) with *trans*-4-iodocyclohexan-1-ol (266) afforded a 1:2 mixture of *cis/trans* isomers[102]. The report[105] that the alkylation of the complex (267) with chiral S-2-iodooctane gave completely racemic material and together with the previous results suggested that a simple nucleophilic substitution was not involved. A single election transfer process may be inferred from the report[105] that *m*-dinitrobenzene, a radical anion scavenger, inhibited the

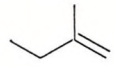
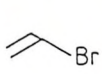
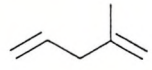
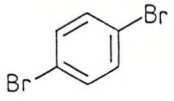
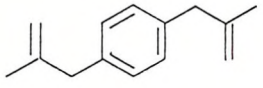
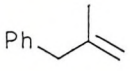
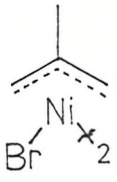
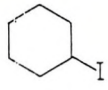
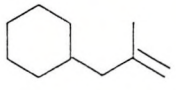
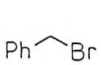
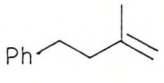
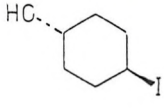
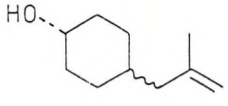
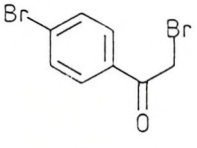
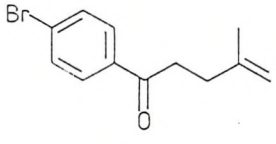
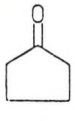
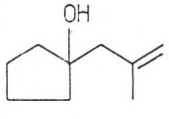
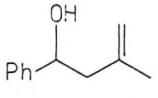
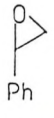
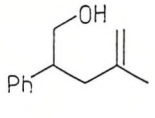
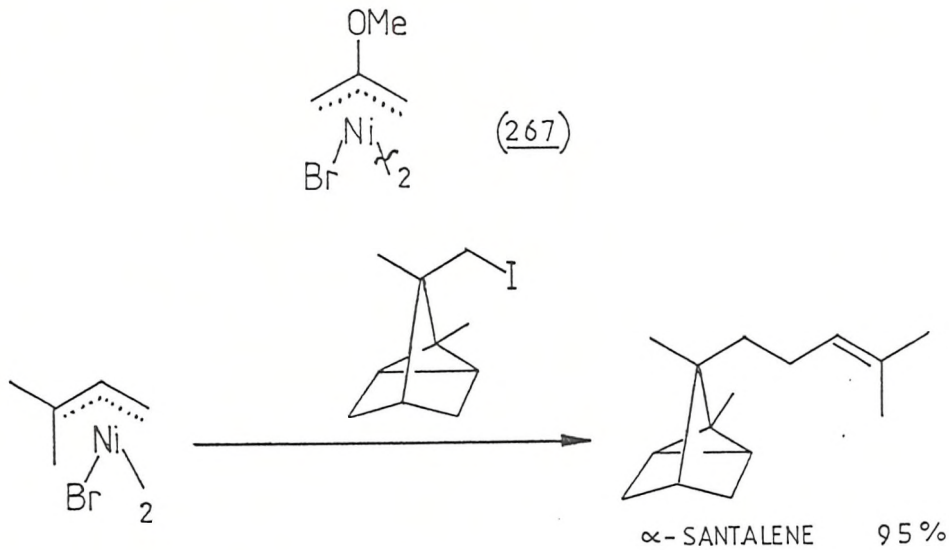
Substrate	Product	Yield	
MeBr		90%	
		70 %	
		97 %	
PhI		98 %	 (265)
		91 %	
		91 %	
		88 %	1:2 cis/trans mixture
		75 %	
		50 %	
		87%	
		60%	
Acid Chlorides	No Reaction		
Nitriles	No Reaction		
Esters	No Reaction		

TABLE 4 - The reaction of complex (265) with a variety of organic substrates.

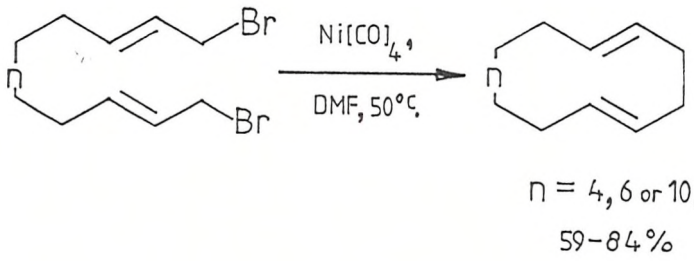
reaction of a π-allyl nickel halide with alkyl and vinyl halide.

The regioselectivity of π-allyl complexes was illustrated by the synthesis of ∝-santalene[102] where the reaction occurs exclusively at the less substituted position in 95% yield (Scheme 55).



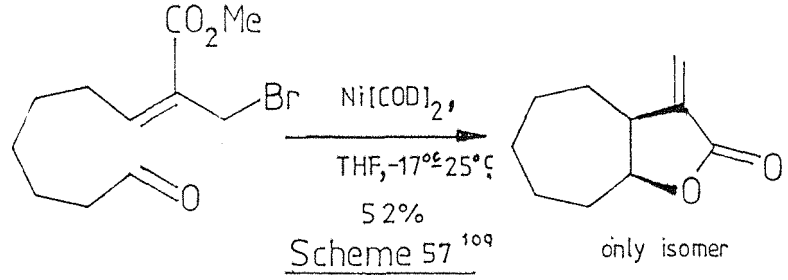
Scheme 55

Another notable use of π-allyl nickel chemistry was in the synthesis of 1,5 dienes: Corey and Hamamaka[106] have shown this coupling to be an attractive method for ring closure (Scheme 56). This cyclisation has been applied to the synthesis of the natural products cembrane[107] and casbene[108] but the yields achieved have never approached those obtained in the simpler cases.

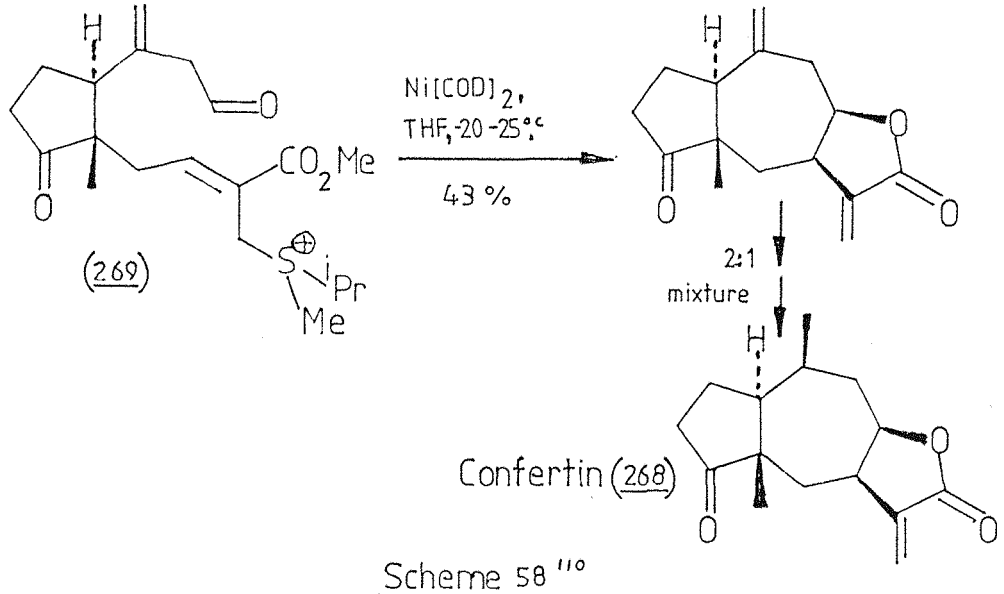


Scheme 56

The reaction of π-allyl nickel complexes with aldehydes and ketones afforded homoallylic alcohols in good to excellent yields. In the case of a π-(2-carboethoxyallyl)nickel bromide, the product formed after lactonisation was an α-methylene-γ-lactone[109] (Scheme 57). This methodology has been used in a synthesis of confertin (268)[110] but in this case the allylic sulphonium salt (269) was used as the precursor to the intermediate organometallic (Scheme 58).

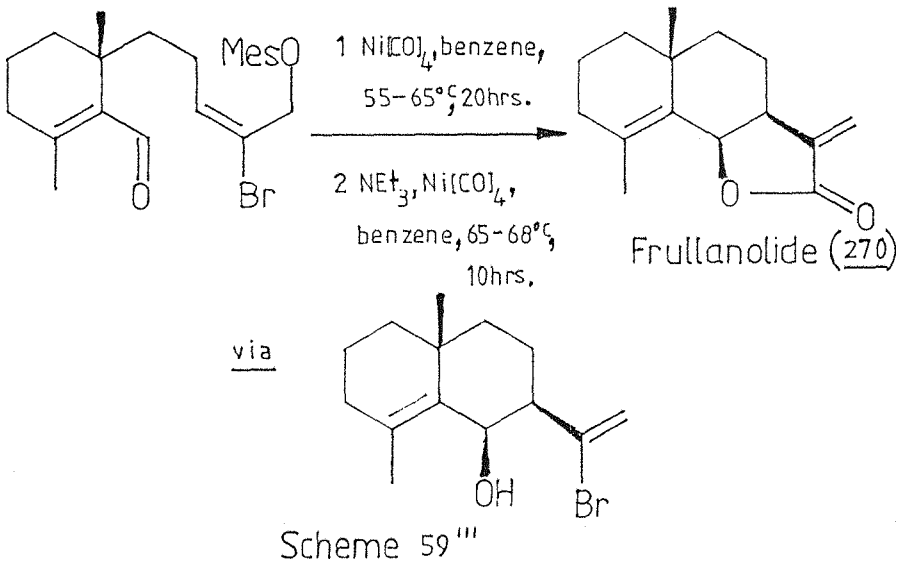


Scheme 57[109] only isomer



Scheme 58[110]

The ability of nickel tetracarbonyl to form both a π-allyl complex and undergo a carbon monoxide insertion reaction with a vinyl bromide has been demonstrated in the synthesis of frullanolide (270)[111] (Scheme 59).



Scheme 59[111]

In these last two cases, the alternative leaving groups were employed because the use of the requiste allylic bromide as a precursor to the intermediate π-allyl complex proved difficult. Since the initial results of the unusual reactivity of π-allyl nickel complexes towards organic substrates, there have been a few further investigations. Each study has highlighted one specific aspect and, in general, culmulated in the synthesis of a natural product. In many cases, nickel complexes have been employed in an intramolecular manner to form small (6-7)or large (15+) membered rings which presumably exploited the template effect of the transition metal.

Results and Discussion

The α-methylene-γ-butyrolactone moiety is present in a range of structurally diverse natural products which often exhibit biological activity[112]. Although many methods are available for the introduction of this functionality[113], they are not generally applicable to the α-methylene-δ-valerolactone system. In most strategies, the α-methylene functionality was added to a preformed δ-valerolactone. It was envisaged that the reaction of π(2-carboethoxyallyl)nickel bromide with an epoxide would provide the α-methylene-δ-valerolactone directly after lactonization had occurred(Figure 20).

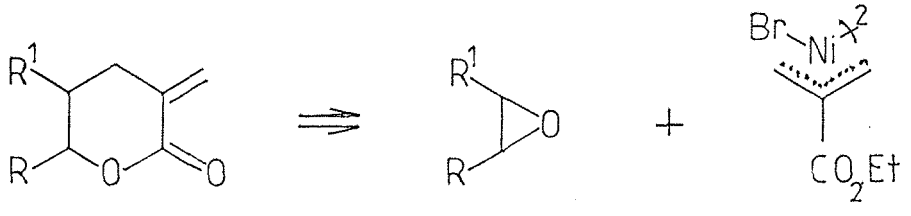


Figure 20

The reaction of π-allyl nickel bromide complexes with epoxides had not been previously reported in the literature. In preliminary studies in this department[114], the reactivity of π-(2-methallyl) nickel bromide with a series of epoxides (Table 5). These encouraging results led to the study of the reaction of π-(2-carboethoxyallyl) nickel bromide with styrene oxide.

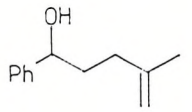
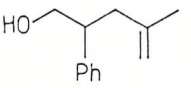
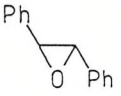
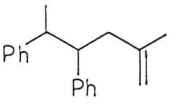
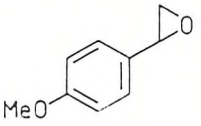
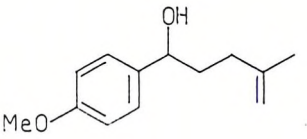
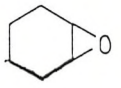
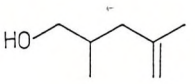
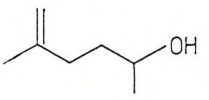
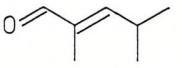
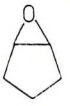
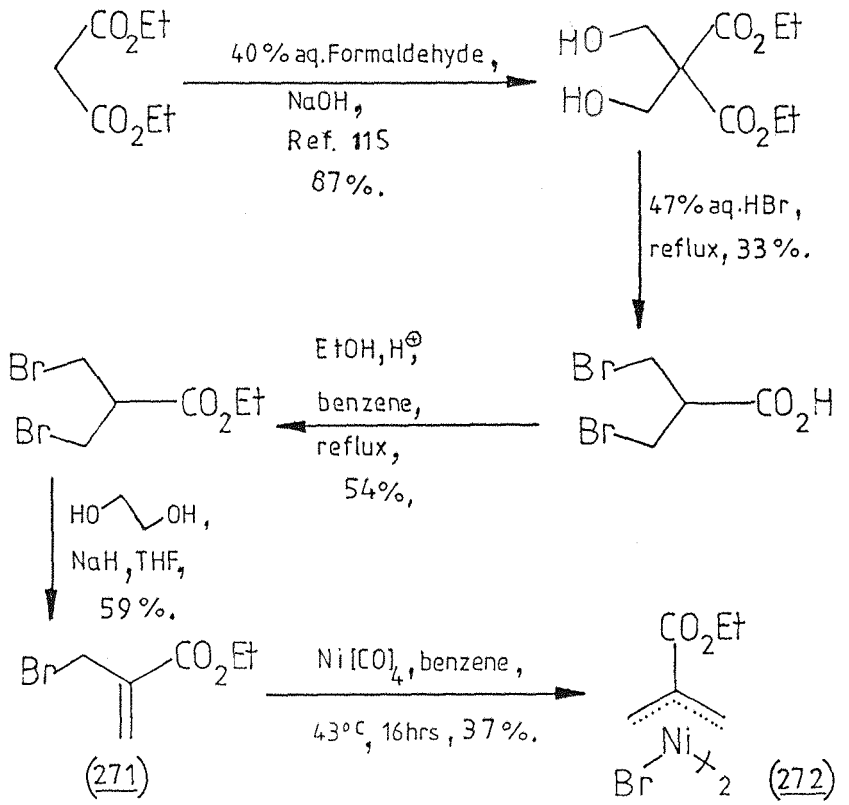
Epoxide	Product	Yield	Reference
		30 %	
		55 %	60 %[102] 30-40 %[119]
		23 %	
		27 %	
	No Reaction		
		16 %	
		12 %	
		72 %	
	No Reaction		30-40 %[119]

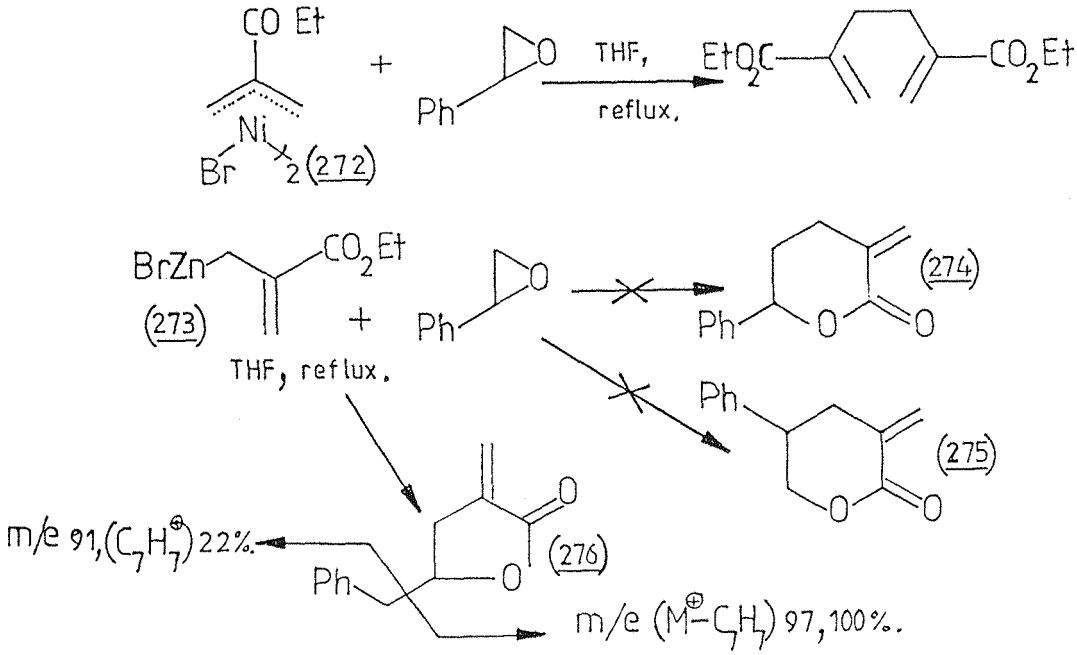
Table 5 The reaction of π(2-methallyl)NiBr(265) with various epoxides[114].



Scheme 60

The allylic bromide (271) was available by the method of Ferris[116] (Scheme 60), but superior syntheses of the halide (271) have since appeared[117,118]. Treatment of the allylic bromide (271) with the volatile and highly toxic nickel tetracarbonyl under an argon atmosphere led to the π-allyl nickel complex (272) in 37% yield. Addition of styrene oxide to the complex (272) in DMF under an argon atmosphere afforded a green solution after being stirred overnight at 50 °C. Isolation of the crude product resulted in an oil which was shown by nmr spectroscopy to contain dimer as the major component (Scheme 61). In Table 5 it can be seen that several inconsistencies exist between the results of Corey[102], Hegedus[119] and Sims[114]. Hegedus *et al*[119] claimed that, in general, π-allyl nickel halide complexes were unreactive towards epoxides. Furthermore, π-(2-carboethoxyallyl)nickel bromide (272) was reported to be less reactive, thermally less stable and more prone to dimerization then other π-allyl nickel complexes. An alternative explanation offered by

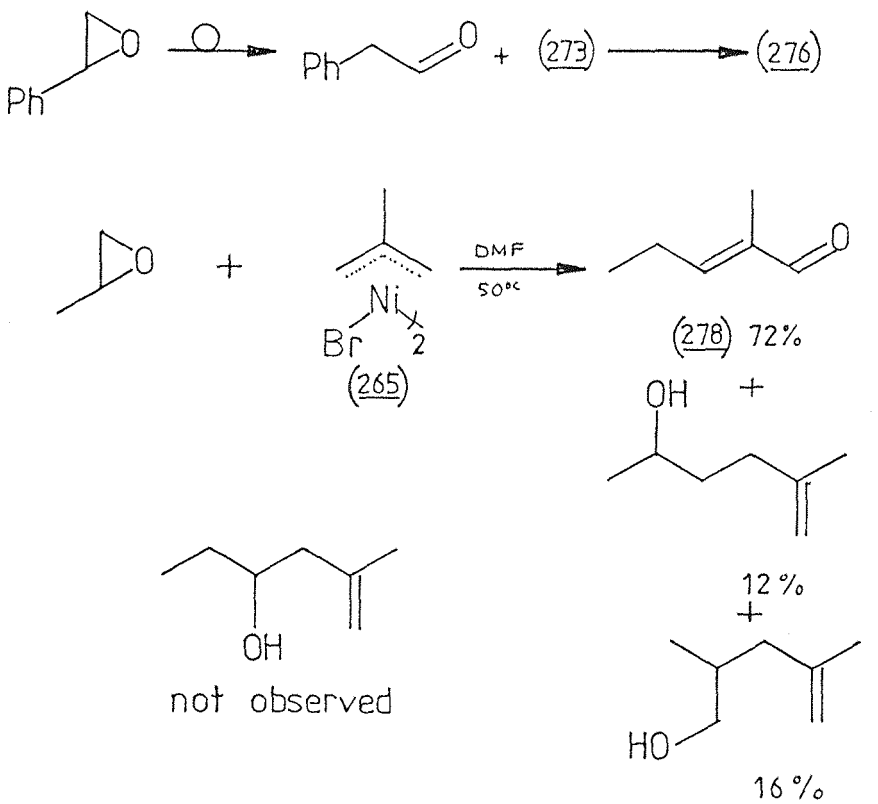
Sato *et al*[120] was that the nickel complex (272) was so reactive that dimerization occurred so fast that quenching reactions could not be observed.



Scheme 61

In an effort to achieve the initial proposal, the more reactive organometallic zinc system (273) was treated with styrene oxide. The organometallic was formed *in situ* in a Reformatsky-type reaction of the allyl bromide (271) with freshly activited zinc dust. The allylic bromide (271) was added slowly to a styrene oxide/zinc mixture in dry refluxing THF and a major product was isolated, after lactonization, by column chromatography. Comparison of the spectral data indicated that the compound was not the δ-valerolactone (274) or (275). The mass spectrum indicated the presence of the tropylium ion (m/e 91) and in spectrum showed that the compound contained a strained lactone carbonyl at 1750 cm^{-1} (Scheme 61). The major product was assigned the structure (276) and its formation must have occurred by the reaction of the intermediate (273) with phenyl acetaldehyde (277).

Consequently, the styrene oxide must have suffered a Lewis acid-catalysed rearrangement to the aldehyde (277) and this convertion of epoxides into aldehydes by organometallic species has been reported elsewhere[121]. Sims[114] found that in the reaction of π-(2-methallyl) nickel bromide with propylene oxide, the major product (278) resulted from the self condensation of propanal. Presumably, the nickel complex (265) catalysed the rearrangement of propylene oxide to propanal and surprisingly no addition of the π-allyl ligand to propanal was observed (Scheme 62).



Scheme 62

After identification of the α-methylene-γ-lactone (276), it was found that this compound had previously been prepared in 20% yield by the same procedure[122]. With these results in hand, no further investigations were initiated and an alternative research topic was pursued.

EXPERIMENTAL

Infra red spectra (IR) were recorded on a Perkin Elmer 157 G spectrometer with polystyrene used as a reference and the absorption (v max) quoted in units of cm^{-1}. 60 $MHz^{1}H$ nmr spectra were recorded on a Perkin Elmer R12 instrument and deuteriochloroform used as the solvent for such spectra with tetramethylsilane employed as the internal reference. Mass spectra were recorded on a Kratos MS30 spectrometer equipped with the DS 50S data system. All spectra were recorded at 70 eV and the major ion fragments are reported as m/e values and as percentages of the base peaks. Melting points were determined using an Electrothermal electral electrically heated block and are incorrected. Elemental analyses were carried out at the Microanalytical laboratory, University College, London.

Flash column chromatography as described by W. C. Still *et al*[93] was performed on M. N. Keiselgel 60(230-400 mesh). The solvents distilled before use and petroleum ether refers to the fraction distilling between 40-60 °C. Thin layer chromatography was performed on precoated silica gel plates (MN Kieselgel . 60) and visualised by a combination of Iodine vapour, UV light and 1% vanallin in an acidic methanol solution.

All glassware for anion and nickel reactions were assembled hot and flame dried before use under a positive pressure of a dry inert atmosphere. Experiments involving the use of nickel tetracarbonyl were carried out in an efficient fume hood and all exhaust gases were passed through bromine water and the apparatus left in bromine water to decompose any of the highly toxic and volatile nickel tetra carbonyl. An argon atmosphere and argon purged solvents were used in all reactions involving nickel complexes. DMF used for such reactions was pre-dried over calcium hydride, fractionated at reduced pressure, purged and stored under an argon atmosphere.

Zinc dust was activated by washing sequentially with 1MHCl, distilled water, ethanol, acetone and dry ether and finally dried at reduced pressure. THF was distilled from sodium/benzophenone under

a dry nitrogen atmosphere. Other reagents were purified by standard procedures.

Diethyl-22-di(hydroxy methyl) malonate

To a solution of diethyl malonate, (250 g,1.56 moles), form aldehyde (2.5 l of 40% aqueous solution) and Thymol blue (catalytic amount) was added drop wise 10% sodium hydroxide (w/v) whilst maintaining the pH below 9. The mixture was stirred for 48 hours at room temperature and then the reaction was saturated with salt (*ca* 350 g) and extracted with ether (6 x 200 mls). The organic extracts were combined and dried over magnesium sulphate, the solvent was removed at reduced pressure and this afforded the title compound as an orange oil (299 g, 87%)[115].

2-(Bromo methyl)-3 bromo-propanoic acid

A solution of the above diester (299 g, 1.35 moles) in 47% hydro bromic acid (1.4 l) was heated under reflux for 2 hours and the ethyl bromide produced was removed by distillation. The remaining red/orange solution was maintained at the point of reflux for a further 6 hours. After cooling, no crystals were obtained, the solution was concentrated by distillation. This produced 2-(Bromo methyl)-3-bromo-propanoic acid (110 g, 33%) as off white needles.

mp 100 °C lit[116] 100 °C - 102 °C
yield 33% lit[116] 66 %

Ethyl, 2-(bromo methyl)-3-bromo-propanoate

A solution of 2-(bromo methyl)-3 bromo-propanoic acid (110 g, 0.45 moles) ethanol (330 mls) benzene (1.1 l) and concentrated sulphuric acid (1ml) was heated at the point of reflux overnight and the condensing liquid passed through a thimble of magnesium sulphate (*ca* 50 g) by means of a Soxlet apparatus. After cooling to room temperature, the reaction mixture was added to ice cold saturated sodium hydrogen carbonate (250 mls). The aqueous phase was extracted with ether (3 x 100 mls), the organic extracts were combined, dried over magnesium sulphate and the solvent removed at reduced pressure. The residue was distilled at reduced pressure and afforded the title compound as a colourless oil (66.3 g, 54%).

bp 120 °C 0.15 mm Hg, lit[115] 59-61°C 3.9 mm Hg

IR. (film) 3000 (CH), 1730 (C=O), 1200(C-O) and 1035 (c-O).

^{1}HNMR($CDCl_3$) 1.3 (t, 3H, J = 6.5 Hz, CH_2 of Et), 3.15 (quintet, J = 5 Hz, 1H, $CH(CO_2Et_2)$, 3.75(d, J = 6.5 Hz, 4H, CH_2 Br x 2) and 4.25 (q, J = 5Hz, 2H, CH_2 of Et).

Ethyl 2-(bromo methyl)-prop-2-enoate(271)

To a suspension of sodium hydride (10.6 g 50% dispersion) 0.23 moles)in dry THF (50 mls) under dry nitrogen atmosphere was added ethane 1,2 diol (22.6 g, 0.36 moles)in dry THF (50 mls) and the resulting mixture was heated at the point of reflux overnight. The mixture was allowed to cool and the Ethyl-2-(bromo methyl)-3 bromo propanoate (48 g, 0.18 moles)in dry THF (50mls) was the added and the resulting mixture stirred for 3 hours. After which time the reaction mixture was poured into water (50 mls) and extracted with DCM (4 x 50 mls). The combined organic extracts were dried over magnesium sulphate and the solvent removed at reduced pressure. The resulting oil was distilled at reduced pressure and afforded Ethyl-2(bromo methyl)-prop-2-enoate (271) (20 g, 59%).

bp °C lit[116] 44-45°C 1.7 mm Hg

IR (film) 3000 (CH), 1730 (GO) 1630 (C=C) and 1200 (C-O)

^{1}H NMR ($CDCl_3$)1.35 (t, J = 6.5 Hz, 3H, CH_3 of Et), 4 - 4.5 (m, 4H, CH_2, Bn, CH_2 and Et)

5.95 (bs, 1H, C*H syn* to ester) and 6.3 (bs, 1H, C*H anti* to ester)

π-(2-carboethoxy allyl) nickel bromide (272)

Ethyl-2-(bromo methyl) prop-2-enoate (271) (20 g, 0.1 moles) was added to nickel tetra carbonyl (15 mls, 0.12 mls) in benzene (100 mls) under an argon atmosphere with the exhaust gases being verted through bromine water and the reaction carried out in a good fume hood. The reaction mixture was stirred overnight at 43 °C and this afforded a pink crystalline precipitate and a dark red solution. The benzene and excess nickel tetra-carbonyl were removed *in vacuo* and afforded a brick red solid. Argon purged pentane (50 mls) was then added and the solid filtered using a Schlenk apparatus. The resulting yellow/orange solid was transferred to a Schlenk tube and the complex dried *in vacuo*.

This gave the complex (272) (9.7 g, 37%) lit[163].

Phenyl oxirane

A solution of styrene (5.2 g, 0.05 moles) in DCM (50 mls) was treated with 3-chloro-peroxy benzoic acid (9.5 g, 0.05 mls). The mixture was stirred overnight and then filtered. The resulting solution was washed with saturated sodium bicarbonate (20 mls), 10% aqueous sodium thio sulphate (20 mls) and again with saturated sodium bicarborate (20 mls). The organic phase was dried over magnesium sulphate and the solvent removed at reduced pressure. The resulting oil was distilled at reduced pressure to afford phenyl oxirane (4.53 g, 75%)

bp 82 ^{o}C/16 mm Hg lit[114] 78-80 ^{o}C/15 mm Hg

The attempted preparation of ± 3 methylene-6-phenyl tetra hydro pyran-2-one, using the allyl nickel complex (272).

Phenyl oxirane (0.5 g, 4.1 mls) in dry DMF (10 mls) was added to π-(2-carbo-ethoxy allyl) nickel bromide (272) (0.8 g, 3.6 nmls) in dry DMF (10 mls) under an argon atmosphere. The reaction mixture was stirred overnight at 50 ^{o}C. The resultant green solution was poured into 10% hydrochloric acid (10 mls) and extracted with ether (2x50 mls). The organic phase was then washed with saturated brine (2x20 mls) and dried over magnesium sulphate. The solvent was removed at reduced pressure and the resultant oil (0.3 g) was shown by nmr to consist mainly of drive (*ca* 70%).

^{1}HNMR ($CDCl_3$) 1.3(t, J = 6.5 Hz, *Me* of Et), 2.5 (s, 4H, CH_2 allylia) 4.2(q, J = 6.5 Hz, 4H, CH_2 of Et), 5.5 (brs, 2H vinyl *CH syn* to ester) and 6.1 (brs, 2H vinyl *CH anti* to ester)

The reaction of 2-carboethoxyallyl zinc bromide (273) with phenyl oxirane

Phenyl oxirane (0.62 g, 5.2 moles) in THF (10 mls) was added to freshly activated zinc (0.37 g, 5.7 moles) and the resultant slurry was slowly treated with Ethyl-2(bromo methyl)-2-prop-2-enoate (271) (1.0 g, 5.2 moles) in THF (20 mls). The solution was heated at the point of reflux overnight and after cooling the reaction mixture was then poured into 4% aqueous hydro chloric acid (10 mls). After extraction with ether (3x20 mls), the combined organic phase was

washed with brine (2 x 10 mls) and dried with potassium carbonate. The solvent was then removed at reduced pressure and the resultant yellow oil was subjected to flash column chromatography (ether/ petroleum ether, 1:1). This afforded an oil (500 mgs) which solidified on standing. Recrystallization from ether gave 3-methylene-5(phenyl methyl)-dihydro furan-2-one (276) (310 mgs, 32%).

mp 58 - 60 ^{o}C (32%) lit[122] 63 - 64 ^{o}C 26% yield

IR ($CDCl_3$ solution) 3010 (CH), 2910 (CH), 1750 (C = O), 1670(C = O) 1270 (C - O), 1250, (C - O) 1150 (C - O) and 1120 (C-O)

^{1}HNMR ($CDCl_3$) 2.6 - 3.1 (m,4H,PhC*H*$_2$,CH_2 allylic), 4.75 (quintet, H = 6.5 H), 1H(C*H*O), 5.55(t,J=2.5 H_z,1H,vinyl C*H* *syn* to lactone), 6.28(t,J=2.5 H_z,1H,vinyl C*H* *anti* to lactone) and 7.5(s,5H, aromatic).

ms. (ei) 188 ($M^{\oplus}$, 13%), 143 ($M^{\oplus}$ - CO, 1.7%) 98, (5%), 97 ($M^{\oplus}$ - C_7H_7, 100%)
92 ($C_7H_8^{\oplus}$, 12%), 91 ($C_7H_7^{\oplus}$, 22%) and 69(33%)

Accurate mass	calculated	188.0837
	found	188.0797

Chemical analysis	calculated	C 76.57%	H 6.43%
	found	C 76.24%	H 6.40%

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