Approaches to the core structure of the squalestatins

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A THESIS
entitled

Approaches to the core structure of the squalestatins

submitted by

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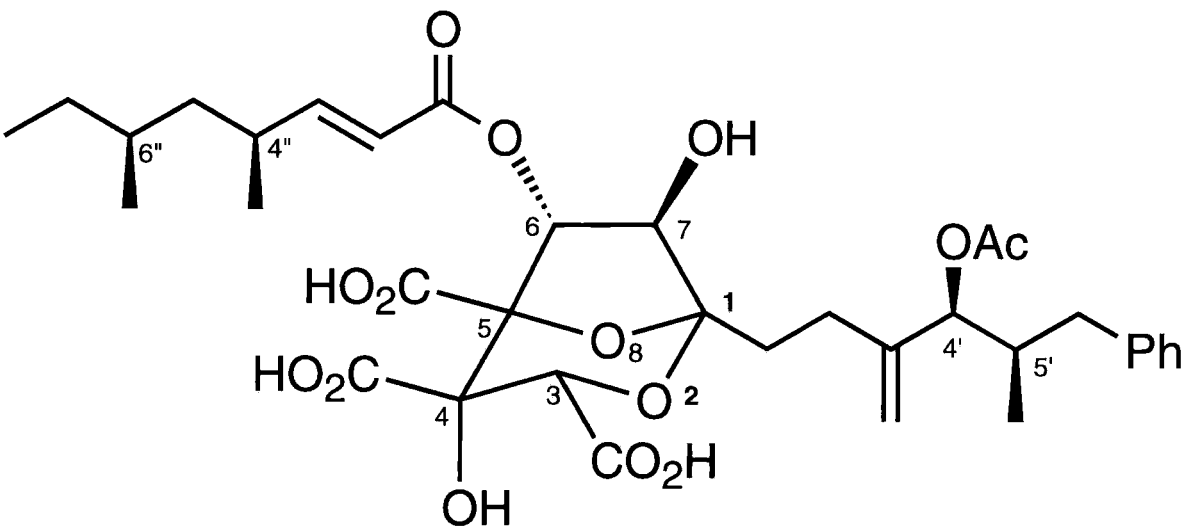

Squalestatin 1

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A special mention must go to the late Andy Ridge, who it was a pleasure to know and work with.

Memorandum

The work described in this thesis was carried out in the University of Durham between October 1993 and September 1996. This thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree.

Part of this work has been presented at:

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December, 1995

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University of St. Andrews
March, 1996.

University of Durham Graduate Colloquia
May, 1996

BOSS-6
Gent, Belgium
July, 1996.

Abbreviations

The following are used throughout the thesis.

Ac	: acetyl
BINAL	: binaphthol aluminium
9-BBN	: 9-borabicyclo[3.3.1]nonane
Bn	: benzyl
Bu	: butyl
CI	: chemical ionisation
d	: doublet
de	: diastereomeric excess
DCM	: dichloromethane
DIBAL	: diisobutylaluminium hydride
DMAP	: 4-dimethylaminopyridine
DMF	: *N,N* dimethylformamide
DMSO	: dimethyl sulphoxide
EI	: electron impact
Et	: ethyl
Ether	: diethyl ether
GC-MS	: gas chromatography-mass spectroscopy
IR	: infra red
LDA	: lithium diisopropyl amide
LHMDS	: lithium hexamethyldilisazide
m	: multiplet
Me	: methyl
m.p.	: melting point
MS	: mass spectroscopy
MOM	: methoxy methyl
NMO	: *N*-morpholine-*N*-oxide
NMR	: nuclear magnetic resonance
PCC	: pyridinium chlorochromate
Petrol	: petroleum ether (40-60°C)
PMB	: *para*-methoxybenzyl
PTSA	: *para*-toluenesulphonic acid
q	: quartet
s	: singlet

SEM	: 2-(trimethylsilyl)ethoxymethyl
t	: triplet
TBDMS	: *tert*-butyldimethylsilyl
TBDPS	: *tert*-butyldiphenylsilyl
TBS	: *tert*-butyldimethylsilyl
THF	: tetrahydrofuran
tlc	: thin layer chromatography
TMS	: trimethylsilyl
TFA	: trifluoroacetic acid
TFAA	: trifluoroacetic anhydride
TPAP	: tetrapropylammonium perruthenate
TsOH	: *para*-toluenesulphonic acid

Abstract

Approaches to the core of the squalestatins

Alison M. Reid
Ph.D. 1996

The squalestatins are a new family of natural products which display potent cholesterol lowering effects. Common to all these natural products is the highly oxidised bicyclic core and the aim of this project was to achieve a concise synthetic route to this core unit.

Initial studies were carried out using 2-benzyloxycyclohexanone as a model template. Following conversion to the 2-oxa-3-oxo-spiro<4.5>decan-6-one *via* addition of the dianion of 3-(*para*-tolylsulphonyl)propionic acid, coupling of a C(2) fragment was explored. Addition of carboethoxymethylenetriphenylphosphorane, followed by oxidation to the diol and protection as the acetonide led to the formation of 4-Ethoxycarbonyl-(2,2-dimethyl-5"-oxodispiro[perhydro[1,3]dioxolane-4,1'-cyclohexane-2',2"-(5"-H-furan)]-5-yl. The alternative order of addition of the C(4) and C(2) units has also been undertaken.

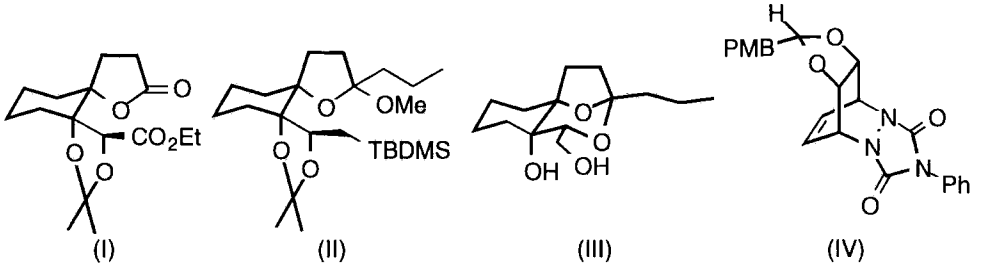
Manipulation of the ester group to a silyl ether afforded a less reactive functionality and C(4) was manipulated to allow for the coupling of the next fragment to form the spiro lactone. The addition of the dianion of 3-(*para*-tolylsulphonyl)propionic acid to 4-(^{t}butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-one failed and another route to the spiro lactone was explored.

Formation of 4-(^{t}butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecan-8-one (**I**) was achieved by allylation at C(4) followed by hydroboration of the double bond and subsequent oxidation. The C(1) side chain could be added to the spiro lactone using allyl magnesium bromide without compromising the other functionality present.

Acid treatment of 4-(^{t}butyldimethylsilyloxymethyl)-8-methoxy-2,2-dimethyl-8-propyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecane (**II**) promoted deprotection of the acetonide followed by concomitant cyclisation to the desired 6-hydroxy-9-propyl-8,12-dioxatricyclo<7.2.1.0>dodec-7-yl-1-methanol (**III**). This showed the viability of the retrosynthetic analysis as a route to core analogues of the squalestatins.

Studies to the fully substituted core were commenced using cis-cyclohexadiene diol. The diol was protected as its *p*-anisaldehyde acetal before the formation of the Diels Alder adduct (**IV**) using 4-phenyl-1,3,5-triazolinone. However a lack of time prevented its manipulation to the α-alkoxy ketone species through Lewis Acid mediated cleavage of the acetal.

In a second retrosynthetic plan 2-benzyloxycyclohexanone was coupled with methyl tetronate prepared following the procedure of Pelter. Preliminary studies towards the addition of the C(1) side chain have been undertaken and initial results seem promising.



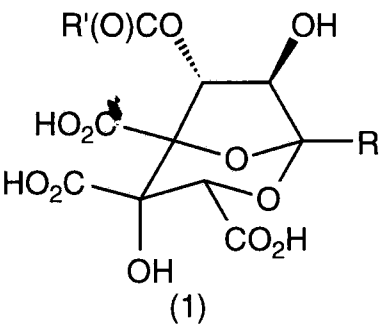
(I) (II) (III) (IV)

Contents

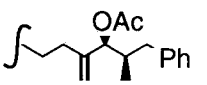
Chapter 1 : Introduction and Background

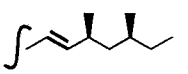
1.1 Introduction

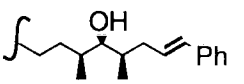
This thesis describes work directed towards a synthesis of the core unit of the squalestatins. These natural products belong to a group of fungal metabolites which have been found to inhibit squalene synthase, a key enzyme in the cholesterol biosynthetic pathway. Hence, the squalestatins have potential as therapeutic agents for a number of ailments including fungal diseases and hypercholesterolemia.

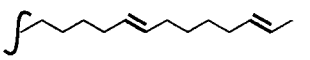


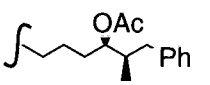
(1)

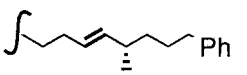
Squalestatin 1 / Zaragozic acid A R = 

R' = 

Zaragozic acid B R = 

R' = 

Zaragozic acid C R = 

R' = 

Scheme 1.1.1

1.2 Isolation and Structure Analysis of Squalestatin 1

1.2.1 Isolation

Screening programmes were set up to aid the discovery of compounds which inhibit squalene synthase and, in 1992, workers at Glaxo[1] and Merck[2] simultaneously reported the discovery of a new family of natural products which display picomolar inhibition of squalene synthase in cell cultures.[3] Glaxo named this new family Squalestatins because of their squalene synthase inhibitory effects and Merck named them Zaragozic Acids as the cultures were isolated from samples taken from the Jola River in Zaragoza, Spain. The squalestatins contain a highly oxidised bicyclic core unit, with a run of three contiguous carboxylic acids and differ only in the C(1) alkyl side chain and C(6) O-acyl side chain, Scheme 1.1.1.

Isolation of the squalestatins was carried out through a four step procedure by taking advantage of their unusual amphipathic nature. Initial extraction was undertaken using a combination of water and methanol. Chromatography was then carried out, followed by the acidification and extraction of the protonated acids with dichloromethane. The strongly acidic nature of the squalestatins was exploited using anion exchange chromatography before final purification by HPLC. Altogether, from 23 litres of broth mixture, 24mg was purified by HPLC to afford squalestatin 1 as a pale yellow oil.

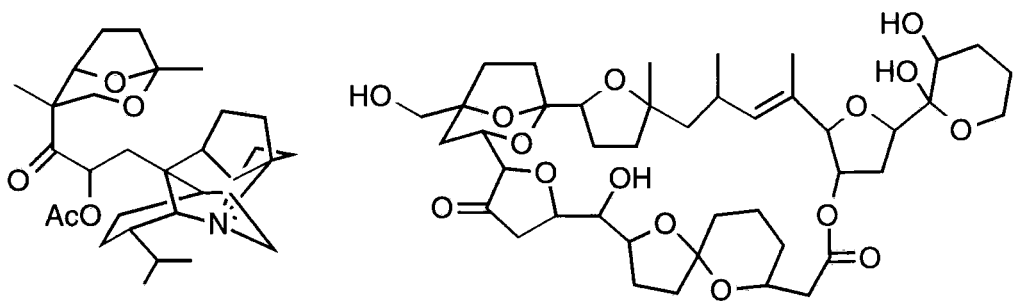
1.2.2 Structure Determination

A knowledge of the absolute stereochemistry of a compound is a prerequisite before studies can be carried out to fully understand the influence of the structure on biological activity. Merck research laboratories reported the initial chemistry and absolute stereochemistry in 1992.[4]

The empirical formula of squalestatin 1 ($C_{35}H_{46}O_{14}$) was deduced from HR EIMS and ^{13}C NMR analysis of its penta-TMS derivative. The tricarboxylic acid moiety was elucidated by FAB MS of the lithium adduct of a trilithium salt formed on spiking with lithium acetate. The ^{13}C data and formula indicated 5

double bonds and 5 carboxylate/ester groups. The structures of the C(1) and C(6) side chains were elucidated from NMR studies of their respective acids after degradation by base hydrolysis.[5] Deuterium isotope induced ^{13}C shifts ruled out the presence of a hemiketal function.

The absolute stereochemistry of the core unit was established using CD measurements of a bisbromobenzoate derivative. From this, it was found that the configuration of C(3) and C(4) were both (S) and that of C(6) and C(7) were (R). Oxidative degradation of the C(1) alkyl side chain suggested an (R) configuration at the C(5') atom. O-methyl mandelate derivatives provided the evidence for the (S) configuration at C(4'). Confirmation of these stereochemical assignments was obtained through X-ray analysis of the easily prepared tetrakis(trimethylsilyl) and tri^{t}butyl ester derivatives of squalestatin 1. As can be seen from Figure 1.2.1, this highly oxidised core unit exists as a six membered ring (C(1)-O(2)-C(3)-C(4)-C(5)-O(8)) in the chair conformation. Although this central core is not unique - it is present in a plant alkaloid[6](**2**) and a shellfish toxin[7](**3**), Figure 1.2.1, it has not previously been observed with such heavy substitution.



Daphniphylline (2) Pectenotoxin-1 (3)

Figure 1.2.1

Overall, squalestatin 1 has nine stereogenic centres with six of them confined to the core unit. In summary, these centres have been defined C(1)(S), C(3)(S), C(4)(S), C(6)(R), C(7)(R), C(4')(S), C(5')(R), C(4")(S), C(6")(S) as decribed in Figure 1.2.2.

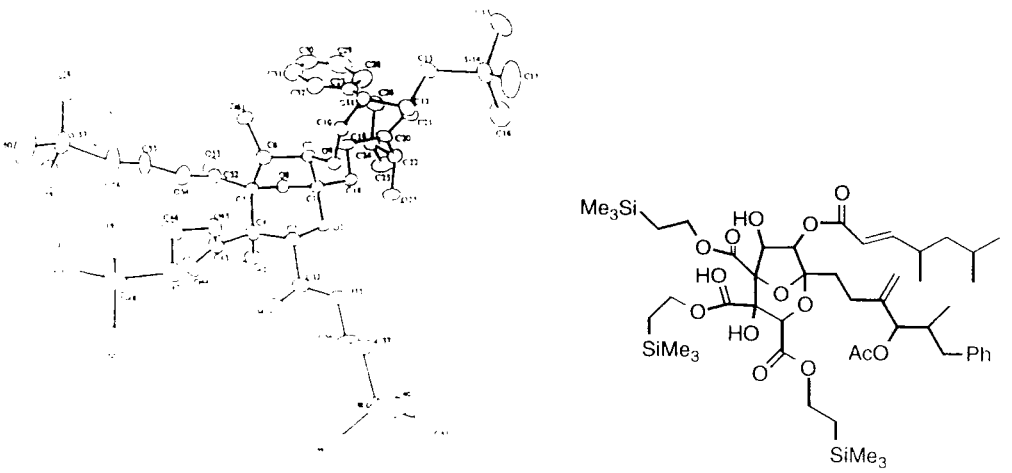


Figure 1.2.2

This work also unveiled some of the chemical properties of squalestatin 1. Selective removal of either the 4'-O-acetyl residue or the 4,6-dimethyl octenoyl residue was accomplished. In addition, it was observed that selective manipulation of the individual carboxyl functions was also feasible. The reactivity of carbomethoxy derivatives was found to be C(3)>C(5)>C(4) at least with respect to attack by small nucleophiles at the carbonyl carbon. The difference in reactivity could arise from a combination of steric factors and electronic assistance from the C_4 hydroxyl group through hydrogen bonding with carbonyl oxygens of the esters at C(3) and C(5).

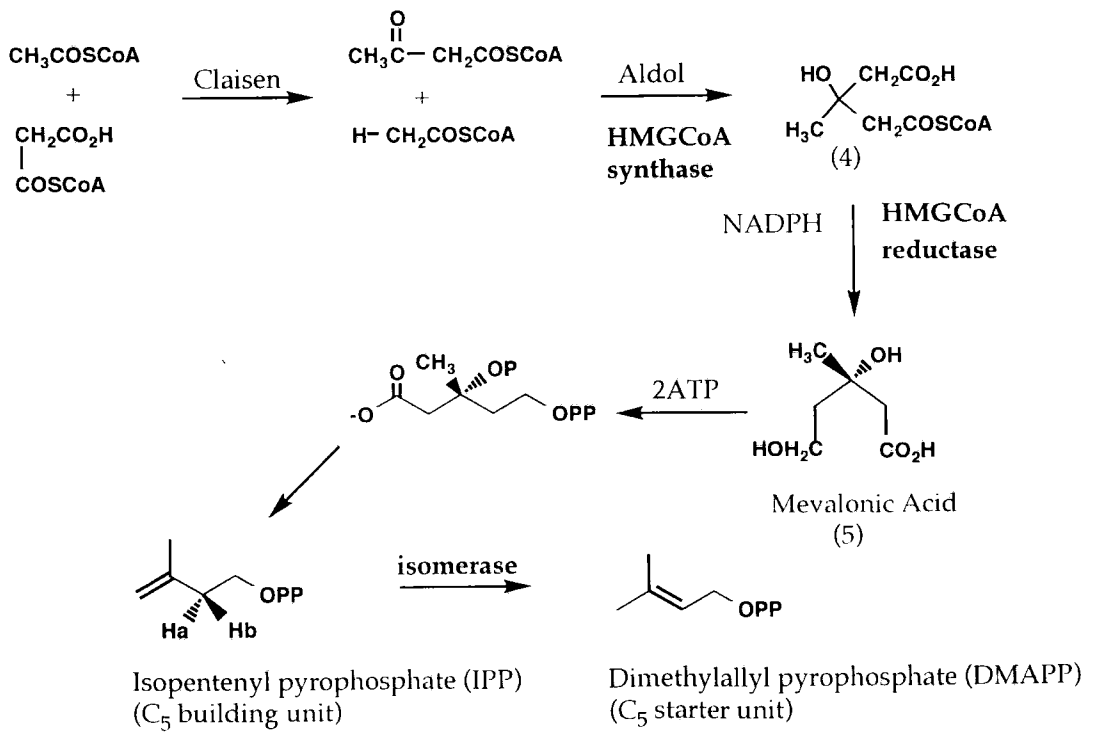
1.3 Cholesterol and its Regulation

1.3.1 Introduction

Atherosclerosis and hypercholesterolemia affect a significant percentage of the population in the western world today. Furthermore, elevated serum cholesterol is well established as a risk factor for coronary disease and a number of studies have shown that reducing raised levels of serum cholesterol in man, leads to a reduction in the incidence of coronary-related deaths.[8] Therefore much effort has been put into understanding and regulating the cholesterol biosynthetic pathway. This section will describe the approaches to the search of potent inhibitors of cholesterol.

1.3.2 Cholesterol Biosynthesis

Cholesterol is biosynthesised from the condensation of isoprene units to form long lipophilic chains which ultimately cyclise to form first lanosterol, then after a series of steps, cholesterol, Scheme 1.3.2. The isoprenoid pathway forms the building blocks to sterol synthesis and commences with the formation of malonyl CoA from acetyl CoA, Scheme 1.3.1.[9] An aldol condensation produces 3-hydroxy-3-methylglutaryl coenzymeA (HMGCoA) (**4**) and an enzyme known as HMGCoA reductase catalyses its reduction to mevalonic acid (**5**). This is known to be a rate limiting step in the isoprenoid pathway and drugs which inhibit this enzyme are well known as effective therapeutic agents for hypercholesterolemia. Manipulation of mevalonic acid produces isopentenyl pyrophosphate (IPP), a C_5 building block in the synthesis of cholesterol. Isomerase catalyses the formation of dimethylallyl pyrophosphate (DMAPP) which is the C_5 starter unit in the polyprenoid pathway.

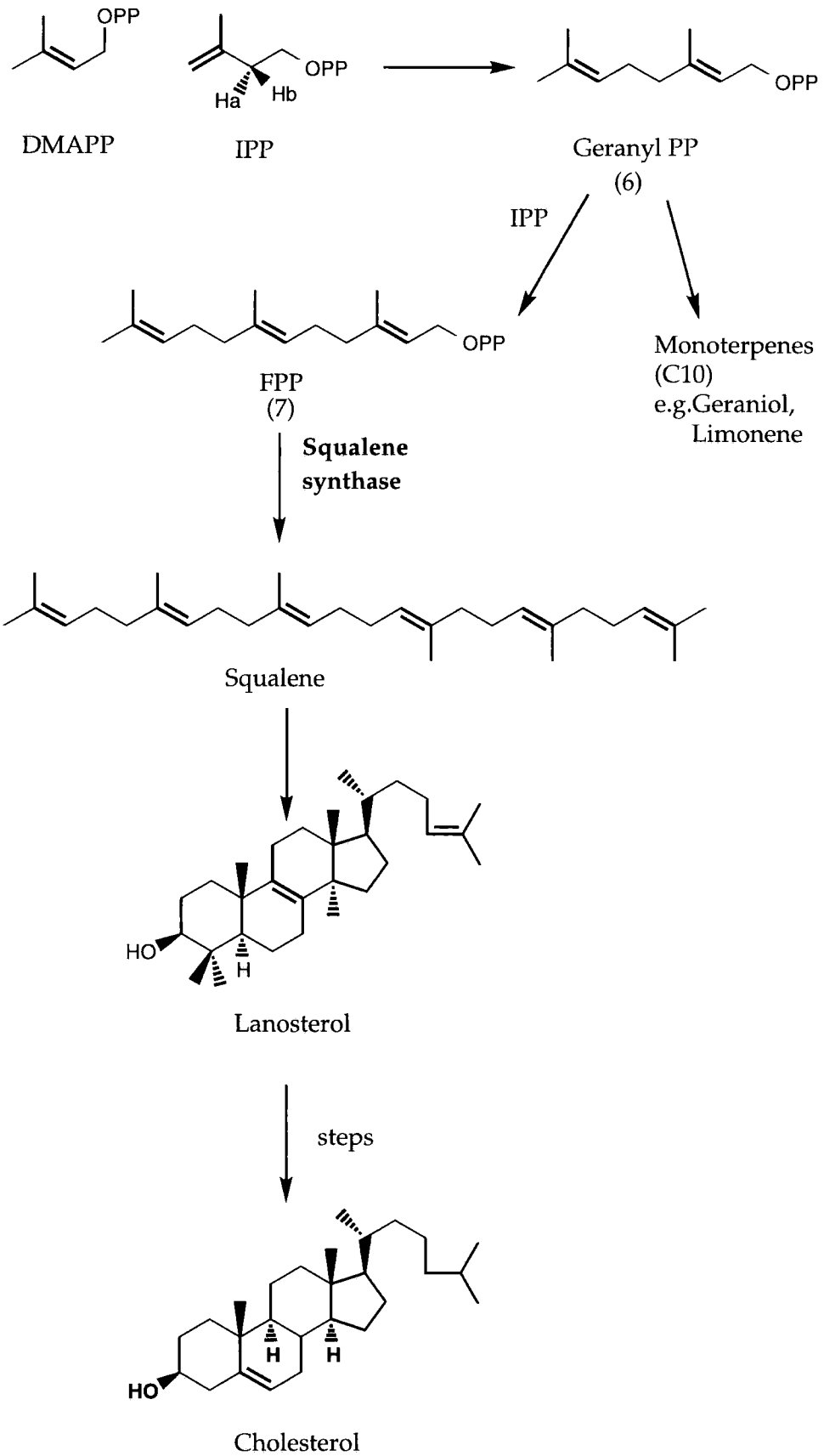


Isopentenyl pyrophosphate (IPP) (C_5 building unit)

Dimethylallyl pyrophosphate (DMAPP) (C_5 starter unit)

Scheme 1.3.1

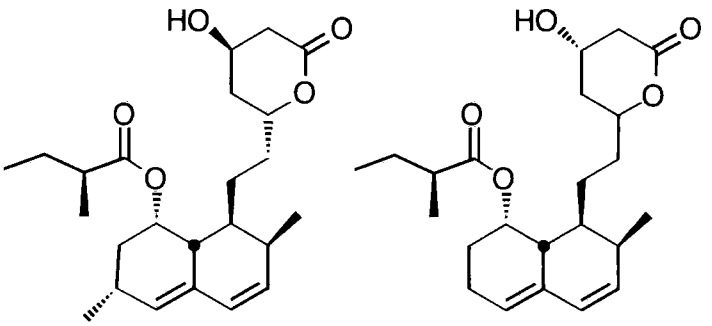
Scheme 1.3.2 shows the construction of cholesterol *via* the condensation of DMAPP units to an IPP starter unit. The addition of one molecule of DMAPP to one molecule of IPP forms geranyl pyrophosphate (**6**) upon the elimination of a pyrophosphate group. The pathway diverges at this point, with the possibility of chain extension through the addition of more DMAPP or manipulation to form monoterpenes such as dolichol and geraniol. Farnesyl pyrophosphate (FPP) (**7**), a C_{15} chain, is formed from the addition of two DMAPP molecules to IPP. Squalene synthase is the enzyme which catalyses the head to head ligation of two FPP molecules to form squalene in the first committed step to cholesterol.


OPP
OPP
Ha
Hb
OPP
DMAPP
IPP
Geranyl PP
(6)
IPP
OPP
Monoterpenes
(C10)
e.g.Geraniol,
Limonene
FPP
(7)
Squalene
synthase
Squalene
HO
H
Lanosterol
steps
H
H
HO
Cholesterol

Scheme 1.3.2

1.3.3 Current Medicinal Chemical Approach

Screening of fermentation cultures for natural products which inhibit specific enzymatic steps in the synthesis of cholesterol has resulted in discoveries of mevinolin[10] (**8**) and compactin[11] (**9**), Figure 1.3.1. These compounds are potent inhibitors of HMGCoA reductase and are clinically established as highly effective cholesterol reducing agents in man. The lactone portion of these chemical structures bear a strong resemblance to HMGCoA and their mode of action is thought to involve mimicking HMGCoA.



Mevinolin (8) Compactin (9)

Figure 1.3.1

The cholesterol biosynthetic pathway not only forms sterols but also produces dolichol, ubiquinone, the farnesyl group of heme A, prenylated proteins and the isopentyl side chain of isopentyl adenine. The pathways for the synthesis of these isoprenoids diverge from the synthesis of cholesterol after the formation of HMGCoA. Thus current therapeutic agents for the lowering of serum cholesterol will also inhibit the formation of other isoprenoids. Ideal candidates for the the control of hypercholesterolemia would be specific cholesterol inhibitors as these drugs often have to be prescribed for the rest of the patient's lifespan to ensure that toxic side effects will be as minimalised.

The squalestatins are a new family of fungal metabolites that are picomolar inhibitors of an enzyme known as squalene synthase. The pathways for the synthesis of these other isoprenoids diverge from the synthesis of cholesterol

either at or before squalene synthase. This enzyme is involved in the first committed step to cholesterol and therefore poses an attractive target for the regulation of cholesterol biosynthesis.

1.3.3 Biological Activity

Squalestatin 1 was shown to be a potent, selective inhibitor of squalene synthase, a key enzyme in cholesterol biosynthesis[3]. As this is the first step after the pathway branches to other isoprene derived compounds, it has been proposed that a specific inhibition of squalene synthase should serve to inhibit cholesterol synthesis and not adversely affect the synthesis of other isoprenoids. Squalene synthase catalyses the head to head ligation of two molecules of farnesyl diphosphate to form first presqualene pyrophosphate, then squalene. Farnesyl pyrophospate (FPP), the substrate for squalene synthase is water soluble and may be readily metabolised. Thus squalene synthase inhibition of cholesterol biosynthesis is safe and specific. Inhibitors of this enzyme based on substrate analogues have been studied previously by Biller *et al*[12] but these compounds have shown only weak inhibition of squalene synthase and were not suitable for evaluation *in vivo*, Figure 1.3.2. Squalestatin 1 has been shown to have an unusually high affinity for Ca^{2+} ions and readily inserts into model membranes[13]. Ca^{2+} plays an important role in membrane stabilisation, in activating membrane bound enzymes and in triggering intracellular events.

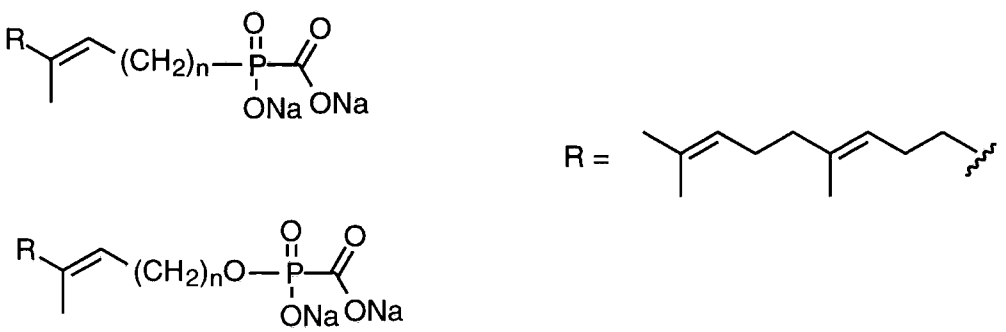
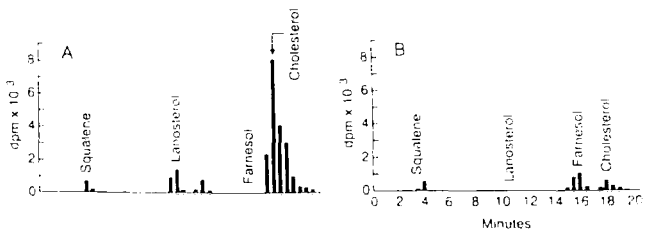


Figure 1.3.2

Initial studies on inhibition of squalene synthase by the squalestatins[3] showed an IC_{50} of ~5nM in assays with 5μM FPP and a protein concentration of 110μg/ml. Only when the protein concentration was decreased by a factor of 50 did the inhibition by the squalestatins become independent of protein concentration. This activity suggests that the squalestatins are very potent reversible inhibitors.

The squalestatins were shown to inhibit cholesterol synthesis in Hep G2 cells. These cells were incubated with the squalestatins and labelled with [^{3}H] mevalonate. Cells were extracted to obtain a nonsaponifiable fraction, a FPP fraction and an organic acid fraction. The incorporation of [^{3}H] mevanolate into cholesterol was shown to be inhibited upon the addition of the squalestatins and also showed a dose dependent decrease in cholesterol synthesis with IC_{50} values ranging from 0.6-6μM within this new family of natural products. The disappearance of label from the usual nonsaponifiables was indicative of inhibition of cholesterol synthesis at a step prior to squalene synthesis, Figure 1.3.3.

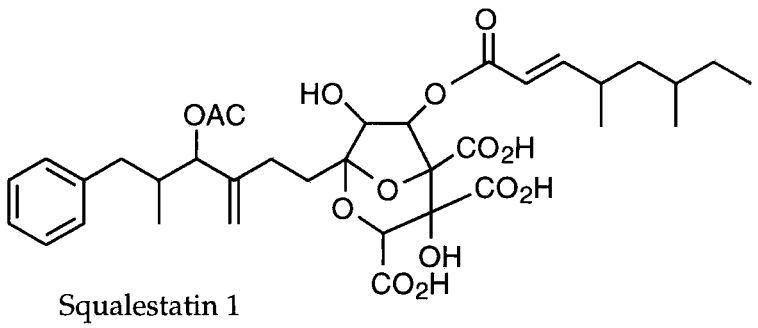


HPLC analysis of the nonsaponifiables labeled with [^{3}H]mevalonate in Hep G2 cells were incubated with no additions (A) or with 10μg of zaragozic acid A per ml (B). Fractions were collected every 0.5min and ^{3}H content of the fractions was determined. The retention times of squalene, lanosterol, farnesol and cholesterol standards are shown.

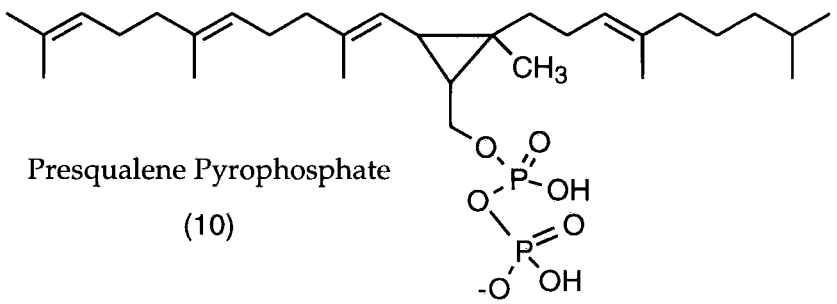
Figure 1.3.3[3]

Squalestatin 1 was also shown to inhibit hepatic cholesterol synthesis in mice with an ED_{50} ~0.2mg/kg. In contrast to Hep G2 cells, labelled farnesol was not detected in the mice. Furthermore, when squalestatin 1 was administered orally to marmosets, a species with a lipoprotein profile similar to that of man[14], a 50% reduction in serum cholesterol was observed at a dose of 10mg/kg/day for 7 days. The squalestatin family of natural products show potent inhibition of squalene synthase both *in vitro* and *in vivo*. Squalene synthase catalyses a two step

sequence in which presqualene pyrophosphate (**10**) is an intermediate. It is thought that the squalestatins inhibit squalene synthase, in part, by effectively mimicking the binding of presqualene pyrophosphate to the enzyme. Both structures contain two long hydrophobic side chains and a cyclic core with polar acidic functions, Figure 1.3.4.



Squalestatin 1



Presqualene Pyrophosphate

(10)

Figure 1.3.4

1.3.4 Toxicity

Some brief reports on the toxicity of the zaragozic acids have been published. One possible consequence of blocking squalene synthase is that FPP accumulates, since it cannot be processed through the cholesterol pathway. The excess levels of FPP are rapidly catabolised to a range of farnesyl-derived dicarboxylic acids (FDDCAs) in the liver. Such dicarboxylic acids are then excreted in the urine.[15] When rats were treated with a dosage of 15mg/kg per day of squalestatin 1 and a bile acid sequestrant, the levels of FDDCAs in the urine rapidly became very high and the animals became very moribound, a symptom of acidosis. Acidosis is a

disease associated with abnormal pH serum levels. It was therefore suggetsted that the toxic side effects associated with squalestatin 1 are a result of the acidosis caused by massive overproduction of FDDCAs from an increase in FPP. However, the toxicity was totally eliminated by co-dosage with a HMGCoA reductase inhibitor.

1.3.5 Structure Activity Relationships

As part of the programme aimed at the discovery of potent cholesterol inhibitors, the key structural features responsible for the biological activity of the squalestatins were studied. Modifications of squalestatin 1 have been carried out to identify the requisite structural features responsible for biological activity.

It was discovered[16] that long chain analogues of the C(6) side chain were generally more potent than C(6) short chain derivatives with the optimal potency for squalene synthase inhibition obtained with 12 atom chain lengths. It has also been reported that replacement of the phenyl group with a ^{t}butyl or cyclohexyl group in the C(1) side chain resulted in a significant loss of squalene synthase inhibitory activity.[17] This could be attributed to the fact that the aromatic ring of squalestatin 1 may be providing additional binding to the enzyme, analogous to that provided by the double bond in the farnesyl chains of FPP. Loss of activity observed with shortening of the C(6) side chain is also consistent with the observation that truncated FPP analogues are poor inhibitors of squalene synthase.[18] Replacement of the C(6) O-acyl group with a hydroxyl group was well tolerated and squalene synthase inhibitory activity remained potent[1].

The role of the tricarboxylic acid moiety was elucidated by a group at Glaxo[19] and it was observed that inhibitory activity of both C(3) and C(4) mono methyl esters of squalestatin 1 retained potent enzyme inhibitory activity (IC_{50} 7nM & 4nM respectively). Furthermore, the C(3), C(4) dimethyl ester also retained significant enzyme inhibitory activity. In contrast, however, the C(5) mono methyl ester showed no significant potency along with the C(3), C(5) and C(4),

C(5) dimethyl esters[20]. This data strongly suggests that the C(5) carboxylic acid is crucial for enzyme inhibitory activity to be retained.

The C(6) hydroxyl analogue of squalestatin 1 was prepared by a group at Glaxo[21] and *in vitro* studies showed potent inhibitory activity. However, the corresponding C(3) and C(4) mono methyl esters showed a significant loss of potency. Again, the C(5) mono methyl ester showed no inhibition of squalene synthase.

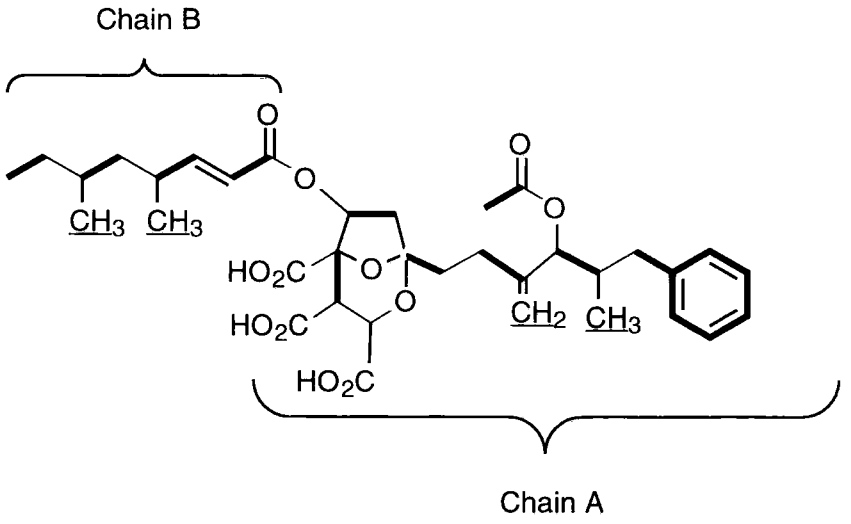
These results suggest that the C(6) side chain critically affects the *in vitro* squalene synthase inhibitory activity for modifications made in other parts of the molecule.[22]

It has been proposed that analogues of squalestatin 1 mimic the biosynthetic intermediate presqualene pyrophosphate while the related C(6) hydroxyl derivatives are FPP mimics[23]. In both series, the highly functionalised 2,8-dioxabicyclo[3.2.1]octane ring system acts as a diphosphate mimic.

Potent squalene synthase inhibition is retained only in those analogues which possess C(1) and C(6) substituents closely similar to those found in the natural product itself.

1.4 Biosynthesis

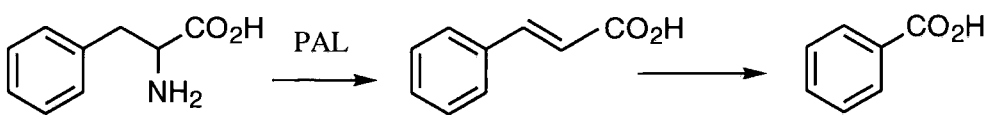
The biosynthesis of squalestatin 1 was elucidated by a group at Bristol University in collaboration with Glaxo[24] through a variety of labelling experiments using ^{13}C and ^{14}C isotopically enriched precursors. It was shown that squalestatin 1 is derived from two polyketide chains, Scheme 1.4.1.



Scheme 1.4.1

The first chain (chain A) forms the C(1) alkyl unit and core and is derived from the condensation of a benzoate group with five acetates in normal polyketide fashion. The terminal four carbon atoms (at C(3) - C(4)) appear to arise from the condensation of one succinate group although citric acid cannot be ruled out as a source of the tricarboxylic acid moiety (terminal six atoms).

The aromatic starter unit is derived from the metabolism of phenylalanine with phenylalanine ammonia lyase (PAL) to form first, *trans* cinnamic acid, then benzoic acid, by β-oxidation and truncation, Scheme 1.4.2. Such aromatic starter units are rare in polyketide biosynthesis.[25]



Scheme 1.4.2

In chain B, the C(6) O-acyl unit, is generated from four acetate units. Interestingly, the branching methyl and methylene groups are formed by C-methylation with L-methyl methionine rather than the incorporation of propionate into the polyketide pathway.

1.5 Previous Synthetic Approaches

A large amount of interest in devising synthetic routes to squalestatin has arisen due to the potential of these fungal metabolites as therapeutic agents in the lowering of serum cholesterol. They also possess a wide range of antifungal activity.[3] This raises the possibility of developing new antifungal agents targeted to the inhibition of fungal squalene synthase. This could prove useful as the number of immunosuppressed patients is on the increase due to the development of transplant operations. Drugs to combat opportunistic fungii are in great demand.

Since the start of this project, three total syntheses and a number of partial syntheses[26] of the squalestatins have been published.

At the end of 1994, three total syntheses were published by Carreira *et al*,[27] Nicolaou *et al* [28]and Evans *et al*[29] in collaboration with researchers at Merck, Sharp and Dohme. All three research groups introduce the C(6) O-acyl side chain in the final step and all form the bicyclic core through a ketalisation step by acetal formation of a 4,6-dihydroxyketone using standard procedures. Apart from these aspects, the synthetic pathways differ.

Evans *et al* chose to explore the synthesis of zaragozic acid C through an acyclic precursor assuming that internal ketalisation would lead to the desired ketal core unit rather than its structural isomer, Figure 1.5.1.

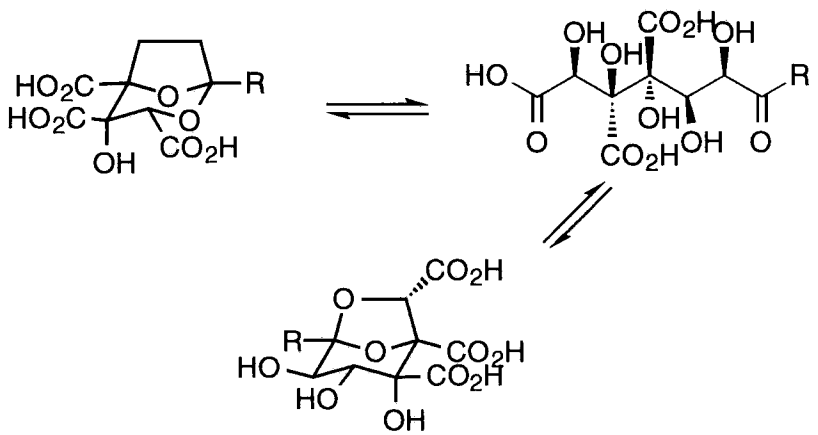
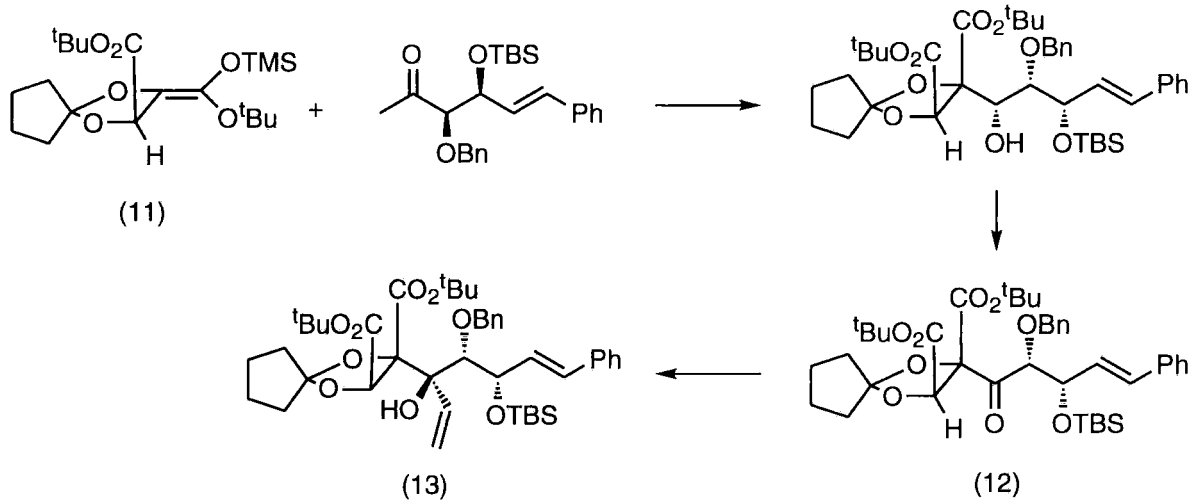
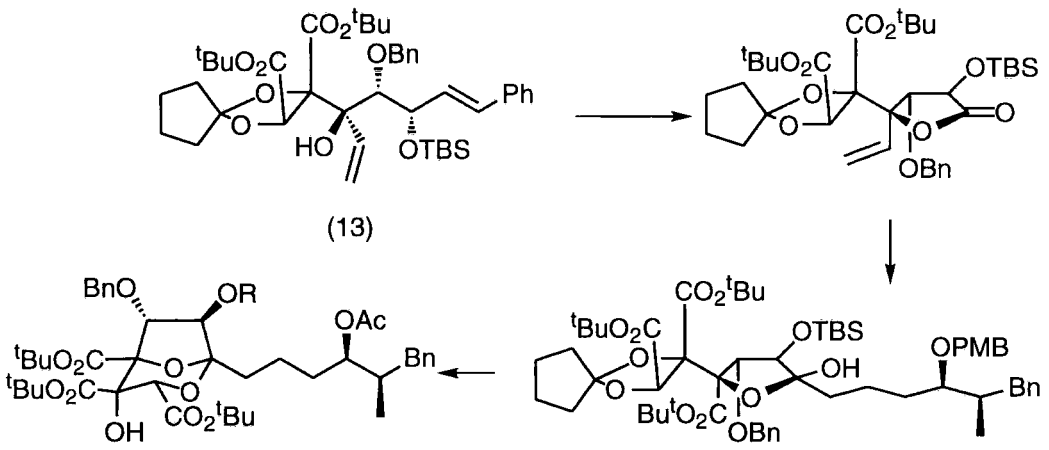


Figure 1.5.1

The synthesis was initiated using a Lewis acid catalysed chiral aldol addition of a tartaric acid derivative (**11**) which served to make up the C(3), C(4) and C(6), C(7) centres of the acyclic analogue of the core unit. Another critical step stereoselectively introduced the C(5) nucleophilic carboxylate fragment by means of a chelated Grignard addition to the ketone (**12**) outlined in Scheme 1.5.2a and Scheme 1.5.2b.



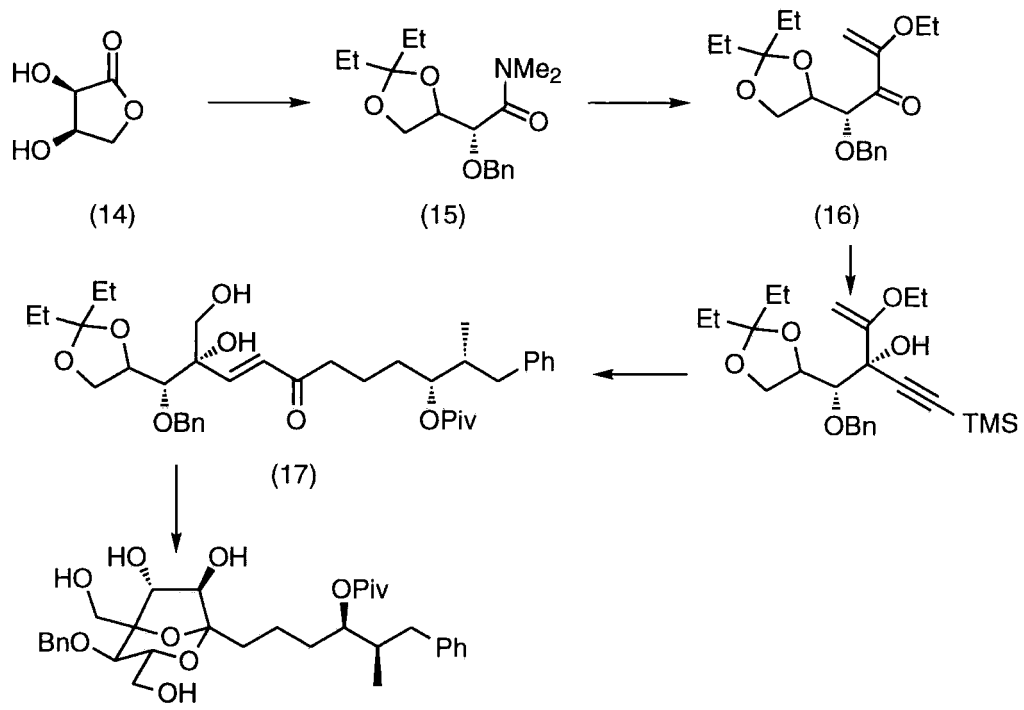
Scheme1.5.2a



Scheme 1.5.2b

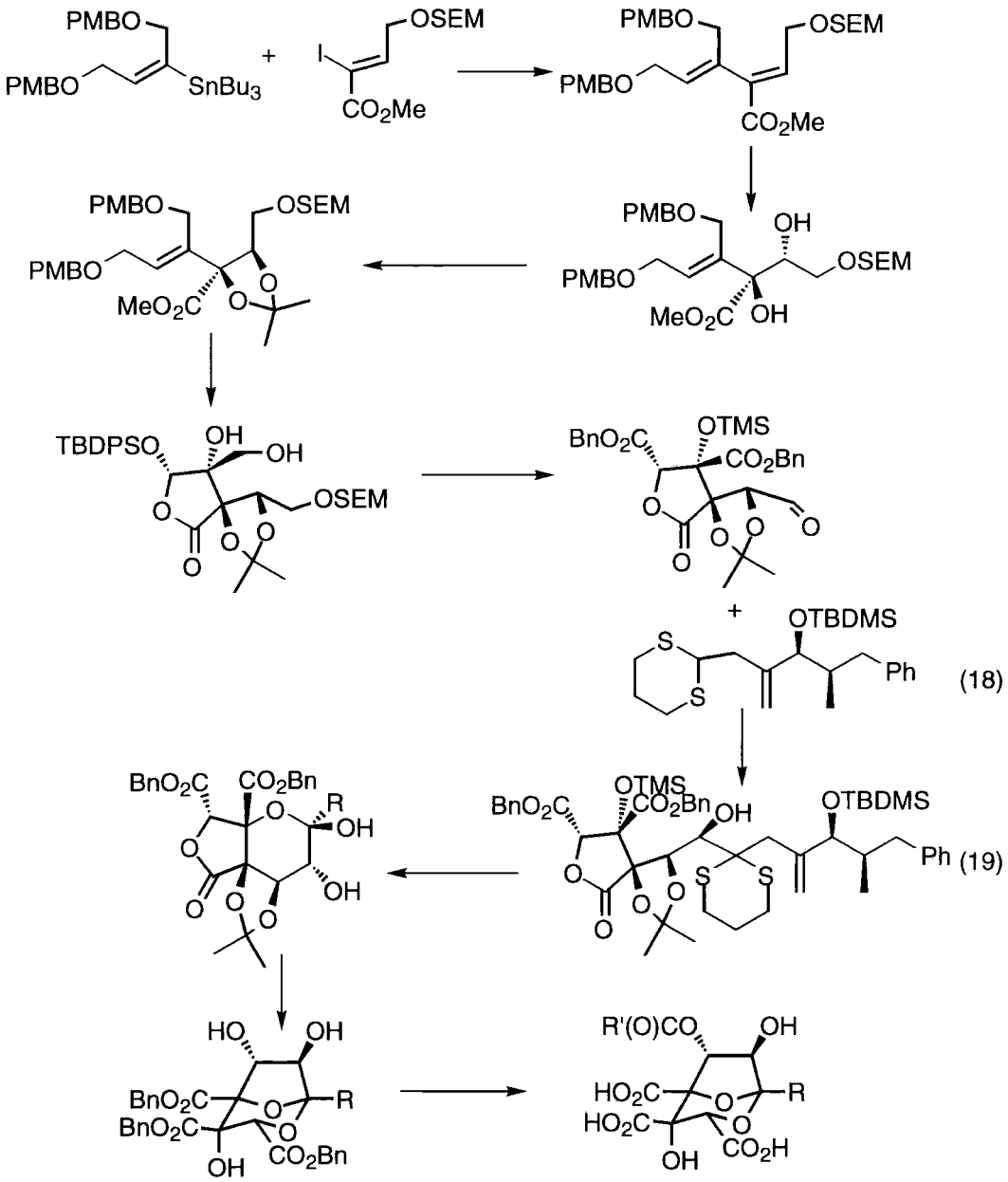
The strategy which Carreira and coworkers followed for the preparation of zaragozic acid C involves initial removal of the C(6) O-acyl and C(1) alkyl side

chains, Scheme 1.5.3. Treatment of (**15**), readily accessible from (**14**), with ethoxyvinyl lithium generated the ketone (**16**). Subsequent reaction with magnesium acetylide afforded the key tertiary alcohol in greater than 90% de. Further elaboration led to the protected hydroxyketone (**17**) with the other stereogenic centres being incorporated by Sharpless asymmetric dihydroxylation. In the final ketalisation step the diol (**17**) is cyclised under acidic conditions to give the dioxabicyclo[3.2.1]octane acetal.



Scheme 1.5.3

The synthesis of squalestatin 1, carried out by Nicolaou, is summarised below, Scheme 1.5.4, with four of the five stereogenic centres constructed using Sharpless dihydroxylations. However, addition of a dithiane protected C(1) side chain (**18**) forms the alcohol (**19**) in an unselective manner. These isomers must be separated by flash column chromatography.

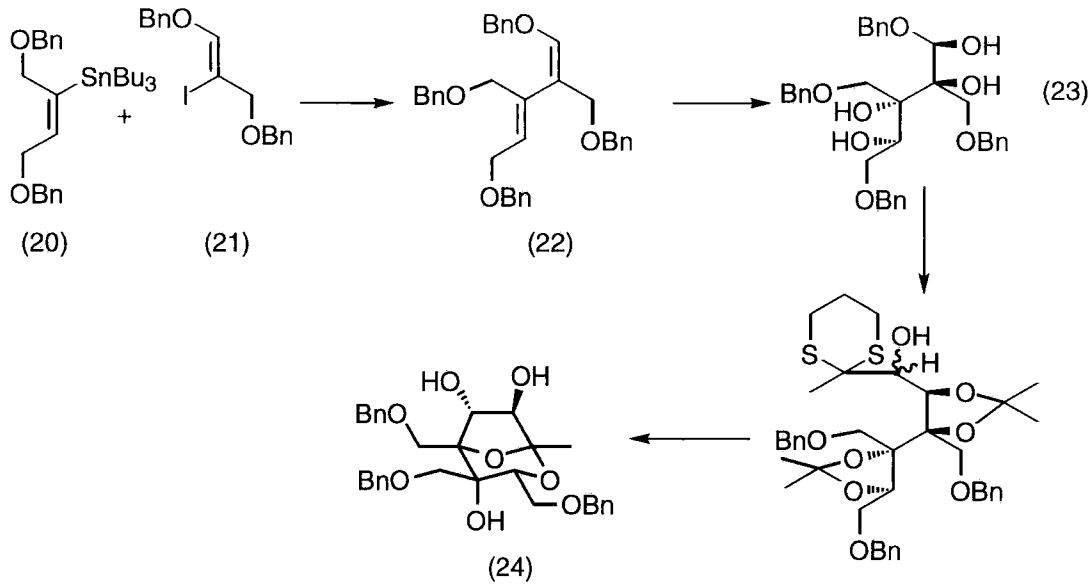


Scheme 1.5.4

In a more recent report[30] Armstrong *et al* published a short and stereoselective synthesis of the squalestatin core, again featuring the use of a double Sharpless asymmetric dihydroxylation reaction to control the stereochemistry. In this case, the reaction was carried out as a one pot synthesis and high stereoselectivity was achieved.

The core unit was, as with Nicolaou, initially disconnected through the ketal, forming a linear core analogue (**24**), which, itself, was obtained through a double

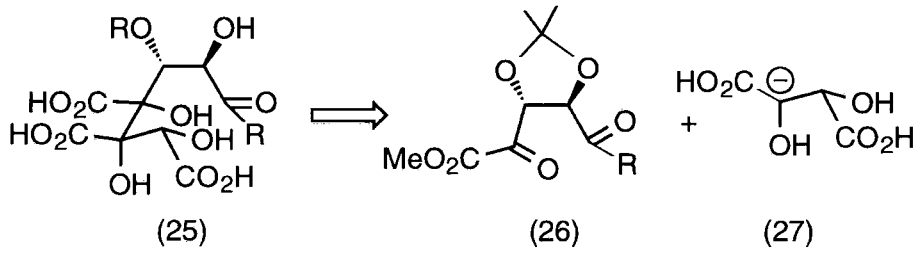
Sharpless dihydroxylation of (**22**) with 76%ee. The diene (**22**) was synthesised from a Stille coupling between a stereodefined vinyl stannane (**20**) and a vinyl iodide (**21**) as outlined in Scheme 1.5.5, below.



Scheme 1.5.5

All three total syntheses are examples of modern, efficient natural product syntheses. The two research groups of Carreira and Nicolaou have been the first to cross the finish line in the race for the synthesis of the squalestatins with overall yields of 1% in each case. Evans however, has formed each new stereogenic centre with high selectivity and completed the synthesis in only 21 steps with an overall yield of 15%. Many partial syntheses of the squalestatins have been reported, some of which are dicussed below.

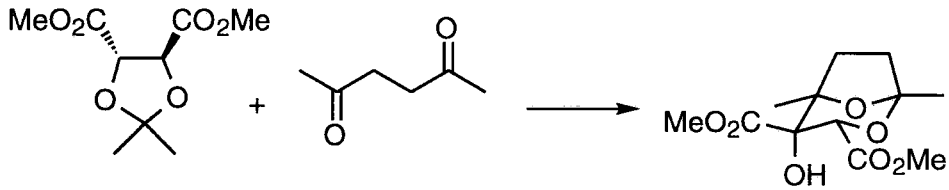
The first synthesis of a novel 2,8-dioxabicyclo[3.2.1]octane ring system, a key feature of the squalestatins, was carried out by Aggarwal and coworkers[31] at the University of Sheffield. Here, the initial disconnection step was that of the ketal to give (**25**) followed by a disconnection that would require the addition of synthon (**27**) to the α-keto ester (**26**), Scheme 1.5.6.



(25) (26) (27)

Scheme 1.5.6

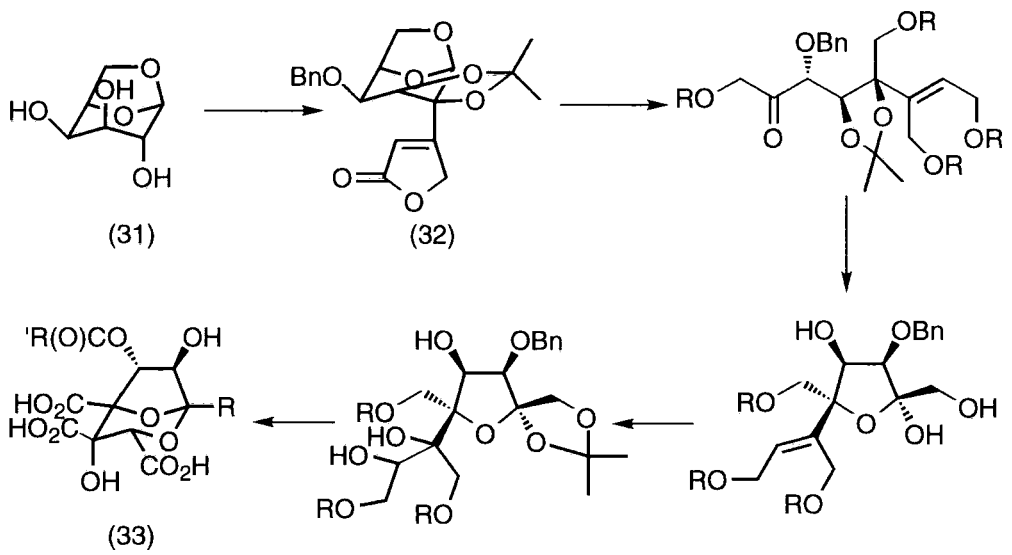
One such equivalent of the synthon was found to be the enolate of the acetonide of (S,S)-dimethyl tartrate (**28**). The anion was prepared by the use of 12-crown-4 with LDA, upon addition to a 1,4 diketone (**29**) to form a mixture of isomeric products, Scheme 1.5.7. These were treated with acid and cyclisation ensued, resulting in a bicyclic core analogue, Scheme1.5.6. It was discovered that due to thermodynamics, the product was formed as essentially one single isomer (**30**).



(28) (29) (30)

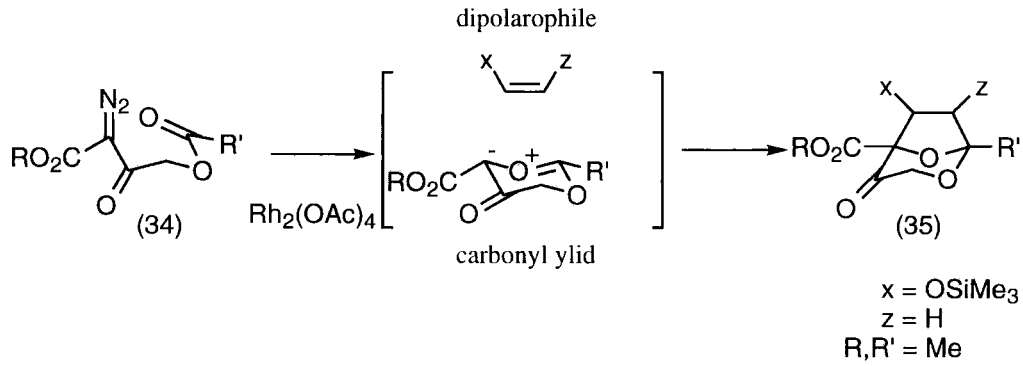
Scheme 1.5.7

In 1994, Roberts[32], in collaboration with a group at Glaxo, reported the synthesis of an analogue of the squalestatin core unit. Here, D-(+)-1,6-anhydrogalactose (**31**), a commercially available material, was converted into the butenolide (**32**) which was eventually converted into the dioxabicyclo[3.2.1]octane core (**33**), a major intermediate for the preparation of squalestatin 1, *via* a late stage ketalisation step. An outline of this strategy is described in Scheme 1.5.8.



Scheme 1.5.8

A novel synthetic approach towards the core structure of the squalestatins was reported by Merck in 1994[33]. The strategy used did not involve a ketalisation step as such, but was based on the tandem cyclisation-cycloaddition of dipolarophiles and carbonyl ylids. With this methodology it was possible to assemble bicyclic core analogues in a single step. The carbonyl ylids were generated from the respective diazo esters (**34**) in the presence of rhodium carboxylate and trapped with the appropriate dipolarophiles. In all of the cases studied, the reaction proceeded regio- and stereoselectively, resulting in a single cyclisation-cycloaddition product from each reaction. Although the cases yielding the "carboxylic version" of the core structure went smoothly, the low yield for formation of (**35**) with an oxygen in the 2-position was rather disappointing, Scheme 1.5.9.



Scheme 1.5.9

1.6 Proposed Work

1.6.1 Introduction

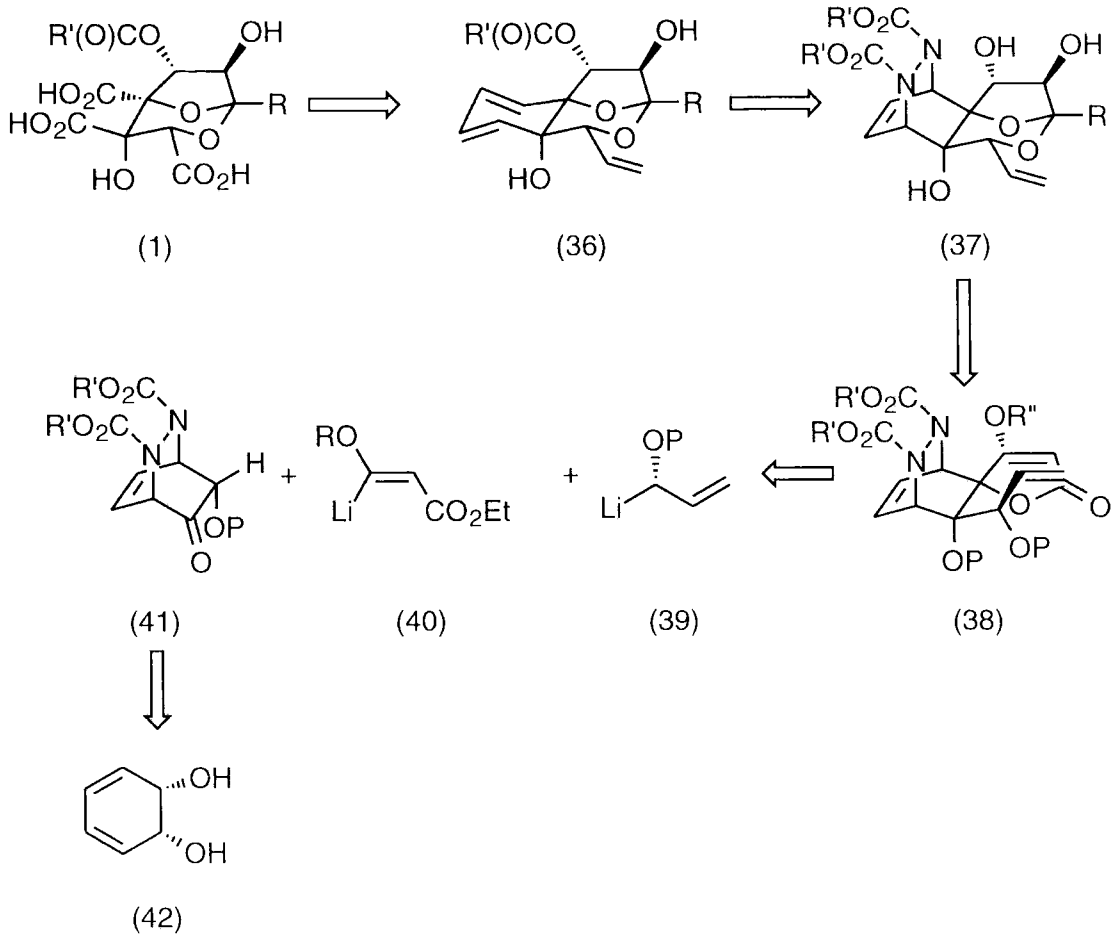
The squalestatin family of natural products exhibit potent cholesterol lowering effects. It would threrefore be desirable to devise a synthesis towards these fungal metabolites which is easily adaptable for analogue synthesis. Consequently we, in line with previous approaches, have disconnected at the C(1) alkyl and C(6) O-acyl side chains first.

1.6.2 Restrosynthetic Plan A

The tricarboxylic acid moiety is a key feature of the highly oxidised bicyclic core of squalestatin 1 but it was envisaged that these functional groups would prove difficult to handle. Consequently, we opted to mask the carboxylic acids as olefins as these could be easily cleaved by ozonolysis followed by an oxidative workup. Furthermore, tethering of two of the olefins to form a diene (**36**) and a Diels Alder reaction with a dieneophile would introduce a rigid tricyclic structure aiding stereochemical control (**37**). This intermediate can be formed through a triply convergent route from a lithioacrylate (**40**), an α-alkoxy lithium (**39**) and an α-alkoxy ketone (**41**) to allow for maximum variation. The ketone can be easily prepared from *cis*-cyclohexadiene diol (**42**).

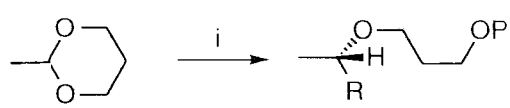
Early disconnection of the C(1) and C(6) side chains of the core unit of squalestatin should enable the production of a variety of analogues at a late stage

in the synthesis. With these points in mind, the retrosynthetic strategy outlined in Scheme 1.6.1 was developed.



Scheme 1.6.1

Asymmetry of the core unit could be incorporated either by using chlorobenzene as a substrate for *Pseudomonas putida* or through a desymmetrisation process *via* asymmetric cleavage of acetals using chiral Lewis acids to give compounds such as (**43**), Scheme 1.6.2.



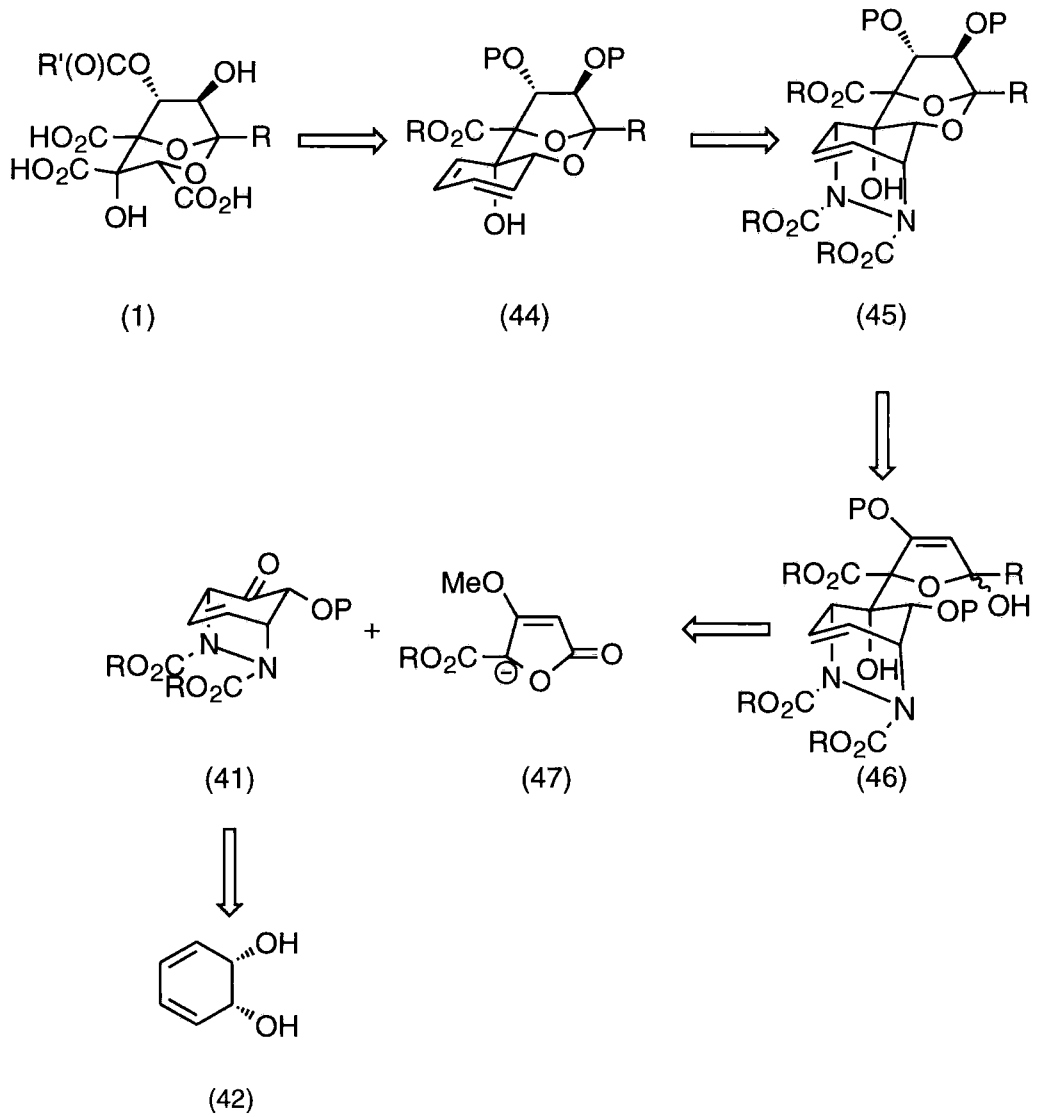
(43)

Reagents: i. ML_n, RLi; ii. OH protection

Scheme 1.6.2

1.6.3 An Alternative Route

Using the same strategy as above, the tethering of two olefins to form a cyclic diene and the subsequent Diels Alder reaction again forms a rigid tricyclic structure. This retrosynthesis differs from the previous approach by the fact that the Diels Alder adduct (**46**) does not contain the spiro ketal moiety as described previously (**38**). Thus the adduct can be approached through a doubly convergent route using the same protected form of *cis*-cyclohexadiene diol (**41**) and a tetronate derivative (**47**), Scheme 1.6.3.



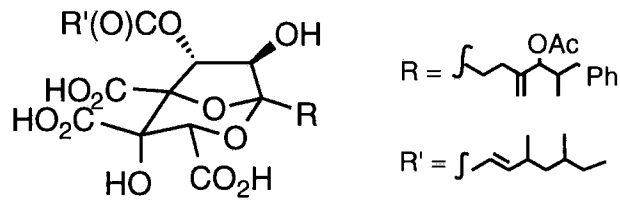
Scheme 1.6.3

Initial studies were carried out using a simplified substrate to test each synthetic plan before studies to the fully substituted core unit were commenced. This work will be discussed in detail in the next chapter.

Chapter 2 : Results and Discussion

2.1 Introduction

The principal aim of this project was the synthesis of the core unit of squalestatin 1 (**1**), Figure 2.1.1 and its analogues. A retrosynthetic plan was developed and initial model studies were carried out to test its viability.

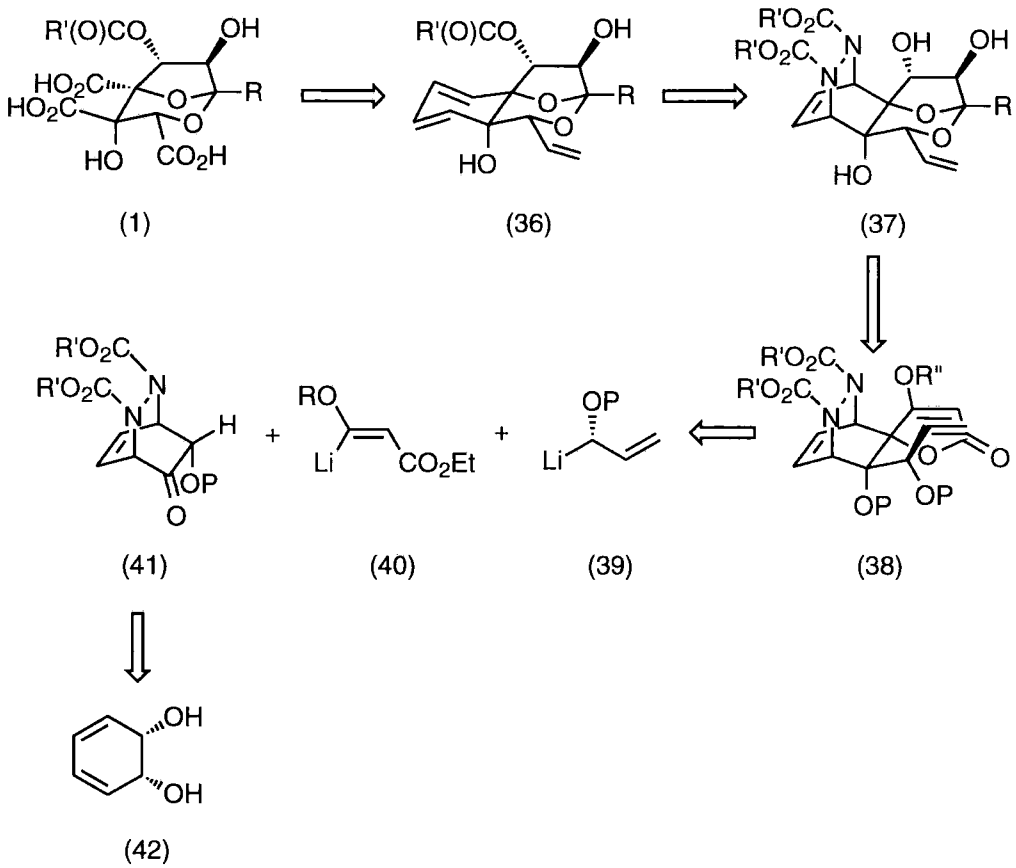


(1)

Figure 2.1.1

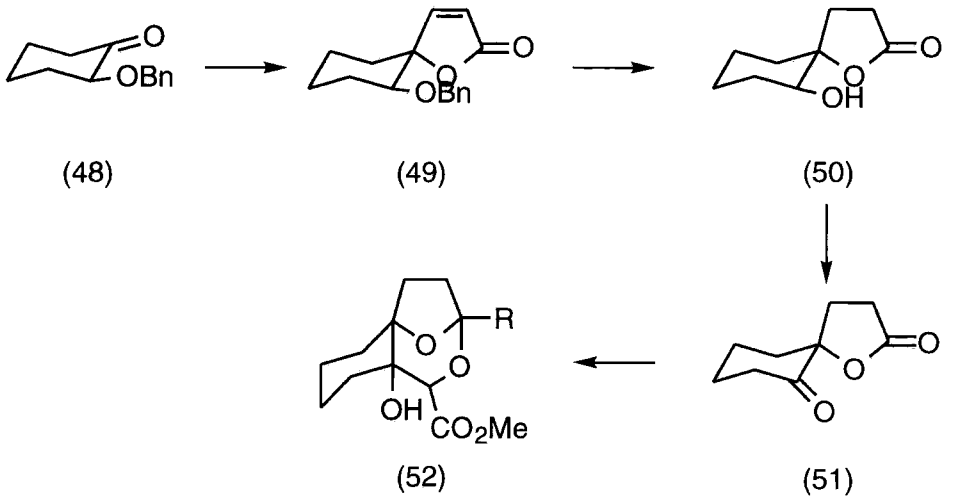
With six stereogenic centres, stereoselective reactions were a major consideration in the proposed synthetic route to the bicyclic core. Key to the biological activity of squalestatin 1 is its tricarboxylic acid moiety. Since this functionality would be difficult to handle, we adopted the strategy of masking these carboxylate groups as olefins with easy recovery of the tricarboxylic acid moiety *via* ozonolysis. With these points in mind, the retrosynthetic strategy outlined in Scheme 1.6.1 was developed.

The first step in the retrosynthesis of the core unit (**1**) chemically ties two of the equatorial carboxylic acids together to form diene (**36**) which can, in turn, be protected by Diels Alder addition of a diazene, forming compound (**37**). In addition to protecting the sensitive diene, it was thought that utilisation of this adduct would enable stereochemical control during synthetic manipulations.



Scheme 1.6.1

Early disconnection of the C(1) R group would also allow analogues to be made at a late stage of synthesis. Cleavage of the acetal (**37**) leads to the spirolactone (**38**) and further disconnection leads to the protected hydroxyketone (**41**) *via* disconnection of the two side chain units (**39**) and (**40**). The hydroxyketone (**41**) can be obtained from the readily available, *cis*-cyclohexadiene diol (**42**) Initially, it was thought that the use of olefins as masking groups for the carboxylic acids might raise some synthetic obstacles, and to test these early steps a simplified structure (**52**) was adopted as a model target, Scheme 2.1.1.



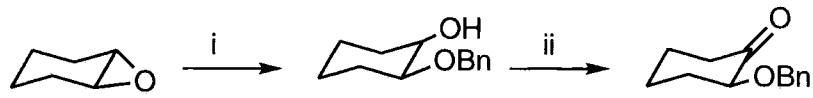
(48) (49) (50) (52) (51)

Scheme 2.1.1

Thus, following this synthetic plan, we required access to 2-benzyloxycyclohexanone (**48**) as an initial starting material.

2.2 Preparation of 2-benzyloxycyclohexanone (48)[34, 35]

Desmaele[34] has reported a synthesis of 2-benzyloxycyclohexanone through treatment of cyclohexene oxide (**53**) with the sodium salt of benzyl alcohol followed by oxidation with Jones' reagent, Scheme 2.2.1. However, in our hands the initial steps of this procedure led to problems in separation of the desired alcohol. This difficulty was overcome through use of excess cyclohexene oxide and thus the monoprotected diol (**54**) was obtained in 93% yield after purification by either vacuum distillation or flash chromatography. IR analysis showed a broad band at 3430cm^{-1} characteristic of the hydroxyl functionality. The appearance of an AB quartet and a multiplet at δ7.28-7.24 in the ^{1}H NMR was typical of a benzylic moiety. Subsequent oxidation to the desired alkoxy ketone (**48**) was attempted using both Jones' reagent and PCC, though these methods proved unsatisfactory. However, excellent yields (>90%) were achieved *via* Swern oxidation.[35]



(53) (54) (48)

Reagents: i. $PhCH_2OH$, NaH; ii. Oxalyl chloride, DMSO, Et_3N

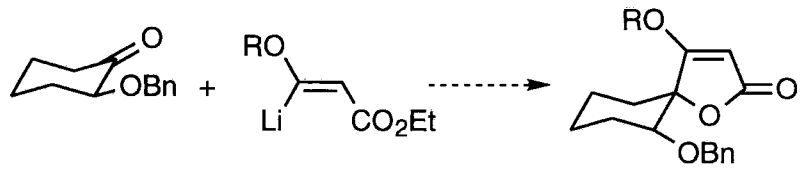
Scheme 2.2.1

Disappearance of the OH stretch at 3479cm^{-1} and the appearance of a strong absorption at 1723cm^{-1} in the IR spectrum confirmed that the ketone (**48**) had been formed. The presence of a peak at δ210.6 in the ^{13}C NMR spectrum is characteristic of the ketonic carbonyl group. Further evidence was obtained from CI-MS which showed a molecular ion peak at *m/z* 222 ($M+NH_4^+$, 94%).

2.3 Preparation of the Spirolactone

2.3.1 Introduction - Application of a Lithium Methacrylate Species

A three carbon homoenolate equivalent (**41**) must now be synthesised to add to the carbonyl group of 2-benzyloxycyclohexanone (**48**) and the adduct subsequently cyclised to form the desired butenolide (**55**), Scheme 2.3.1.

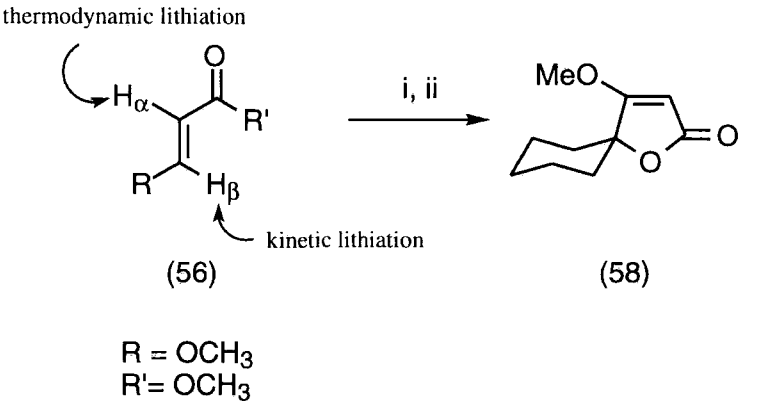


(48) (41) (55)

Scheme 2.3.1

Methyl β-methoxyacrylate (**56**) can be lithiated regioselectively at the β- position to afford the nucleophile necessary for the formation of the spirolactone (**55**) and Schmidt *et al*[36] have reported the application of a functionalised acrylate (**57**).

Kinetic lithiation of the β– carbon, achieved by the addition of LDA at -90°C for 2min, followed by addition of cyclohexanone resulted in the formation of the butenolide (**58**),[37] Scheme 2.3.2.



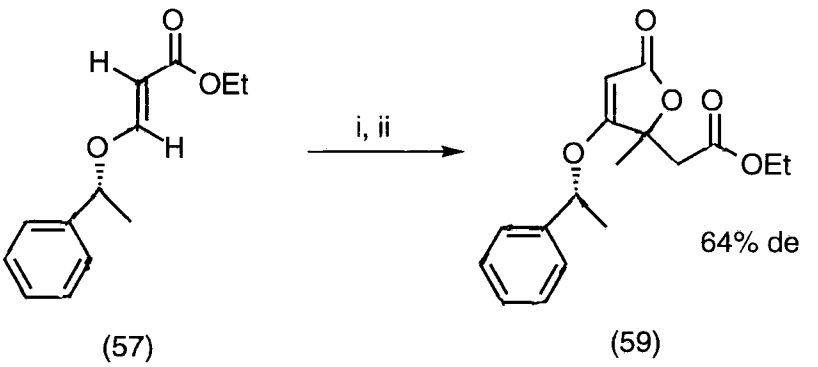
Reagents: i. LDA, -90°C, 2min; ii. cyclohexanone

R	R'	Reaction conditions [°C/min]	Ratio β : α
OCH_3	$-OC_2H_5$	LDA [-90/2]	95 : 5
		LDA [-90/20]	82 : 18
		LDA [-90/150]	64 : 36
		LDA [-90/300]	57 : 43
	$-OC_2H_5$	LDA [-113/10]	100 : 0
	-CN	LDA [-76/60]	0 : 100

Scheme 2.3.2

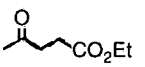
It can be seen from the table above that changing the sbstituents on the acrylate can afford different ratios of α- and β- lithiated species. Furthermore, these ratios can be manipulated by changing the temperature and length of deprotonation. Schmidt *et al*[38] have also described in a more recent paper, the use of a chiral β-alkoxyacrylate (**57**) in the stereoselective synthesis of a (-) Vertinolide precursor

(**59**), Scheme 2.3.3. In this case 64% de was observed and it was thought that this would be useful in asymmetric studies towards the fully substituted core of the squalestatins.



(57) (59)

Reagents: i. LDA, -100°C, 45min; ii. ethyl levulinate (**60**), -100°C to -60°C, 1h



(**60**)

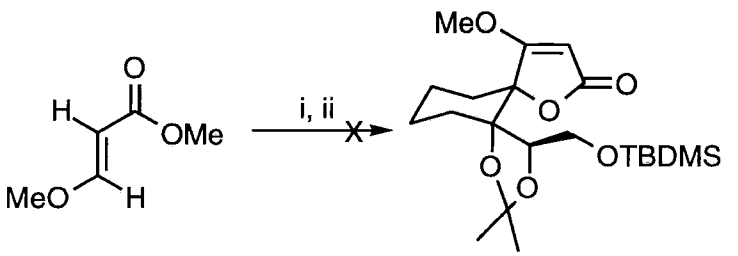
Scheme 2.3.3

Selective deprotonation was achieved by the addition of LDA at -100°C for 45 min. Addition of the ketone (**60**) then afforded the Vertinolide precursor (**59**).

2.3.2 Preparation of a Lithium Homoenolate

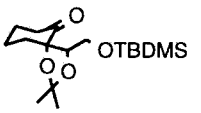
The methodology of Schmidt, described above, was followed using cyclohexanone, Scheme 2.3.2. Deprotonation of the methacrylate (**56**) by LDA at -90°C for 2min followed by the addition of cyclohexanone at -90°C afforded only recovered starting materials upon work up and purification. Repeating the reaction at higher temperatures again resulted in the recovery of starting materials. As we were unable to repeat the chemistry of Schmidt it was decided to temporarily abandon this approach and examine other routes to afford access to the butenolide, see next Section. Later on in this project the formation of the ketone (**56**) was achieved (Section 2.6.3) and it was thought that the now more

experienced chemist would be able to attempted the addition of the β-methoxyacrylate anion to the ketone (**61**) to afford the butenolide (**62**), Scheme 2.3.4. The methodology of Schmidt was repeated and deprotonation of the methoxyacrylate was attempted using LDA at -90°C for 2min. However, addition of the ketone (**61**) afforded only recovered starting materials upon work up and purification by column chromatography. The longer deprotonation time of 45min at the lower temperature of -100°C was also employed for the addition of methyl acrylate (**56**) to the ketone (**61**). Again, product formation was not observed and flash column chromatography gave complete recovery of starting materials.



(56) (62)

Reagents: i. LDA, -90°C, 2min; ii. ketone (**61**)



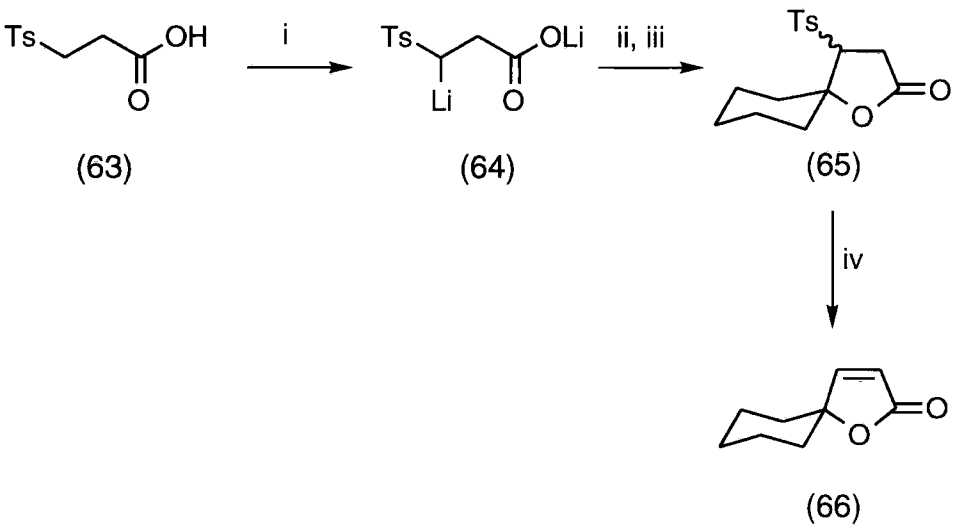
(61)

Scheme 2.3.4

Obviously, there is a fine balance between kinetic and thermodynamic deprotonation so to avoid equilibration of these two species, the electrophilic addition process must be fast. One possible reason for the lack of reactivity between the ketone (**61**) and the lithio acrylate could be due to the fact that competing enolisation was taking place because of the basicity of the lithium anion. Hence, upon quenching and extracting only starting materials were recovered.

2.3.3 Application of 3-(*para* -tolylsulphonyl)propionic acid (63)

Following the failure of the above methodology, we next examined the use of 3-(*para*-tolylsulphonyl)propionic acid (**63**) as the precursor to the formation of a related spiro compound (**49**). Najera *et al*[39] have reported the use of lithiated 3-(*para*-tolylsulphonyl)propionic acid (**64**) as the required homoenolate equivalent by its addition to cyclohexanone *en route* to butenolide synthesis, Scheme 2.3.5.



(63) (64) (65) (66)

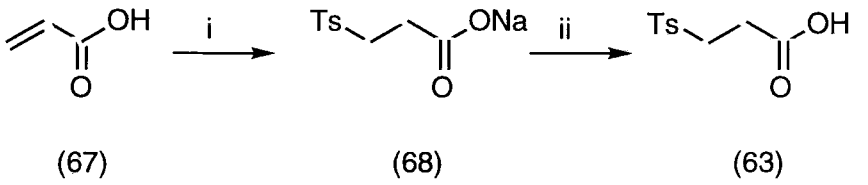
Reagents: i. 2eq BuLi, THF, -78°C; ii. cyclohexanone, -40°C; iii. TFAA, -30°C; iv. Et_3N

Scheme 2.3.5

Formation of the dianion (**64**) was achieved by careful addition of butyl lithium to the acid (**63**) at -78°C. Cyclohexanone was added and the mixture warmed to -40°C for 2h before the addition of trifluoroacetic anhydride. After 1h at -30°C, triethylamine was added and the reaction quenched with saturated $NaHCO_3$ to afford the butenolide (**66**).

Following the procedure of Kamogawa *et al*[40] sodium 3-(*para*-tolylsulphonyl)propionate was prepared by addition of acrylic acid (**67**) to sodium *para*-toluenesulphinate dihydrate in ethanol. Acidification of the sodium salt (**68**) and subsequent recrystallisation from hexane afforded the desired acid (**63**) in

70% yield, Scheme 2.3.6. The presence of doublets at δ7.79 and δ7.38 and a singlet at δ2.42 in the ^{1}H NMR corresponded to the tosyl group. Concomitant loss of the olefinic protons at δ6.64-5.95 associated with the acrylic acid was also observed. IR also showed the disappearance of a sharp peak at 1622cm^{-1} corresponding to the double bond and formation of the acid (**63**) was confirmed by a molecular ion peak observed at *m/z* 246 ($M+NH_4^+$, 92%).



(67) (68) (63)

Reagents: i. $TsNa.2H_2O$, EtOH; ii. HCl

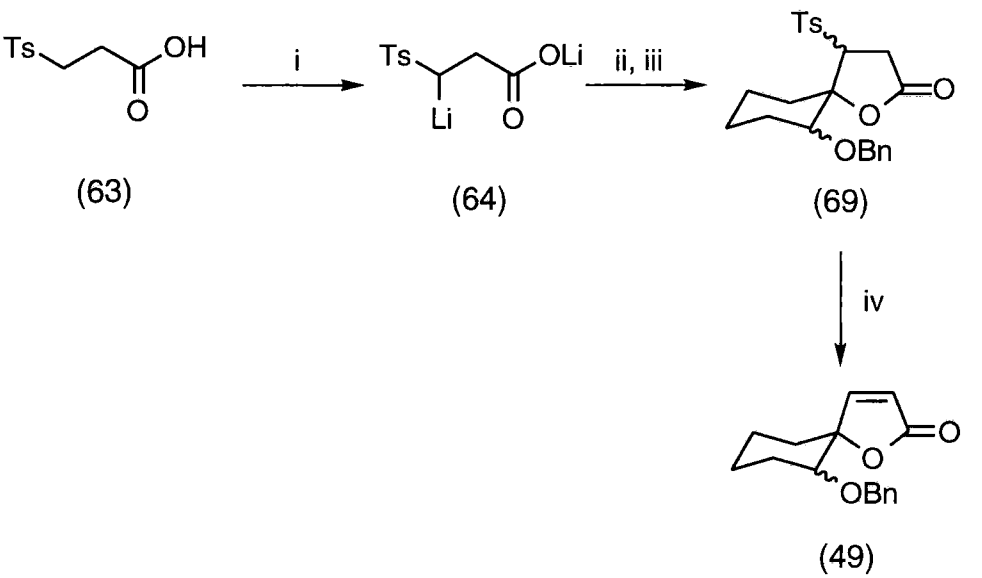
Scheme 2.3.6

With the acid in hand, formation of the butenolide (**66**) using cyclohexanone was attempted. Following the procedure of Najera, it was found that dianion formation was critically dependent upon the reaction conditions. In particular, it was necessary to ensure a vigorously anhydrous environment and, as mentioned in the literature, the Butyl lithium must be added very slowly, so as to prevent addition of the acid to itself. The butenolide (**66**) was obtained in only 16% yield due to the fact that addition of the dianion (**64**) to carbonyl groups was a reversible process at temperatures above -40°C and keeping temperatures constant initially proved difficult, Scheme 2.3.5.

Formation of the desired butenolide (**66**) by elimination of the tosylate group was achieved by addition of excess triethylamine (10 eq).

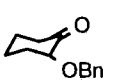
It was decided to revert back to the use of the ketone (**48**) in model studies of spirolactone synthesis rather than the more precious precursor (**61**) used in the previous section (see Scheme 2.3.4).

Analogous reaction of the acid (**63**) with 2-benzyloxycyclohexanone (**48**) gave 48% yield of the required adduct (**69**), Scheme 2.3.7, after treatment with trifluoroacetic anhydride. A mixture of isomers was obtained as well as substantial recovery of starting material (**48**) (50%) and flash chromatography was used to separate unreacted ketone (**48**) from the crude reaction mixture. One possible suggestion for the low conversion is that 2-benzyloxycyclohexanone (**48**) quenched the dianion through competing enolisation. Although the butenolide (**49**) formed by this method was not as functionalised as the previous attempt using methoxyacrylate, Scheme 2.3.4, the double bond of the α,β-unsaturated lactone (**49**) could be manipulated towards the desired functionality (*i.e.* a diol) for the core unit of the squalestatins.



(63) (64) (69) (49)

Reagents: i. 2eq BuLi, THF, -78°C; ii. **48**, -40°C; iii. TFAA, -30°C; iv. LDA



(48)

Scheme 2.3.7

Subsequent elimination of the tosylate group was attempted by the addition of excess triethylamine to the isomeric mixture. This resulted in low yields of the

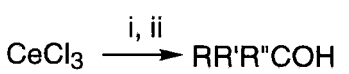
desired butenolide (**49**) (19%). Alternatively, the use of freshly distilled DBU[41] gave increased yields of the eliminated product (**49**) (40-50%), though required longer reaction times. More recently, LDA was utilised and complete consumption of the sulphonyl lactone (**69**) was observed after only 12h. With this modification, the desired butenolide (**49**) was therefore obtained in a 33% overall yield as a 1.4:1 mixture of isomers, Scheme 2.3.7. The appearance of two 1H doublets in the ^{1}H NMR at δ7.56, δ6.02 (major isomer) and δ7.12, δ5.87 (minor isomer) relating to the olefinic protons and an AB coupling at δ4.46 (major isomer) and δ4.41 (minor isomer) of the benzyl moiety was observed. ^{13}C NMR also showed peaks at δ171.3 (major isomer) and δ172.6 (minor isomer) corresponding to the lactone carbonyl.

Although the overall yield for the lactone synthesis was 33%, the reaction proceeded cleanly and it was possible to recycle unreacted ketone (**48**) to obtain the butenolide (**49**) in multigram quantities. It was also hoped that the diastereoselectivity could be increased by the use of a bulkier alkoxy unit than the current benzyloxy group in the ketone.

This method was not totally unsatisfactory and it became the method of choice but it was obviously desirable to look for less basic nucleophiles so as to reduce the competing enolisation effect.

2.3.4 Application of Cerium Homoenolates

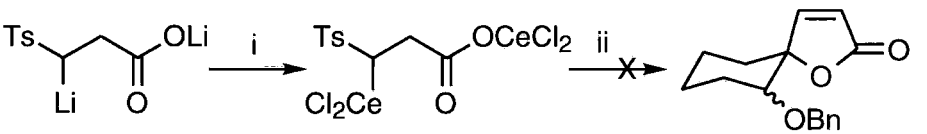
Cerium homoenolates are known to be less basic than their lithium counterparts, but highly nucleophilic. These species have also been reported to add to ketones under mild conditions. The method of Greeves *et al*[34], which involved the transmetallation of organolithium reagents was employed, Scheme 2.3.8.



Reagents: i. RLi, -78°C; ii. R'R"CO

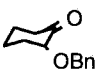
Scheme 2.3.8

Special characteristics of organolanthanoids include high lipophilicity and strong nucleophilicity, but weak basicity for a carbonyl group. This last property was of special interest to us as one of the problems in using 2-benzyloxycyclohexanone (**48**) was that competing enolisation often took place when using very basic nucleophiles (*vide supra*).



(64) (70) (49)

Reagents: i. $CeCl_3$, -78°C; ii. **48**



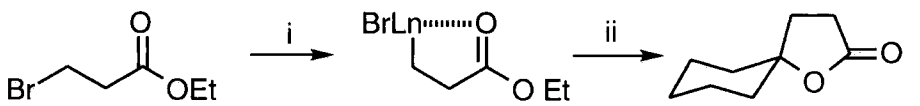
(48)

Scheme 2.3.9

Cerium(III) chloride heptahydrate was finely ground and placed in a flask which was heated *in vacuo* to 135-140°C/0.5mmHg for 16h. Argon was introduced into the flask which was then cooled in an ice bath before the addition of THF, followed by sonication at room temperature for 1h. The resulting white slurry was cooled to -78°C and a solution of the organolithium (propionic acid dianion (**64**)) in THF was added dropwise[35]. The reaction mixture was stirred for a further 1h before adding 2-benzyloxycyclohexanone (48) and stirring for 40h at room temperature, Scheme 2.3.9. No addition was observed to have taken place and flash chromatography led to complete recovery of the ketone (**48**). We attributed this negative result to non-formation of the desired organocerium.

Another method for the production of organocerium reagents has been reported by Fukuzawa *et al*[36] who observed that direct reaction of ethyl 3-bromopropionate with lanthanoid metals in THF produced lanthanoid ester homoenolates. These reacted with ketones to give γ-lactones in good yields under

mild conditions, Scheme 2.3.10. The cerium homoenolate (**71**) was prepared by the addition of a solution of ethyl 3-bromopropionate (**72**) to cerium powder and iodine as illustrated. Formation of the cerium homoenolate was verified by IR analysis and addition of cyclohexanone afforded the desired lactone (**73**) in 55% yield.



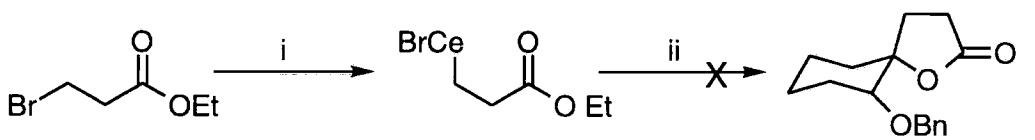
(72) (71) (73)

Reagents: i. Ln, I_2; ii. cyclohexanone

Ln = La, Ce, Nd, Sm

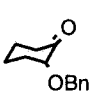
Scheme 2.3.10

In our hands however, we were unable to verifiy the formation of the cerium homoenolate, as the lanthanoid homoenolate (**71**) was extremely air and moisture sensitive and was therefore not isolated. Treatment of 2-benzyloxycyclohexanone (**48**) with the resulting solution at room temperature did not afford the desired lactone (**74**), Scheme 2.3.11. The reaction was repeated several times, but without success.



(72) (71) (74)

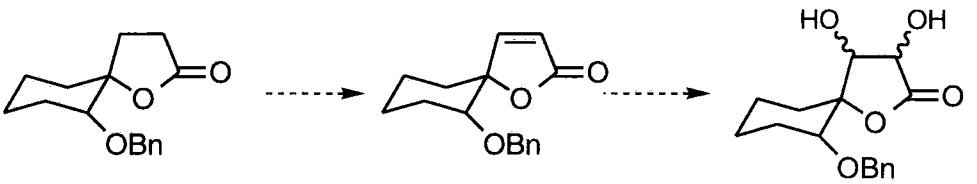
Reagents: i. Ce, I_2; ii. **48**



(48)

Scheme 2.3.11

One possibility for the lack of formation of the desired product could be due to the fact that cerium homoenolates are very unstable and perhaps decomposition occurred before the ketone (**48**) could react. It was therefore desirable to search for a more stable metal homoenolate that would also react with ketones. Again there would be no functionality at the α-and β- positions of the lactone (**74**) but this could have been overcome using selenium reagents to create an α,β-unsaturated lactone which could subsquently be manipulated to a diol functionality (**75**), Scheme 2.3.12.



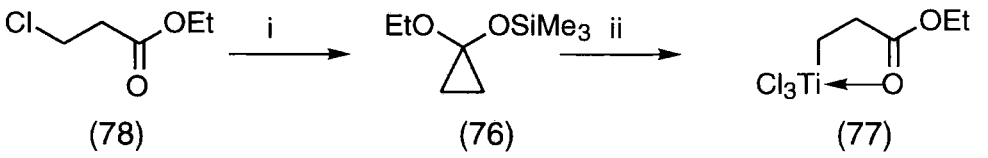
(74) (49) (75)

Reagents: i. PhSeCl, H_2O_2; ii. OsO_4, NMO, ^{t}butanol

Scheme 2.3.12

2.3.5 Application of titanium homoenolates

A survey of the literature for the preparation of homoenolate anions and their equivalents revealed that the use of titanium homoenolates[45] could become a viable option. It has been found that the addition of (**76**) to a carbonyl compound is readily achieved in the presence of titanium(IV) chloride[46]. Further analysis showed the reactive species to be a titanium homoenolate (**77**), Scheme 2.3.13. These reagents are highly nucleophilic but react under mild conditions. Furthermore, the problem of the masking and unmasking procedures required by the "synthetic equivalents" approach[47] is circumvented.



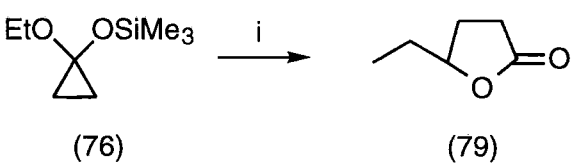
Reagents: i. Na, TMSCl; ii. $TiCl_4$

Scheme 2.3.13

Nakamura and co-workers[48] reported the preparation of the titanium homoenolate (**77**), Scheme 2.3.13. The silyloxycyclopropane (**76**), was obtained from the reductive silylation of ethyl 3-chloropropionate (**78**) by the addition of sodium sand and trimethylsilyl chloride. Careful addition of titanium(IV) chloride to the silyloxycyclopropane (**76**) afforded the desired homoenolate (**77**) which could be purified by recrystallisation under argon or prepared *in situ* and reacted directly with a ketone or aldehyde.

Following the literature procedure, the precursor to the titanium homoenolate, trimethylsilyloxy-1-ethoxy cyclopropane, (**76**) was prepared by the addition of sodium sand and trimethylsilyl chloride. The addition of 4 equivalents of sodium sand rather than the recommended 2 equivalents was necessary as the scale of the reaction was very small. The product was dissolved in ether, filtered, concentrated and purified by careful distillation to afford the desired product (**76**) in 87% yield. ^1H NMR analysis revealed a (4H) multiplet at δ0.9, characteristic of the cyclopropyl ring and a (9H) singlet at δ0.2, indicative of the trimethylsilyl group. GC-MS also showed a molecular ion peak at *m/z* 101.

With the cyclopropane (**76**) in hand, a model study to form 4-hydroxyhexanoic lactone (**79**) was conducted, Scheme 2.3.14.

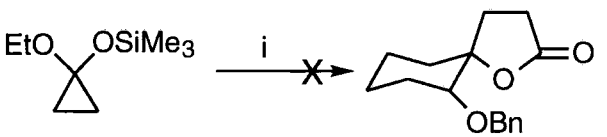


Reagents: i. $TiCl_4$, propionaldehyde

Scheme 2.3.14

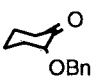
In this, the titanium homoenolate (**77**) was prepared *in situ* by the addition of titanium(IV) chloride to the silyloxypropane (**76**) followed by addition of propionaldehyde at -78°C. The mixture was stirred at 0°C for 1h before quenching with water and extracting with benzene. TsOH was added and the mixture was heated to reflux for 16h to obtain the desired lactone (**79**) in 77% yield. ^{13}C NMR showed a peak at δ177.6 corresponding to the carbonyl and ^{1}H NMR showed a (3H) triplet at δ0.9 and a (1H) multiplet at δ4.4 corresponding to the methyl group and the carbinol proton, respectively. IR showed a stretch at 1772cm^{-1} indicating the presence of the lactone functionality and CI-MS contained a molecular ion peak at *m/z* 132 confirming that synthesis of the desired lactone (**79**) had been achieved.

Familiar with this chemistry, we could now proceed with the synthesis of the spirolactone (**74**) using 2-benzyloxycyclohexanone (**48**) following the methodology of Nakamura *et al*[37], Scheme 2.3.15.



(76) (74)

Reagents: i. $TiCl_4$, **48**



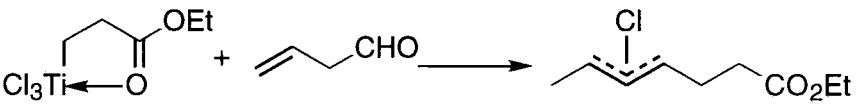
(48)

Scheme 2.3.15

A solution of the silyloxycyclopropane (**76**) was added to a yellow suspension of titanium(IV) chloride and 2-benzyloxycyclohexanone (**48**) in DCM at -78°C. The resulting mixture was warmed to room temperature and stirred for 16h. However,

no addition occurred and purification by flash chromatography resulted in complete recovery of ketone (**48**).

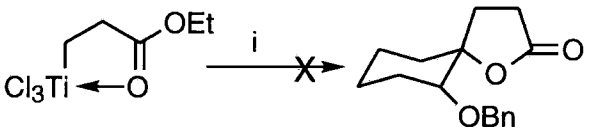
It was thought that the lack of reactivity of the titanium homoenolate (**77**) was due to its low nucleophilicity. Another potential problem with the use of this homoenolate was that chlorinated by-products have been shown to arise in reactions with enals[38], Scheme 2.3.16.



Scheme 2.3.16

Nakamura has reported that replacing the electron withdrawing chlorine ligands, with alkoxides makes the homoenolate more nucleophilic and also reduces the formation of chlorinated by-products observed in reactions with enals[13]. For example, this ligand exchange was utilised in an addition to acetophenone where it was found that product formation increased by more than 30%. Furthermore, the addition of 0.5 eq of titanium(IV) isopropoxide also facilitated the reaction of cyclohexanone with the titanium homoenolate (**77**). Considering this result, it was envisaged that addition of a titanium(IV) alkoxide would similarly facilitate the addition reaction of the silyloxycyclopropane (**76**) to 2-benzyloxycyclohexanone (**48**). Following the procedure for the addition of an alkoxide modified homoenolate[13], the addition of the 3 carbon unit (**77**) to 2-benzyloxycyclohexanone (**48**) was attempted.

Thus, a solution of titanium(IV) isopropoxide was added to a solution of purified titanium homoenolate (**77**) at 0°C. After 5min, 2-benzyloxycyclohexanone (**48**) was added and the mixture quenched after 10min. The reaction was repeated and this time warmed to room temperature after addition of the ketone (**48**) but in neither case was the formation of addition products observed.



(76) (74)

Reagents: i. $Ti(O^iPr)_4$, **48**

(48)

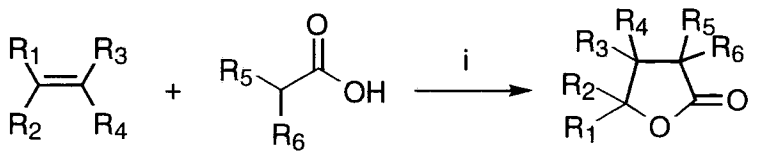
Scheme 2.3.17

It appeared to be that the titanium homoenolate was not reactive enough to afford the desired lactone (**74**). However, it has been reported that these homoenolates are very sensitive to steric interactions and the carbonyl used in this case contains a benzyloxy group in the α-position. As well as causing some degree of hindrance, the alkoxy moiety could also be deactivating the carbonyl group due to its electron withdrawing properties.

2.3.6 Application of Radical Carboxylates

Perusal of the literature revealed a paper by Heiba and Dessau[39] which described a novel, one-step, synthesis of γ–lactones by the use of manganic carboxylates. The general reaction, depicted in Scheme 2.3.18, consisted of the addition of a carboxylic acid (containing an α-hydrogen) to the double bond of an olefin. This proceeded in the presence of various metal oxidants (Mn(III), Ce(IV), V(V)). Manganic acetate dihydrate was chosen as this could be readily prepared *in situ* by permanganate oxidation of manganese(II) acetate tetrahydrate. When synthesising the lactone, it was found advantageous to add 10-30% potassium acetate or another carboxylate salt to the reaction mixture. The addition of the acetate ion served to shorten the reaction time by raising the reflux temperature of

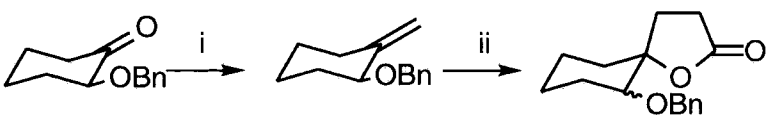
the reaction mixture and also led to decreased formation of side products, resulting in higher lactone yields.



Reagents: i. $Mn(OAc)_3.2H_2O$, KOAc, AcOH

Scheme 2.3.18

The olefin needed to obtain lactone (**74**), Scheme 2.3.19 was the alkene (**80**) which was readily prepared by the addition of a Wittig reagent to the ketone (**48**). This Wittig reagent (**81**) was prepared from the related bromide salt, methyltriphenylphosphonium bromide[40] upon deprotonation with butyl lithium. After stirring for 4h, a solution of 2-benzyloxycyclohexanone (**48**) was added and the mixture allowed to stir at room temperature for 20h, following which, purification by flash chromatography afforded the desired alkene (**80**) in 39% yield with 48% recovery of starting material (**48**). The alkene (**74**) was characterised by the loss of the ketone carbonyl peak at δ210.6 in the ^{13}C NMR. ^1H NMR also showed the generation of two olefinic protons at δ4.79 and δ4.18. Addition of the methylene unit was confirmed by the presence of a molecular ion peak at *m/z* 202 in the EI-MS.

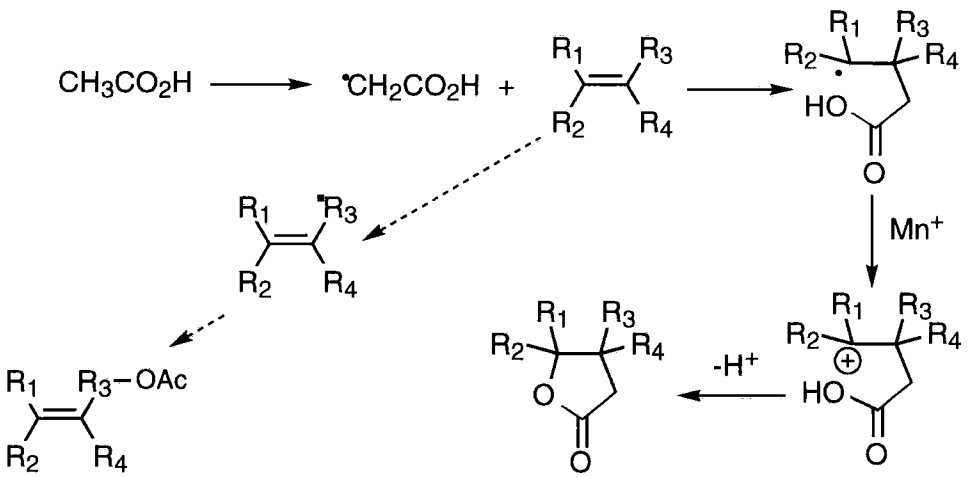


(48) (80) (74)

Reagents: i. $Ph_3P{=}CH_2$ (**81**), ii. $Mn(OAc)_3.2H_2O$, KOAc, AcOH

Scheme 2.3.19

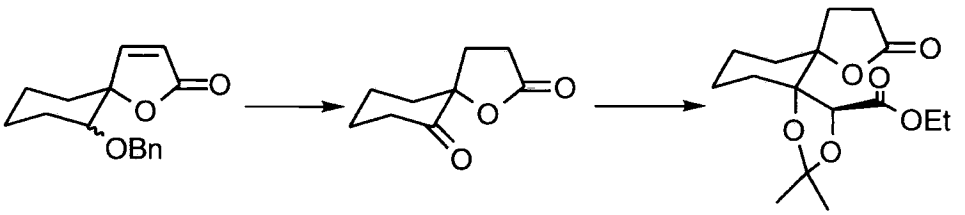
A solution of the olefin (**80**) in glacial acetic acid was heated to reflux in the presence of manganese acetate and potassium acetate, until the brown manganic colour disappeared. After 45h the solution was quenched with water, then purified by column chromatography to afford one single lactone isomer in 11% yield as a colourless oil, Scheme 2.3.19. This was characterised by the appearance of the lactone carbonyl at δ174.4 in the ^{13}C NMR. HRMS also showed a value of 261.1491 corresponding to the theoretical mass of the lactone. The formation of the lactone is thought to proceed through a radical process, in which a carboxymethyl radical is generated, adds to the olefin and the product is subsequently oxidised by the metal oxidant, Scheme 2.3.20. Ring closure then affords the lactone.



Scheme 2.3.20

Although this procedure generated the desired lactone (**74**) the very harsh conditions, coupled with low yields would be of limited use in studies towards the fully substituted core of the squalestatins. Consequently, this method of lactonisation was not pursued further.

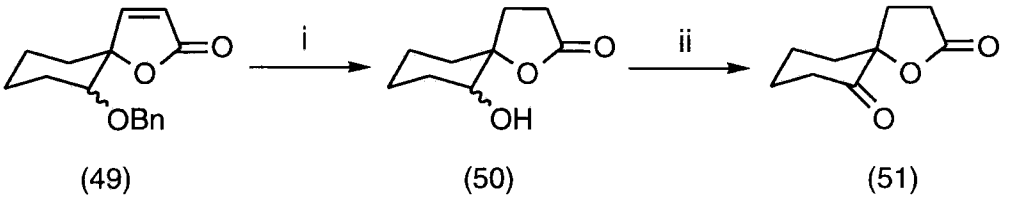
2.3.7 Preparation of 2-benzyloxy-2-oxa-3-oxospiro<4.5>decan-6-one (51)



(49) (51) (82)

Scheme 2.3.21

These results led to the conclusion that the formation of a spirolactone species (**49**) was best achieved using the methodology of Najera, Section 2.3.2. To allow elaboration towards a core analogue of the squalestatins the spirolactone (**49**) had to be modified to permit stereoselective addition, Scheme 2.3.21. It should be noted that changing the functionality at the benzyl ether to a ketone would also eliminate the diastereomers present in the starting material (**49**). The benzyl ether (**49**) was therefore cleaved and the resulting alcohol oxidised to a ketone (**51**). It was initially hoped that the relative reactivity of the benzyl ether would be greater than that of the conjugated olefin, allowing selective reduction to occur. Palladium on carbon seemed the ideal catalyst to use but was unsuccessful. One possible reason for this could have been due to the fact that trace amounts of sulphur (from the tosyl elimination step) were still present. Use of the stronger reagent, palladium hydroxide, afforded the alcohol (**50**), albeit with concomitant reduction of the double bond. The reaction proceeded with a good yield of 87%. Appearance of a broad band at 3438cm^{-1} in the IR confirmed the presence of an alcohol functionality and the disappearance of the characterisic benzylic AB quartet in ^{1}H NMR confirmed loss of the benzyl group. Reduction of the double bond was also confirmed through the disappearance of the doublet at δ6.0 in the ^{1}H NMR spectrum. CI-MS concluded our evidence with a peak of 100% for at *m/z* 188 corresponding to $C_9H_{18}NO_3$.



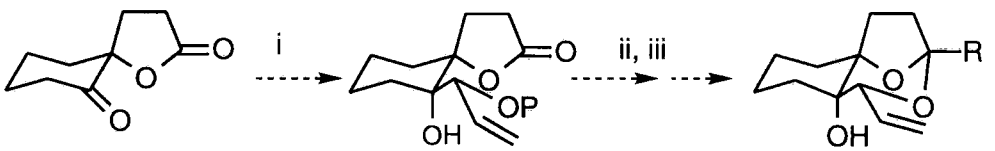
(49) (50) (51)

Reagents: i. $Pd(OH)_2$, H_2, MeOH; ii.oxalyl chloride, DMSO, Et_3N

Scheme 2.3.22

Oxidation of the secondary alcohol (**50**) to the ketone (**51**) was successfully achieved by using the now familiar procedure of Swern *et al*[35] which proceeded with good yield (85%), Scheme 2.3.22. IR showed loss of the OH stretching frequency at 3438cm^{-1} and the appearance of a carbonyl stretch at 1758cm^{-1}. Elemental analysis confirmed the correct empirical formula and HRMS revealed the correct mass of 169.0865.

Insertion of a 2 carbon unit was necessary to obtain (**83**) before ketalisation to afford a core analogue of the squalestatins (**84**), Scheme 2.3.23.



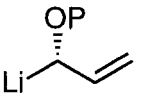
(51) (83) (84)

Reagents: i. C_2 unit; ii. RMgX; iii. H_3O^+

Scheme 2.3.23

A study of the addition of the final 2 carbon unit to the ketone functionality was now possible and this work is discussed in the following section.

2.4 Addition of an α-Alkoxylithium Species



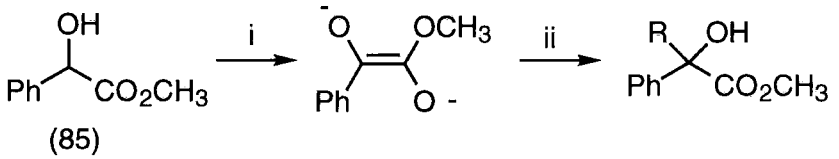
(39)

2.4.1 Introduction

With the ketolactone (**51**) in hand it was neccessary to develop a method for the introduction of the C_2 side chain. This formally requires the addition of an α-alkoxylithium unit (**39**). The preparation of the lithium species (**39**) proved to be more difficult than expected but it was noted that an ester group could be used as a carboxylic acid equivalent instead of an olefin. Consequently preliminary studies using methyl glycolate were undertaken and are described below.

2.4.2 Initial Studies using a Vinyl Dianion

In 1977, Boeckmann and co-workers[53] reported the preparation of dianions derived from α–hydroxyesters (**85**) by reaction with LDA, Scheme 2.4.1.



(85)

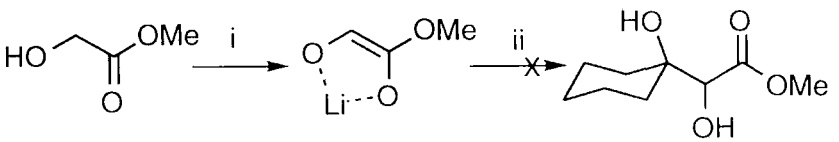
Reagents: i. LDA, -78°C; ii. RX, -78°C

Scheme 2.4.1

We opted to use 2-benzyloxycyclohexanone (**48**) as a test substrate to examine this procedure. The lithium reagent chosen was the lithium dianion of methyl glycolate (**86**), Scheme 2.4.2. Methyl glycolate (**87**) was prepared by methylation of glycolic acid (**88**). Several methods were studied[54], with the most efficient being the addition of diazomethane[55] to glycolic acid (**88**) with a yield of 26%.[56] ^{1}H NMR showed the appearance of a singlet at δ3.63 related to the methyl group

of the ester. The IR spectrum also showed the disappearance of the OH stretch at 3391cm^{-1} corresponding to the acid moiety and a shift of absorption from 1725cm^{-1} to 1741cm^{-1} arising from the carbonyl stretch of the ester group.

The *cis*-dianion of methyl glycolate was prepared by the addition of LDA at -78°C in THF. The mixture was stirred for 1h before addition of the electrophile, Scheme 2.4.2. Cyclohexanone was used initially, since it should be more reactive than the α-alkoxyketone, 2-benzyloxycyclohexanone (**48**). The mixture was warmed to room temperature, but formation of the desired product was not observed. The reaction was repeated using a more hindered base, LHMDS, and a more reactive electrophile, benzaldehyde. Again, no reaction occurred, and starting materials were recovered by flash column chromatography.



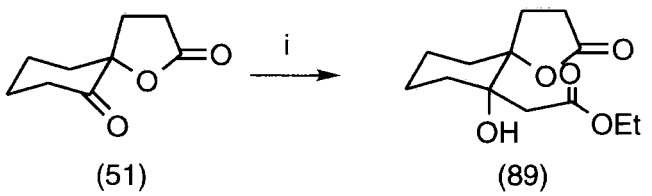
(88) (86)

Reagents: i. 2eq LDA, -78°C; ii.cyclohexanone

Scheme 2.4.2

It was thought that the formation of the dianion (**86**) was proving to be the problematic step so studies using a species without an α-alkoxy group were carried out. The addition of ethyl acetate to the ketone (**51**) was successfully achieved *via* the use of LHMDS, Scheme 2.4.3. Ethyl acetate was added to a solution of LHMDS in THF at -78°C. After 1h a solution of ketone (**51**) was added and the reaction mixture warmed to room temperature and after a further 2h the mixture was quenched by the addition of sat. NH_4Cl. Purification by column chromatography yielded 14% of one single isomer of the adduct (**89**) as a colourless oil. Analysis of ^{13}C NMR data showed peaks at δ176.8 and δ173.4 corresponding to the lactone and ester carbonyl groups, respectively. A

molecular ion peak was observed at *m/z* 274.1654 indicating that the desired compound (**89**) had been produced.

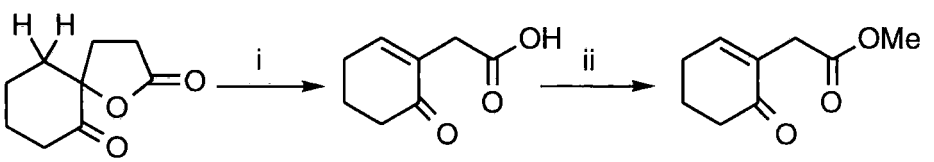


(51) (89)

Reagents: i. LHMDS, ethyl acetate, -78°C

Scheme 2.4.3

The low yield was surprising as complete consumption of starting materials was observed by tlc. In order to determine the mass balance the aqueous layer generated during the work up of the reaction was acidified with HCl and extracted with ethyl acetate. Drying ($MgSO_4$) and concentrating afforded an additional compound which accounted for the mass balance and contained an OH stretch in the IR spectrum at 3455cm^{-1} corresponding to an acid group. Diazomethane was then used to methylate this acid. The appearance of a 3H singlet at δ3.50 in the ^{1}H NMR suggested that methylation had occurred. A peak at δ6.6 also suggested the presence of an olefinic proton. Furthermore, the IR spectrum showed the disappearance of the OH stretching mode at 3455cm^{-1}. A molecular ion peak was observed at *m/z* 182 in the CI-MS. This evidence suggested that the ketolactone (**51**) had deprotonated, opening up the lactone to form the acid (**90**), Scheme 2.4.4.

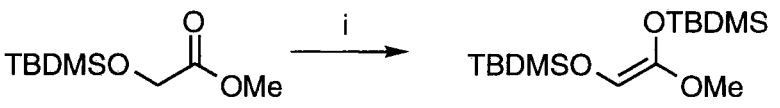


(51) (90) (91)

Reagents: i. LHMDS; ii. diazomethane

Scheme 2.4.4

We considered that it might be better to protect the alcohol moiety of methyl glycolate (**87**) before deprotonating to form the anion. A paper by Yamamoto *et al*[41] reported a method for the stereoselective synthesis of silyl ketene acetals from α-hydroxyesters. It was shown that the *Z*-silyl ketene acetal (**92**) could be selectively prepared from the addition of LHMDS to silyloxy methyl glycolate (**93**), which was then trapped with TBDMS chloride, Scheme 2.4.5.

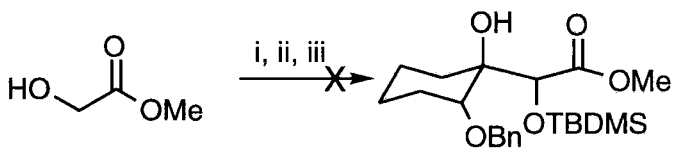


(93) (92)

Reagents: i. LHMDS, TBDMSCl, -78°C

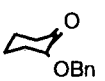
Scheme 2.4.5

Thus, it was thought that the enolate of (**93**) could be trapped using 2-benzyloxycyclohexanone (**48**) to form the addition product (**94**), Scheme 2.4.6.



(87) (94)

Reagents: i. TBDMSCl, Imidazole; ii. LHMDS, -100°C; iii. **48**



(48)

Scheme 2.4.6

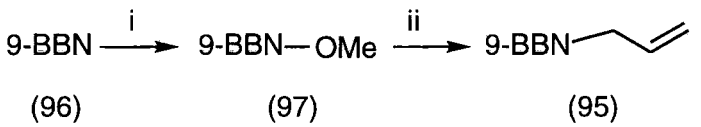
Methyl glycolate (**87**) was protected as the silyl ether (**93**) by the addition of imidazole and TBDMS chloride. Following purification by flash column chromatography the desired ether (**93**) was isolated in 86%. Care was taken during removal of solvent as the silyl ether was found to be highly volatile. ^{1}H

NMR showed the presence of a 9H singlet at δ0.91 and a 6H singlet at δ0.09 corresponding to the TBDMS group. Subsequent deprotonation was carried out by the addition of the silyl ether (**93**) to LHMDS at -100°C. 2-benzyloxycyclohexanone (**48**) was then added and the mixture warmed to room temperature. However product formation was not observed and the ketone (**48**) was recovered upon purification by flash column chromatography. Again, this was attributed to competing enolisation of the alkoxy ketone (**48**).

With these disappointing results it was felt that the α-alkoxyenolates were too basic and this approach was discontinued.

2.4.3 Addition of an Allyl Boron Reagent

In the task of finding a suitably reactive α-alkoxyallyl lithium equivalent, boron chemistry was explored. *B*-allyl-9-BBN (**95**) was prepared in the hope that addition would occur selectively to 2-benzyloxycyclohexanone (**48**), Scheme 2.4.7.



(96) (97) (95)

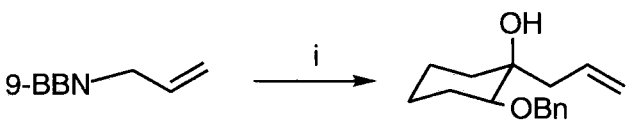
Reagents: i. MeOH; ii. Allylmagnesium bromide, 0°C

Scheme 2.4.7

The method employed followed the procedure of Brown and Racherla[42] for the synthesis of Ipc_2B-allyl. Thus, methanol was added to a cooled solution of 9-BBN (**96**) at 0°C, then the solvents were removed. The resulting 9-BBN-OMe (**97**) was dissolved in ether and an ethereal solution of allylmagnesium bromide added. Purification by vacuum distillation (42°C, 0.5mmHg) afforded B-allyl-9-BBN (**95**) as a colourless oil. This preparation permitted the synthesis of allyl borane reagents free of MgBr(OMe) or Mg^{2+} salts as the rate of reaction is reported to be retarded in the presence of these species. One suggestion for this rate suppression was that MgBr(OMe) complexes with the highly electrophilic boron atom. In doing so, the resulting complex becomes increasingly more stable

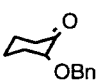
as the reaction temperature is lowered. Consequently, the rate of allylboration diminishes considerably at -78°C, in the presence of Mg^{2+} salts, due to the low concentration of the reactive boron species. A standard procedure for the allylboration of ketones was used[43]. 2-benzyloxycyclohexanone (**48**) was added to a solution of *B*-allyl-9-BBN and the mixture stirred for 2h, after which, ethanolamine was added and the solution stirred for a further 1h. Purification by flash column chromatography afforded 13% of desired product (**98**) and 44% of recovered starting material (**48**) , Scheme 2.4.8. The alcohol was characterised by analysis of ^{1}H NMR which showed the presence of three olefinic protons at δ5.91-5.79 (1H) and δ5.11-5.03 (2H) and an AB quartet associated with the benzyl group. IR also showed the presence of a broad OH stretch at 3574cm^{-1}. Analogous reaction with allylmagnesium bromide afforded the allylated product (**98**) in 98% yield as a 1.3:1 mixture of isomers. In the allylboration reaction only the major isomer was obtained.

The low product yield obtained from this reaction can be attributed to the low nucleophilicity of the allylboron combined with the low electrophilicity of the ketone (**48**). It was therefore decided not to pursue with the synthesis of an α-alkoxyboron reagent as this would prove to be even less reactive. The corresponding stannanes, however, tend to be more nucleophilic and react with aldehydes to give addition products in high yields. The synthesis of such C_3 stannanes is described in the next section.



(95) (98)

Reagents: i. **48**, ethanolamine

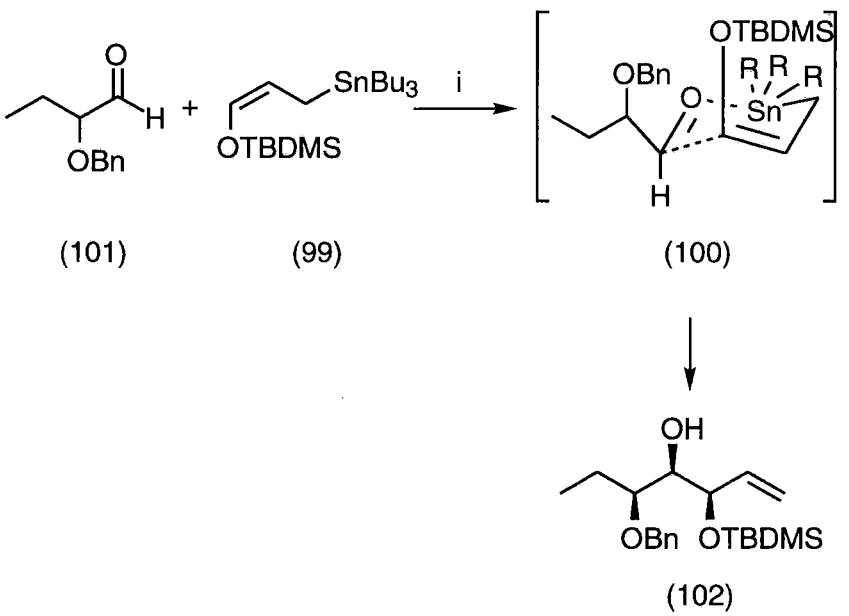


(48)

Scheme 2.4.8

2.4.4 Preparation of a γ-Alkoxy Stannane

Another synthetic equivalent of the α-alkoxylithium is a γ-alkoxystannane (**99**). This species adds to carbonyl groups *via* a six membered transition state (**100**)[60], Scheme 2.4.9. Following this precedent we opted to investigate the potential of γ-silyloxystannane (**99**) as such stannanes had been observed to react with α-benzyloxyaldehydes, Scheme 2.4.9, although the corresponding reaction with ketones has not been reported. For example, Keck *et al*[61] reported the addition of the γ-alkoxystannane (**99**) to α-benzyloxyaldehydes (**101**) in the presence of magnesium bromide, Scheme 2.4.9. The products were obtained with diastereofacial selectivity consistent with 'chelation control' and *syn* disposition of substituents about the newly formed bond was found to be highly favoured.



(101) (99) (100)

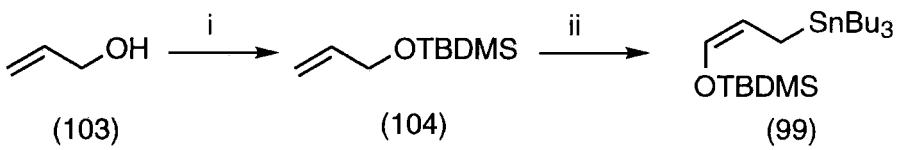
(102)

Reagents: i. $MgBr_2.OEt_2$, -23 - 0°C

Scheme 2.4.9

The stannane (**99**) was prepared using methodology reported by Keck,[61] Scheme 2.4.10. Allyl alcohol (**103**) was added to sodium hydride at 0°C, followed by TBDMS chloride.[62] The resulting mixture was stirred for 14h at room temperature. Extraction and purification by high vacuum transfer afforded the

desired silylether (**104**) in 89% yield. Its formation was characterised in the ^1H NMR by the appearance of a 9H singlet at δ0.84 and a 6H singlet at δ0.06 relating to the silyl ether protecting group. In addition, the IR indicated the disappearance of a characteristic OH stretch indicating that protection had occurred successfully.



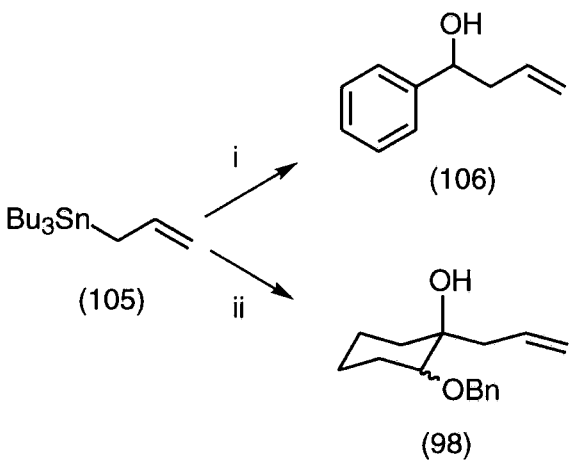
Reagents: i. NaH, TBDMSCl; ii. BuLi, HMPA, Bu_3SnCl, -78°C

Scheme 2.4.10

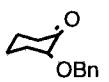
Conversion to the stannane (**99**) was achieved by the addition of butyl lithium and HMPA to the silyl ether (**104**) and trapping of the resultant anion with tributyltin chloride. The reaction was warmed to room temperature, then quenched by the addition of sat. NH_4Cl. Although the crude product could be could be used directly, in our hands the stannane (**99**) was purified by column chromatography giving the required compound in 78% yield. Formation of the stannane (**99**) was shown by the appearance of a large multiplet at δ1.79-0.82 in the ^1H NMR corresponding to the tributyl tin moiety. A molecular ion peak was observed at *m/z* 403 in the EI-MS, corresponding to loss of the ^{t}butyl group.

Following the procedure mentioned above, the stannane (**99**) was added to a mixture of magnesium bromide and 2-benzyloxycyclohexanone (**48**) in DCM at -23°C. No reaction was observed at this temperature, so the mixture was warmed to room temperature and stirred for 16h. Again, product formation was not observed. The reaction was heated to reflux for 6h but purification of the crude mixture by flash column chromatography led to complete recovery of starting materials. The reaction was repeated using benzaldehyde as the electrophile but also proved unsuccessful and again unreacted starting materials were recovered.

Allylation of benzaldehyde was carried out using allyl tributyltin (**105**) and magnesium bromide, Scheme 2.4.11, as it was thought that allyl tributyltin should be more reactive than the corresponding α-alkoxy stannane. After 16h at room temperature formation of a new compound was observed and the reaction was quenched with saturated NH_4Cl. Purification was achieved by flash column chromatography affording 37% desired alcohol (**106**) and 24% recovered benzaldehyde. The appearance of multiplets at δ5.79-5.68 (1H) and δ5.12-5.06 (2H) in the ^1H NMR correspond to the three olefinic protons and the presence of a broad OH stretch at 3603cm^{-1} in the IR suggested that addition to the benzaldehyde had taken place. Furthermore, confirmation of the molecular structure (**106**) was obtained from EI-MS which showed a peak at *m/z* 130.



Reagents: i. benzaldehyde, $MgBr_2$; ii. **48**, $TiCl_4$,-78°C



(48)

Scheme 2.4.11

Allylation of 2-benzyloxycyclohexanone (**48**) with magnesium bromide failed but the use of titanium(IV) chloride, a stronger Lewis acid, gave 100% allylated product (**98**) after only 6h at -78°C. 2-Benzyloxycyclohexanone (**48**) was added

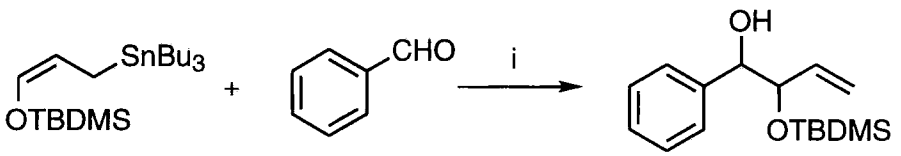
to a stirred solution of titanium(IV) chloride followed by the addition of allyl tributyltin at -78°C. After work up and chromatography, the desired homoallyl alcohol (**98**) was obtained in 100% yield and was characterised by an AB splitting pattern typical of the benzyl grouping and the presence of three multiplets in the olefinic region δ5.82-4.95 in the ^{1}H NMR. IR showed the appearance of an alcohol moiety which, coupled with the loss of the carbonyl peak at δ210.6 in the ^{13}C NMR, suggested that addition at the carbonyl centre had taken place.

The excellent yield obtained upon allylation of the ketone (**48**) with titanium(IV) chloride suggested that this Lewis acid could be ideal for the addition of the less reactive silyloxyallyl stannane (**99**) to 2-benzyloxycyclohexanone (**48**). This reaction was therefore carried out at -78°C but no product formation was observed. Furthermore, the silyloxyallyl stannane decomposed in the presence of titanium(IV) chloride at temperatures above -10°C and ^{1}H NMR showed the disappearance of the 9H and 6H singlets characteristic of the TBDMS group.

Attempts to add silyloxyallyl stannane (**99**) to benzaldehyde in the presence of titanium(IV) chloride were also unsuccessful. Benzaldehyde was added to a solution of titanium(IV) chloride at -78°C and after 15min, a solution of stannane (**99**) was added. The reaction mixture turned black almost immediately. After purification by flash column, ^{1}H NMR analysis indicated decomposition of the stannane had occurred with the loss of a 9H singlet at δ0.84 and a 6H singlet at δ0.06 corresponding to the loss of a TBDMS group. Concomitant with this observation, Keck also reported side reactions arising from the result of the relatively low nucleophilicity of the silyloxyallylstannanes, which require somewhat higher temperatures to be employed with these reagents than with equivalent allylbutylstannanes. Lewis acid mediated cleavage of acid sensitive groups (e.g. silyl ethers) can compete with the desired addition process.

In our hands, attempts to add the silyloxystannane (**99**) to benzaldehyde in the presence various Lewis acids showed that a 'titanium blend' gave the highest yield of the allylated product (**107**), Scheme 2.4.12. In this procedure a 1M solution of titanium(IV) chloride was added to a 1M solution of titanium(IV) isopropoxide in

DCM at -78°C. The mixture was stirred for 1h before the addition of benzaldehyde and then for a further 20min before quenching with saturated $NaHCO_3$. Purification by flash column yielded 27% of a colourless oil identified as the adduct (**107**). IR showed an OH stretch at 3550cm^{-1} and a peak at δ-3.1 in the ^{13}C NMR corresponded to a methyl attached to a silicon atom. The presence of three peaks in the olefinic region of the ^{1}H NMR suggested that allylation had occurred and a large peak at *m/z* 106 in the CI-MS corresponded to a fragmentation of the molecular ion at the silyl ether.

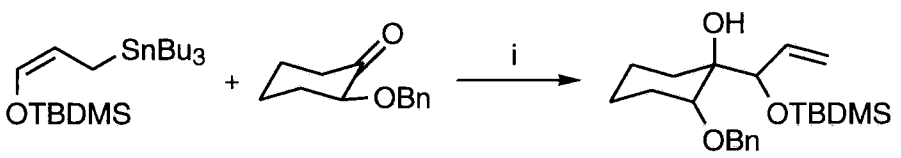


(99) (107)

Reagents: i. $TiCl_4$, $Ti(O^iPr)_4$

Scheme 2.4.12

It was therefore decided to use the titanium blend for the addition of the stannane (**99**) to 2-benzyloxycyclohexanone (**48**), Scheme 2.4.13. However, at -78°C, there appeared to be no addition products forming and, upon warming the reaction slowly, decomposition of the stannane (**99**) occurred. The procedure was repeated a number of times, varying the reaction conditions, with the results summarised in Table 2.4.1, below.



(99) (48) (108)

Reagents: i.Lewis acid (see table)

Scheme 2.4.13

Lewis Acid	Temperature (°C)	Yield
1.1eq $MgBr_2$[a]	-23	No reaction
1.1eq $TiCl_4$[a]	-78	Stannane decomposition
0.55eq $TiCl_4$/ 0.55eq $Ti(O^iPr)_4$[a]	-78 - RT	Stannane decomposition
1.1eq $TiCl_4/Ti(O^iPr)_4$[a]	0	Stannane decomposition
1.1eq $Cl_2Ti(O^iPr)_2$[a]	RT	Stannane decomposition
1.1eq BBr_3[a]	-78	Stannane decomposition
1.1eq $BF_3.OEt_2$[a]	-78 - RT	Stannane decomposition
1.1eq $AlCl_3$[a]	RT	18%
5eq $AlCl_3$[a]	-78 - RT	Stannane decomposition
1.1eq $AlCl_3$[b]	-78 - RT	22%
1.1eq $EtAlCl_2$[b]	-78 - RT	12%

[a]Lewis acid added to the ketone (**48**) before the addition of the stannane (**99**) at -78°C

[b]Lewis acid added to a solution of ketone (**48**) and stannane (**99**) at -78°C

Table 2.4.1

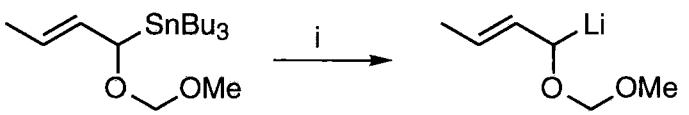
It was found that optimum conditions, in which aluminium(III) chloride was used as the Lewis acid yielded 22% of the desired product (**108**) as a single isomer. A solution of stannane (**99**) was added to a solution of 2-benzyloxycyclohexanone (**48**) at -78°C. After 15min aluminium(III) chloride was added and the mixture stirred for 5h. The reaction was then warmed to room temperature and quenched with saturated $NaHCO_3$. Purification was achieved through column chromatography to afford 22% of the desired colourless oil (**108**) and 54% recovered ketone (**48**), Scheme 2.4.13. The IR spectum of (**108**) contained an OH stretch suggesting that the addition had occurred at the ketone centre. ^1H NMR showed the presence of three olefinic protons at δ5.88 integrating for 1H and

δ5.21, integrating for 2H. Peaks at δ -3.5 and δ -4.6 in the ^{13}C NMR correspond to the methyl groups attached to the silicon atom.

Although formation of the desired adduct (**108**) had been achieved, a more nucleophilic precursor might increase the 22% yield obtained from the addition of the γ-alkoxy stannane (**99**) to 2-benzyloxycyclohexanone (**48**). A report by Chong[44] showed that transmetallation of α-alkoxy stannanes to the equivalent alkoxy lithium was possible. This would be a more nucleophilic reagent which might afford higher yields upon addition to 2-benzyloxycyclohexanone (**48**). The preparation and addition of such a reagent is described in the following section.

2.4.4 Applications of an α-Alkoxy Lithium

Another alternative for the synthesis of an α-alkoxylithium (**109**) is the transmetallation of an α-alkoxystannane (**110**), Scheme 2.4.14, potentially available by the method outlined by Chong.[63]

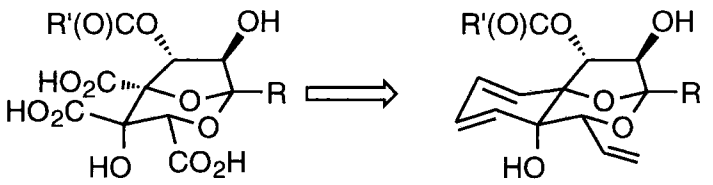


(109) (110)

Reagents: i. BuLi, -78°C

Scheme 2.4.14

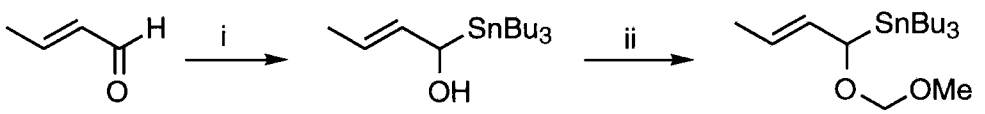
It should also be noted that the terminal substitution on the alkene (**109**) is unimportant since this would be cleaved by ozonolysis in the final step towards the synthesis of the core unit of the squalestatins, Scheme 2.4.15.



(1) (36)

Scheme 2.4.15

The α-alkoxystannane (**109**) was prepared using the procedure reported by Thomas *et al* ,[64] Scheme 2.4.16. Tributyltin hydride was added to a solution of LDA, at -78°C, with stirring. Crotonaldehyde (**111**) was then added dropwise to the mixture. The allyl alcohol (**112**) was isolated after quenching with saturated NH_4Cl. Subsequent protection of the alcohol (**112**) was achieved by the addition of MOM chloride and diisopropylethylamine, affording the desired α-alkoxystannane (**109**) in 82% yield, after purification by flash chromatography. ^1H NMR showed an AB splitting pattern corresponding to the two diastereotopic protons of the MOM group and a multiplet at δ5.57 and δ5.39 arising from the two alkenic protons of the product.



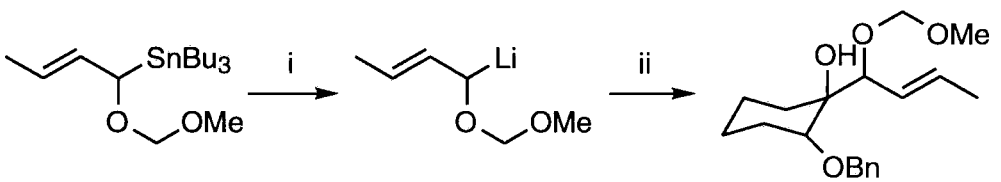
(111) (112) (109)

Reagents: i. LDA, Bu_3SnH, -78°C; ii. MOMCl, diisopropylethylamine

Scheme 2.4.16

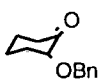
Following Chong's described procedure for the transmetallation of stannanes,[59] butyl lithium was added to a solution of stannane (**109**) and allowed to stir for 10min. A solution of 2-benzyloxycyclohexanone (**48**) was then added and the reaction warmed to room temperature after 2h. Purification by column

chromatography yielded only a very small amount of product, Scheme 2.4.17, but this was subsequently improved by increasing the transmetallation time to 1h affording the desired allylated product (**113**) in 13% yield as a single isomer. This was characterised by the presence of two AB quartets indicative of the MOM group and the benzyl group, respectively. A band at 1665cm^{-1} in the IR showed that the compound possessed an olefinic group and a stretch at 3488cm^{-1} indicated the presence of the hydroxyl functionality. HRMS observed a mass of 259.1698 identical to the calculated mass of the molecular ion.



(109) (110) (113)

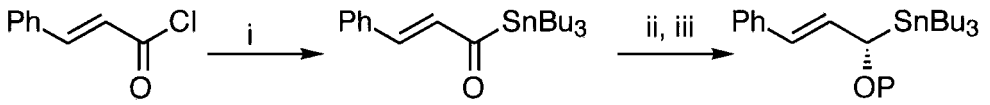
Reagents: i. BuLi, -78°C, 4h; ii. **48**



(48)

Scheme 2.4.17

This reaction, however, was not enantioselective as the stannane contained one chiral centre which was not controlled, so was therefore generated as a racemic mixture. The addition of lithium tributyltin to the aldehyde (**111**) results in the formation of an enantiomeric mixture (**112**), Scheme 2.4.16. This could be overcome by the formation of the ketostannane (**114**) from the palladium catalysed addition of the acid chloride (**115**) to hexamethylditin, Scheme 2.4.18. This ketostannane (**114**) could then be stereoselectively reduced with a chiral reagent, for example, (R)- or (S)-BINAL, then protected to yield the corresponding α-alkoxystannane (**116**).



(115) (114) (116)

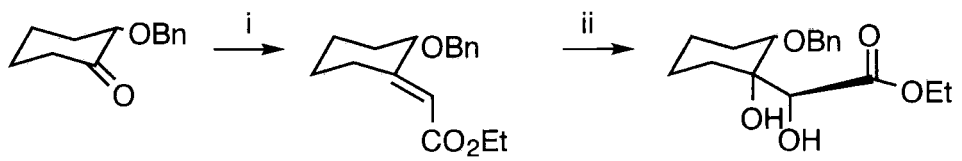
Reagents: i. hexamethylditin, $(Ph_3P)_4Pd$; ii. (S)-BINAL; iii. MOMCl, diisopropylethylamine

Scheme 2.4.18

Preparation of the stannane (**114**) has been reported[65] and its formation is catalysed by a palladium (0) species. Tetrakis (triphenylphosphine) palladium (0) was found to be both expensive as well as air sensitive. Consequently, all attempts to produce the ketostannane were unsuccessful due to decomposition of the palladium reagent.

Although the addition of the α-alkoxylithium (**110**) component proceeded with low yields, this is as yet unoptimised but as described below, it was discovered that simpler methodology could be used to achieve addition of the C_2 unit. Although an increased number of steps was needed, an excellent overall yield was obtained.

2.4.5 Alternative Preparation of a C_2 Unit



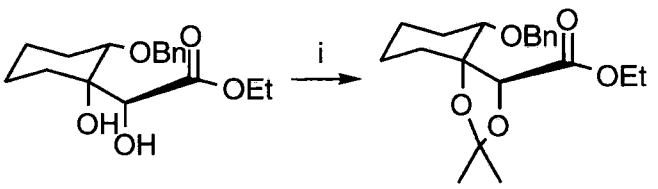
(48) (118) (119)

Reagents: i. $Ph_3P{=}CHCO_2Et$ (**117**), PhH; ii. OsO_4, NMO, ^{t}butanol

Scheme 2.4.19

The addition of the Wittig reagent (**117**) to 2-benzyloxycyclohexanone (**48**) afforded the alkene (**118**) in 94% yield, characterised by the appearance of an

The addition of the Wittig reagent (**117**) to 2-benzyloxycyclohexanone (**48**) afforded the alkene (**118**) in 94% yield, characterised by the appearance of an olefinic 1H singlet at δ5.93 in the ^{1}H NMR. CI-MS also showed a large molecular ion peak at *m/z* 141. This, together with HRMS analysis which correlated with the calculated mass of 275.1647 provided firm evidence that the alkene (**118**) had indeed been synthesised. Furthermore a 8:1 mixture of separable *E* and *Z* isomers was obtained. This was elucidated by analysis and comparison of alkene (**126**) which allowed for complete assignment of the alkene (**118**). Conversion of the major *E* isomer to the diol (**119**) was achieved upon heating to 30°C, in the presence of osmium(IV) oxide and NMO[45]. Purification by column chromatography afforded the diol (**119**) in 100% yield as a colourless oil. ^{1}H NMR showed the disappearance of the olefinic proton at δ5.93 and a broad band was observed at 3497cm^{-1} in the IR spectrum corresponding to the OH stretch with no absorption in the alkenic region (~1655cm^{-1}). HRMS observed a mass of 309.1702 which correlates with the calculated mass. Subsequent protection of the diol as the acetal (**120**) was achieved by heating the diol (**119**) at reflux with 2,2-dimethoxypropane and a catalytic quantity of trifluoroacetic acid in chloroform[46]. Molecular sieves were used to extract the water evolved upon protection, driving the equilibrium towards the formation of the acetonide. On large scale protection, the sieves were renewed periodically. Purification by flash column chromatography afforded the desired acetonide (**120**) in 97% yield. The disappearance of the broad band at 3497cm^{-1} in the IR suggested that the diol had been protected as the acetal. Furthermore, the presence of two 3H singlets at δ1.49 and δ1.31 in the ^{1}H NMR correspond to the two methyl groups of the acetal and EI-MS showed a molecular ion peak at *m/z* 349 confirming that the acetonide (**120**) had been formed, Scheme 2.4.20.



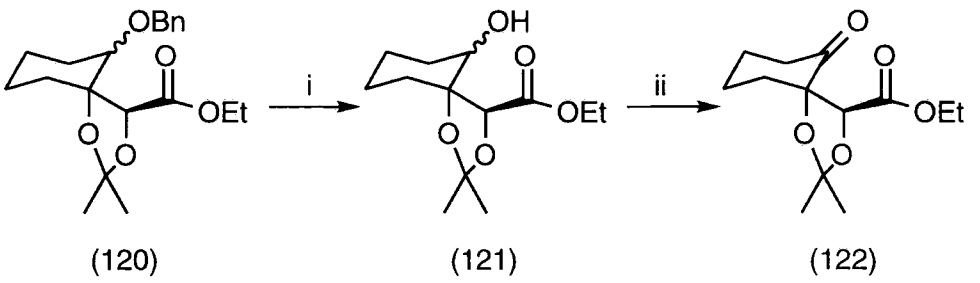
(119) (120)

Reagents: i. 2, 2 dimethoxypropane, TFA, $CHCl_3$

Scheme 2.4.20

The next step in the synthesis was to remove the benzyl ether (**120**) to allow further elaboration at this centre, Scheme 2.4.21. This was achieved by hydrogenolysis using palladium catalyst and hydrogen. Several catalysts were used[47] from which it was found that palladium hydroxide was the most efficient, giving the desired alcohol (**121**) in 99% yield after purification by flash column chromatography. ^1H NMR showed the disappearance of a 5H multiplet at δ7.36-7.18 and the AB quartet relating to loss of the benzyl moiety. An absorption at 3474cm^{-1} in the IR arose from the appearance of the OH group and MS showed a moleceular ion peak at *m/z* 258 corresponding to $C_{13}H_{22}O_5$. Initial oxidation to the ketone (**122**) was achieved using TPAP[69]. In this process, a catalytic amount of TPAP was added to a solution of the alcohol (**121**) and NMO. The mixture was stirred at room temperature for 10h, then filtered and concentrated to afford the crude product (**122**). Purification by flash column chromatography gave the ketone (**122**) in 80% yield. It was, however, less expensive to conduct large scale oxidation of the ketone using Swern methodology which also gave an increased yield of 100%. IR showed the disappearance of the broad OH stretch at 3474cm^{-1} which was replaced with a strong absorption at 1757cm^{-1} corresponding to the ketone. Two 1H multiplets at δ2.88-2.84 and δ2.40-2.36 in the ^1H NMR corresponded to the two protons α- to the ketone. A peak at δ208.7 in the ^{13}C NMR was also characteristic of the formation of the ketone (**122**). A HRMS

value of 257.1389 corresponded to the theoretical mass confirming that oxidation had occurred forming the desired ketone (**122**).



(120) (121) (122)

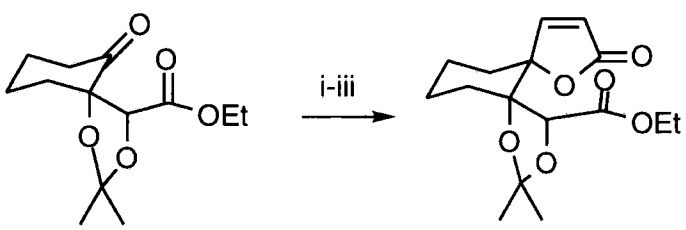
Reagents: i. $Pd(OH)_2$, MeOH; ii. oxalyl chloride, DMSO, Et_3N

Scheme 2.4.21

Methodology for the addition of a C_2 unit had been achieved in excellent overall yield. It now remains to couple this with the C_3 unit using Najera's[39] chemistry, to form the spiro lactone. The order of addition of these two units is also considered and this work is described below in Section 2.4.7.

2.4.6 Preparation of the Spirolactone (123)

In order to form the spiro lactone (**123**) it was neccessary to form the dianion of 3-(*para*-tolylsulphonyl) propionic acid (**63**) before addition to the ketone (**122**), Scheme 2.4.22. This was achieved by following the procedure of Najera and co-workers which has been described previously in Section 2.3.3.



(122) (123)

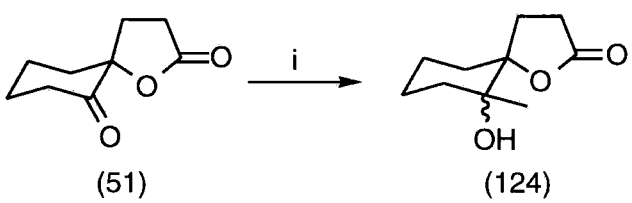
Reagents: i. $TsCH_2CH_2CO_2H$, 2eq BuLi, -78°C then **122**, -40°C; ii. TFAA, -30°C; iii. LDA, -78°C - RT

Scheme 2.4.22

Butyl lithium was added to a stirred solution of 3-(*para*-tolylsuphonyl)propionic acid (**63**) at -78°C. After 1h a solution of the ketone (**122**) was added and the mixture stirred at -40°C for 30h, before trifluoroacetic anhydride was added and the reaction warmed to -30°C for 4h. Quenching with sat. $NaHCO_3$ afforded the sulphonyl lactone which was subsequently eliminated by the addition of LDA to afford the desired lactone (**123**) as a 1.3:1 mixture of separable isomers in 35% overall yield. This was characterised by the presence of two peaks in the ^{13}C NMR spectrum at δ171.9, δ168.7 (major isomer) and δ174.4, δ168.0 (minor isomer) corresponding to the lactone and ester carbonyl groups, respectively. Furthermore, the presence of two doublets in at δ7.52, δ6.13 (major isomer) and δ7.54, δ6.21 (minor isomer) in the ^{1}H NMR showed that formation of the α,β-unsaturated lactone had been achieved. The HRMS value of 328.1760 for each isomer confirmed that the correct structure had been formed.

The disappointing yield in this sequence was attributed to the competing enolisation which was postulated as being an important factor of this addition step. The only side product of this reaction was, however, the unreacted ketone (**122**) and this material could be recycled to give large amounts of the desired butenolide (**123**). It was thought that the selectivity of both the Wittig reaction and dihydroxylation of the double bond could be increased by forming the spiro lactone first before the formation of the alkene.

2.4.6 Initial Selectivity Studies of the Ketolactone (51)

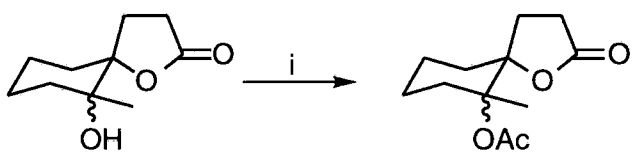


(51) (124)

Reagents: i. MeLi, -78°C

Scheme 2.4.23

In order to test the selectivity of nucleophilic addition to the ketolactone (**51**), methyl lithium was added to a solution of ketolactone (**51**) in THF at -78°C, Scheme 2.4.23. Purification yielded a mixture of diastereomeric products which proved difficult to separate. ^{1}H NMR showed the presence of two singlets in a ratio of 1.3:1. These were separable with difficulty after repeated flash column chromatography. The ^{1}H NMR spectra showed a 3H singlet at δ1.24 for one isomer and 3H singlet at δ1.48 for the other. The appearance of an OH stretch at 3497cm^{-1} in the IR and ^{13}C NMR analysis showed the lactone (C=O, δ177.4) to have remained intact. Further elaboration of the alcohol (**124**) to the ester (**125**) confirmed the addition of methyl lithium to the ketone position. This conversion was achieved by the addition of acetyl chloride and triethylamine to a solution of the lactone alcohol (**124**) to afford a 38% yield of the desired ester (**125**), Scheme 2.4.24. Appearance of singlets at δ1.94 and δ2.26 respectively corresponded to the acetate methyl groups. The formation of the ester (**125**) also facilitated the separation of the two isomers resulting from addition of methyl lithium. Preferential reactivity at the ketone centre was to be expected but the rather unselective manner of addition was disappointing. The reaction was repeated using methylmagnesium bromide but an identical mixture of isomers was obtained.



(124) (125)

Reagents: i. AcCl, Et_3N

Scheme 2.4.24

2.4.7 Preparation of the Spirolactone (82) from the Ketolactone (51)

The Wittig methodology discussed in Section 2.4.6 was repeated using the ketolactone (**51**) in order to study the effect of the lactone on the selectivity of each reaction. The alkene (**126**) was obtained in a 12:1 ratio of separable isomers, Scheme 2.4.25. Utilising the techniques of HETCOR, COSY and NOE difference spectroscopy enabled full assignment of ^{1}H and ^{13}C NMRs, Figure 2.4.1. Furthermore, it was found that, of the two diastereoisomers, the double bond of the major diastereomer existed in the (*E*) configuration. Comparative methods were used to analyse the isomeric ratio of the previous alkene (**118**) formed from 2-benzyloxycyclohexanone (**48**). HRMS value of 256.1549 corresponds with the calculated mass for each isomer. Addition of a catalytic amount of osmium(IV) oxide to a solution of the alkene (**126**) and NMO in ^{t}butanol afforded two unseparable diastereomeric diols (**127**) in 77% yield. ^{13}C NMR showed 26 peaks concluding that two species must be present. The diastereomers were observed in a ratio of 2:1, however we were unable to assign the configuration of the major isomer. A broad OH band at 3444cm^{-1} in the IR suggested that the diol had been formed. The loss of the olefinic singlet at δ5.9 (major isomer) δ5.60(minor isomer) in the ^{1}H NMR showed that the alkene moiety was no longer present. Protection of the diol (**127**) *via* the addition of 2,2-dimethoxypropane in the presence of a catalytic amount of trifluoroacetic anhydride gave the desired acetal (**82**). A yield of 78% of one isomer was obtained after purification by flash chromatography. The disappearance of the broad band at 3444cm^{-1} characteristic of the alcohol functionality indicated that protection had taken place. ^{1}H NMR also showed the presence of two 3H triplets at δ1.53 and δ1.37 corresponding to the two methyl groups of the acetal and EI-MS also showed a large molecular ion peak at *m/z* 330. Overall, the selectivity of the addition reactions was increased slightly but the yields of each step remained similar.

AMR 16-1
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2D Spectral width 3051.1 Hz
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Relaxation delay 1.000 sec
Pulse width 18.5 usec
First pulse width 45.0 degrees
Ambient temperature
No. repetitions 8
No. increments 512
Double precision acquisition
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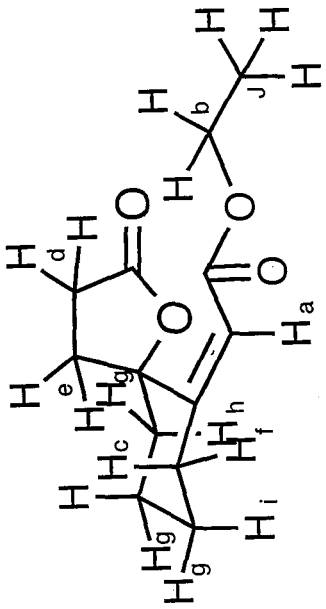
Sine bell squared 0.126 sec
Shifted by -0.084 sec
FT size 1024
F1 DATA PROCESSING
Sine bell square 0.126 sec
Shifted by -0.084 sec
FT size 1024
Total acquisition time 85 minutes



(126)

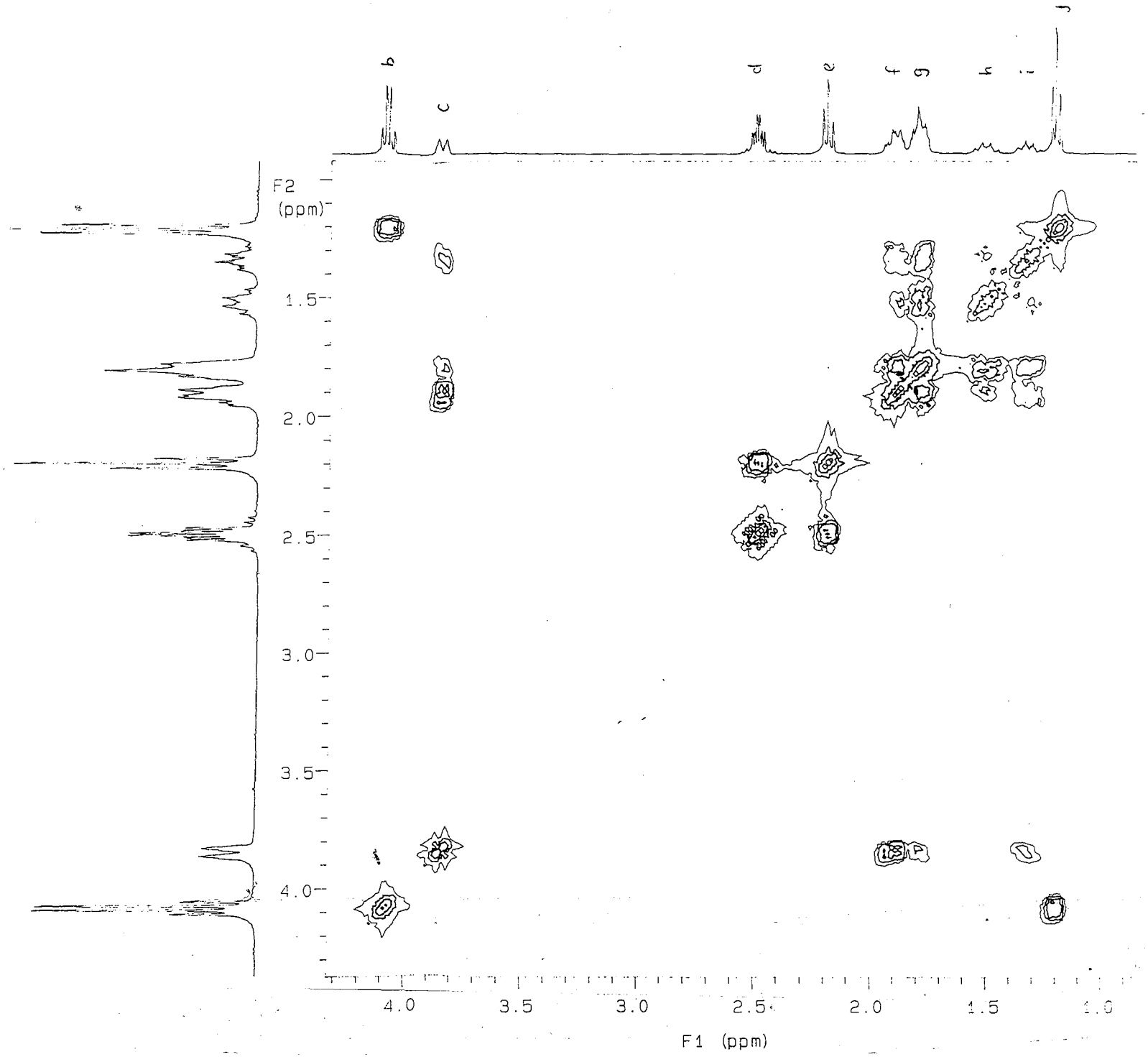


Figure 2.4.1 (COSY of alkene **126**)

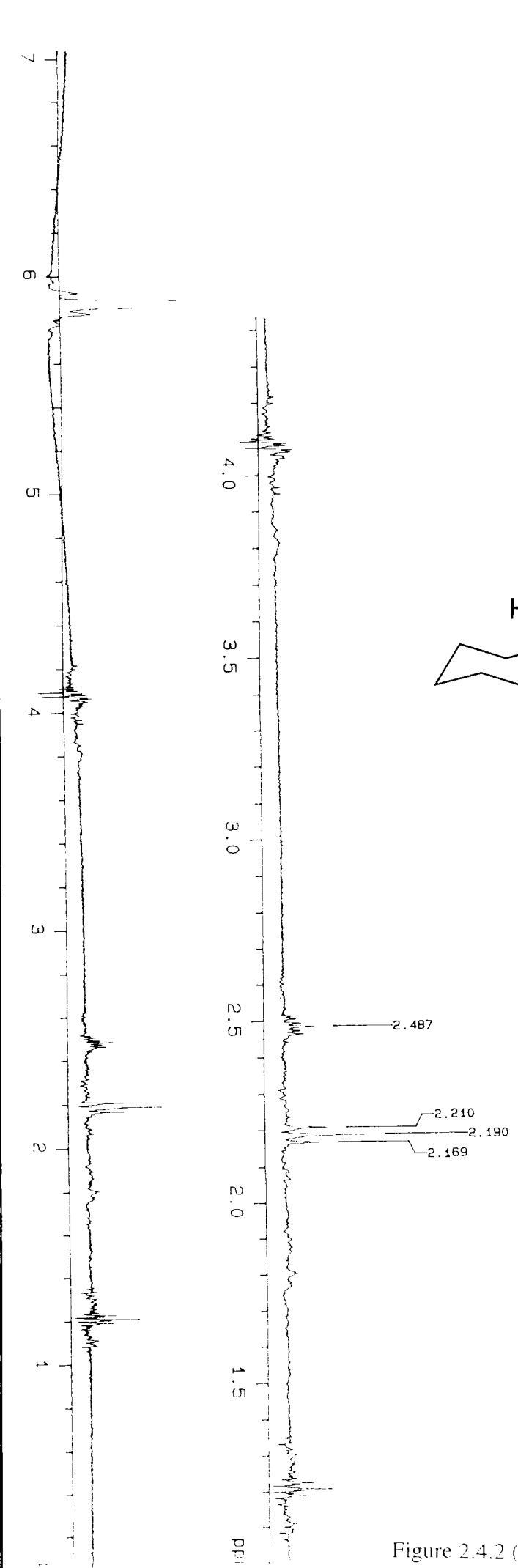
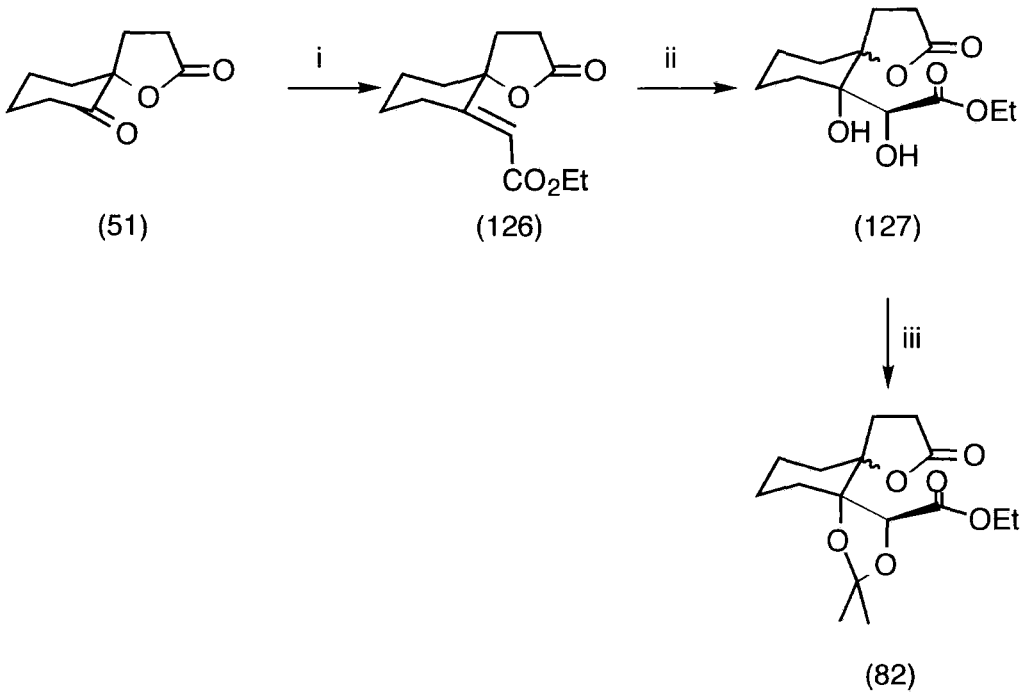


Figure 2.4.2 (NOE spectrum of alkene **126**)



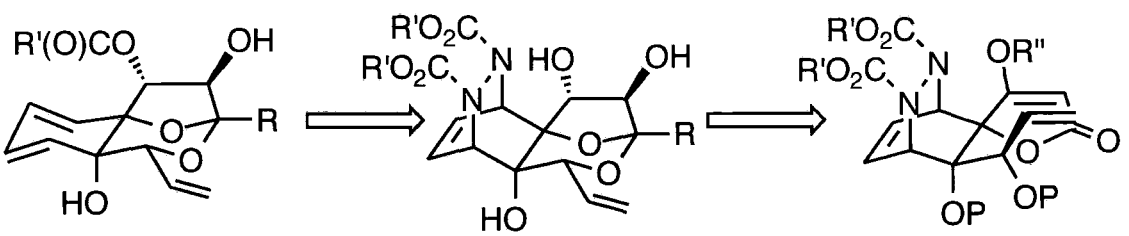
(51) (126) (127) (82)

Reagents: i. $Ph_3P{=}CHCO_2Et$ (**117**), toluene, 110°C; ii. OsO_4, NMO; iii. 2,2-dimethoxypropane, TFA, chloroform

Scheme 2.4.25

With the addition of the C_2 and C_3 units achieved, the next step in the synthesis was the addition of the C(1) side chain. This would functionalise the lactone at the carbonyl group to form a lactol. Initially, we opted to use methyl lithium or methyl magnesium reagents for this purpose but eventually an allyl reagent would be used as this could afford chain extension ultimately forming a variety of analogues of the squalestatins at a late stage in the synthesis.

2.5 Functionalisation of the Lactone - Addition of a C(1) Side Chain



(1) (36) (38)

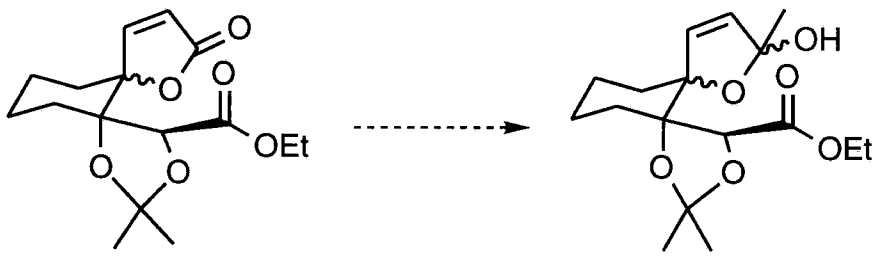
Scheme 2.5.1

2.5.1 Introduction

The introduction of a C(1) alkyl group at a late stage in the synthesis was essential for the preparation of a number of core analogues without having to dramatically vary the core synthesis, Scheme 2.5.1.

2.5.2 Attempted Addition of an Alkyl Lithium

Preliminary studies were undertaken to determine whether the ester or lactone functionality of the butenolide (**123**) would be the most reactive to nucleophiles. It was thought that the lactone carbonyl would react first, due to the fact that there would be a certain amount of release of ring strain on converting this carbon to an sp^3 configuration, Scheme 2.5.2

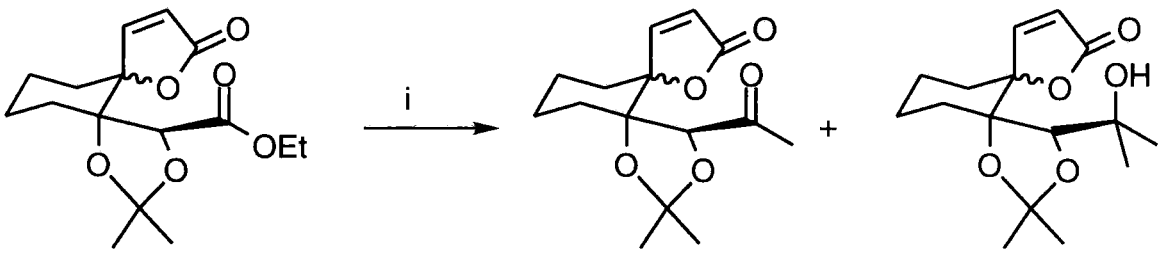


(123) (128)

Scheme 2.5.2

However, the addition of 1.2 equivalents of methyl lithium resulted in the recovery of 59% starting material (**123**) and the isolation of an alcohol (**129**) in 25% yield. After purification by flash column chromatography. ^1H NMR showed two 3H singlets at δ1.24 and δ1.15 corresponding to the two methyl groups on the alcohol (**129**). Reaction of the ethyl ester was also characterised by the disappearance of an apparent 2H quartet at δ4.22 and a 3H triplet at δ1.31 in the ^1H NMR with the development of a strong OH stretch at 3496cm^{-1} in the IR. The presence of a carbonyl peak at δ158.9 in the ^{13}C NMR corresponded to the lactone carbonyl and not the ester carbonyl which occurs at δ168.0 in the starting

material (**123**). The data suggests that the alkyl lithium had selectively added to the ester carbonyl rather than the lactone carbonyl, Scheme 2.5.3. Careful chromatography also yielded a small amount of ketone (**130**) in 9% yield. This was characterised in ^{13}C NMR by the presence of two carbonyl peaks at δ207.6 and δ157.3 corresponding to ketone and lactone carbonyls respectively. Once formed, (**130**) is obviously more reactive than an ester or lactone group and preferentially reacts with any available methyl lithium. This double methylation means that large amounts of starting material (**123**) will be recovered. Similar products were obtained from reaction of methyl lithium with the other lactone isomer.



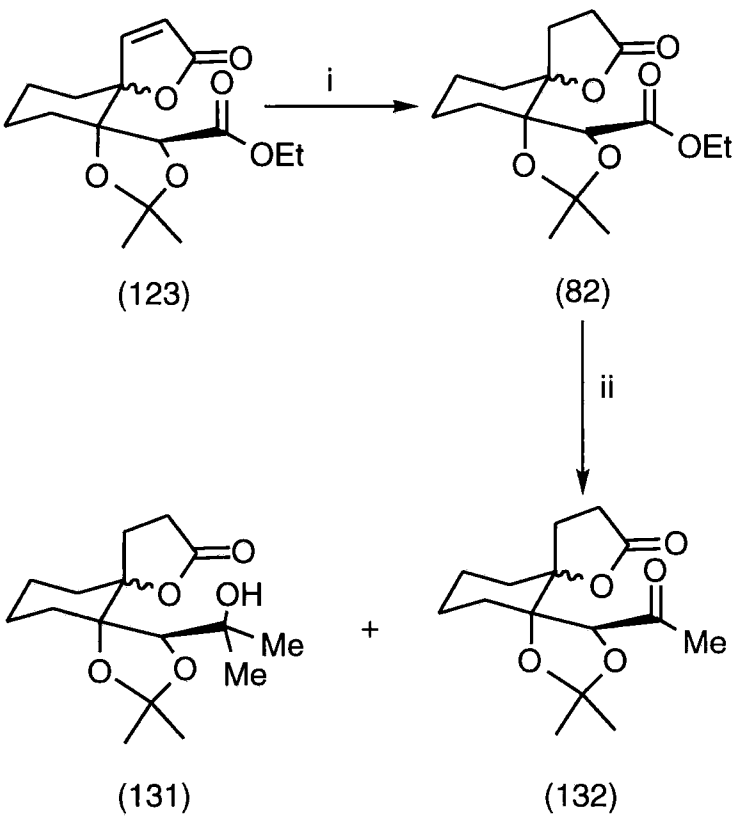
(123) (130) (129)

Reagents: i. MeLi, -78°C

Scheme 2.5.3

One reason for the lack of reactivity of the lactone carbonyl could be due to its conjugation which could be deactivating the carbonyl group. The double bond can be oxidised to form a diol through which Squalestatin 1 can be accessed by esterification of the C(6) side chain. To obtain this functionality, oxidation of the double bond was studied. Attempts to form an epoxide with ^{t}butyl hydroperoxide and butyl lithium[70] were unsuccessful so it was decided to reduced the double bond instead forming a saturated structure and this was readily accomplished using palladium hydroxide (**82**), Scheme 2.5.4. ^{1}H NMR showed the disappearance of two 1H doublets at δ7.62, δ6.13 (major isomer) and δ7.51,

δ6.41 (minor isomer) corresponding to the α- and β- protons of the lactone. HRMS also showed peaks in the CI corresponding to the calculated masses of 330.1917. Subsequent reaction with methyl lithium yielded the analogous alcohol (**131**) in 37% yield and starting material (**82**) in 52% yield as observed previously. Again, these were characterised by the disappearance of the ethyl ester in ^{1}H NMR {masked quartet and triplet at δ4.28-4.08, δ1.24 (major isomer) δ4.30-4.17, δ1.3 (minor isomer)}. This was the case for both lactone isomers and studies with other nucleophiles such as methylmagnesium bromide yielded identical products.



Reagents: i. $Pd(OH)_2$, MeOH; ii. MeLi, THF, -78°C

Scheme 2.5.4

This was rather disappointing as it called for a review of the synthetic plan. The use of an ester functionality as protection of a carboxylic acid was obviously too

reactive for our needs and the search for a less reactive protecting group was undertaken.

2.6 Alternative Protection of a carboxylic acid

2.6.1 Introduction

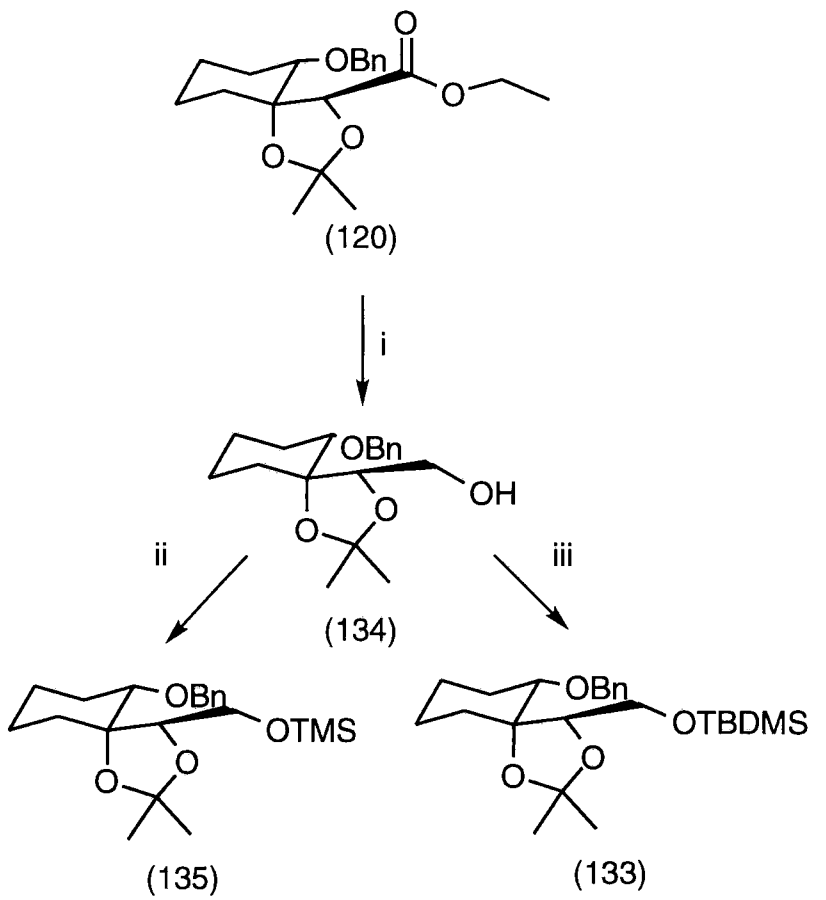
Rather than devise a different synthesis to incorporate a less reactive protecting group for an acid, it was noted that the ester group could be reduced to an alcohol using DIBAL. Subsequent silyl protection would obtain a functionality stable to nucleophilic attack.

2.6.2 Conversion of the Ester (120) to a Silyl Ether (133)

DIBAL was added to a solution of the ester (**120**) in THF, Scheme 2.5.5. After the careful addition of methanol and water, celite was added and the mixture extracted with ethyl acetate. Purification by column chromatography afforded the desired alcohol (**134**) in 99% yield. Absence of a peak at δ170.2 in the ^{13}C NMR indicated that the ester had been reduced in addition to disappearance of a masked 2H quartet at δ4.17-4.02 and a 3H triplet at δ1.16 in the ^{1}H NMR. IR also showed the disappearance of the peak at 1744cm^{-1} corresponding to the ester functionality and the appearance of an OH stretch at 3455cm^{-1} confirmed that the ester (**120**) had been reduced to the alcohol (**134**).

TMS protection of the alcohol (**134**) was achieved by the simple addition of TMS chloride and triethylamine using standard methodology[71]. The appearance of a 9H singlet at δ0.06 indicated the formation of the silyl ether (**135**). IR also showed the loss of an OH stretching absorption at 3455cm^{-1}. Subsequently, this protecting group proved too labile for our purposes so a sterically larger silyl group was used. Similar protection of the alcohol (**134**) with TBDMS chloride and imidazole[48] gave the desired silyl ether (**133**) in 90% yield, Scheme 2.6.1. ^{1}H NMR contained a 9H singlet at δ0.87 arising from the ^{t}butyl silyl group. MS showed a peak in the EI at *m/z* 420 corresponding to the molecular ion. HRMS

observed a mass of 420.2696 in accordance with the calculated mass for the proposed molecular ion.



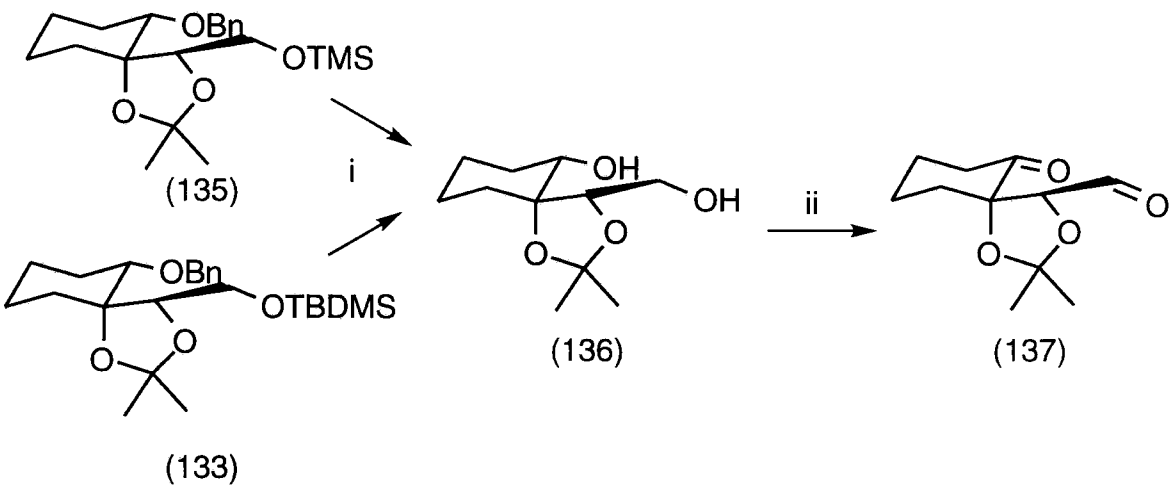
Reagents: i. DIBAL; ii. TMSCl, Et_3N; iii. TBDMSCl, Imidazole

Scheme 2.6.1

2.6.3 Preparation of the Silyl Ketone (61)

A solution of benzyl ether (**135**) was hydrogenated over palladium, Scheme 2.6.2. This method was previously found to be the most successful in forming the secondary alcohol. After purification, ^1H NMR showed the disappearance of the 5H aromatic multiplet and the AB system relating to the benzylic moiety. However, analysis of the ^1H NMR spectrum also showed the disappearance of the 9H singlet corresponding to the silyl ether. Subjection of the TBDMS protected benzyl ether (**133**) to hydrogenation afforded an identical product. MS showed a molecular ion *m/z* 216 indicating that the diol (**136**) had been formed.

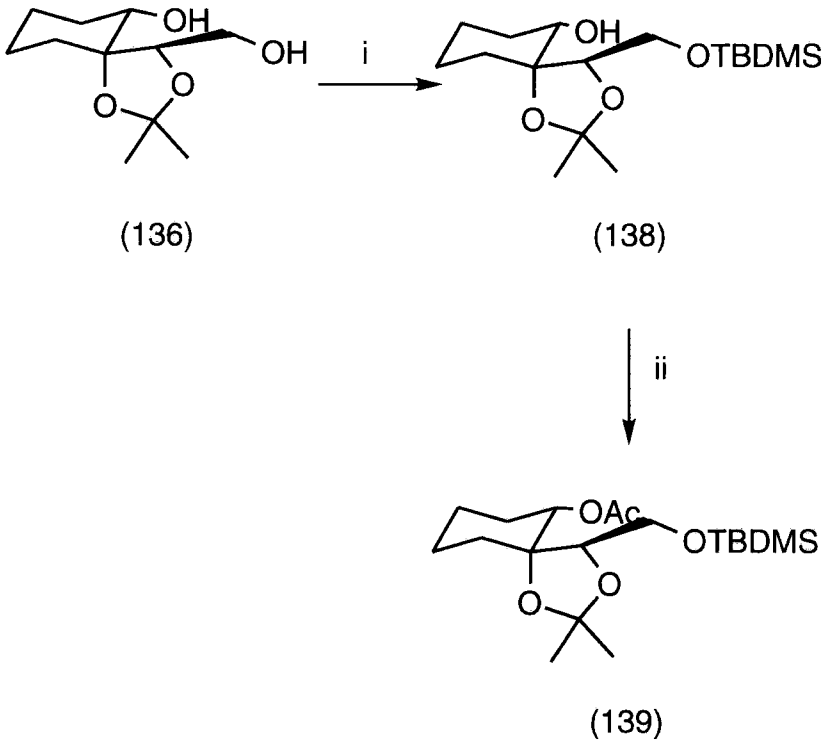
To prove the assignment of the diol (**136**), Swern oxidation was carried out to produce a waxy solid which gave rise to a 1H singlet at δ9.67 in the ^{1}H NMR. This suggested that the compound isolated contained an aldehyde (**137**). ^{13}C NMR also showed two carbonyl functionalities at δ208.9 and δ200.8, arising from the presence of the aldehyde and the ketone respectively, Scheme 2.6.2. This proved that the diol was indeed formed in the previous reduction.



Reagents: i. $Pd(OH)_2$, MeOH; ii. oxalyl chloride, DMSO, Et_3N

Scheme 2.6.2

It is a well known fact that primary alcohols are more reactive than secondary alcohols so it was possible to selectively protect the primary alcohol leaving the secondary alcohol intact. Thus TBDMS chloride and imidazole were added to a solution of the diol (**136**) in DMF. After 20h the reaction was quenched, concentrated and purified by flash chromatography to afford the protected alcohol (**138**) as a white solid in 97% yield. The appearance of two very low frequency peaks at δ0.93 (9H) and δ0.08 (6H) in the ^{1}H NMR was indicative of the presence of a TBDMS ether, Scheme 2.6.3.



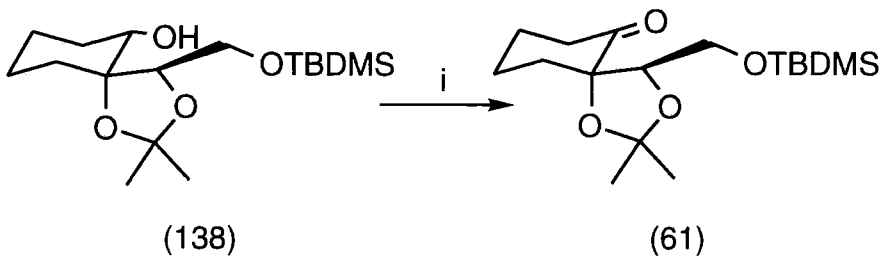
Reagents: i. TBDMSCl, imidazole; ii. Ac_2O, DMAP, pyridine

Scheme 2.6.3

The secondary alcohol (**138**) was then protected as the acetate (**139**) to confirm the location of the silyl ether moiety. A solution of the alcohol (**138**), acetic anhydride, and DMAP in pyridine was stirred for 40h at room temperature. The crude oil was washed with a saturated aqueous copper sulphate solution to remove the pyridine. Purification by column chromatography gave 63% of the desired ester (**139**). This was characterised by the appearance of a 3H singlet at δ2.07 in the ^1H NMR corresponding to the methyl group and a multiplet at δ3.97-3.70 corresponding to the α-alkoxy proton. ^{13}C NMR also showed a carbonyl peak at δ169.9 suggesting that acetylation had occurred. HRMS showed a *m/z* peak with a mass of 373.2410 in agreement with the theoretical mass.

Simple Swern oxidation of the remaining secondary alcohol afforded the ketone (**61**) in 69% yield, Scheme 2.6.4. IR showed the disappearance of the OH stretch at 3408cm^{-1} and the appearance of a stretch at 1719cm^{-1} corresponding to the

presence of a carbonyl group. HRMS showed a *m/z* peak with a mass of 329.2148 identical to the calculated mass for the ketone (**61**).



(138) (61)

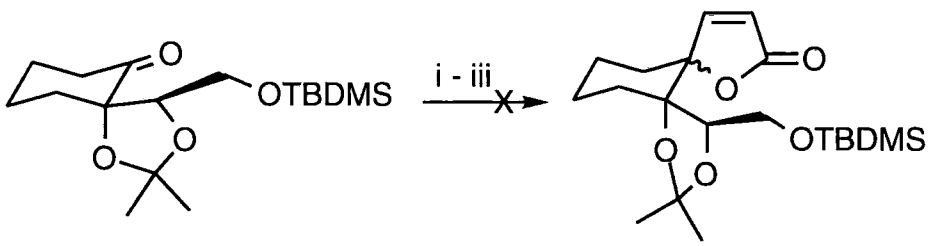
Reagents: i. oxalyl chloride, DMSO, Et_3N

Scheme 2.6.4

Formation of the ketone (**61**) was carried out employing this method affording good overall yield and further elaboration to the spirolactone was subsequently carried out (*vide infra*).

2.6.4 Preparation of the Spirolactone

The Najera methodology (Section 2.3.3) previously used to form the spirolactone was employed, Scheme 2.6.5. The dianion of the propionic acid (**63**) was formed upon the addition of two equivalents of ^{n}butyl lithium. This, however, failed to add to the ketone (**61**) carbonyl. This disappointing result was rationalised by the fact that the addition step is sensitive to steric interactions and the silyl ether could possibly be too bulky to allow such an addition.

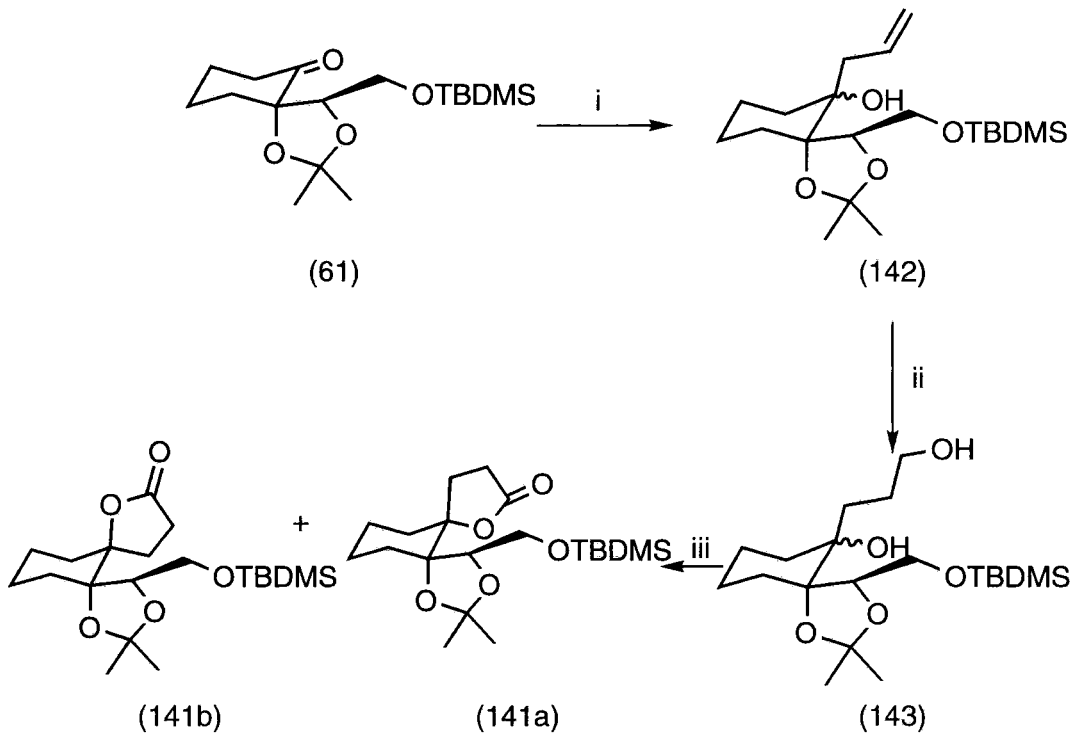


(61) (140)

Reagents: i. $TsCH_2CH_2CO_2H$, 2eq BuLi, -78°C; ii. **61**, -40°C, TFAA, -30°C; LDA

Scheme 2.6.5

Well known methodology[49] was therefore used to form the saturated lactone (**141**), Scheme 2.6.6. Allylmagnesium bromide was added to a solution of the ketone (**61**) to form the alkene (**142**) as a 1.3:1 mixture of separable isomers. The major isomer was characterised by an OH stretch at 3419cm^{-1} in the IR and the presence of three olefinic protons, one as a multiplet at δ5.95 and two at δ5.06 in the ^{1}H NMR. The minor isomer differs spectroscopically by the presence of a 1H multiplet at δ4.35 corresponding to C<u>H</u>CH$_2$OSi. This occurs at δ4.24 in the major isomer. HRMS value of 370.2539 corresponded identically with the calculated value for each isomer. The diastereomers were separated and subsequent reactions were carried out on each isomer individually. At this point we didn't know which was which but later results (*vide infra*) enabled us to determine that the major isomer was (**142a**) and the minor isomer was (**142b**). Both were carried through the following steps concurrently, however in the interests of clarity only the process involving isomer (**142a**) (the one that worked) will be described in detail.



Reagents: i. AllylMgBr, THF, -78°C; ii. BH_3.THF, H_2O_2; iii. PCC

Scheme 2.6.6

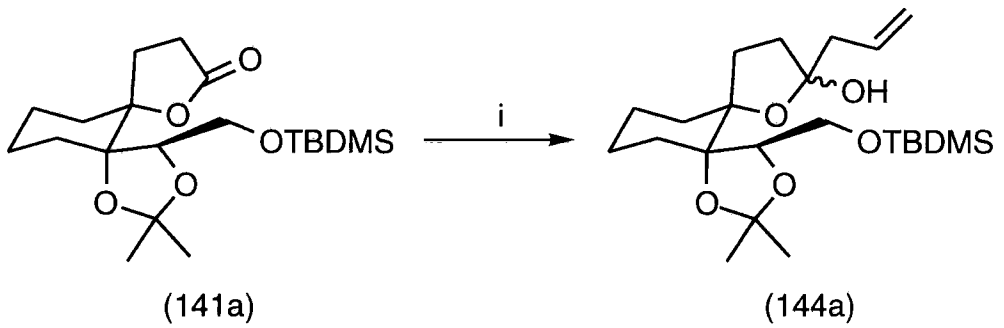
Hydroboration of the major isomer (**142a**) with borane followed by oxidative workup with hydrogen peroxide afforded the diol (**143a**) in 63% yield. This was characterised by a large OH stretch at 3392cm^{-1} in the IR spectrum with concomitant disappearance of the olefinic stretch at 1640cm^{-1}. Oxidation to the lactone *via* the lactol was explored using a number of oxidation processes[73]. An optimised yield of 80% was obtained by using PCC[74] as the oxidant. Formation of the lactol could be observed by tlc and isolation was possible but it was more convenient to drive the reaction to the formation of the lactone before purification by flash column chromatography. Purification was achieved by column chromatography and an IR spectrum was obtained showing the disappearance of the OH stretch at 3392cm^{-1}. A peak at δ176.6 in the ^{13}C NMR corresponded to a lactone carbonyl group and elemental analysis confirmed that the lactone had indeed been formed.

Although the lactone (**141a**) was obtained through a multi step process, the yields of each step were such that multigram scale preparation was possible. Incorporation of the less reactive silyl ether protecting group had been accomplished. It was now possible to proceed with the incorporation of the C(1) side chain by the addition of a magnesium reagent to the lactone. Nucleophilic attack should only occur at the lactone functionality unlike previous attempts to add a C(1) side chain (Section 2.5.2) where the more reactive ester functionality was also present.

2.6.5 Functionalisation of the Lactone - Addition of a C(1) Allyl Unit

Allylmagnesium bromide was added to a solution of lactone (**141a**). Almost immediately, tlc showed that starting material had been consumed and products formed. After purification by column chromatography, ^{1}H NMR showed a 1.2:1 mixture of unseparable diastereomers to be present, Scheme 2.6.7. Allylation was characterised by the presence of signals around δ5-6 in the ^{1}H NMR, corresponding to the olefinic proton. These diastereomers are anomers (**144a**) of each other so cyclisation studies were carried out without further purification.

Only 200MHz ^{1}H NMR data was obtained as the molecule proved to be very unstable. Decomposition seemed to occur with migration of the double bond to form an allyl alcohol together with a number of unidentifiable products (see Scheme 2.7.4).

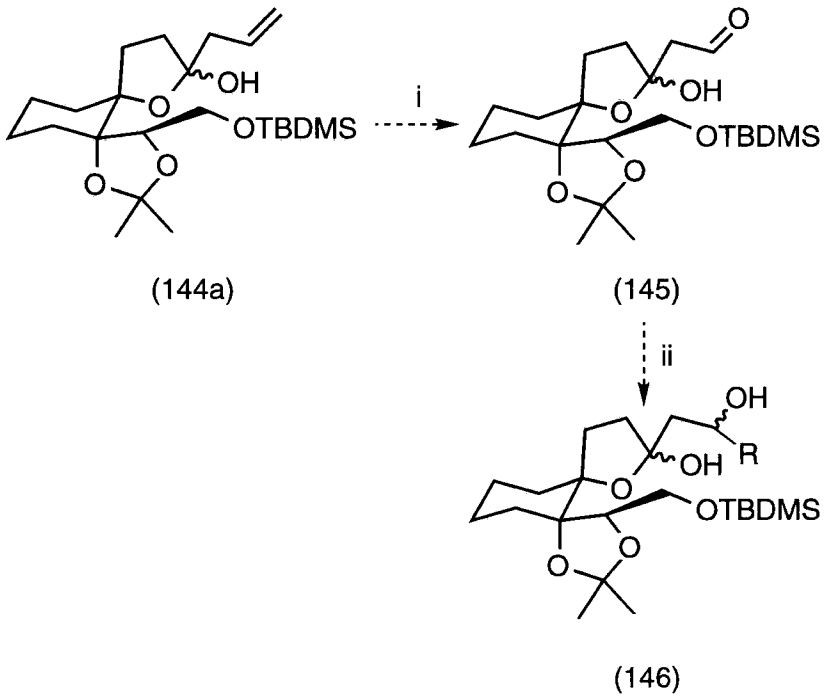


(141a) (144a)

Reagents: i. AllylMgBr, THF, -78°C

Scheme 2.6.7

The addition of a C(1) side chain had been accomplished in excellent yields. Furthermore, the nature of this side chain should enable further elaboration to analogues of the squalestatins as the alkene (**144a**) can be oxidised to an aldehyde (**145**) which could undergo further addition reactions (**146**), Scheme 2.6.8.



(144a) (145) (146)

Reagents: i. O_3, DMS; ii. RMgBr

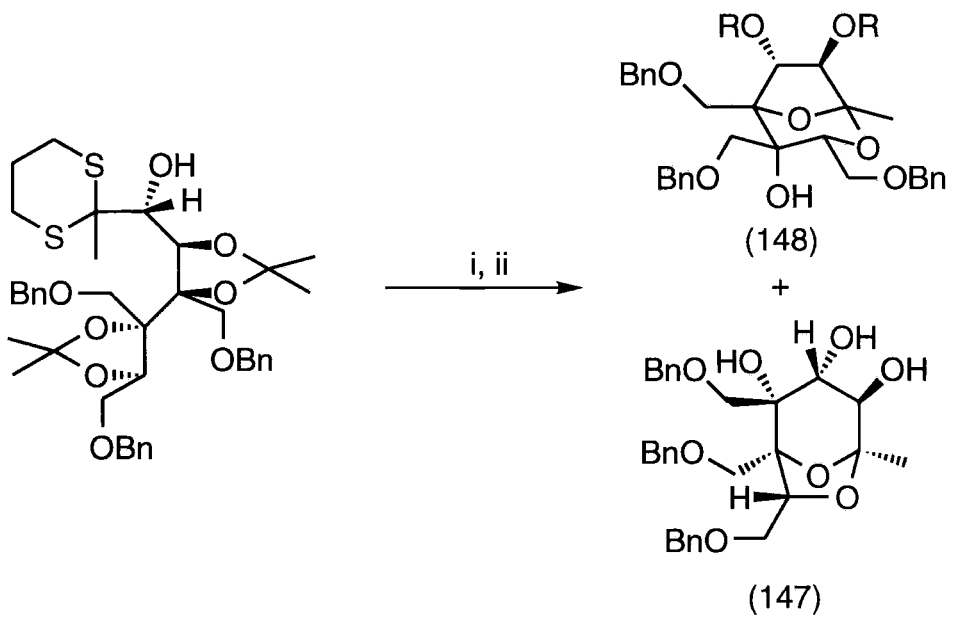
Scheme 2.6.8

Functionalisation of the lactone had been achieved so now ketalisation studies to form a core analogue of the squalestatins could be carried out and this work is described below.

2.7 Cyclisation Studies

2.7.1 Introduction

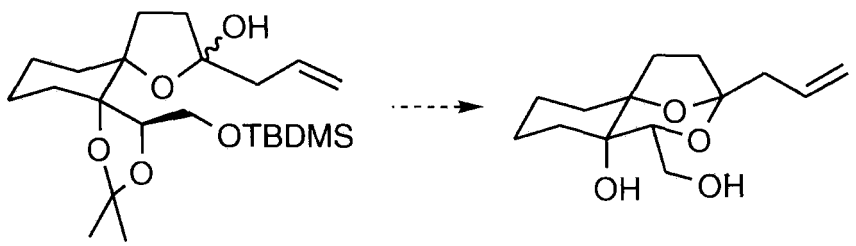
With the lactol (**144a**) in hand it remained to test the ketalisation step to afford a core analogue of the squalestatins. Armstrong[30] has carried out a number of experiments showing the possibility of forming bicyclic rings (**147**) other than the desired ketal (**148**) present in the bicyclic core of squalestatin 1, Scheme 2.7.1. Nicolaou has also noted this feature[28].



Reagents: i. $Hg(ClO_4)_2$, $CaCO_3$, 5:1 THF:H_2O, 30min; ii. 2% HCl, MeOH, RT, 10.5h

Scheme 2.7.1

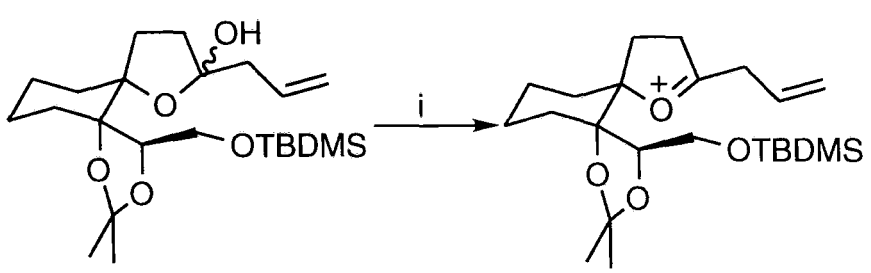
As shown above, it is possible to form a variety of 5 and 6-membered bicyclic rings but we undertook cyclisation studies on an analogue containing a cyclohexane ring. In our case, the cyclohexane ring would provide a conformationally more rigid core analogue. This group should serve to promote cyclisation to the desired product without the formation of isomeric side products due to restriction by the cyclohexane group. The desired product (**149**) also appeared to be the most thermodynamically feasible in our case, Scheme 2.7.2.



(144a) (149)

Scheme 2.7.2

It was hypothesised that, of the two possible lactone isomers formed (**141**), only one would have the correct stereochemistry to afford the core analogue. Furthermore, the unselective formation of two lactol isomers (**144**) upon allylation of the lactone (**141**), should not prove to be a problematic as they are anomers of each other. Interconversion of these anomers is possible during acid cyclisation of the isomeric mixture *via* an oxycarbenium ion intermediate (**150a**) and this should afford only one isomeric tricyclic structure, Figure 2.7.1.



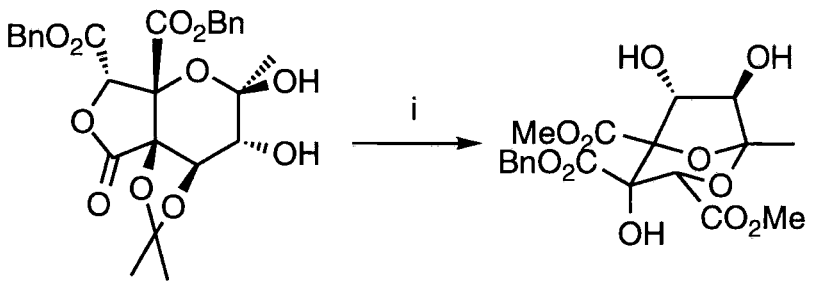
(144a) (150a)

Reagents: i. H_3O^+

Figure 2.7.1

The use of aqueous acid is a well known procedure for the deprotection of an acetal to its component diol and carbonyl.[50] In this case, concomitant cyclisation of the diol to the ketal (**149**) should then occur.

Nicolaou *et al*[28] used this procedure in the ketalisation step towards the total synthesis of squalestatin 1 where methanolic HCl was used to deprotect the acetonide (**151**) and catalyse the cyclisation step necessary to obtain the bicyclic core (**152**) of squalestatin 1, Scheme 2.7.3



(151) (152)

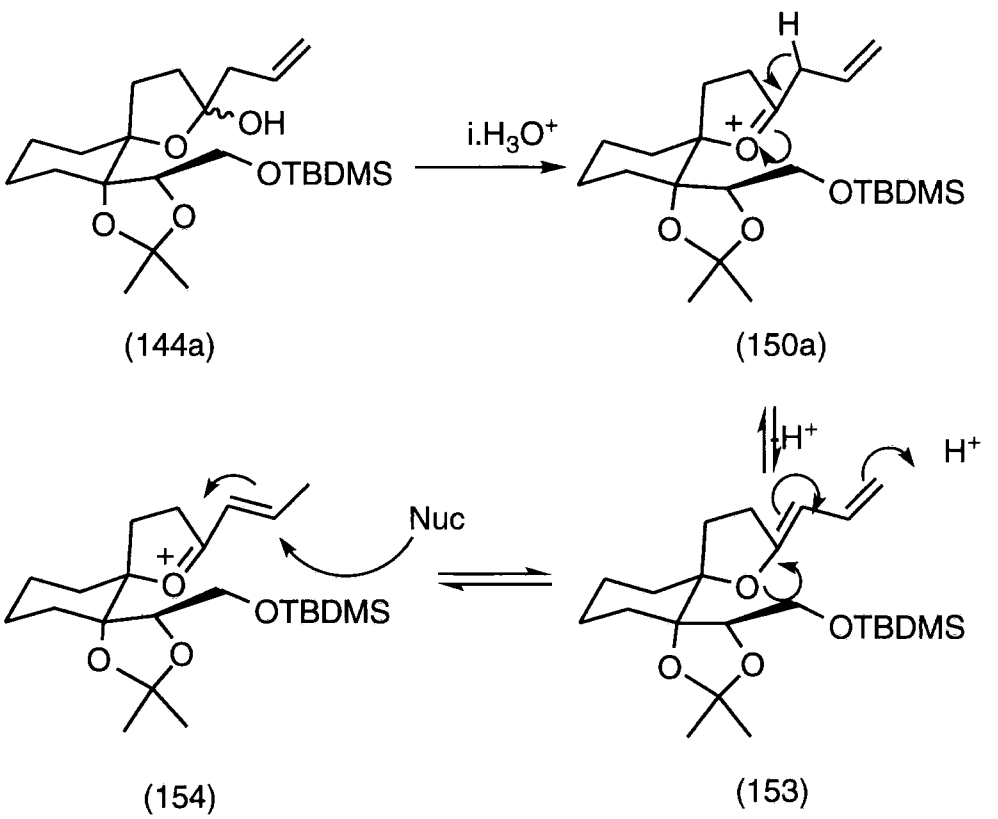
Reagents: i. 2% HCl in MeOH, 68°C, 18h

Scheme 2.7.3

Surprisingly, following this precedent, the lactol (**144a**) failed to undergo cyclisation to the desired core analogue (**149**). In particular, the formation of an intractable mixture of compounds occurred. Crude ^{1}H NMR showed the disappearance of a multiplet at δ5.89 corresponding the allylic proton and also two 3H singlets at δ0.90 and δ0.08 corresponding to the TBDMS group. The presence of two methyl peaks at δ1.42, δ1.34 (major isomer) suggested that the acetonide was unaffected by the reaction conditions. Variations of temperature did not produce any change in the crude ^{1}H NMR's obtained.

Consequently we opted to use TsOH to catalyse the deprotection of the acetal (**144a**). This again, resulted in the formation of decomposition products. The

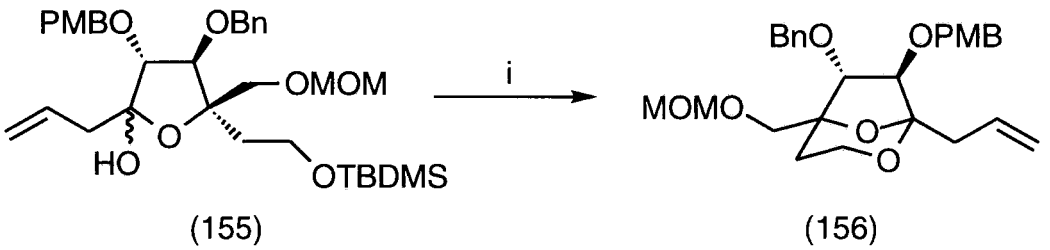
loss of the olefinc signals in the ^1H NMR suggested that migration of the double bond was somehow linked to the decomposition. This and the formation of many unisolable compounds could be due to that fact that the glycosidic alcohol may be lost as water, forming the oxonium ion (**150a**) which, in turn, would be susceptible to intermolecular additions, Scheme 2.7.4.



Scheme 2.7.4

Rizzacasa *et al*[51] have used a ketalisation step in the production of a core analogue of squalestatin 1, Scheme 2.7.5. Here, the C_1 side chain is also replaced by an allyl group (**155**), permitting further elaboration or extension of this chain. Deprotection of the TBDMS alcohol with concomitant cyclisation would afford the desired tricyclic analogue (**156**). A source of fluoride ions was used to remove the silyl ether protecting group and cyclisation occurred without the loss of the allylic moiety. It should, therefore, be possible to retain the allylic side

chain in our synthesis as long as strongly acidic conditions are avoided. This remains to be tested with compound (**144a**).



(155) (156)

Reagents: i. HF, MeCN, H_2O

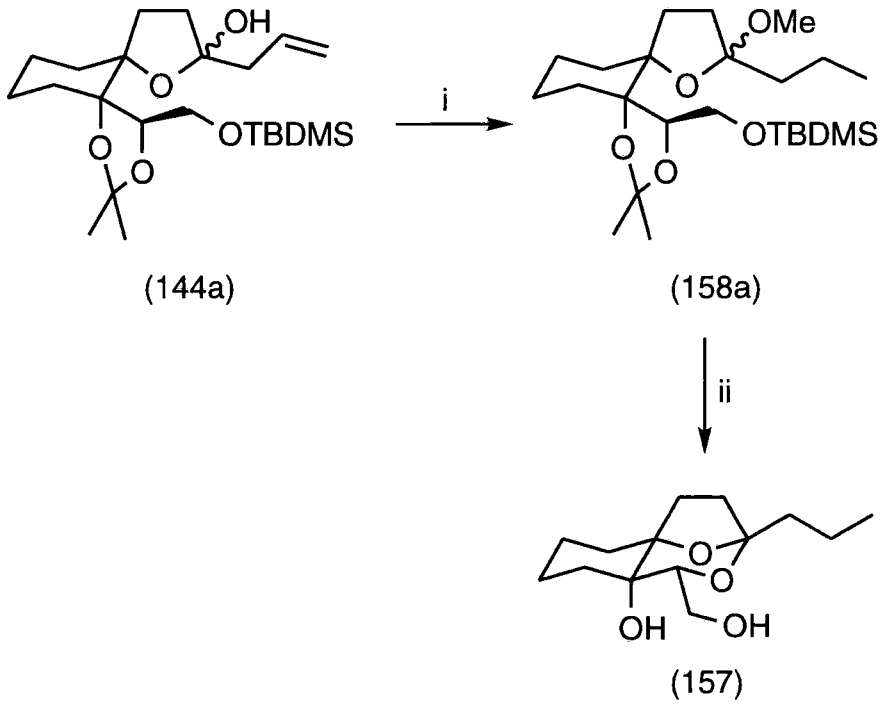
Scheme 2.7.5

The lack of cyclisation could also be due in part, to the fact that the cyclohexane ring restricts such a process. This would invalidate the retrosynthetic scheme as an accessible route to the core unit of the squalestatins. However, it seemed more probable that the allylic double bond was the problem so cyclisation studies were undertaken on a saturated analogue (*vide infra*).

2.7.2 Preparation of the Saturated Analogue (157)

A sample of the lactols (**144a**) was hydrogenated under standard conditions using methanol as solvent, producing the methyl glycoside (**158a**) in 94% yield, Scheme 2.7.6, in which the glycosidic alcohol had been displaced by methanol during the reaction. ^{1}H NMR showed the presence of a 1H triplet at δ4.12 corresponding to C<u>H</u>CH_2OSi and a 3H singlet at δ3.18 corresponding to the methoxy group. Disappearance of the olefinic multiplet at δ5.89 and the appearance of a triplet at δ1.46 corresponding to the methyl terminal of the propyl side chain proved that the double bond had been reduced. Cyclisation studies were carried out without further purification. Using the procedure reported by Nicolaou *et al* (methanolic HCl), the reaction was warmed to 40°C for 12h

whereupon tlc showed the formation of one product only. Purification by flach column chromatography afforded 37% of the desired core anaologue (**157**). ^{13}C NMR DEPT experiment showed the presence of one methyl, nine methylene and one methine carbon which corresponded exactly with the suggested structure. IR also showed the presence of hydroxyl functionality at 3690cm^{-1} and CI-MS showed a molecular ion peak at *m/z* 257. HRMS value also corrresponded with the calculated mass of 257.1753. The spectroscopic data corresponds well with that published for other analogues of the squalestatins.[31]



(144a) (158a) (157)

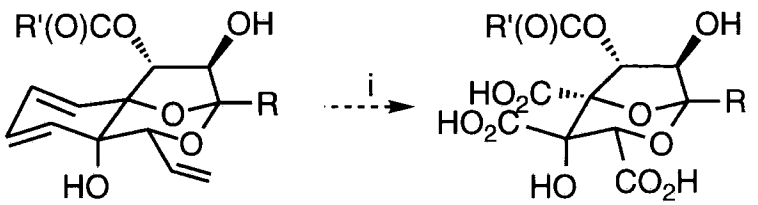
Reagents: i. $Pd(OH)_2$, MeOH, H_2; ii. 2% HCl, MeOH, 40°C

Scheme 2.7.6

As mentioned earlier, this procedure was also carried out on the other isomer (**142b**) obtained from allylation of (**61**). This procedure was successful up to the final step when the desired cyclisation did not occur and only decomposition was observed. It was this difference in outcome that enabled us to determine which isomer of (**142**) was which.

This result proved the viability of the retrosynthetic plan and studies towards the fully substituted core were commenced.

Obviously, the cyclohexane ring did not prevent cyclisation. Therefore, access to the fully substituted core through ozonolysis of a cyclohexadiene ring, Scheme 2.7.7, should not pose a problem in the ketalisation step although this moiety would be flatter and more rigid than the cyclohexane group.

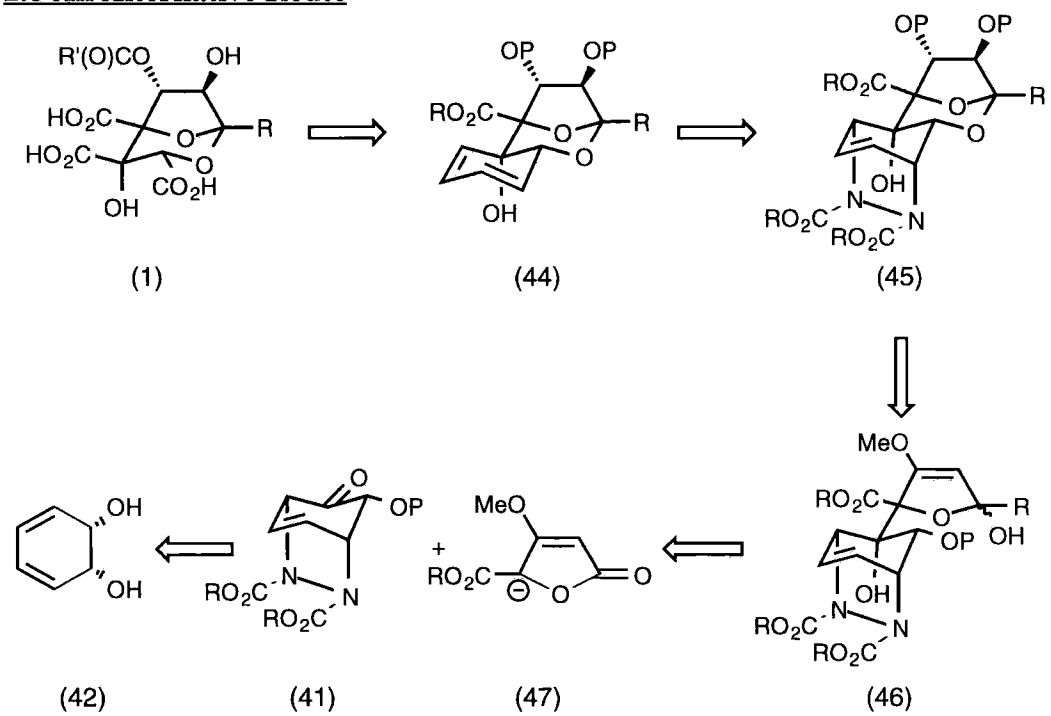


Reagent: i. O_3, DMS

Scheme 2.7.7

Using the same strategy as descibed previously, an analogous retrosynthetic plan was developed to give a more direct route to the core unit of the squalestatins.

2.8 An Alternative Route



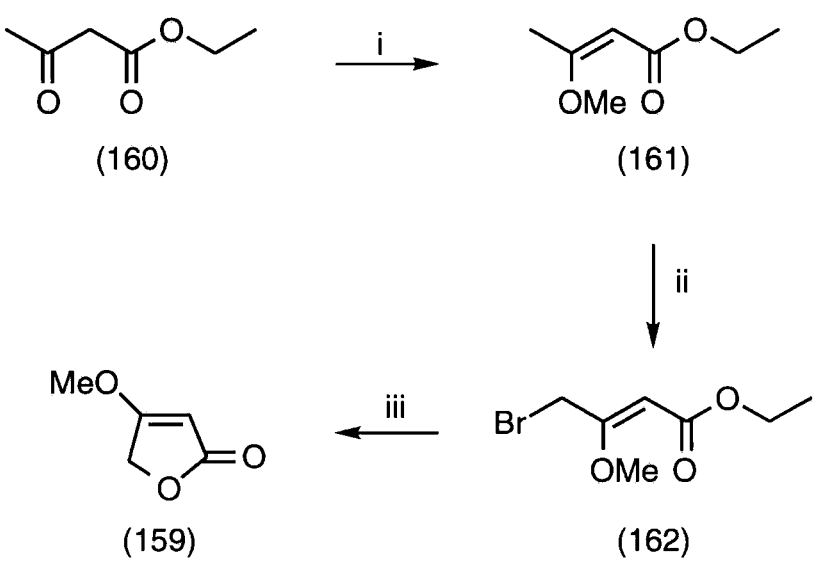
Scheme 2.8.1

2.8.1 Introduction

The previous route, Scheme 2.1.1, appeared to provide access to the core unit of squalestatin 1 but difficulty was encountered in the attempt to synthesise a spirolactone moiety, See Scheme 2.1.1. Although successful, the yield of this step was optimised to only 33% and obviously it was desirable to devise a similar route to the squalestatins without encountering the spirolactone synthesis. Using a similar strategy it was observed that the alternative tethering of the C(3) and C(4) olefins would afford a lactone (**46**) without the spirocyclic centre, Scheme 2.8.1.

Further disconnection generates a doubly convergent route from the tetronate derivative (**47**) and the α-alkoxy ketone (**41**). This could provide easier access to the core unit with a concomitant reduction in the number of synthetic steps.

The methodology was again tested using cyclohexane diol rather than the more expensive *cis*--cyclohexadiene diol (**42**). Synthesis of the tetronate precursor was carried out and is described below.



(160) (161) (162) (159)

Reagents: i. $HC(OMe)_3$, HCl; ii. NBS; iii. $ZnBr_2$

Scheme 2.8.2

2.8.2 Preparation of the lactone (163)

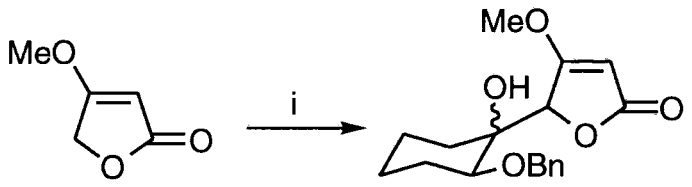
Formation of the tetronate (**159**) was accomplished using reported methodology[52], Scheme 2.8.2, through a three step procedure. All intermediate compounds were unstable, so were used immediately.

Trimethyl orthoformate was added to a solution of ethyl acetoacetate (**160**) in methanol and HCl catalysed the formation of ethyl 3-methoxybut-2-enoate (**161**) at 190°C. The mixture was immediately distilled through an efficient fractionating column to give the desired prodct (**161**), quantitatively. Subsequent bromination was achieved by the addition of *N*-bromosuccinimide at a temperature above 100°C. Distillation gave the desired bromide (**162**) in 95% yield. Lewis acid catalysed cyclisation of the bromide (**162**) gave the tetronate (**159**). The brown solid obtained was purified by recrystallisation from a mixture of ethyl acetate in petrol. A melting point of 67°C (lit. 65°C) was obtained and a 3H singlet at δ3.91 due to the methoxy group was apparent in the ^{1}H NMR. EI-MS also showed a molecular ion peak at *m/z* 114. This corresponded well with the published data.

The tetronate was then used in addition studies to 2-benzyloxy cyclohexanone (**48**). Deprotonation of the tetronate was achieved using the methodology of Pelter *et al*[75] by the careful addition of the tetronate (**159**) to a solution of butyl lithium in THF at -78°C. It was also discovered that by reversing the addition of the reagents, that is the addition of butyl lithium to the tetronate, resulted in other addition by-products.

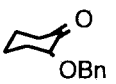
A solution of 2-benzyloxycyclohexanone (**48**) was then added to the dienolate and the reaction warmed to room temperature for 12h. Purification by chromatography afforded the desired product as a 1.3:1 mixture of separable isomers with a combined yield of 54%, Scheme 2.8.3. This was characterised by ^{1}H NMR which showed the appearance of two 1H singlets at δ5.12, δ5.06 (major isomer) and δ4.81, δ4.50 (minor isomer) corresponding to the two single protons attached to the tetronate group. A broad band in the IR spectrum at 3154cm^{-1} shows the presence of an OH group and ^{13}C NMR contains a carbonyl peak at

δ182.1 In addition, a substantial amount of 2-benzyloxycyclohexanone (**48**) (33%) was recovered. One reason for this could be that the deprotonated tetronate is extracting a proton from the α position of the ketone (**48**) forming the enolate. Aqueous work up would protonate this species recovering the ketone (**48**).



(159) (163)

Reagents: i. BuLi, -78°C, 4h, then **48**

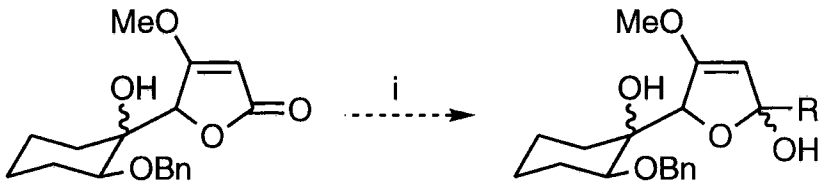


(48)

Scheme 2.8.3

The addition of the tetronate (**159**) to 2-benzyloxycyclohexanone (**48**) had been achieved and although the yield was only 53%, it was possible to recycle unreacted starting material to form large amounts of the desired alcohol. The next step in the synthesis would be to functionalise the carbonyl group through the addition of either organo lithium or magnesium reagents.

2.8.3 Functionalisation of the Tetronate



(163) (164)

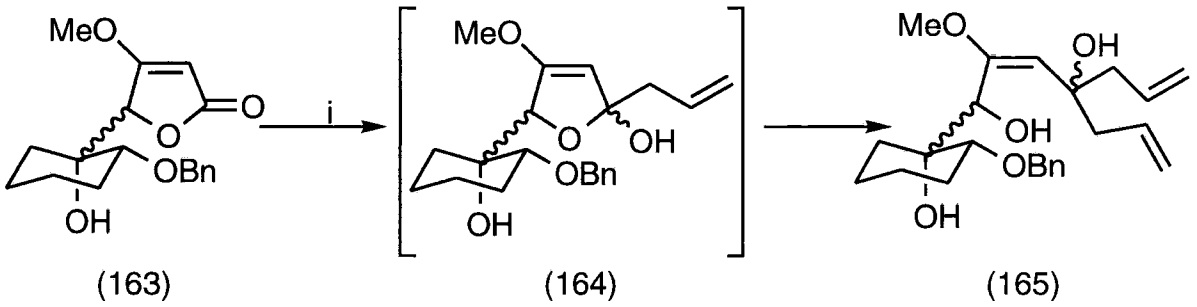
Reagents: i. RMgBr

Scheme 2.8.4

With the addition of the tetronate (**159**) to the α-alkoxy ketone (**48**) accomplished, the next step was to functionalise the tetronate carbonyl group, Scheme 2.8.4. This proved to be more difficult than was first imagined.

1.2 equivalents of allylmagnesium bromide was added to a solution of tetronate (**163**) in THF at -78°C. The solution was allowed to warm to room temperature for 4h and quenched. Purification by column chromatography resulted in the recovery of starting material (**163**) only. A white precipitate formed upon addition of the magnesium reagent. This could be due to quenching of the reagent by its abstraction of the alcohol proton. The reaction was repeated using 2.2 equivalents of allylmagnesium bromide. However, again only starting material was recovered. The reaction was carried out varying the temperature and solvent conditions.

Allylation did occur upon addition of 2 equivalents of magnesium reagent at 0°C. ^{1}H NMR showed a 2H multiplet at δ5.80, characteristic of an allylic proton. However, MS showed a molecular ion peak at *m/z* 403, suggesting the desired product had not been formed but instead the lactone had opened and double allylation (**165**) had occurred, Scheme 2.8.5.

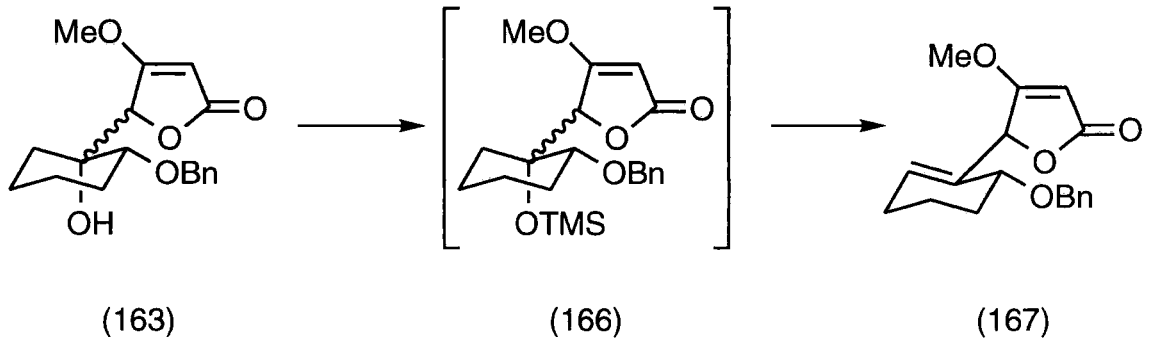


(163) (164) (165)

Reagents: i. AllylMgBr

Scheme 2.8.5

To overcome the difficulty of functionalising the tetronate (**163**), protection of the alcohol was attempted. The addition of TMS chloride and triethylamine to the tetronate (**163**) afforded only recovered starting material (**163**) upon purification by flash column. Similar reaction with TMS triflate and triethylamine did not afford the protected alcohol (**166**). Tlc showed complete consumption of starting material with the development of a single spot further up the plate. Analysis of spectral data showed the presence of two protons at δ6.94 and δ6.18 in the olefinic region as well as two 1H singlets at δ5.26 and δ4.70 suggesting that the two isolated protons attached to the tetronate part of the molecule were still intact. There were no characteristic singlets between δ0-1 typifying the presence of a trimethyl silyl protecting group. This suggested that elimination had occurred forming a double bond in the molecule. The fact that ^{1}H NMR showed two olefinic protons to be present suggested that elimination had occurred in the cyclohexane ring, Scheme 2.8.6.

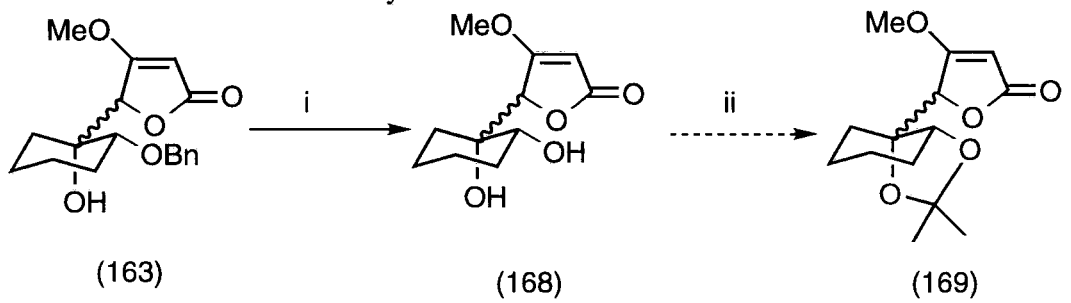


(163) (166) (167)

Reagents: i. TMSOTf, Et_3N or TMSCl, Et_3N

Scheme 2.8.6

It was thought that the lack of electrophilicity at the tetronate (**163**) carbonyl was due to the fact that it is a homologous ester and perhaps reduction of the double bond would allow for nucleophilic insertion. Palladium hydroxide was the catalyst used for the hydrogenation. This was the same method used for the cleavage of benzyl ethers and it was hoped that the reaction would be selective. This was indeed the case but it was the benzyl ether which was cleaved to form the diol (**168**), Scheme 2.8.7. Purification by flash chromatography afforded a white solid. ^1H NMR analysis showed the disappearance of the benzylic protons around δ5. EI-MS showed a molecular ion at *m/z* 229 proving the formation of the diol (**168**). Subsequent hydrogenation of the diol (**168**) did not afford reduction of the double bond. This was a little disappointing but there still remained the possibility of elaboration by protection of the diol as an acetal, Scheme 2.8.7. This work has yet to be carried out.

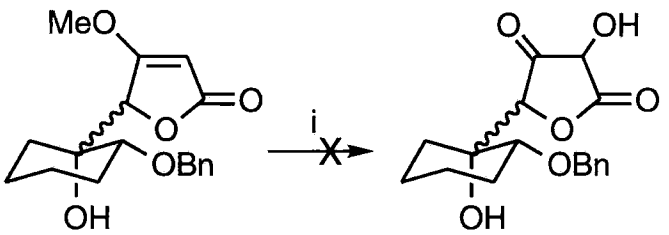


(163) (168) (169)

Reagents: i. $Pd(OH)_2$, MeOH; ii. 2, 2 dimethoxypropane, TFA

Scheme 2.8.7

Another method of manipulating the double bond of the tetronate was to oxidise the double bond to a diol. Attempts to form (**170**) were carried out using osmium(IV) oxide and NMO. The mixture was stirred for 18h but no reaction occurred and purification by column chromatography allowed complete recovery of starting material (**163**). Epoxidation of the double bond was also considered. The reagent chosen was mCPBA and this was added to a solution of tetronate in DCM. The mixture was stirred for 17h but tlc showed no reaction to have taken place, Scheme 2.8.8.

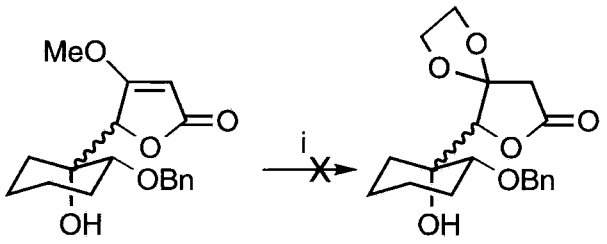


(163) (170)

Reagents: i. OsO_4, NMO, ^{t}butanol

Scheme 2.8.8

A search was undertaken to find alternative methods for protection of the alcohol. It was noted that the methoxy functionality of the tetronate (**163**) was a ketone equivalent and attempts to form the acetal at this centre were carried out. A mixture of tetronate (**163**) and ethylene glycol was refluxed in benzene with an acid catalyst for 27h. Purification by flash column chromatography afforded only recovered starting material (**163**), Scheme 2.8.9.



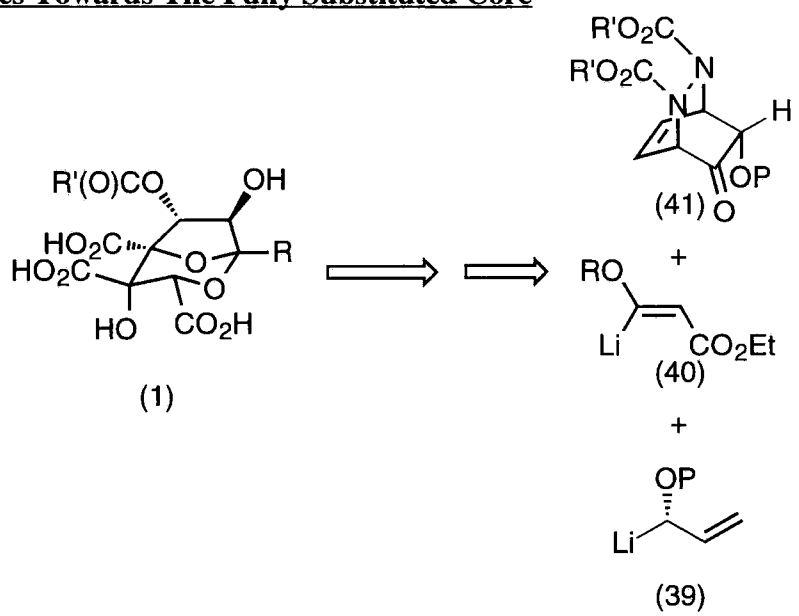
(163) (171)

Reagents: i. ethylene diol, TFA

Scheme 2.8.9

The lack of reactivity of the double bond is a setback to this approach, though is probably related to its conjugation to the lactone carbonyl group. Because of time restrictions further investigation was not possible, however the addition of nucleophilic oxidising agents (eg hydrogen peroxide) to the α,β-unsaturated system should be studied. In addition, the successful mono addition of a nucleophile to the carbonyl group should be examined further. So far, discussion has been centred around testing the viability of the two retrosynthetic plans. This was attempted using 2-benzyloxycyclohexanone and studies towards the fully substituted core starting with *cis*-cyclohexadiene diol (**42**) will now be discussed.

2.9 Studies Towards The Fully Substituted Core

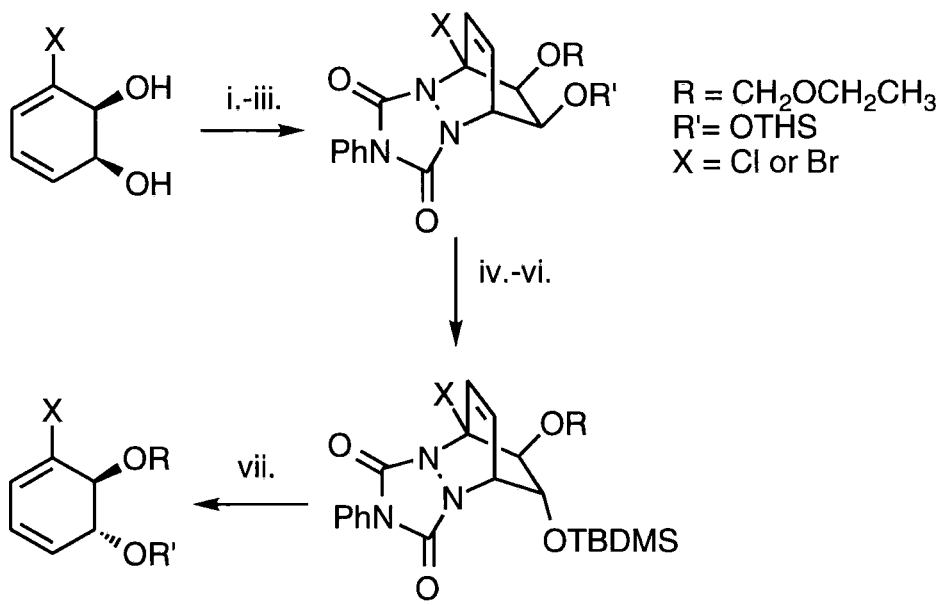


Scheme 2.9.1

2.9.1 Introduction

Retrosynthetic plan A (see Section 2.1.1) was shown to be viable through the synthesis of a core analogue of the squalestatins. This synthesis was tested by using a cyclohexane diol model as a starting material rather than the more expensive *cis*-cyclohexadiene diol (**42**) needed for elaboration to the full substituted core unit. *Cis*-cyclohexadiene diol (**42**) is easily obtained from an oxidation process of benzene using *Pseudomonas putida.*

The retrosynthetic scheme involves the protection of the diene moiety through a Diels Alder reaction with diazodicarboxylate (**41**), Scheme 2.9.1. However, a recent report published by Hudlicky[76] showed that the same diene could be efficiently protected by Diels Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (**172**), Scheme 2.9.2.



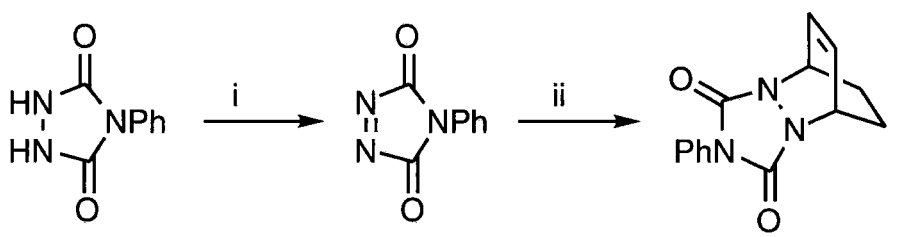
Reagents: i. THSCl, Imidazole, 0°C; ii. $ClCH_2OCH_2CH_3$, $EtN(iPr)_2$, 0°C; iii. 4-phenyl-1,2,4-triazoline-3,5-dione, -60°C; iv. TBAF -55°C; v. Tf_2O, pyridine, 0°C; CsOAc, 18-crown-6, 70°C; K_2CO_3; vi. TBSOTf, 2,6-lutidine, 0°C; vii. 2N KOH

Scheme 2.9.2

The triazoline group was chosen for the cycloaddition step as the reaction is easily reversed under basic conditions to reveal the diene. This was a crucial requirement for the dienophile to be used in our synthetic plan.

2.9.2 Preparation of the Diels Alder adduct

The dienophile (**172**) was easily prepared upon the addition of dinitrogen tetroxide to 4-phenyl urazole (**173**)[77], Scheme 2.9.3. Red crystals immediately formed and further purification, *via* sublimation, could be carried out but normally was not necessary. IR showed the appearance of a band at 1624cm^{-1} corresponding to the triazoline double bond. In a model study, Diels Alder studies were carried out with the reaction of the triazolinone (**172**) with cyclohexadiene. In this, the addition of 1,4 cyclohexadiene to the triazolinone (**172**) was found to produce the Diels Alder adduct (**174**) at -78°C almost immediately, Scheme 2.9.3. A colour change from red to yellow was observed and a yield of 82% was obtained after recrystallisation from ethyl acetate and petrol. ^{1}H NMR studies showed the white crystals to contain two olefinic protons at δ6.51 indicating that the desired Diels Alder reaction had taken place. Furthermore, CI-MS showed a large parent molecular ion peak at 256 and elemental analysis was found to be correct for the desired structure (**174**).

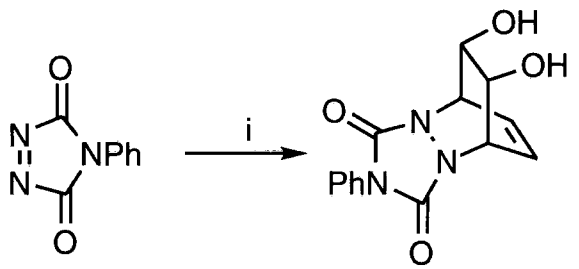


(173) (172) (174)

Reagents: i. N_2O_4, O°C; ii. 1, 4 cyclohexadiene, -40°C

Scheme 2.9.3

With the success of the previous reaction it was possible for proceed with the addition of the triazoline group to *cis*-cyclohexadiene diol (**42**). This was achieved using the previous method. *Cis*-cyclohexadiene diol (**42**) was much less reactive than the equivalent diene but addition occurred upon raising the temperature of the reaction to -40°C. The solid (**175**) was purified by flash column chromatography but proved to be very insoluble in most organic solvents. This could possibly explain the low yield of 23%. Spectral data was obtained using DMSO as a deuterated solvent.



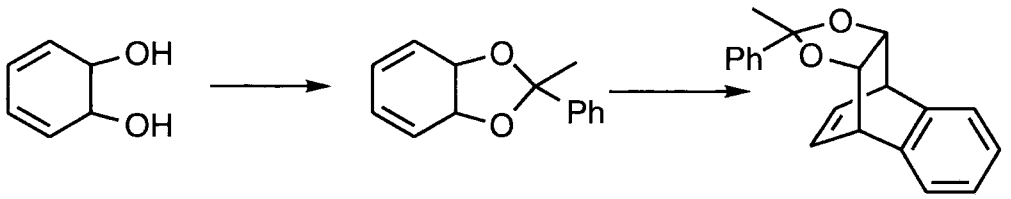
(172) (175)

Reagents: i. *cis*-cyclohexadiene-2,3-diol (**41**), -40°C

Scheme 2.9.4

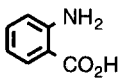
The problem of low yield and the lack of solubility was solved by first protecting the diol as an acetal before carrying out the Diels Alder reaction.

A recent paper by Grubbs *et al*[78] shows the preparation of benzobarrelenes using cyclohexadiene diol. Here, *cis*-cyclohexadiene-2,3-diol (**42**) is protected *in situ* by the formation of an acetal (**176**) before reaction with a benzyne dienophile formed from (**177**), Scheme 2.9.5



(42) (176) (178)

Reagents: i. $PhCH(OMe)_2$, PTSA; ii. anthrilic acid (**177**), isoamyl nitrite



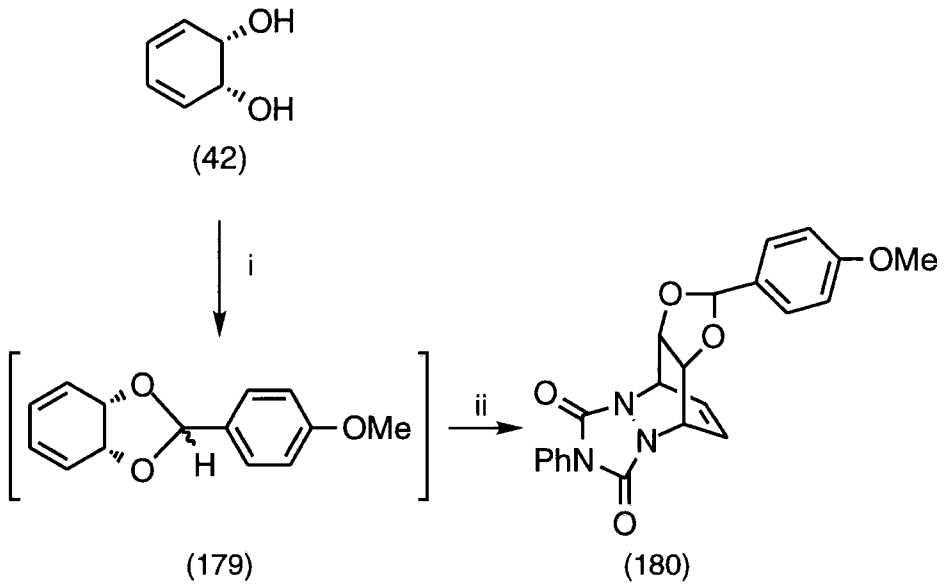
(177)

Scheme 2.9.5

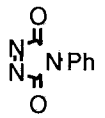
Similar methodology to that reported by Grubbs was used to form an acetal from *para*-anisaldehyde dimethyl acetal. *para*-Anisaldehyde dimethyl acetal was chosen for the fact that the acetal formed is more reactive to cleavage than the benzaldehyde equivalent. Following reductive cleavage, the alcohol could subsequently be oxidised to a ketone allowing nucleophilic insertion of the C(2) or C(3) precursor of the synthetic scheme.

Initially, *p*-anisaldehyde dimethyl acetal was added to *cis* -cyclohexadiene-2,3-diol (**42**) in the presence of acid. The reaction was carried out at room temperature but this resulted in decomposition. The reaction was followed by ^1H NMR and showed the loss of a multiplet at δ6.00 in the diol, corresponding to the proton on the alcohol bearing carbon. This was due to the fact that the *cis*-cyclohexadiene-2,3-diol (**42**) is sensitive to acid and easily eliminates water, re-aromatising to form phenol. The reaction was repeated at -78°C but it wasn't until the mixture was warmed to -40°C that reaction took place. ^1H NMR showed the development of two 2H doublets at δ7.80 and δ6.95 and a singlet at δ5.35. This was compared with the ^1H NMR of *para*-anisaldehyde. The acetal (**179**) was not isolated but the mixture was quenched by the addition of excess $NaHCO_3$ before

addition of the triazoline dienophile (**172**). Again, the Diels Alder reaction was carried out at -40°C and monitored by ^{1}H NMR, Scheme 2.9.6.



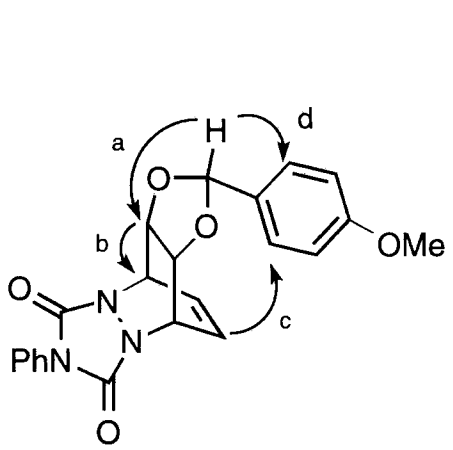
Reagents: i.*para*-anisaldehyde dimethyl acetal, PTSA, -40°C; ii. **172**, -40°C



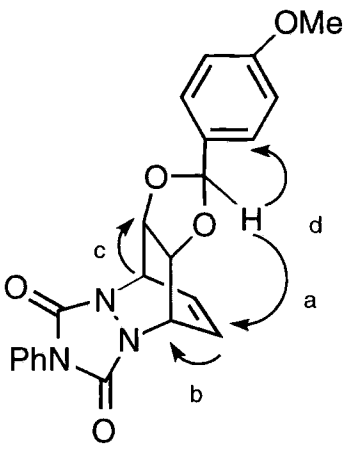
(172)

Scheme 2.9.6

Purification of the Diels Alder adduct (**180**) by flash column chromatography afforded a 1.3:1 mixture of isomers in a 53% yield. Again the products formed were only sparingly soluble in ethyl acetate and yields were increased to 60% upon purification by recrystallisation. NOE and COSY showed that only two isomers were formed. There are a number of possible isomers but analysis of spectral data suggested that the isomers were formed at the acetal centre rather than the formation of *exo* and *endo* Diels Alder mixtures, Scheme 2.9.7.



major isomer (**180**)

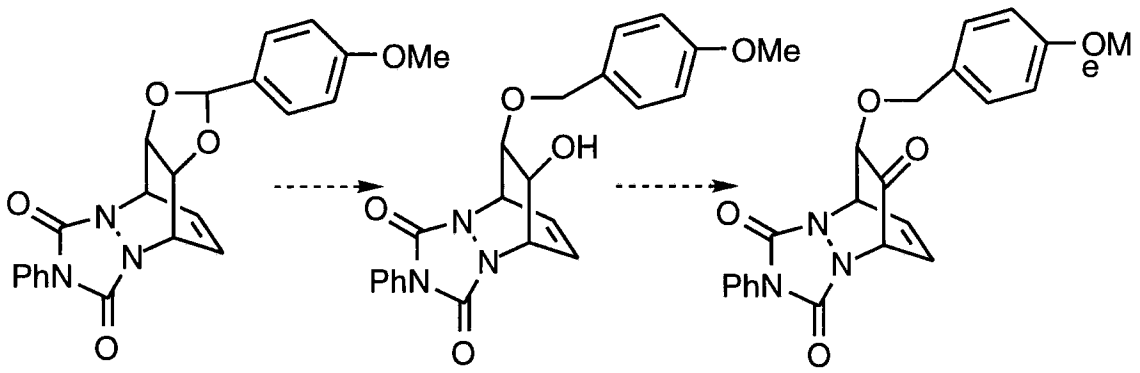


minor isomer (**180**)

From analysis of NOE data

Scheme 2.9.7

Manipulation of the acetal (**180**) to afford deprotection of one alcohol (**181**) was desirable so that oxidation to the carbonyl (**182**) could be carried out and subsequent manipulation to the spiroenone could be attempted, Scheme 2.9.8.

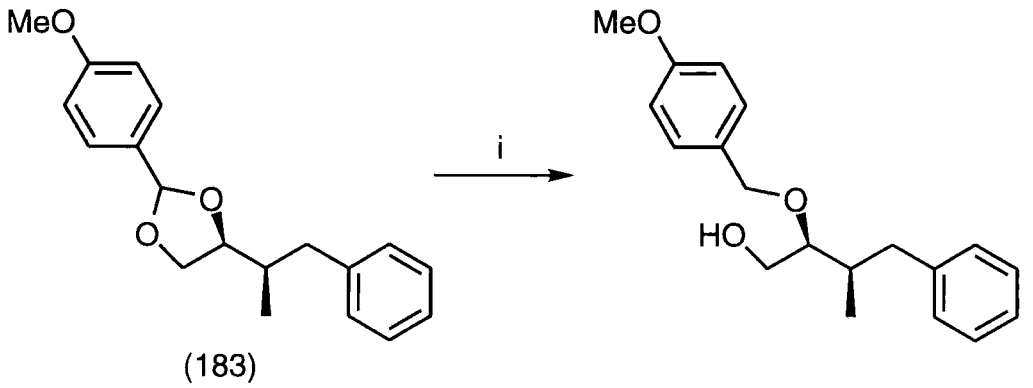


(180) (181) (182)

Scheme 2.9.8

2.9.3 Attempted Actetal Cleavage

Nicolaou *et al* [28, 79] showed that it was possible to cleave a similar acetal (**183**) by use of DIBAL, Scheme 2.9.9.



(183)

Reagents: i. 1.2eq DIBAL, -78 - -22°C, 2h

Scheme 2.9.9

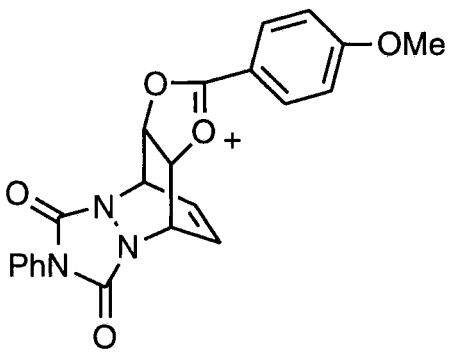
This reaction was therefore carried out with the acetal (**180**) we had prepared earlier. The substrate cleaved by Nicolaou needed temperatures between -78 - -22°C for the reaction to occur. The reaction conditions were varied extensively but without success. Table 2.9.1 shows the different attempts carried out to cleave the acetal with DIBAL.

Nucleophile	**Lewis Acid**	**Temperature (°C)**	**Result**
1eq DIBAL	-	-78	No reaction
1.1eq DIBAL	-	0	No reaction
2eq DIBAL	-	RT	No reaction
1.1eq Et_3SiH	1.1eq $TiCl_4$	-78 - 0	No reaction
1.1eq Et_3SiH	1.1eq $BF_3.OEt_2$	-78 - 0	No reaction
1.1eq Et_3SiH	2.5eq $BF_3.OEt_2$	0 - RT	No reaction
10eq Et_3SiH	2.5eq $BF_3.OEt_2$	0 - RT	No reaction
10eq Me_3SiH	2.5eq $BF_3.OEt_2$	0 - RT	No reaction
1.1eq AlH_2Cl	-	0 - RT	No reaction
1.1eq $ZnBH_4$	-	0 - RT	No reaction

Table 2.9.1

Work is currently being carried out within our group to cleave acetals asymmetrically, therefore distinguishing between the two alcohol moieties. This route involves Lewis acid formation of an oxonium ion followed by nucleophilic cleavage to the alcohol and ether.

The first Lewis acid to be used was titanium(IV) chloride with triethyl silane as the external nucleophile. A solution of titanium(IV) chloride was added to a solution of acetal in DCM. After 10min triethylsilane was added and the reaction stirred for 6h. Tlc showed that no reaction had occurred and purification by column chromatography allowed complete recovery of starting material (**180**). The reaction was repeated varying the temperature but without success. Titanium(IV) chloride was replaced with boron trifluoride and the reaction carried out. Again, the temperature was varied but no products were obtained. Increasing the amount of Lewis acid to 2.5 and 10 equivalents was also considered but no products were observed. It was noted, however, that, upon addition of the boron Lewis acid to a mixture of isomers, only one isomer was ever recovered. Addition of $BF_3.OEt_2$ to a 1:1 mixture of acetal isomers, without the addition of a nucleophile, confirmed this observation. This suggested that the oxonium ion (**184**) was indeed forming and isomerisation was taking place, Figure 2.9.1.



(184)

Figure 2.9.1

This result meant that the Lewis acid had formed the oxonium ion (**184**) but nucleophilic attack was not taking place. Addition of 10 equivalents of triethylsilane was then carried out but again only starting material was recovered. A more reactive form of silane is trimethylsilane and reactions were carried out using this nucleophile but to no avail.

A typical procedure to cleave acetals is the use of aluminium dihydrogen chloride[53]. This reducing agent is prepared from the addition of lithium aluminium hydride to aluminium trichloride[81]. It was possible to make aluminium dihydrogen chloride *in situ* but unreacted lithium aluminium hydride could reduce the amide bonds present in the molecule (**180**). The reducing agent was therefore isolated before cleavage of the acetal (**180**) was attempted. Aluminium dihydrogen chloride was added to a solution of acetal in DCM and stirred for 10h. Purification by flash column chromatography yielded only recovered acetal. Another method for the cleavage of acetals is through the use of zinc borohydride[82], prepared from the addition of zinc chloride to sodium borohydride.[83] The use of this reagent with TMS chloride is very effective in the reductive cleavage of acetals under mild conditions. The zinc reagent was added to a solution of acetal (**180**) closely followed by the addition of TMS chloride at 0°C. The reaction was stirred at this temperature for 4h but no reaction occurred so the mixture was warmed to room temperature but no products were observed upon purification by flash column chromatography. Cerium ammonium nitrate is also a well known reagent for the ring opening of acetals.[84] To a solution of the acetal (**180**) in acetonitrile and water (4:1) was added ceric ammonium nitrate at 0°C. The mixture was stirred for 15h however cleavage was not observed. The result of these experiments show reductive cleavage of the acetal (**180**) to be unsuccessful. An attempt to cleave the acetal (**180**) by an oxidative method was therefore carried out. Ozonolysis has been known to react smoothly with acetals to give the corresponding esters.[85] A solution of acetal (**180**) in ethyl actetate was ozonised for 10min at -78°C before dimethyl sulphide was added and the

resulting mixture warmed to room temperature. However decomposition occurred. The Diels Alder adduct (**180**) contains a strained double bond and it was this moiety that was found to be the more reactive resulting in decomposition products. ^{1}H NMR showed the presence of a singlet at δ8.74 sugesting that the double bond had been oxidised to give an aldehyde.

A report by Seeley *et al*[86] discussed the cleavage of acetals by the use of *N*-bromosuccinimide and water. One drop of hydrobromic acid was added to a mixture of NBS and water at 0°C before addition of the acetal (**180**). After 2h, the mixture was still red in colour so $NaHCO_3$ was added and the mixture stirred at room temperature for 23h. No product formation was observed and the acetal was recovered quantitatively by flash column chromatography. Although cleavage of the acetal (**180**) proved to be problematic, this could be overcome by considering the use of other acetals as protection for the diol moiety.

2.1.0 Conclusion

Model studies using 2-benzyloxycyclohexanone have shown that retrosynthetic plan A, Scheme 2.1.1, is a viable route to the core unit of the squalestatins. Work undertaken towards the fully substituted core has been slightly hindered due to the fact that the acetal (**180**) has proven difficult to cleave. Perhaps the use of a different protecting group for the *cis*-cyclohexadiene 2,3 diol would alleviate the problem. There is precedent in the literature for the preparation of the acetonide.[76] The *para*-methoxybenzylidene functionality was chosen due to the fact that it is more reactive to nucleophiles allowing cleavage to occur readily, however, this has proven not to be the case with our substrate. Alternatively, chlorobenzene could be used as a substrate for *Pseudomonas putida* as again there is literature precedent for the selective protection of each alcohol.[76]

With cleavage achieved, oxidation to the ketone should allow further addition and elaboration. Addition of an α-alkoxylithium equivalent could be carried out. The *para* methoxybenzylidene group could aid stereocontrol allowing selective addition to form the *syn* product. Alternatively, the propionic acid (**63**) could be

added to the ketone forming the spirolactone. Further reduction of the *para* methoxybenzyl ether to afford the alcohol, followed by oxidation to the ketone would enable elaboration of this carbonyl group.

Functionalisation of the spirolactone would afford a variety of analogues at a late stage in the synthesis.

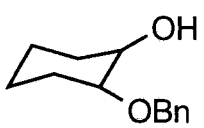
Chapter 3: Experimental

3.1 Introduction

All reactions were undertaken in an inert gas atmosphere of dry nitrogen or argon in pre dried glassware. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Gemini 200 (^{1}H at 199.975 MHz, ^{13}C at 50.289 MHz), Varian XL-200 (^{1}H at 200.057 MHz) and Varian VXR-400(s) (^{1}H at 399.952 MHz, ^{13}C at 100.577 MHz), spectrometers with $CDCl_3$ as solvent ($\delta = 7.26$) and are recorded in ppm (δ units) downfield of tetramethylsilane (δ=0). Infra Red (IR) spectra were recorded on a Perkin Elmer FT-IR 1720X spectrometer. Low resolution mass spectra were recorded on a VG Analytical 7070E organic mass spectrometer, and gas chromatography - mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph connected to a VG mass Lab trio 1000. Flash Column Chromatography was performed on silica (60-240 mesh). Melting points were determined using Gallenkamp melting point apparatus and are uncorrected. All solvents were distilled prior to use following standard protocols. Petroleum ethers refer to the fraction boiling in the 40-60°C range unless otherwise stated. Butyl lithium used was 1.4M n-butyl lithium solution in hexanes unless otherwise stated. All Grignard reagents used were 1.4M solutions in ether unless otherwise stated.

3.2 Experimental Detail

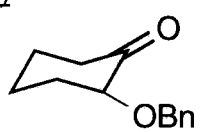
2-benzyloxycyclohexanol[34] (**54**)



Benzyl alcohol (9.50ml, 92mmol) was added to a stirred suspension of sodium hydride (4.90g of a 60% dispersion in oil, 122mmol) in DMF (100ml) at 0°C. After addition the mixture was stirred under argon at room temperature for 60min. Cyclohexene oxide (**53**) (10.40ml, 102mmol) was then added and the

solution was heated at 80°C for 16h. When tlc (12:1, petrol:ethyl acetate) indicated complete consumption of benzyl alcohol the reaction was quenched with water and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford a yellow oil which, when purified by fractional distillation, yielded 2-benzyloxycyclohexanol (**54**) (17.8g, 94.3%) ; b.p. 116-118°C/0.15mmHg (116°C, 0.15mmHg[lit.]); ν_{max} ($CDCl_3$ solution) 3430 (OH), 2932, 2860, 1668, 1452, 1075cm^{-1}; $\delta(^1H)$(200MHz) 7.28-7.24 (5H, m, $C_6\underline{H}_5$), 4.65 & 4.48 (1H each, AB system J = 11.6Hz, $OC\underline{H}_2C_6H_5$), 3.48-3.32 (1H, m, $C\underline{H}OCH_2C_6H_5$), 3.18-3.03 (1H, m, $C\underline{H}OH$), 2.65 (1H, broad, $O\underline{H}$), 2.10-2.00 (1H, m, $\underline{H}CHCHOCH_2C_6H_5$), 1.98-1.85 (1H, m, $\underline{H}CHCHOCH_2C_6H_5$), 1.68-1.55 (2H, m, $C\underline{H}_2CHOH$), 1.27-1.05 (4H, m, $C\underline{H}_2C\underline{H}_2CH_2CHOH$); $\delta(^{13}C)$(50MHz) 139.1 (Ar), 129.0 (Ar), 128.3 (Ar), 128.2 (Ar), 84.0, 74.3, 71.3, 32.6, 29.7, 24.7, 24.5; MS (CI, (NH_3)) *m/z:*224 ($M+NH_4^+$, 100%), 207 (MH^+, 9), 108 ($C_6H_5CH_2OH^+$, 87), 91 ($-CH_2C_6H_5$, 57).

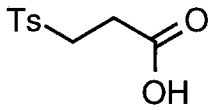
2-benzyloxycyclohexanone[35] (**48**)



Dimethyl sulphoxide (0.82ml, 11.65mmol) in DCM (3ml) was added dropwise, *via* cannula, to a solution of oxalyl chloride (0.51ml, 5.825mmol) in DCM (40ml) cooled to -78°C. After stirring for 10min a solution of the alcohol (**54**) (1.00g, 4.85mmol) in DCM (30ml) was added. The reaction mixture was stirred for a further 50min before triethylamine (3.44ml, 24.27mmol) was added and the reaction allowed to warm to room temperature. The resultant mixture was diluted with DCM and washed with 2M HCl, sat. NH_4Cl, dried ($MgSO_4$) and concentrated to afford a yellow oil which was purified by flash column chromatography (8:1, petrol:ether) producing 0.89g (90.3%) of the desired ketone. ν_{max} ($CDCl_3$ solution) 3031, 2866, 1723, 1497, 1112cm^{-1}; $\delta(^1H)$(200MHz) 7.45-7.25 (5H, m, $C_6\underline{H}_5$), 4.78 & 4.49 (1H each, AB system, J =

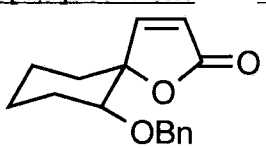
11.7Hz, $OC\underline{H}_2C_6H_5$), 3.9 (1H, m, $CH_2C\underline{H}OCH_2C_6H_5$), 2.6-1.6 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CO$); $\delta(^{13}C)$(50MHz) 210.6 (C=O ketone), 138.5 (Ar), 128.9 (Ar), 128.2 (Ar), 128.2 (Ar), 82.2, 72.1, 41.1, 35.1, 28.1, 23.6; MS (CI, (NH_3)) *m/z*:222 ($M+NH_4^+$, 94%), 108 ($C_6H_5CH_2OH^+$, 100).

3-(*para*-tolylsulphonyl)propionic acid[40] (**63**)



A suspension of sodium *para*-toluene sulphinate dihydrate (10.50g, 50mmol) and acrylic acid (3.57ml, 50mmol) in ethanol (60ml) was stirred at room temperature for 12h to afford white crystals. These crystals were dissolved in water, acidified to pH4 and the solution was extracted with ethyl acetate. The combined organic extracts were then dried ($MgSO_4$) and concentrated to obtain white crystals of the desired acid. Purification by recrystallisation in DCM/hexane produced a yield of 7.4g (70%) of the desired white crystals. ν_{max} ($CDCl_3$ solution) 3687, 3048, 2359, 1493, 1204, 1184cm^{-1}; $\delta(^1H)$(200MHz) 7.79 (2H, d, J = 8Hz, $C_6\underline{H}_4$), 7.38 (2H, d, J = 8Hz, $C_6\underline{H}_4$), 3.35 (2H, t, J = 8Hz, $C\underline{H}_2CH_2CO_2H$), 2.73 (2H, t, J = 8Hz, $C\underline{H}_2CO_2H$), 2.42 (3H, s, $C\underline{H}_3$); $\delta(^{13}C)$(50MHz) 176.1 (C=O acid), 143.2, (Ar) 135.7, (Ar) 130.6 (Ar), 128.7 (Ar), 51.7, 28.2, 22.2; MS (CI, (NH_3)) *m/z* 246 ($M+NH_4^+$, 100%), 139 ($CH_3C_6H_4SO$, 22).

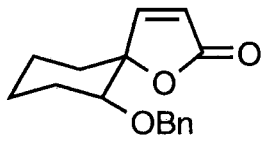
6-benzyloxy-2-oxa-3-oxo-spiro[4,5]dec-4-ene[39, 41] (**49**)



A solution of 3-(*para*-tolylsulphonyl)propionic acid (5.85g, 26.68mmol) in THF (300ml) was stirred at -78°C and butyl lithium (33.43ml, 53.51mmol) was slowly added. The resulting yellow solution was stirred for 1h before 2-benzyloxycyclohexanone (**48**) (4.37g, 21.40mmol) in THF (50ml) was added and

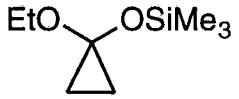
the mixture allowed to warm to -40°C for 16h. Trifluoroacetic anhydride (7.18ml, 51.36mmol) was then added and the solution stirred for 4h at -30°C. The mixture was quenched with sat. $NaHCO_3$, extracted with ether, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (1:1, petrol: ether) gave 4.26g (48%) of tosyl diastereoisomers (**69**) and 2.18g (50%) recovered 2-benzyloxycyclohexanone (**48**). This mixture (**69**) was then redissolved in THF (100ml) and added to a 1M solution of LDA (12.35ml, 12.35mmol) in THF at -78°C under argon and subsequently warmed to room temperature. After stirring for a further 12h, the reaction was quenched with sat. NH_4Cl, extracted with ether, washed with sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated to yield a yellow oil, which was purified by flash column chromatography (3:1, petrol : ether) resulting in 1.75g (66%) yield of two separable diastereoisomers of the desired oil (**49**). The overall yield of the two steps was calculated to be 33%. **Major isomer:** ν_{max} ($CDCl_3$ solution) 2937, 2859, 1756, 1496, 1453, 1262, 1207, 1160, 1097cm^{-1}; $\delta(^1H)$(400MHz) 7.56 (1H, d, J = 5.6Hz, C<u>H</u>=CHCO), 7.29-7.19 (5H, m, C_6<u>H_5</u>), 6.02 (1H, d, J = 5.6Hz, CH=C<u>H</u>CO), 4.52 & 4.39 (1H each, AB system, J = 12Hz, OC<u>H_2</u>C_6H_5), 3.41 (1H, m, <u>H</u>COC$H_2C_6H_5$), 1.92-1.17 (8H, m, (C<u>H_2</u>)$_4$); $\delta(^{13}C)$(100MHz) 171.3 (C=O), 157.4, 136.9 (Ar), 127.3 (Ar), 126.7 (Ar), 126.6 (Ar), 120.5, 89.3, 77.8, 70.9, 31.3, 26.7, 21.2, 19.9; MS (CI, (NH_3)) *m/z* 276 ($M+NH4^+$, 100%), 259 (MH^+, 51); HRMS (CI, (NH_3)) $C_{16}H_{22}NO_3$ *m/z* Calc. 276.1600; Found 276.1600. **Minor isomer:** ν_{max} ($CDCl_3$ solution) 2933, 2867, 1767, 1494, 1450, 1350, 1267, 1206, 1133, 1100cm^{-1}; $\delta(^1H)$(400MHz) 7.24-7.14 (6H, m, C_6<u>H_5</u>, C<u>H</u>=CHCO), 5.87 (1H, d, J = 5.6Hz, CH=C<u>H</u>C=O), 4.46 & 4.36 (1H each, AB system, J = 12Hz, OC<u>H_2</u>C_6H_5), 3.34 (1H, dd, J_1 = 10.4Hz, J_2 = 4.4Hz, <u>H</u>COC$H_2C_6H_5$), 1.91-1.12 (8H, m, -(C<u>H_2</u>)$_4$-); $\delta(^{13}C)$(100MHz) 172.6 (C=O), 157.8, 138.0 (Ar), 128.1 (Ar), 127.4 (Ar), 127.3 (Ar), 121.3, 90.2, 77.2, 71.1, 33.8, 27.7, 23.2, 21.4; MS (CI, (NH_3)) *m/z* 276 ($M+NH4^+$, 100%), 259 (MH^+, 57); HRMS (CI, (NH_3)) $C_{16}H_{22}NO_3$ *m/z* Calc. 276.1600; Found 276.1600.

Attempted preparation of 6-benzyloxy-2-oxa-3-oxo-spiro<4.5>dec-4-ene[42] (**49**)



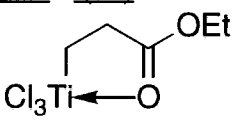
A solution of 3-(*para*-toylsulphonyl)propionic acid (**63**) (0.69g, 3.00mmol) in THF (10ml) was stirred at -78°C and butyl lithium (3.91ml, 6.00mmol) was added. The resulting yellow solution was stirred for 1h whereupon anhydrous cerium(III) chloride (2.19g, 6.00mmol) was added and the solution stirred for a further 1h. A solution of ketone (**48**) (0.50g, 2.45mmol) in THF (2ml) was then cooled to -78°C and added *via* cannula to the reaction mixture. The resulting solution was allowed to warm to -40°C and stirred for 30h before trifluoroacetic anhydride (0.85ml, 6.00mmol) was added and the mixture warmed to -30°C for 4h. The mixture was quenched with sat. $NaHCO_3$, extracted with ether, dried ($MgSO_4$) and concentrated to afford only starting material (**48**).

1-Ethoxy-1-trimethylsilyloxycyclopropane[49] (**76**)



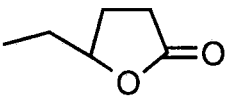
A suspension of sodium sand (0.37g, 16.10mmol) in ether (2ml) and trimethylsilyl chloride (0.51ml, 4.00mmol) was stirred vigorously. Ethyl 3-chloropropionate (**78**) (0.50ml, 3.72mmol) was added at such a rate that continuous refluxing occurred. The mixture was stirred for a further 45min and filtered *in vacuo*. The filtrate was concentrated and purified by distillation (b.p. 44-45°C, 12mmHg) to produce a colourless liquid (0.56g, 87.4%). ν_{max} ($CDCl_3$ solution) 2975, 1436, 1310, 1225, 1062, 1012cm^{-1}; $\delta(^1H)$(200MHz) 3.66 (2H, q, J = 7.1Hz, $OC\underline{H}_2CH_3$), 1.17 (3H, t, J = 7.1Hz, $OCH_2C\underline{H}_3$), 0.87 (4H, m, $C\underline{H}_2C\underline{H}_2$), 0.18 (9H, s, $Si(C\underline{H}_3)_3$); $\delta(^{13}C)$(50MHz) 87.3, 62.6, 16.3, 14.2, 1.0; MS (EI) *m/z* 101 (MH^+, 15%), 73 ($Si(CH_3)_3$, 100%), 45 (OCH_2CH_3, 12).

Ethyl-3-(trichlorotitanio)propionate[50] (**77**)



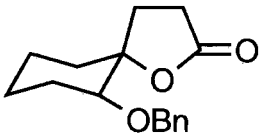
Silyloxycyclopropane (**76**) (0.50g, 2.87mmol) was added dropwise to a solution of titanium(IV) chloride (0.32ml, 2.87mmol) in hexane (6ml) at room temperature. The initial milky white suspension rapidly turned brown and deep purple coloured microcrystals precipitated. Evolution of heat continued for several minutes whereupon the supernatant was removed and the resulting crystals washed with hexane to afford the crude product 0.73g (96.2%) which was used without further purification.

4-hydroxyheptanoic lactone[87] (**79**)



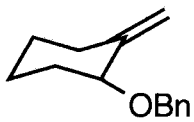
A solution of silyloxycyclopropane (**76**) (2.00g, 11.51mmol) in DCM (5ml) was added over a period of 5min to a thick yellow suspension of titanium(IV) chloride (2.06g, 10.50mmol) and propionaldehyde (0.71g, 12.2mmol) in DCM (7ml) at -78°C. The resulting dark brown solution was stirred for 15min at -78°C then for 1h at 0°C. The reaction was quenched by slow addition of water and the crude product consisted mainly of the expected lactone by ^{1}H NMR. Treatment of the crude lactone with *para*-toluene sulphonic acid hydrate (2.20g, 10.51mmol) in benzene (5ml) at reflux gave, upon purification by flash column chromatography (9:1, petrol:ethyl acetate), 1.15g (87%) of the desired lactone. ν_{max} ($CDCl_3$ solution) 2970, 2939, 2881, 1772, 1461, 1353, 1189, 1175, 1130, 1017cm^{-1}; δ(^{1}H)(200MHz) 4.4 (1H, m, $\underline{H}CO$), 2.5 (2H, m, $C\underline{H}_2CO$), 2.3 (1H, m, $\underline{H}CHCH_2CO$), 1.9-1.6 (3H, m, $-C\underline{H}_2CH_3$, $HC\underline{H}CH_2CO$), 0.9 (3H, t, J = 7.1Hz, $C\underline{H}_3$); δ(^{13}C)(50MHz) 177.6 (C=O lactone), 82.2, 29.3, 28.2, 27.3, 9.2; MS (CI, (NH_3)) *m/z* 132 ($M+NH_4^+$, 100%), 115 (MH^+, 5).

Attempted Preparation of 1-oxa-spiro<4.5>dec-6-benzyloxy-2-one[50] (**74**)



A solution of silyloxycyclopropane (**76**) (0.39g, 2.70mmol) in DCM (3ml) a -78°C was added over a period of 5min to a yellow suspension of titanium(IV) chloride (0.33ml, 2.94mmol), titanium(IV) isopropoxide (0.44ml, 1.47mmol) and 2-benzyloxycyclohexanone (**48**) (0.50g, 2.45mmol) in DCM (20ml) at -78°C, under an atmosphere of nitrogen. The reaction mixture was stirred for 15min before warming to room temperature when tlc (6:1 petrol:ether) indicated that no reaction had occurred. After 50h the reaction was quenched by the addition of water, extracted with ether, dried ($MgSO_4$) and concentrated to afford only starting material (**48**).

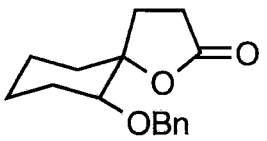
2-Benzyloxycyclohexylidene (**80**)



To a solution of methyltriphenylphosphonium iodide (2.38g, 5.88mmol) in THF (25ml) was added butyl lithium (3.67ml, 5.88mmol). After 4h a solution of 2-benzyloxycyclohexanone (**48**) (1.0g, 4.9mmol) in THF (5ml) was added and the solution stirred for a further 20h. Upon filtration and concentration, a crude yellow oil was obtained. Purification by flash column chromatography (50:1 petrol:ether) afforded 0.467g, (39.3%) desired alkene (**80**) and 0.48g (48.4%) recovered starting material (**48**). Data for (**80**) ν_{max}($CDCl_3$ solution) 2937, 2860, 1601, 1091cm^{-1}; $\delta(^1H)$(400MHz) 7.29-7.19 (5H, m, $C_6\underline{H}_5$), 4.18 (1H, br, C=C$\underline{H}$H), 4.79 (1H, b, C=CH$\underline{H}$), 4.50 & 4.31 (1H each, AB system, J = 12.4Hz, $OC\underline{H}_2C_6H_5$), 3.76 (1H, m, C$\underline{H}OCH_2C_6H_5$), 2.31-2.25 (1H m, HC$\underline{H}$C=CH_2), 2.30-1.64 (1H, m, $\underline{H}$CHC=CH_2), 1.78-1.36 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2C=CH_2$); $\delta(^{13}C)$(100MHz) 148.4 ($\underline{C}$=CH_2), 139.1 (Ar), 128.3 (Ar), 127.5 (Ar), 127.3 (Ar),

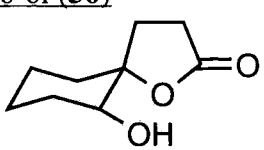
108.8, 79.0, 69.7, 45.2, 34.0, 32.3, 28.0; MS (EI) *m/z* 202 (M^+, 18%), 91 ($CH_2C_6H_5^+$, 100); HRMS (CI) $C_{14}H_{18}O$*m/z* Calc. 202.1358; Found 202.1358.

1-oxa-spiro<4.5>dec-6-benzyloxy-2-one[51] (**74**)



To a solution of alkene (**80**) (0.20g, 0.99mmol) in glacial acetic acid (9.9ml) was added manganese triacetate dihydrate (0.53g, 1.98mmol) and potasium acetate (2.97g). The reaction was heated at reflux for 45h whereupon it was allowed to cool to room temperature, diluted with water, extracted with ether, dried ($MgSO_4$) and concentrated to afford 0.029g (11.1%) of the desired product (**74**) as a single diastereoisomer and 0.57g (30.8%) recovered starting material (**80**) after purification by flash column chromatography (8:1 petrol:ether). Data for (**74**) ν_{max}(KBr disc) 2937, 2836, 1761 (C=O lactone), 1092cm^{-1}; $\delta(^1H)$(400MHz) 7.34-7.26 (5H, m, $C_6\underline{H}_5$), 4.59 & 4.53 (1H each, AB system J = 11.2Hz, $OC\underline{H}_2C_6H_5$), 3.48 (1H, dd, J_1 = 10.4, J_2 = 4.4Hz, $C\underline{H}OCH_2C_6H_5$), 2.71-2.63 (1H, m, $HC\underline{H}C$=O), 2.53-2.43 (2H, m, $\underline{H}CHC$=O, $HC\underline{H}CH_2C$=O), 2.06-2.00 (1H, m, $\underline{H}CHCH_2C$=O), 1.85-1.66 (3H, m, $C\underline{H}_2CHOCH_2C_6H_5$, $HC\underline{H}COC$=O), 1.46-1.25 (5H, m, $C\underline{H}_2C\underline{H}_2CH_2CHOCH_2C_6H_5$, $\underline{H}CHCOC$=O); $\delta(^{13}C)$(100MHz) 174.4 (C=O lactone), 138.2 (Ar), 128.4 (Ar), 127.7 (Ar), 127.3 (Ar), 88.6, 81.2, 72.1, 36.6, 29.5, 28.3, 27.0, 23.1, 22.2; MS (EI) *m/z* 261 (MH^+, 32%), 170 (MH^+-$CH_2C_6H_5$, 100); HRMS (CI) $C_{16}H_{21}O_3$*m/z* Calc. 261.1491; Found 261.1491.

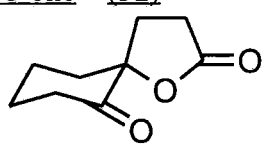
2-oxa-3-oxo-spiro<4.5>decan-6-ol (**50**)



6-benzyloxy-2-oxa-3-oxospiro<4.5>dec-4-ene (**49**) (0.69g, 2.69mmol) was dissolved in methanol (20ml) and added, *via* cannula, to a suspension of

palladium hydroxide (0.29g, 0.27mmol) in methanol (5ml). The mixture was degassed and stirred vigorously for 6h under hydrogen. On completion of the reaction, (tlc ether), the mixture was filtered through celite, washed with methanol and concentrated to afford a yellow liquid. Upon purification by flash column chromatography (neat ether) 0.4g of a clear liquid was obtained to give an overall yield of 87.3% of a 1.3:1 mixture of separable isomers. **Major isomer:** ν_{max} ($CDCl_3$ solution) 3438, 2939, 2864, 2341, 1758, 1450, 1210cm^{-1}; $\delta(^1H)$(400MHz) 3.4 (1H, dd, J_1 = 10.4Hz, J_2 = 4Hz, C<u>H</u>OH), 2.72-2.32 (3H, m, -C<u>H</u>HC<u>H</u>$_2$CO), 1.91-1.18 (9H, m, -(C<u>H</u>$_2$)$_4$C<u>H</u>HCO)); $\delta(^{13}C)$(100MHz) 177.7 (C=O lactone), 87.7, 74.4, 35.9, 30.9, 30.3, 29.1, 23.4, 21.5; MS (CI, (NH_3)) *m/z* 188 ($M+NH_4^+$, 100%), 171 (MH^+, 38); HRMS (CI, (NH_3)) $C_9H_{15}O_3$ *m/z* Calc. 171.1021 Found 171.1021. **Minor isomer:** $\delta(^1H)$(400MHz) 3.84 (1H, dd, J_1 = 10.0Hz, J_2 = 4.0Hz, C<u>H</u>OH), 2.72-2.32 (3H, m, -C<u>H</u>HC<u>H</u>$_2$CO), 1.91-1.20 (9H, m, -(C<u>H</u>$_2$)$_4$C<u>H</u>HCO).

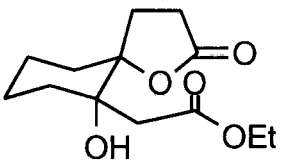
<u>2-oxa-3-oxo-spiro<4.5>decan-6-one</u>[35] (**<u>51</u>**)



Dimethyl sulphoxide (0.87ml, 12.40mmol) in DCM (120ml) was added dropwise, *via* cannula, to a suspension of oxalyl chloride (0.54ml, 6.21mmol) in DCM (60ml) at -78°C. After stirring for a further 10min, a solution of the alcohol (**50**) (0.88g, 5.17mmol) in DCM (50ml) was added. The resulting solution was then stirred for 50min before triethylamine (3.67ml, 25.9mmol) was added and the reaction warmed to room temperature. This mixture was diluted with DCM and washed with 2M HCl, sat. $NaHCO_3$ dried ($MgSO_4$) and concentrated to produce 0.74g (85.0%) of the desired ketone after purification by flash column chromatography (2:1, ether : petrol). ν_{max} ($CDCl_3$ solution) 3544, 3422, 2944, 2867, 1772 (C=O lactone) , 1722 (C=O ketone), 1420, 1319, 1250cm^{-1}; $\delta(^1H)$(400MHz) 2.53 (2H, m, C<u>H</u>$_2$C=O lactone), 2.39 (3H, m, C<u>H</u>$_2$C=O,

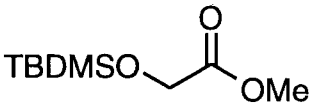
HCHCH$_2$C=O lactone), 2.04 (1H, m, HCHCH$_2$C=O lactone), 1.8-1.6 (6H, m, (CH$_2$)$_3$CH$_2$C=O); δ(^{13}C)(100MHz) 205.7 (C=O ketone), 175.3 (C=O lactone), 88.0, 38.5, 38.4, 28.7, 27.6, 26.2, 21.2; MS (EI) *m/z* 169 (MH$^+$, 100%); HRMS (EI) $C_9H_{13}O_3$ *m/z* Calc. 169.0865; Found 169.0865

Ethyl 1-oxa-2-oxospiro<4.5>dec-6-hydroxy-6-acetate[53] (**89**)



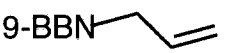
Butyl lithium (0.89ml, 1.43mmol) was slowly added to a solution of hexamethyldisilazide (0.28ml, 1.31mmol) in THF (2ml) at -78°C. The mixture was allowed to stir for 50min before a solution of ethyl acetate (0.12g, 1.19mmol) in THF (10ml) was added. The reaction mixture was allowed to stir for 1h whereupon a solution of 2-oxa-3-oxo-spiro<4.5>deca-6-one (**51**) (0.18g, 1.07mmol) in THF (10ml) was added *via* cannula to the reaction mixture at -78°C. The solution was kept at constant temperature for 16h but tlc (neat ether) indicated that no reaction had occured. The mixture was then allowed to warm to room temperature for 2h whereupon tlc showed development of a new compound. The reaction was quenched with sat. NH_4Cl, extracted with ether, washed with sat. $NaHCO_3$, dried and concentrated to afford a yellow oil whch, upon flash column chromatography (1:2 petrol:ether) afforded 0.035g (13%) of the desired product (**89**) as a single isomer. ν_{max}($CDCl_3$ solution) 3479 (OH), 2954, 2875, 1774 (C=O lactone), 1714 (C=O ester) cm^{-1}; δ(^{1}H)(400MHz) 4.17-4.06 (2H, m, CO$_2$CH$_2$CH$_3$), 2.75-2.41 (6H, m, CH$_2$CH$_2$C=O, CH$_2$CO$_2$Et), 1.80-1.27 (8H, m, CH$_2$CH$_2$CH$_2$CH$_2$COH), 1.22 (3H, t, J = 7.2Hz, OCH$_2$CH$_3$); δ(^{13}C)(100M Hz) 176.8 (C=O lactone), 173.4 (C=O ester), 89.3 (C-O-C=O), 74.5 (C-OH), 61.0, 37.2, 35.1, 34.9, 29.1, 28.1, 21.8, 13.9; MS (CI, (NH_3)) *m/z* 274 (M+NH_4^+, 100%), 257 (MH$^+$, 38); HRMS (CI, (NH_3)) $C_{13}H_{24}NO_5$ *m/z* Calc. 274.1654; Found 274.1654.

Methyl 2-^{t}butyldimethylsilyloxy ethanoate[72] (**93**)



A solution of methyl glycolate (**88**) (0.20g, 2.63mmol) , ^{t}butyldimethylsilyl chloride (0.49g, 3.24mmol) and imidazole (0.90g, 6.75mmol) in DMF (3ml) was stirred at room temperature for 10h. The reaction was quenched with water, extracted with petrol, washed with sat. NH_4Cl solution, dried ($MgSO_4$) and concentrated. This afforded a yellow oil which upon purification by flash column chromatography (12:1, petrol:ethyl acetate) gave the desired product (0.53g, 86.7%). ν_{max} ($CDCl_3$ solution) 2944, 2856, 1764 (C=O ester), 1742, 1472, 1436, 1362, 1255, 1213, 1150cm^{-1}; δ(^{1}H)(400MHz) 4.24 (2H, s, -C$\underline{H}_2$), 3.72 (3H, s, OC$\underline{H}_3$), 0.9 (9H, s, Si$^{t}\underline{Bu}$), 0.09 (6H, s, Si(C$\underline{H}_3$)$_2$); δ(^{13}C)(100MHz) 172.0 (C=O ester), 62.1, 52.4, 26.2, 25.4, 25.3; MS (EI) *m/z* 147 (M^+-^{t}Bu, 63%), 89 (M^+-Si(CH$_3$)$_2$^{t}Bu, 100).

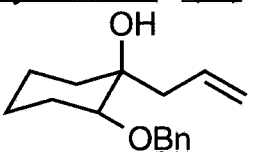
B-allyl-9-BBN[58] (**95**)



9-BBN (**96**) (32.8ml, 1.7M solution, 55.76mmol) was added by syringe into a dry two necked round bottomed flask containing a stirrer bar. The THF was evaporated *in vacuo* to leave neat 9-BBN (2.0g, 16.4mmol). Next, anhydrous ether (17ml) was added and the resulting suspension cooled to 0°C for 1h. While stirring, similarly cooled anhydrous methanol (0.80ml, 19.7mmol) was added dropwise over a period of 0.5h. After evolution of hydrogen gas ceased, a clear solution was formed indicating methanolysis had taken place. Finally, ether and excess methanol were evaporated *in vacuo* to leave 9-BBN-OMe (**97**). Ether (16ml) was then added, the solution was stirred vigorously at 0°C and allylmagnesium bromide(17.14ml, 14.40mmol) was added. Following completion of the addition, the reaction mixture was stirred vigorously for 1h at 25°C, whereupon the solvents were removed under vacuum (14mmHg) . The

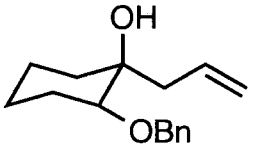
residue was extracted with pentane and stirring was discontinued to allow salts formed to settle. The clear supernatant extract was transferred from the flask using a double ended needle with Kramer filter. Evaporation of pentane (14mmHg, 1h; 2mmHg, 1h) afforded *B*-allyl-9BBN (**95**) in almost quantitative yield. Purification was achieved by distillation (b.p. 41.5-42°C, 0.5mmHg).

1-allyl-1-hydroxy-2-benzyloxycyclohexane[87] (**98**)



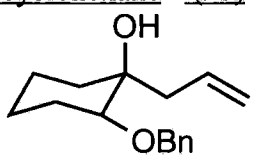
To an oven dried, nitrogen flushed, flame dried, round bottomed flask, was added *B*-allyl-9BBN (3.15ml, 3.15mmol) in pentane (3.15ml). To this stirred solution was added 2-benzyloxycyclohexanone (**48**) (0.64g, 3.15mmol) and the mixture allowed to stir for 2h whereupon ethanolamine (0.19ml, 3.15mmol) was added and the solution stirred for a further 1h. The supernatant was then allowed to settle and was decanted. The precipitate was washed with pentane and the extracts were concentrated and purified by flash column chromatography (7:1 petrol:ether) to afford the alcohol (**98**) (0.10g, 13.5%) and starting material (**48**) (0.28g, 44.3%). Data for (**98**): ν_{max}($CDCl_3$ solution) 3574, 3068, 2939, 2862, 1431, 1090, 1074cm^{-1}; $\delta(^1H)$(400MHz) 7.36-7.30 (5H, m, $C_6\underline{H}_5$), 5.91-5.79 (1H, m, $C\underline{H}=CH_2$), 5.11-5.03 (2H, m, $CH=C\underline{H}_2$), 4.58 & 4.36 (1H each, AB system, J = 11.2Hz, $OC\underline{H}_2C_6H_5$), 3.27 (1H, dd, J_1 = 8.8Hz, J_2 = 4Hz, $C\underline{H}OCH_2C_6H_5$), 2.45-2.29 (3H, m, $C\underline{H}_2CH=CH_2$, $HC\underline{H}CHOCH_2C_6H_5$), 1.89-1.12 (8H, m, $\underline{H}CHC\underline{H}_2C\underline{H}_2C\underline{H}_2CO\underline{H}$); $\delta(^{13}C)$(100MHz) 138.5(Ar), 134.2 ($\underline{C}H=CH_2$), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 117.6 ($CH=\underline{C}H_2$), 80.1, 73.1, 70.6, 48.1, 34.2, 25.9, 22.9, 21.2; MS (EI) *m/z* 246 (M^+, 18%), 228 (M^+-H_2O, 45%), 91 ($CH_2C_6H_5$, 100).

1-allyl-1-hydroxy-2-benzyloxycyclohexane (**98**)



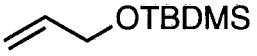
To a stirred solution of 2-benzyloxycyclohexanone (**48**) (0.12g, 0.59mmol) in ether (5ml) at -78°C was slowly added allyl magnesiumbromide (0.08ml, 0.59mmol). After 1.5h (tlc 10:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (10:1 petrol:ether) to afford the alcohol (**98**) (0.16g, 98%).

1-allyl-1-hydroxy-2-benzyloxycyclohexane[62] (**98**)



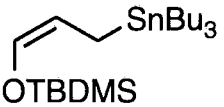
To a stirred solution of titanium(IV) chloride (0.54ml, 0.54mmol) in DCM (2.5ml) at -78°C was added 2-benzyloxycyclohexanone (**48**) (0.1g, 0.49mmol) in DCM (1ml). After 10min a solution of allyl stannane (**105**) (0.16ml, 0.54mmol) in DCM (0.5ml) was added and the mixture stirred for 6h. The reaction was then quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$), and concentrated to afford 0.13g, 100% desired product (**98**) after purification by flash column chromatography (10:1 petrol:ether). $\delta(^1H)$(400MHz) 7.28-7.24 (5H, m, $C_6\underline{H}_5$), 5.82-5.71 (1H, m, $C\underline{H}=CH_2$), 5.01-4.95 (2H m, $CH=C\underline{H}_2$), 4.58 & 4.36 (1H each, AB system, J = 11.6Hz, $OC\underline{H}_2C_6H_5$), 3.18 (1H, m, $C\underline{H}OCH_2C_6H_5$), 2.31-2.21 (3H, m, $C\underline{H}_2CH=CH_2$, $HC\underline{H}CHOCH_2C_6H_5$), 1.74-1.25 (8H, m, $\underline{H}CHC\underline{H}_2C\underline{H}_2C\underline{H}_2CO\underline{H}$); $\delta(^{13}C)$(100MHz) 138.5 ($\underline{C}H=CH_2$), 134.2 (Ar), 128.3 (Ar), 127.6 (Ar), 127.6 (Ar), 117.6 ($CH=\underline{C}H_2$), 80.0, 73.0, 70.6, 43.6, 34.2, 25.9, 22.9, 21.2; MS (EI) *m/z* 246 (M^+, 22%), 228 (M^+-H_2O, 48), 91 ($CH_2C_6H_5$, 100).

^{t}Butyldimethylsilyloxyprop-2-ene[62] (**104**)



To a stirred solution of sodium hydride (2.04g, 51mmol) in ether (160ml) was added allyl alcohol (**103**) (2.00g, 34.21mmol) at 0°C. The reaction mixture was stirred at room temperature for 30min whereupon it was cooled to 0°C and ^{t}butyldimethylsilylchloride (6.00g,40.80mmol) was added. The solution was then warmed to room temperature and stirred until tlc (10:1 petrol:ether) indicated complete consumption of starting material. The reaction was quenched with water, extracted with ether, dried ($MgSO_4$) and concentrated to afford 5.20g (88.9%) of the desired colourless oil (**104**) after purification by high vacuum transfer. ν_{max}($CDCl_3$ solution) 3083, 2956, 2930, 2857, 1255, 1136, 1073cm^{-1}; δ(^{1}H)(400MHz) 5.85 (1H, ddt, J_1 = 17.2Hz, J_2 = 10.4Hz, J_3 = 4.4Hz, C<u>H</u>=CH_2), 5.19 (1H, ddt, J_1 = 17.2Hz, J_2 = 3.6Hz, J_3 = 1.6Hz, CH=CH<u>H</u>), 5.01 (1H, ddt, J_1 = 10.4Hz, J_2 = 3.6Hz, J_3 = 1.6Hz, CH=C<u>H</u>H), 4.10 (2H, dt, J_1 = 4.4Hz, J_2 = 1.6Hz, CH_2OSi), 0.84 (9H, s, Si^{t}<u>Bu</u>), 0.06 (6H, s, Si(CH_3)$_2$); δ(^{13}C)(100MHz) 137.4 (<u>C</u>H=CH_2), 113.9 (CH=<u>C</u>H_2), 64.1 (<u>C</u>H_2OSi), 25.9 (SiC(<u>C</u>H_3)$_3$), 25.6 (Si<u>C</u>(CH_3)$_3$), -5.3 (Si(<u>C</u>H_3)$_2$); MS (EI) *m/z* 115 (M^+-^{t}Bu, 45%).

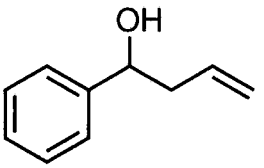
3-(^{t}butyldimethylsilyloxy)allyl tributyltin[61] (**99**)



To a solution of ^{t}butyldimethylsilylallyl ether (**104**) (0.50g, 2.90mmol) in THF (8ml) at -78°C was added ^{t}butyl lithium (2.05ml, 3.49mmol) and HMPA (0.71ml, 4.06mmol). After 15min tributyltin chloride (0.87ml, 3.20mmol) was added and a colour change from yellow to clear was observed. After an additional 15min the mixture was allowed to warm to room temperature and then poured onto hexane (10ml), washed with sat. NH_4Cl, then water, dried ($MgSO_4$) and concentrated to afford 1.05g (78.2%) desired stannane after purification by distillation (195°C, 0.1mmHg). ν_{max}($CDCl_3$ solution) 2955, 2926, 2854, 1586,

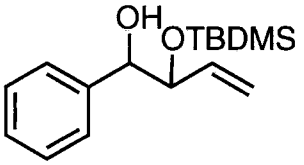
1251cm^{-1}; δ(^{1}H)(400MHz) 6.02 (1H, dt, J_1 = 6Hz, J_2 = 1.2Hz, CH=C<u>H</u>OSi), 4.58 (1H, td, J_1 = 7.6Hz, J_2 = 6Hz, C<u>H</u>=CHOSi), 2.63 (2H, d, J = 7.6Hz, C<u>H</u>$_2$CH=CH), 1.79-0.82 (27H, m, (C<u>H</u>$_3$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$)$_3$Sn), 0.93 (9H, s, Si^t<u>Bu</u>), 0.11 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ(^{13}C)(100MHz) 134.9 (SiO<u>C</u>H=CH), 109.0 (SiOCH=<u>C</u>H), 29.2, 27.4, 26.9, 25.7 (Si<u>C</u>(CH$_3$)$_3$), 13.7, 9.3, 5.6, -5.3 (Si(<u>C</u>H$_3$)$_2$); MS (EI) *m/z* 403 (M$^+$-^{t}Bu, 40%), 115 (M$^+$-Bu$_3$SnCH$_2$CH=CH, 40).

<u>1-phenyl but-3-en-1-ol</u>[62] <u>(**106**)</u>



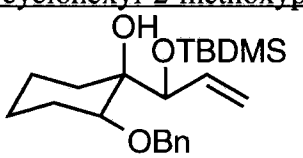
To a stirred solution of magnesium bromide (0.19g, 1.04mmol) in DCM (2ml) at -78°C was added benzaldehyde (0.1g, 0.94mmol) in DCM (1ml) . After 10min a solution of allyl stannane (**105**) (0.32ml, 1.04mmol) in DCM (1ml) was added. After addition the mixture was allowed to warm to room temperature and stirred for 20h. The reaction was then quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford 0.05g, 36.7% desired product (**106**) as a single isomer and 23.6% recovered benzaldehyde. Data for (**106**): ν_{max}($CDCl_3$ solution) 3603, 3154, 3082, 2980, 2903, 1640, 1468, 1454, 1382cm^{-1}; δ(^{1}H)(400MHz) 7.29-7.18 (5H, m, C$_6$<u>H</u>$_5$), 5.79- 5.68 (1H, m, C<u>H</u>=CH$_2$), 5.12-5.06 (2H, m, CH=C<u>H</u>$_2$), 4.69-4.66 (1H, m, C<u>H</u>OH), 2.47-2.42 (2H, m, C<u>H</u>$_2$CH=CH$_2$), 2.00 (1H, br, O<u>H</u>); δ(^{13}C)(400MHz) 143.8 (<u>C</u>H=CH$_2$), 134.4 (Ar), 128.4 (Ar), 127.5 (Ar), 125.8 (Ar), 118.5 (CH=<u>C</u>H$_2$), 73.3 (<u>C</u>HOH), 43.8 (<u>C</u>H$_2$CH=CH$_2$); MS (EI) *m/z* 130 (M$^+$-H$_2$O, 100%), 77 (M-CH(OH)CH$_2$CH=CH$_2$, 57).

2-(^{t}butyl dimethylsilyloxy)-1-phenyl-but-3-en-1-ol[88] (**107**)



To a stirred solution of titanium(IV) chloride (0.52ml, 0.52mmol) in DCM (1ml) at -78°C was added titanium(IV) isopropoxide (0.154ml, 0.52mmol) in DCM (1ml). This was allowed to stir for 1h at -78°C whereupon benzaldehyde (0.10g, 0.94mmol) in DCM (1ml) was added. After 10min a solution of stannane (**99**) (0.48g, 1.03mmol) in DCM (1ml) was added and the mixture was stirred for 20min. The reaction was then quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$), and concentrated to afford 0.07g (27.3%) desired product (**107**) and 0.05g (53.6%) recovered benzaldehyde. Data for (**107**): ν_{max}($CDCl_3$ solution) 3550, 3086, 3033, 2955, 2930, 2886, 2857, 1256cm^{-1}; δ(^{1}H)(400MHz) 7.33 (5H, m, $C_6\underline{H}_5$), 5.78 (1H, m, C$\underline{H}$=CH_2), 5.13 (2H, m, CH=C$\underline{H}_2$), 4.49 (1H, m, $\underline{H}$COSi), 4.15 (1H, dd, J_1 = 6.4Hz, J_2 = 5.6Hz, C$\underline{H}$OH), 3.05 (1H, br, O$\underline{H}$), 0.91 (9H, s, OSi^{t}B$\underline{u}$), 0.00 (3H, s, SiC$\underline{H}_3$), -0.06 (3H, s, C$\underline{H}_3$SiCH_3); δ(^{13}C)(100MHz) 141.8, 138.8 (Ar), 129.2 (Ar), 128.8 (Ar), 128.2 (Ar), 118, 80.1, 78.6, 27.0, 19.4, -3.1 (($\underline{C}H_3$)Si(CH_3)), -4.0 ((CH_3)Si($\underline{C}H_3$)); MS (CI, (NH_3)) *m/z* 106 (MH^+-(CH_3)$_2$^{t}BuSiO, CH_2=CH_2, 100); HRMS (CI, (NH_3)) $C_{16}H_{27}O_2Si$ *m/z* 279.1780; Found 279.1780.

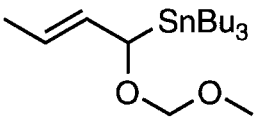
2-(^{t}butyl dimethylsilyloxy)-1-cyclohexyl-2-methoxyphenyl-but-3-en-1-ol[88] (**108**)



To a stirred solution of aluminium trichloride (0.01g, 0.49mmol) in DCM (2.5ml) at -78°C was added 2-benzyloxycyclohexanone (**48**) (0.10g, 0.49mmol) in DCM (1ml) . After 10min a solution of allyl stannane (**99**) (0.25g, 0.54mmol) in DCM (1ml) was added and the mixture was allowed to warm to room temperature and stirred for 20h. The solution was then quenched with sat. NH_4Cl, extracted with

ether, dried ($MgSO_4$), and concentrated to afford 0.04g (22.0%) desired product (**108**) and 0.05g (51.4%) recovered starting material (**48**). Data for (**108**): ν_{max}($CDCl_3$ solution) 3497, 3065, 3031, 2949, 2933, 2857, 1720, 1253, 1089, 1073cm^{-1}; $\delta(^1H)$(400MHz) 7.28 (5H, m, $C_6\underline{H}_5$, 5.88 (1H, m, $C\underline{H}=CH_2$), 5.21 (2H, m, $CH=C\underline{H}_2$), 4.64 & 4.42 (1H each, AB system, J = 11.2Hz, $OC\underline{H}_2C_6\underline{H}_5$), 4.31 (1H, d, J = 6.8Hz, $\underline{H}COSi$), 3.64 (1H, dd, J_1 = 11.2Hz, J_2 = 4.8Hz, $C\underline{H}OCH_2C_6H_5$), 2.26 (1H, br, $O\underline{H}$) ; 2.01-0.92 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOCH_2C_6H_5$), 0.89 (9H, s, $OSi^t\underline{Bu}$), 0.00 (3H, s, $C\underline{H}_3SiCH_3$), -0.08 (3H, s, $C\underline{H}_3SiCH_3$); $\delta(^{13}C)$(100MHz) 138.9 (Ar), 137.9 ($\underline{C}H=CH_2$), 128.3 (Ar), 127.4 (Ar), 127.3 (Ar), 117.3 ($CH=\underline{C}H_2$), 77.4, 75.7, 75.3, 70.0, 28.5, 26.4, 26.0, 23.8, 20.5, 18.1, -3.5 (($\underline{C}H_3$)Si(CH_3)), -4.6 ((CH_3)Si($\underline{C}H_3$)).

1-Methoxymethoxy-1-tributylstannanyl but-2-ene[64] (**109**)

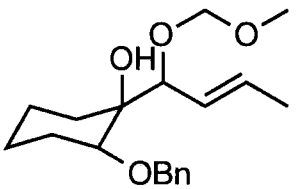


Tributyltin hydride (26.5ml, 100mmol) was added to a solution of LDA (100ml, 100mmol) at 0°C under an atmosphere of nitrogen. After 15min, the green solution was cooled to -78°C, and crotonaldehyde (**111**) (7g, 100mmol) was added dropwise. The reaction was stirred for a further 5min, quenched by the addition of sat. NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$) and warmed to 20°C. The mixture was partitioned between petrol (200ml) and water (200ml), and the organic phase separated, dried ($MgSO_4$) and concentrated under reduced pressure to leave the alcohol (**112**) as an unstable oil used immediately without purification.

Diisopropylethylamine (35ml, 200mmol) was added to the stirred solution of butenol (**112**) (36g, 100mmol) in DCM (250ml) at 0°C and MOM chloride (11.5ml, 150mmol) was added. After 1h, the reaction mixture was poured onto petrol (750ml) and the resulting mixture washed with ice cold 0.5M HCl, water, and sat. $NaHCO_3$. The organic phase was then dried ($MgSO_4$) and concentrated

under reduced pressure to leave 33g (82.2%) of the desired compound (**109**) as a pale yellow oil which could be used without further purification but flash column chromatography (30:1 petrol:ether) was carried out for formal characterisation. ν_{max}($CDCl_3$ solution) 2955, 2924, 2871, 2853, 1463, 1376, 1016cm^{-1}; δ(^1H)(400MHz) 5.57 (1H, m, HC=C<u>H</u>COCH$_2$OCH$_3$), 5.39 (1H, m, <u>H</u>C=CHCHOCH$_2$OCH$_3$), 4.67 & 4.49 (1H each, AB system, J = 6.2Hz, OC<u>H</u>$_2$OCH3), 4.56 (1H, d, J1 = 7.6Hz, <u>H</u>COCH$_2$OCH$_3$), 3.34 (3H, s, OC<u>H</u>$_3$), 1.70-0.82 (30H, m, Sn((C<u>H</u>$_2$)$_3$C<u>H</u>$_3$)$_3$, <u>H</u>$_3$CCH=CH); δ(^{13}C)(100MHz) 132.4, 119.9, 95.0, 72.4, 55.3, 29.1, 27.4, 13.7, 9.1; MS (CI, (NH_3)) *m/z* 362 (MH^+-OCH_3, 8%), 308 ($M+NH_4^+$-$(CH_2)_3CH_3$, 100).

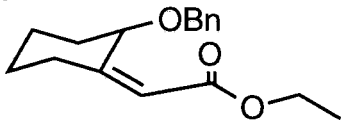
<u>2-Benzyloxy-1-(1-methoxymethoxy-but-2-enyl)-cyclohexanol</u>[63] <u>(**113**)</u>



To a solution of stannane (**109**) (1.0g, 2.22mmol) in DME (15ml) was added n-butyl lithium (1.53ml, 2.44mmol) at -78°C and the mixture stirred for 1h whereupon a solution of 2-benzyloxycycohexanone (**48**) (0.5g, 2.44mmol) in DME (5ml) cooled to -78°C was added. The mixture was then warmed to room temperature and stirred for a further 20h (tlc 8:1 petrol:ether) when it was quenched with sat. NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (10:1 petrol:ether) to afford 0.095g (13.3%) of the desired product (**113**). ν_{max}($CDCl_3$ solution) 3488, 2954, 2940, 2859, 1665, 1454, 1393, 1256, 1246cm^{-1}; δ(^1H)(400MHz) 7.31-7.19 (5H, m, C_6<u>H</u>$_5$), 6.06 (1H, d, J = 6.4Hz, C<u>H</u>OMOM), 4.68 & 4.59 (1H each, AB system, J = 6.4Hz, OC<u>H</u>$_2$OCH$_3$), 4.54 & 4.39 (1H each, AB system, J = 11.2Hz, OC<u>H</u>$_2$C$_6$H$_5$), 4.38 (1H, m, C<u>H</u>=CHCH$_3$), 3.38 (1H, m, C<u>H</u>OCH$_2$C$_6$H$_5$), 3.25 (3H, s, OC<u>H</u>$_3$), 3.22 (1H, m, CH=C<u>H</u>CH$_3$), 2.12 (1H, br, O<u>H</u>), 1.82-0.78 (8H, m,

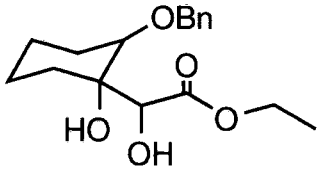
$C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2COH$), 0.94 (3H, d, J = 6.8Hz, $CH{=}CHC\underline{H}_3$); $\delta(^{13}C)$(100MHz) 142.1 ($CH{=}\underline{C}HCH_3$), 139.0 (Ar), 128.2 (Ar), 127.5 (Ar), 127.3 (Ar), 111.2 ($\underline{C}H{=}CHCH_3$), 96.1 ($\underline{C}$HOMOM), 79.0, 74.8, 70.6, 55.6, 34.8, 29.8, 26.2, 23.0, 21.0, 14.8; MS (CI, (NH_3)) *m/z* 259 (MH^+-OCH_2OCH_3, 57%), 167 (M-OCH_2OCH_3, -$OCH_2C_6H_5$, 100); HRMS (CI) $C_{17}H_{23}O_2$ *m/z* Calc. 259.1698; Found 259.1698.

Ethyl 2-benzyloxycyclohexylidene acetate[54] (**118**)



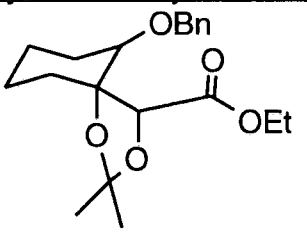
A stirred solution of Wittig reagent (**117**) (13.10g, 37.68mmol) and 2-benzyloxycyclohexanone (**48**) (3.83, 18.8mmol) in toluene (180ml) was heated at reflux for 40h when tlc (5:1 petrol:ether) indicated that (**48**) was still present. The reaction was driven to completion by further addition of Wittig reagent (6.15g, 18.80mmol). The mixture was then concentrated *in vacuo* and purified by flash column chromatography (5:1 petrol:ether) to afford 4.82g (93.6%) of the desired product (**118**) as a mixture of *Z:E* isomers (1:8). **Major isomer:** m.p. 89°C; ν_{max}($CDCl_3$ solution) 2939, 2863, 1708, 1652, 1448, 1216cm^{-1}; $\delta(^1H)$(400MHz) 7.38-7.34 (5H, m, $C_6\underline{H}_5$), 5.93 (1H, s, $C\underline{H}CO_2Et$), 4.58 & 4.49 (1H each, AB system J = 12Hz, $OC\underline{H}_2C_6H_5$), 4.20 (2H, q, J = 6.8Hz, $CO_2C\underline{H}_2CH_3$), 3.72 (1H, m, $C\underline{H}OCH_2C_6H_5$), 3.06 (1H, m, $HC\underline{H}{=}CHCO_2Et$), 2.52 (1H, m, $\underline{H}CH{=}CHCO_2Et$), 1.90-1.16 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOCH_2C_6H_5$), 1.22 (3H, t, J = 6.8Hz, $CO_2CH_2C\underline{H}_3$); $\delta(^{13}C)$(100MHz) 166.7 (C=O ester), 161.1, 138.4 (Ar), 128.3 (Ar), 127.5 (Ar), 127.4 (Ar), 113.0, 80.1, 70.4, 59.7, 34.9, 27.8, 27.3, 22.8, 14.3; MS (CI, (NH_3)) *m/z* 292 ($M+NH_4^+$, 32%), 275 (MH^+, 100%); HRMS (CI, (NH_3)) $C_{17}H_{23}O_3$ *m/z* Calc. 275.1647; Found 275.1647.

Ethyl (2-benzyloxy-1-hydroxy-1-cyclohexyl)-2-hydroxyacetate[66] (**119**)



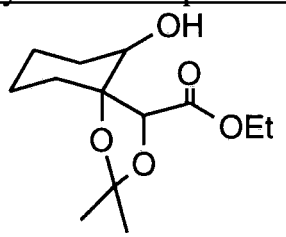
To a stirred solution of the alkene (**118**) (4.82g,17.6mmol) in ^{t}butanol (170ml) was added NMO (3.20g, 26.46mmol), osmium(IV) oxide (0.45g, 1.76mmol) and distilled water (0.03ml, 1.76mmol). The reaction was stirred, under nitrogen, at room temperature. After 16h, tlc (5:1petrol:ether) indicated complete consumption of (**118**) and an excess of sodium metabisulfite was added to the stirred solution. After a further 30min the reaction mixture was filtered through a pad of celite, washed with ethyl acetate and concentrated *in vacuo* to afford 10.10g of a dark yellow oil which was purified by flash column chromatography (5:1 petrol:ether) to afford 5.39g (100%) of the desired diol (**119**). ν_{max}($CDCl_3$ solution) 3497 (OH), 2941, 2856, 1722 (C=O ester), 1459, 1263, 1199cm^{-1}; δ(^{1}H)(400MHz) 7.36-7.18 (5H, m, $C_6\underline{H}_5$), 4.52 & 4.34 (1H each, AB system J = 10.8Hz, $OC\underline{H}_2C_6H_5$), 4.25 (1H, br d, J = 8.4Hz, $C\underline{H}CO_2Et$), 4.17 (2H, q, J = 7.2Hz, $CO_2C\underline{H}_2CH_3$), 3.57 (1H, s, $C\underline{H}OCH_2C_6H_5$), 3.55 (1H, br, OH), 2.77 (1H, br, OH), 1.87-1.29 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOCH_2C_6H_5$), 1.23 (3H, t, J = 7.2Hz, $CO_2CH_2C\underline{H}_3$); δ(^{13}C)(100MHz) 173.7 (C=O ester), 138.2 (Ar), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 77.8, 74.9, 73.7, 71.0, 61.4, 29.7, 24.3, 20.6, 19.5, 14.1; MS (CI, (NH_3)) *m/z* 326 ($M+NH_4^+$, 18%), 309 (MH^+, 41), 108 ($OCH_2C_6H_5$, 100); HRMS (CI, (NH_3)) $C_{17}H_{25}O_5$ *m/z* Calc. 309.1727; Found 309.1702.

4-Ethoxycarbonyl-6-benzyloxy-2,2-dimethyl-1 3-dioxa-spiro<4.5>decane[67] (**120**)



Trifluoroacetic acid (0.14ml,1.76mmol) was added to a stirred solution of diol (**119**) (5.40g, 17.63mmol) and 2,2-dimethoxypropane (5.20ml, 52.81mmol) in chloroform (150ml). The reaction mixture was then heated to reflux in a sohxlet apparatus containing 4Å molecular seives (on large scale the molecular sieves were replaced every 5h). After 10h the mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ dried ($MgSO_4$) and concentrated. Purification by flash column chromotography (2:1 petrol:ether) to yield 5.96g (97.5%) of the desired product (**120**). ν_{max} 2939, 2865, 1744 (C=O ester), 1454, 1372, 1279, 1224, 1201cm^{-1}; $\delta(^1H)$(400MHz) 7.33-7.18 (5H, m, $OCH_2C_6\underline{H}_5$), 4.60 (1H, s, $C\underline{H}CO_2CH_2CH_3$), 4.61 & 4.41 (1H each, AB system, J = 11.6Hz, $OC\underline{H}_2C_6H_5$), 4.17-4.02 (2H, m, $CO_2C\underline{H}_2CH_3$), 3.41 (1H, m, $C\underline{H}OCH_2C_6H_5$), 1.86-1.34 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOCH_2C_6H_5$), 1.49 (3H, s, $C\underline{H}_3CCH_3$), 1.31 (3H, s, $CH_3CC\underline{H}_3$), 1.16 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); $\delta(^{13}C)$(100MHz) 170.2 (C=O ester), 138.7 (Ar), 128.1 (Ar), 127.3 (Ar), 127.2 (Ar), 110.8, 84.7, 81.0, 79.1, 70.7, 60.8, 29.7, 28.7, 25.0, 21.6, 19.5, 14.0; MS (CI, (NH_3)) *m/z* 349 (MH^+, 13%), 291 (MH^+-$(CH_3)_2CO$, 100); HRMS (CI, (NH_3)) $C_{20}H_{29}O_5$ *m/z* Calc. 349.2015; Found 349.2015.

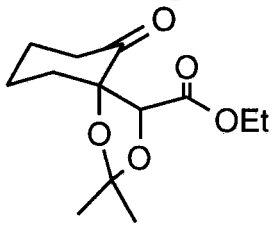
4-Ethoxycarbonyl-2,2-Dimethyl-1 3-dioxa-spiro<4.5>decan-6-ol (**121**)



To a solution of the benzyl ether (**120**) (0.22g, 0.63mmol) in methanol (6ml) was added palladium hydroxide (0.06g, 0.03mmol). This mixture was vigourously stirred under an atmosphere of hydrogen for 16h (tlc 2:1 petrol:ether) whereupon the reaction mixture was filtered through a pad of celite and concentrated *in vacuo* producing a clear oil. Purification was achieved by flash column chromatography (tlc 2:1 petrol:ether) to afford 0.056g (99.2%) of the desired alcohol (**121**). ν_{max}($CDCl_3$ solution) 3474 (OH), 2967, 2859, 1743 (C=O ester),

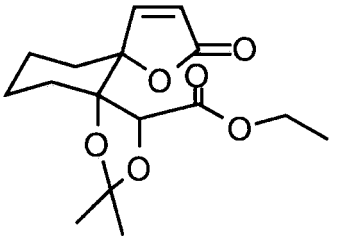
1710, 1216, 1188cm^{-1}; δ(^{1}H)(400MHz) 4.48 (1H, s, C<u>H</u>CO_2Et), 4.28-4.20 (2H, m, $CO_2C\underline{H}_2CH_3$), 3.70 (1H, m, C<u>H</u>OH), 1.71-1.25 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$CHOH), 1.49 (3H, s, $C\underline{H}_3CCH_3$), 1.32 (3H, s, $CH_3CC\underline{H}_3$), 1.27 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); δ(^{13}C)(100M Hz) 170.3 (C=O ester), 109.9, 84.0, 81.0, 72.7, 62.0, 29.3, 28.5, 27.7, 27.3, 21.1, 19.4, 14.1; MS (EI) *m/z* 258 (M^+, 11%), 243 (M^+-CH_3, 57), 59 ($(CH_3)_2COH^+$, 100); HRMS (EI) $C_{13}H_{22}O_5$ *m/z* Calc. 258.1467; Found 258.1467.

<u>4-Ethoxycarbonyl-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-one[35] (**122**)</u>



A solution of dimethyl sulphoxide (1.32ml, 18.6mmol) in DCM (90ml) was added dropwise, *via* cannula, to a solution of oxalyl chloride (0.8ml, 9.3mmol) in DCM (80ml) at -78°C. After stirring for a further 10min, a solution of the alcohol (**121**) (2.0g, 7.75mmol) in DCM (70ml) was added. The resulting solution was stirred for a further 50min before triethylamine (5.5ml, 38.8mmol) was added and the reaction allowed to warm to room temperature. The resulting mixture was diluted with DCM and washed with 2M HCl, sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated to afford 1.97g, (100%) of the desired ketone (**122**) obtained after purification by flash column chromatography (5:1 petrol:ether). ν_{max}($CDCl_3$ solution) 2953, 2869, 1757 (C=O ester), 1724 (C=O lactone), 1186, 1109cm^{-1}; δ(^{1}H)(400MHz) 5.30 (1H, s, C<u>H</u>CO_2Et), 4.25-4.11 (2H, m, $CO_2C\underline{H}_2CH_3$), 2.88-2.84 (1H, m, HC<u>H</u>C=O), 2.40-2.36 (1H, m, <u>H</u>CHC=O) 2.10-1.58 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$C=O), 1.56 (3H, s, $C\underline{H}_3CCH_3$), 1.25 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$), 1.20 (3H, s, $CH_3CC\underline{H}_3$); δ(^{13}C)(100M Hz) 208.7 (C=O ketone), 169.9 (C=O ester), 111.6, 87.1, 77.2, 75.3, 60.96, 38.7, 35.4, 27.6, 26.3, 21.2, 14.1; MS (CI, (NH_3)) *m/z* 257 (MH^+, 100%); HRMS (CI, (NH_3)) $C_{13}H_{21}O_5$ *m/z* Calc. 257.1389; Found 257.1389.

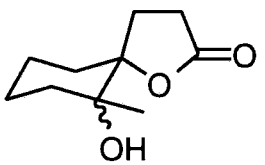
4-Ethoxycarbonyl-(2,2-dimethyl-5"-oxodispiro[perhydro[1,3]dioxolane-4,1'-cyclohexane-2',2"-(5"-H-furan)]-5-yl[39] (**123**)



To a stirred solution of 3-(*para*-toylsulphonyl)propionic acid (**63**) (0.86g, 3.75mmol) in THF (40ml) was slowly added butyl lithium (4.88ml, 7.81mmol) at -78°C. The resulting yellow solution was stirred for 1h whereupon a solution of ketone (**122**) (0.8g, 3.12mmol) in THF (8ml) was cooled to -78°C and added *via* cannula to the reaction mixture.The resulting solution was allowed to warm to -40°C and stirred for 30h before trifluoroacetic anhydride (1.05ml, 7.5mmol) was added and the mixture warmed to -30°C for 4h. The mixture was quenched with sat. $NaHCO_3$, extracted with ether, dried ($MgSO_4$) and concentrated to afford 0.51g (35.2%) tosyl isomers, 0.37g (43%) ketone starting material (**122**) after purification by flash column chromatography (5:1 petrol:ether). The mixture of tosyl isomers was then redissolved in THF, cooled to -78°C and added *via* cannula to a similarly cooled solution of LDA (1.31ml, 1.31mmol) in THF (2ml). The resulting solution was then warmed to room temperature, stirred for 3h and quenched by addition of sat. $NaHCO_3$, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (1:1 petrol:ether) to afford a 1.3:1 mixture of two separable isomers of the desired butenolide 0.18g (52%) as a white solid. **Major isomer**: m.p. 138°C; ν_{max}($CDCl_3$ solution) 2992 (CH), 2844 (CH), 1740 (C=O lactone), 1220 (acetonide), 1102 (acetonide) cm^{-1}; $\delta(^1H)$(400MHz) 7.62 (1H, d, J = 6Hz, C<u>H</u>=CHC=O), 6.13 (1H, d, J = 6Hz, CH=C<u>H</u>C=O), 4.20-4.10 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.11 (1H, s, C<u>H</u>CO_2Et), 2.42-2.35 (1H, m, HC<u>H</u>COC=O), 1.80-1.32 (7H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2(\underline{H})$CHCOC=O), 1.52 (3H, s, $C\underline{H}_3CCH_3$), 1.47 (3H, s,

$CH_3CC\underline{H}_3$), 1.27 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); $\delta(^{13}C)$(100MHz) 171.9 (C=O lactone), 168.7 (C=O ester), 157.3, 121.6, 111.5, 89.9, 84.5, 76.3, 61.4, 34.1, 32.1, 28.8, 26.3, 25.1, 20.5, 14.1; MS (CI, (NH_3)) *m/z* 328 ($M+NH_4^+$, 100%); HRMS (CI, (NH_3)) $C_{16}H_{26}NO_6$ *m/z* Calc. 328.1760; Found 328.1760. **Minor isomer**: m.p. 138-139°C; ν_{max}($CDCl_3$ solution) 2991 (CH), 2942 (CH), 2868 (CH), 1753 (C=O lactone), 1221 (acetonide), 1102 (acetonide) cm^{-1}; $\delta(^1H)$(400MHz) 7.54 (1H, d, J = 6Hz, C$\underline{H}$=CHC=O), 6.21 (1H, d, J = 6Hz, CH=C$\underline{H}$C=O), 4.22-4.12 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.22 (1H, s, C$\underline{H}CO_2$Et), 2.08-1.98 (1H, m, HC$\underline{H}$COC=O), 1.96-1.90 (1H, m, $\underline{H}$CHCOC=O), 1.68-1.18 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2COC$=O), 1.57 (3H, s, $C\underline{H}_3CCH_3$), 1.38 (3H, s, $CH_3CC\underline{H}_3$), 1.31 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); $\delta(^{13}C)$(100MHz) 174.4 (C=O lactone), 168.0 (C=O ester), 157.5, 122.7, 110.6, 89.2, 83.3, 77.8, 61.6, 32.9, 29.7, 28.4, 26.9, 21.0, 20.2, 13.9; MS (CI, (NH_3)) *m/z* 328 ($M+NH_4^+$, 100%); HRMS (CI, (NH_3)) $C_{16}H_{26}NO_6$ *m/z* Calc. 328.1760; Found 328.1760.

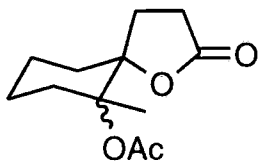
1-oxa-spiro<4.5>dec-6-methyl-6-hydroxyl-2-one (**124**)



To a stirred solution of ketolactone (**51**) (0.10g, 0.60mmol) in ether (6ml) was added a solution of methyl lithium (0.47ml, 0.66mmol) at -78°C. The reaction was followed by tlc (2:1 DCM:ether) . After 1h the reaction was quenched with sat. NH_4Cl and extracted with ether. Purification by flash column chromatography (2:1 DCM:ether) afforded 0.04g (38.9%) of (**124**) as a 4:1 mixture of diastereoisomers. **Major isomer:** ν_{max}($CDCl_3$ solution) 3497 (OH), 2492 (CH), 2866 (CH), 1729 (C=O lactone) cm^{-1}; $\delta(^1H)$(400MHz) 2.62-2.38 (3H, m, HC$\underline{H}C\underline{H}_2$C=O), 1.80-1.32 (10H, m, $\underline{H}CHCH_2C$=O, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CO\underline{H}$), 1.24 (3H, s, $C\underline{H}_3$); $\delta(^{13}C)$(100MHz) 177.4 (C=O lactone), 90.0, 73.6, 36.7, 35.0, 29.2, 27.5, 23.1, 22.0, 21.9; MS (CI, (NH_3)) *m/z*

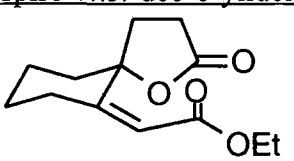
202 ($M+NH_4^+$, 100%), 185 (MH^+, 42); HRMS (CI, (NH_3)) $C_{10}H_{20}NO_3$ *m/z* Calc. 202.1443; Found 202.1443.

1-oxa<4.5>dec-6-methyl-6-O-acyl-2-one (**125**)



Acetyl chloride (0.03ml, 0.34mmol) and triethylamine (0.02ml, 0.02mmol) were added to a stirred solution of the alcohol (**124**) (0.06g, 0.23mmol) in DCM (2ml). The reaction mixture was allowed to stir at room temperature for 40h (tlc 2:1 petrol:ether) after which the solution was quenched with water, extracted with DCM, dried ($MgSO_4$) and concentrated to afford 0.02g (38.5%) acetylated product (**125**) upon purification by flash column chromatography. **Major isomer:** ν_{max}($CDCl_3$ solution) 2947 (CH), 2868 (CH), 2257, 1767 (C=O ester), 1734cm^{-1} (C=O lactone); $\delta(^1H)$(400MHz) 2.57-2.40 (3H, m, HC<u>H</u>C<u>H</u>$_2$C=O), 1.94 (3H, s, C<u>H</u>$_3$), 1.84-1.34 (9H, m, <u>H</u>CHCH$_2$C=O, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CO), 1.36 (3H, s, CH_3); $\delta(^{13}C)$(100MHz) 176.7 (C=O lactone), 169.4 (C=O ester), 88.0, 84.7, 35.1, 31.7, 28.9, 28.8, 28.6, 22.4, 21.4, 18.3; MS (CI, (NH_3)) *m/z* 244 ($M+NH_4^+$, 100%), 227 (MH^+, 96); HRMS (CI, (NH_3)) $C_{12}H_{22}NO_4$ *m/z* Calc. 244.1549; Found 244.1549.

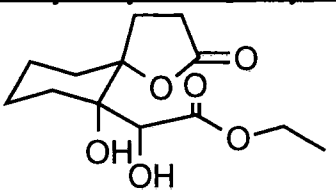
Ethoxycarbonyl-2-oxa-3-oxo-spiro<4.5>dec-6-ylidene (**126**)



The Wittig reagent (**117**) (0.46g, 1.31mmol) was added to a solution of 2-oxa-3-oxo-spiro<4.5>decan-6-one (**51**) (0.20g, 1.19mmol) in benzene (10ml) and the mixture refluxed at 80°C for 12h. When tlc (neat ether) indicated completion of the reaction , the mixture was filtered through celite to afford a yellow oil and

purification by flash column chromatography (1:1 petrol:ether) afforded 0.19g (67%) of (**126**) as a 12:1 mixture of *E*:*Z* isomers and 0.06g (30%) recovered starting material. Data for (**126**): ν_{max} ($CDCl_3$ solution) 2984, 2943, 2865, 2256, 1774 (C=O lactone), 1710 (C=O ester), 1652, 1449, 1374, 1304, 1258, 1195, 1166cm^{-1}; $\delta(^1H)$(400MHz) 5.9 (1H, s, =C<u>H</u>) , 4.08 (2H, q, J = 7.2Hz, OC<u>H</u>$_2$$CH_3$) , 3.84 (1H, broad, HC<u>H</u>$_{ax}$C=CH) , 2.49 (2H, m, -C<u>H</u>$_2$CO) , 2.2 (2H, t, J = 8Hz, C<u>H</u>$_2$$CH_2$CO) , 1.89 (2H, m, HC<u>H</u>$_{eq}$C=CH, HC<u>H</u>$_{ax}$$(CH_2)_2$C=C) , 1.80 (3H, m, (HC<u>H</u>$_{eq}$)$_3$$CH_2$C=) , 1.52 (1H, m, HC<u>H</u>$_{ax}$$(CH_2)_3$C=) , 1.33 (1H, m, H_{ax}C<u>H</u>CH_2C=) , 1.21 (3H, t, J = 7.2Hz, OCH_2C<u>H</u>$_3$); $\delta(^{13}C)$(100MHz) 174.7 (C=O ester), 165.4 (C=O lactone), 158.2, 110.9, 86.2, 59.0, 38.2, 30.3, 26.9, 25.9, 25.6, 22.2, 13.1; MS (CI, (NH_3)) *m/z* 256 ($M+NH_4^+$, 92%), 239 (MH^+, 39), 195 (MH^+-OCH_2CH_3, 100); HRMS (CI, (NH_3)) $C_{13}H_{22}NO_4$ *m/z* Calc. 256.1549; Found 256.1549.

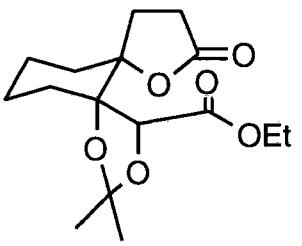
<u>Ethyl [1-oxa-spiro<4.5>dec-6-hydroxy-2-one]-6-hydroxyacetate[66] (**127**)</u>



To a solution of alkene (**126**) (0.12g, 0.49mmol) in ^{t}butanol (5ml) was added NMO (0.06g, 0.50mmol) and a catalytic amount of osmium(IV) oxide. This was stirred for 14h (tlc ether) whereupon excess sodium metabisulfite was added and allowed to stir for 30min . The resulting mixture was filtered through celite, washed with ethyl acetate and concentrated to afford 0.21g of a yellow oil. Purification by flash column chromatography (1:2, petrol:ether) obtained a clear liquid weighing 0.12g which gave a total yield of 77% of two unseparable diastereomers (**127**). ν_{max} ($CDCl_3$ solution) 3444 (OH), 2944, 2867, 2356, 1739 (C=O lactone), 1639 (C=O ester), 1444, 1367, 1256, 1211, 1089, 1016cm^{-1}; $\delta(^1H)$(400MHz) 4.32-4.09 (3H, m, OC<u>H</u>$_2$$CH_3$, C(OH)<u>H</u>) , 3.45-3.05 (2H, broad s, 2 O<u>H</u>) , 2.80-2.45 (3H, m, HC<u>H</u>$_{ax}$COH, C<u>H</u>$_2$CO) , 2.15-1.22 (12H, m,

-($C\underline{H}_2)_3\underline{H}_{eq}CHCOH$, $C\underline{H}_2CH_2CO$, $OCH_2C\underline{H}_3$) ; $\delta(^{13}C)$(100MHz) 177.4 (C=O lactone), 175.9 (C=O lactone), 173.2 (C=O ester), 172.0 (C=O ester), 90.1, 89.3, 76.2, 75.3, 74.1, 73.3, 62.4, 62.2, 36.4, 34.8, 31.7, 31.4, 28.9, 28.7, 28.4, 27.1, 22.2, 21.2, 20.3, 20.0, 14.3, 14.1; MS (CI, (NH_3)) *m/z* 290 ($M+NH_4^+$, 100%), 272 (M^+, 39); HRMS (CI, (NH_3)) $C_{13}H_{24}NO_6$ *m/z* Calc. 290.1604; Found 290.1604.

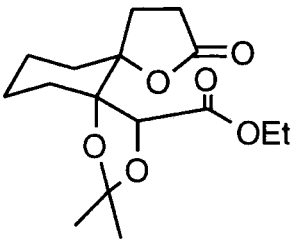
4-Ethoxycarbonyl-2,2,dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecan-8-one (**82**)



Trifluoroacetic acid (0.02g, 0.021mmol) was added to a stirred solution of diol (**127**) (0.05g, 0.21mmol) and 2,2-dimethoxypropane (0.05ml, 0.25mmol) in chloroform (20ml). The reaction mixture was then heated at reflux using sohxlet apparatus containing 4Å molecular seives. After 10h tlc analysis (neat ether) indicated the reaction to be complete and the mixture was cooled to room temperature, quenched with sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated. Purification by flash column chromotography (2:1 petrol:ether) yielded 0.051g, 78% desired product (**82**). $\nu_{max}(CDCl_3$ solution) 1783 (C=O lactone), 1756 (C=O ester), 1733, 1383, 1211cm^{-1}; $\delta(^1H)$(400MHz) 4.64 (1H, s, $C\underline{H}CO_2Et$), 4.32-4.14 (2H, m, $CO_2C\underline{H}_2CH_3$), 2.72-2.46 (3H, m, $C\underline{H}C\underline{H}_2CO$), 2.00-1.28 (9H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2OC\underline{H}CH_2CO$), 1.53 (3H, s, $C\underline{H}_3CCH_3$), 1.37 (3H, s, $CH_3CC\underline{H}_3$), 1.30 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); $\delta(^{13}C)$(400M Hz) 176.3 (C=O lactone), 170.0 (C=O ester), 111.0, 87.8, 86.8, 77.8, 61.5, 35.9, 30.9, 29.3, 29.0, 28.7, 27.0, 21.2, 21.0, 14.0; MS (CI, (NH_3)) *m/z* 330 ($M+NH_4^+$, 100%), 313 (MH^+, 18); HRMS (CI, (NH_3)) $C_{16}H_{28}NO_6$ *m/z* Calc. 330.1916; Found 330.1917.

4-Ethoxycarbonyl-2,2,dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecan-8-one

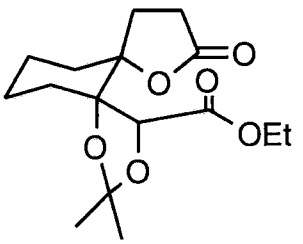
(82) (Major isomer)



The major isomer of butenolide (**123**) (0.13g, 0.41mmol) was dissolved in methanol (2ml) and added, *via* cannula, to a suspension of palladium hydroxide (4mg, 0.08mmol) in methanol (2ml). The mixture was degassed and stirred vigorously for 6h under hydrogen. When tlc (3:2 petrol:ether) showed complete consumption of the butenolide (**123**) the reaction mixture was filtered through a pad of celite, washed with methanol and concentrated to afford a yellow liquid which was purified by flash column chromatography (3:2 petrol:ether) to afford 88mg (68.8%) of the desired saturated lactone (**82**). m.p. 97°C; ν_{max}($CDCl_3$ solution) 2989, 2940, 2868, 1767 (C=O lactone), 1725 (C=O ester), 1219, 1131, 1382, 1372cm^{-1}; $\delta(^1H)$(400MHz) 4.50 (1H, s, C<u>H</u>CO_2Et), 4.30-4.17 (2H, m, $CO_2C\underline{H}_2CH_3$), 2.67-2.61 (2H, m, $HCHC\underline{H}_2CO$), 2.51-2.41 (1H, m, $HC\underline{H}CH_2CO$), 2.15-2.04 (2H, m, <u>H</u>$CHCH_2CO$, C<u>H</u>$COC{=}O$), 1.84-1.26 (7H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2HC\underline{H}COCO$), 1.51 (3H, s, $C\underline{H}_3CCH_3$), 1.46 (3H, s, $CH_3CC\underline{H}_3$), 1.30 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); $\delta(^{13}C)$(100MHz) 176.2 (C=O lactone), 169.9 (C=O ester), 111.4, 87.7, 86.7, 61.6, 33.6, 31.1, 28.8, 28.5, 26.9, 26.3, 22.0, 20.2, 14.1; MS (CI, (NH_3)) *m/z* 330 ($M+NH_4^+$, 38%), 313 (MH^+, 49), 272 (MH^+-OCH_2CH_3, 100); HRMS (CI, (NH_3)) $C_{16}H_{28}NO_6$ *m/z* Calc. 330.1916; Found 330.1917.

4-Ethoxycarbonyl-2,2,dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecan-8-one

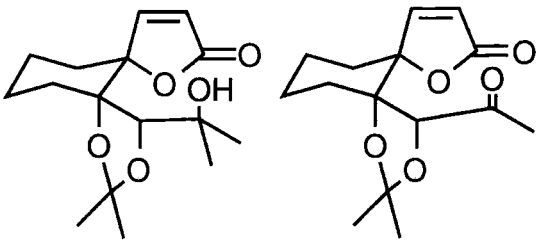
(82) (Minor isomer)



The minor isomer of butenolide (**123**) (0.036g, 0.12mmol) was dissolved in methanol (1ml) and added, *via* cannula, to a suspension of palladium hydroxide (0.0012g, 0.024mmol) in methanol (1ml). The vessel was then degassed and a hydrogen balloon fitted to the top of the flask. The mixture was stirred vigorously for 6h. When tlc indicated complete consumption of starting material the mixture was filtered through a pad of celite, washed with methanol and concentrated to afford a yellow liquid which was purified by flash column chromatography (2:1 petrol:ether) to afford the saturated lactone (**82**) (0.03g, 80.6%) as a white solid. m.p. 97°C; ν_{max}($CDCl_3$ solution) 2988 (CH), 2869 (CH), 2941 (CH), 1770 (C=O lactone), 1751 (C=O ester), 1383, 1374, 1211, 1095cm^{-1}; δ(^1H)(400MHz) 4.59 (1H, s, C<u>H</u>CO_2Et), 4.28-4.08 (2H, m, $CO_2C\underline{H}_2CH_3$), 2.68-2.35 (3H, m, C<u>H</u>C<u>H</u>$_2$CO), 1.96-1.18 (9H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CC\underline{H}CH_2CO$), 1.48 (3H, s, $C\underline{H}_3CCH_3$), 1.31 (3H, s, $CH_3CC\underline{H}_3$), 1.24 (3H, t, J = 7.2Hz, $OCH_2C\underline{H}_3$); δ(^{13}C)(100MHz) 176.5 (C=O lactone), 169.2 (C=O ester), 111.4, 87.0, 86.5, 61.5, 35.9, 30.9, 29.3, 29.0, 28.7, 27.0, 21.2, 21.0, 14.0; MS (CI, (NH_3)) *m/z* 330 ($M+NH_4^+$, 100%), 272 (MH^+-$(CH_3)_2C$, 45); HRMS (CI, (NH_3)) $C_{16}H_{28}NO_6$ *m/z* Calc. 330.1916; Found 330.1917.

1-(2, 2-dimethyl-5"-oxodispiro[perhydro[1, 3]dioxolane-4, 1' cyclohexane-2', 2"-(5"-H-furan)]-5-yl)-1-methyl-1-methanol (**129**)

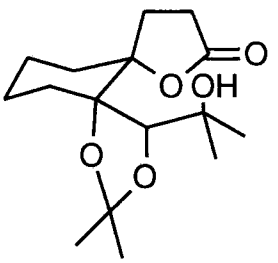
1-(2, 2-dimethyl-5"-oxodispiro[perhydro[1, 3]dioxolane-4, 1' cyclohexane-2', 2"-(5"-H-furan)]-5-yl)-1-ethanone (**130**)



To a stirred solution of the major isomer of butenolide (**123**) (0.64g, 0.21mmol) in THF (2ml) at -78°C was slowly added methylmagnesium bromide (0.18ml, 0.23mmol) . After 2h (tlc 1:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (1:1 petrol:ether) to afford 0.005g (8.8%) of the ketone (**130**) , 0.016g (25.4%) of the alcohol (**129**) and 0.038g (58.8%) recovered starting material (**123**). **Alcohol (129)**: m.p. 147-148°C; ν_{max}($CDCl_3$ solution) 3496 (OH), 2987 (CH), 2940 (CH), 2848 (CH), 1754 (C=O lactone), 1226 (acetonide), 1032 (acetonide) cm^{-1}; $\delta(^1H)$(400MHz) 7.68 (1H, d, J = 6Hz, C<u>H</u>=CHC=O), 6.08 (1H, d, J = 6Hz, CH=C<u>H</u>C=O), 3.47 (1H, s, C<u>H</u>C(OH)Me_2), 2.52 (1H, m, HC<u>H</u>COC=O), 2.16 (1H, m, <u>H</u> CHCOC=O), 1.92 (1H, br, O<u>H</u>), 1.81-1.15 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2COC$=O), 1.46 (3H, s, $C\underline{H}_3CCH_3$), 1.45 (3H, s, $CH_3CC\underline{H}_3$), 1.24 (3H, s, $CH_3C(OH)C\underline{H}_3$), 1.15 (3H, s, $C\underline{H}_3C(OH)CH_3$); $\delta(^{13}C)$(100MHz) 174.5 (C=O lactone), 158.9, 121.0, 107.4, 90.8, 84.7, 80.9, 71.0, 35.1, 32.2, 29.4, 29.1, 28.9, 26.2, 23.3, 20.6; MS (CI, (NH_3)) *m/z* 314 ($M+NH_4^+$, 57%), 279 (MH^+-H_2O, 100); HRMS (CI, (NH_3)) $C_{16}H_{28}NO_5$ *m/z* Calc. 314.1967; Found 314.1967. **Ketone (130)**: m.p. 85-86°C; ν_{max}($CDCl_3$ solution) 2956 (CH), 2908 (CH), 2848 (CH), 1746 (C=O lactone), 1718 (C=O ketone), 1102 (acetonide), 1038 (acetonide) cm^{-1}; $\delta(^1H)$(400MHz) 7.68 (1H, d, J = 6Hz, C<u>H</u>=CHC=O), 6.12 (1H, d, J = 6Hz, CH=C<u>H</u>C=O), 3.95 (1H, s, C<u>H</u>C(O)Me), 2.45 (1H, m, HC<u>H</u> COC=O), 2.24 (3H, s, C=O$C\underline{H}_3$), 1.78-1.12 (6H, m,

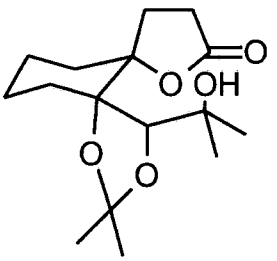
$C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2COC{=}O$), 1.55 (3H, s, $C\underline{H}_3CCH_3$), 1.49 (3H, s, $CH_3CC\underline{H}_3$); $\delta(^{13}C)$(100MHz) 207.6 (C=O ketone), 174.2 (C=O lactone), 157.3 (CH=$\underline{C}$H, 120.0 , 109.5, 88.7, 83.6, 80.3, 33.3, 30.8, 28.0, 27.7, 25.0, 22.2, 19.3; MS (CI, (NH_3)) *m/z* 298 ($M+NH_4^+$, 100%), 281 (MH^+, 50); HRMS (CI, (NH_3)) $C_{15}H_{28}NO_5$ *m/z* Calc. 298.1654; Found 298.1654.

2,2-Dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecane-1-ethanone (**131**) **(Major isomer)**



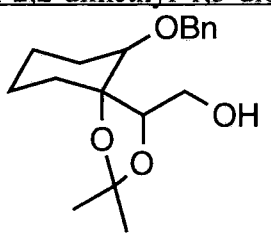
To a stirred solution of lactone (**82**) [derived from the major isomer of (**123**)] (0.80g, 0.26mmol) in THF (2ml) at -78°C was slowly added methylmagnesium bromide (0.25ml, 0.31mmol). After 2h (tlc 1:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (1:1 petrol:ether) to afford 7mg (6.8%) of the alcohol (**131**) and 69mg (85.6%) starting material (**82**). Data for (**131**): ν_{max}($CDCl_3$ solution) 2918, 2849, 1763 (C=O lactone), 1717 (C=O ketone), 1220, 1133; $\delta(^1H)$(400MHz) 4.20 (1H, s, $C\underline{H}CO(OH)Me_2$), 2.66-2.52 (2H, m, $C\underline{H}_2C{=}O$), 2.18-1.98 (2H, m, $C\underline{H}_2CH_2C{=}O$), 1.78-1.22 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2COC{=}O$), 1.55 (3H, s, $C\underline{H}_3CCH_3$), 1.47 (3H, s, $CH_3CC\underline{H}_3$), 1.43 (3H, s, $HOC(CH_3)C\underline{H}_3$), 1.25 (3H, s, $HOC(C\underline{H}_3)CH_3$); $\delta(^{13}C)$(100MHz) 176.2 (C=O lactone), 124.5, 109.1, 86.3, 85.5, 81.2, 33.1, 29.9, 29.3, 28.7, 28.1, 27.7, 25.5, 25.0, 21.1, 19.0; MS (CI, (NH_3)) *m/z* 283 (MH^+, 18%), 115 (MH^+-$(CH_3)_2COC(OH)(CH_3)_2$, 100); HRMS (CI, (NH_3)) $C_{15}H_{23}O_5$ *m/z* Calc. 283.1545; Found 283.1545.

2,2-Dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecane-1-ethanol (**131**) (**Minor isomer**)



To a stirred solution of butenolide (**82**) (25mg, 0.08mmol) in THF (1ml) at -78°C was slowly added methyl magnesiumbromide (0.08ml, 0.10mmol). After 0.5h (tlc 1:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (1:1 petrol:ether) to afford 8mg (36.8%) of the alcohol (**131**) and 0.013g (62.5%) starting material (**82**). Data for (**131**): ν_{max}($CDCl_3$ solution) 3579 (OH), 2985, 2936, 1765 (C=O lactone), 1381, 1372, 1219, 1159cm^{-1}; $\delta(^1H)$(400MHz) 3.66 (1H, s, C<u>H</u>C(OH)$(CH_3)_2$), 2.67-2.39 (3H, m, HC<u>H</u>C<u>H</u>$_2$C=O), 2.00-1.14 (9H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>CHCH$_2$C=O), 1.48 (3H, s, C<u>H</u>$_3$CCH$_3$), 1.41 (3H, s, C(OH)C<u>H</u>$_3$), 1.31(3H, s, CH$_3$CC<u>H</u>$_3$), 1.27 (3H, s, C<u>H</u>$_3$CCH$_3$; $\delta(^{13}C)$(100MHz) 176.5 (C=O lactone), 106.5, 86.7, 84.6, 84.3, 71.4, 37.4, 30.0, 29.7, 29.0, 28.8, 28.4, 27.7, 26.7, 21.0, 20.5; MS (CI, (NH_3)) *m/z* 283 (MH^+, 100); HRMS (CI, (NH_3)) $C_{16}H_{23}O_5$ *m/z* Calc. 283.1545; Found 283.1545.

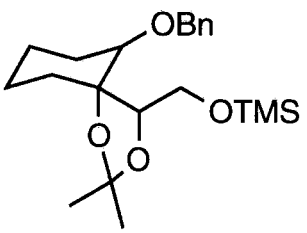
6-Benzyloxy-4-hydroxymethyl-2,2-dimethyl-1,3-dioxa-spiro<4.5>decane (**134**)



To a stirred solution of ester (**120**) (0.25g, 0.72mmol) in THF (10ml) was added DIBAL (1.58ml, 1.58mmol) at -78°C. After 1h the mixture was allowed to warm to room temperature and stirring was continued for a further 1h. The mixture was

then cooled to -78°C and methanol (0.16g, 5.04mmol) was added. Again, the mixture was warmed to room temperature and water (0.09ml, 5.04mmol) then celite was added. This was then filtered, washed with ethyl acetate and concentrated to afford the desired alcohol (0.217g, 99%) after purification by flash column chromatography (4:1 petrol:ether) . ν_{max}($CDCl_3$ solution) 3455, 2983, 2935, 2862, 1249, 1217, 1061, 1085cm^{-1}; δ(^1H)(400MHz) 7.29-7.23 (5H, m, $C_6\underline{H}_5$), 4.58 & 4.31 (1H each, AB system, J_1 = 11.2Hz, $OC\underline{H}_2C_6H_5$), 3.83 (1H, t, J = 6.4Hz, $C\underline{H}CH_2OH$), 3.63 (2H, br, $C\underline{H}_2OH$), 3.33 (1H, m, $C\underline{H}OCH_2C_6H_5$), 2.83 (1H, br, $O\underline{H}$), 1.91-1.36 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOCH_2C_6H_5$), 1.36(3H, s, $C\underline{H}_3CCH_3$), 1.24 (3H, s, $CH_3CC\underline{H}_3$); δ(^{13}C)(100MHz) 137.3 (Ar), 128.5 (Ar), 128.1 (Ar), 128.0 (Ar), 107.7, 83.4, 81.5, 79.6, 63.4, 60.8, 28.6, 27.2, 26.8, 24.6, 20.6 ($\underline{C}H_3CCH_3$), 19.3 ($CH_3C\underline{C}H_3$); MS (CI, (NH_3)) *m/z* 306 (M^+, 22%), 141 (M^+-$(CH_3)_2C(O)O$, $CH_2C_6H_5$, 100); HRMS (CI, (NH_3)) $C_{18}H_{26}O_4$ *m/z* Calc. 307.1909; Found 307.1909.

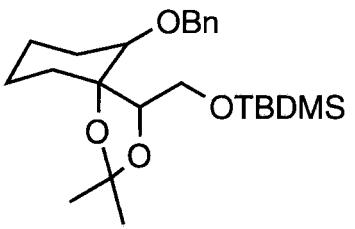
6-Benzyloxy-4-(trimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decane[55] (**135**)



To a stirred solution of alcohol (**134**) (0.18g, 0.59mmol) in THF (6ml) was added triethylamine (0.09ml, 0.65mmol) and trimethylsilyl chloride (0.12ml, 0.97mmol) . Immediately a colour change from clear to white occurred and tlc (2:1 petrol:ether) showed consumption of starting material so the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford 0.13g (60.4%) of the desired colourless oil (**135**) after purification by flash column chromatography (16:1 petrol:ether). ν_{max}($CDCl_3$ solution) 2984, 2936, 2863, 1249, 1216, 1155, 1086, 1061cm^{-1}; δ(^1H)(400MHz) 7.35-7.27 (5H,

m, $C_6\underline{H}_5$), 4.58 & 4.30 (1H each, AB system, J = 11.2Hz, $OC\underline{H}_2C_6H_5$), 3.94 (2H, m, $C\underline{H}_2OTMS$), 3.60 (1H, dd, J_1 = 11.6Hz, J_2 = 9.6Hz, $C\underline{H}CH_2OTMS$), 3.41 (1H, m, $C\underline{H}OCH_2C_6H_5$), 1.98-1.37 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOCH_2C_6H_5$), 1.46 (3H, s, $C\underline{H}_3CCH_3$), 1.34 (3H, s, $CH_3CC\underline{H}_3$), 0.06 (9H, s, $Si(C\underline{H}_3)_3$); $\delta(^{13}C)$(100MHz) 139.1 (Ar), 129.5 (Ar), 128.2 (Ar), 128.3 (Ar), 107.9, 85.3, 81.2, 80.4, 70.1, 63.1, 28.9, 27.4, 26.9, 24.9, 20.6 ($\underline{C}H_3CCH_3$), 19.3 ($CH_3\underline{C}CH_3$), -1.5 ($Si(\underline{C}H_3)_3$); MS (EI) *m/z* 378 (M^+, 38%), 213 (M^+-$(CH_3)_3Si$, $OCH_2C_6H_5$, 37), 91 ($CH_2C_6H_5^+$, 100); HRMS (EI) $C_{21}H_{34}O_4Si$ *m/z* Calc. 378.2226; Found 378.2226.

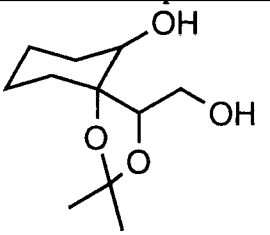
6-Benzyloxy-4-(^{t}butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decane[72] (**133**)



Imidazole (0.27g 2.05mmol) and ^{t}butyldimethylsilyl chloride (0.15g, 0.98mmol) were added to a stirred solution of alcohol (**134**) (0.25g, 0.82mmol) in DMF (4ml). Tlc (4:1 petrol:ether) showed consumption of starting material after 20h so the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (30:1 petrol:ether) afforded 0.29g (89.9%) of the desired compound (**133**). ν_{max}($CDCl_3$ solution) 2931, 2882, 2858, 1253, 1211, 1190, 1087, 1063cm^{-1}; $\delta(^1H)$(400MHz) 7.34-7.31 (5H, m, $OCH_2C_6\underline{H}_5$), 4.63 & 4.37 (1H each, AB system, J = 11.6Hz, $OC\underline{H}_2C_6H_5$), 3.96 (2H, m, $C\underline{H}_2OSi$), 3.66 (1H, m, $C\underline{H}OCH_2C_6H_5$), 3.41 (1H, m, $C\underline{H}CH_2OSi$), 1.97-1.23 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOCH_2C_6H_5$), 1.44 (3H, s, $C\underline{H}_3CCH_3$), 1.32 (3H, s, $CH_3CC\underline{H}_3$), 0.87 (9H,s, $Si^t\underline{Bu}$), 0.03 (3H, s, $Si(CH_3)C\underline{H}_3$), 0.01 (3H, s, $Si(C\underline{H}_3)CH_3$); $\delta(^{13}C)$(100MHz) 138.7 (Ar), 128.2 (Ar), 127.4 (Ar), 127.3 (Ar), 107.6, 84.7, 80.3, 79.5, 70.1, 63.7, 28.9, 27.4, 26.9, 26.0, 25.9, 25.0, 20.7, 17.6,

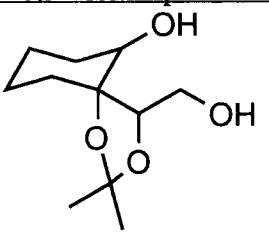
-5.3 ($Si(CH_3)\underline{C}H_3$), -5.3 ($Si(\underline{C}H_3)CH_3$); MS (EI) m/z 420 (M^+, 28%), 255 (M^+-$(CH_3)_2{}^tBuSiOCH_2$, $OCH_2C_6H_5$, 68), 91 ($CH_2C_6H_5^+$, 100); HRMS (EI) $C_{24}H_{40}O_4Si$ *m/z* Calc. 420.2696; Found 420.2696.

4-hydroxymethyl-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-ol (**136**)



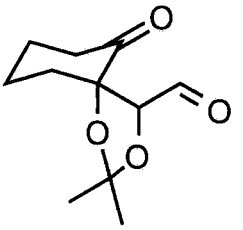
The benzyl ether (**135**) (0.10g, 0.264mmol) was dissolved in methanol (2ml) and added, *via* cannula, to a suspension of palladium hydroxide (0.006g, 0.053mmol) in methanol (1ml). The mixture was degassed and stirred vigorously for 12h under hydrogen. The reaction mixture was filtered through a pad of celite, washed with methanol and concentrated yielding a yellow liquid which was purified by flash column chromatography 4:1 petrol:ether) to afford 0.03g (61.4%) of the diol (**136**) as a white solid. m.p. 86°C; $\nu_{max}(CDCl_3$ solution) 3367 (OH), 2987, 2939, 2865, 2253, 1245, 1219cm^{-1}; $\delta(^1H)$(400MHz) 3.87 (1H, m, $C\underline{H}OH$), 3.75-3.57 (5H, m, $C\underline{H}C\underline{H}_2O\underline{H}$, $CHO\underline{H}$), 1.83-1.22 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CHOH$), 1.36 (3H, s, $C\underline{H}_3CCH_3$), 1.28 (3H, s, $CH_3CC\underline{H}_3$); $\delta(^{13}C)$(100MHz) 107.8 ($\underline{C}(CH_3)_2$), 82.6, 82.2 ($\underline{C}OC(CH_3)_2$), 72.3, 59.9, 29.9, 28.5, 26.8, 26.1, 20.5, 19.2; MS (CI, (NH_3)) *m/z* 216 (M^+, 8%), 141 (MH^+-(CH3)2C(O)O, 100); HRMS (CI, (NH_3)) $C_{11}H_{24}NO_4$ *m/z* Calc. 234.1705; Found 234.1705.

4-Hydroxymethyl-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-ol (**136**)



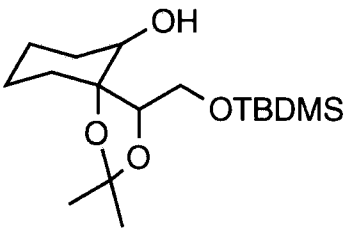
The benzyl ether (**133**) (0.25g, 0.82mmol) was dissolved in methanol (6ml) and added, *via* cannula, to a suspension of palladium hydroxide (0.043g, 0.082mmol) in methanol (2ml) . The vessel was then degassed and a hydrogen balloon fitted to the top of the flask. The mixture was stirred vigorously for 2h before the mixture was filtered through a pad of celite, washed with methanol and concentrated to afford a yellow liquid which was purified by flash column chromatography (4:1 petrol:ether) to afford 0.172g (97.1%) of the diol (**136**) as a white solid. Data as before.

4-Formyl-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-one[35] (**137**)



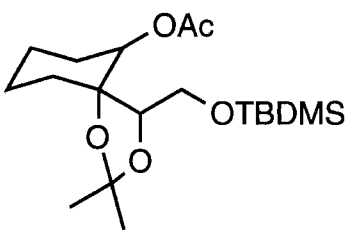
Dimethyl sulphoxide (0.06ml, 0.84mmol) in DCM (8ml) was added dropwise, *via* cannula, to a solution of oxalyl chloride (0.04ml, 0.42mmol) in DCM (4ml) at -78°C. After stirring for a further 10min, a solution of the diol (**136**) (0.08g, 0.35mmol) in DCM (3ml) was added. The solution was stirred for a further 50min before triethylamine (0.25ml, 1.76mmol) was added and the reaction allowed to warm to room temperature. The resulting mixture was diluted with DCM and washed with 2M HCl sat. $NaHCO_3$. Drying ($MgSO_4$), concentrating and purification by flash column chromatography (5:1 petrol:ether) afforded the keto aldehyde (**137**) (0.07g, 92.1%). ν_{max}($CDCl_3$ solution) 2987, 2939, 2867, 1743 (C=O ketone), 1722 (C=O aldehyde) cm^{-1}; $\delta(^1H)$(400MHz) 9.67 (1H, d, J = 1.6Hz, C<u>H</u>O), 5.13 (1H, d, J = 1.6Hz, C<u>H</u>CHO), 2.94 (1H, m, HC<u>H</u>C=O), 2.43 (1H, m, <u>H</u>CHC=O), 2.18-1.14 (6H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_2$C=O), 1.50 (3H, s, C<u>H</u>$_3$CCH$_3$), 1.22 (3H, s, CH$_3$CC<u>H</u>$_3$); $\delta(^{13}C)$(100MHz) 208.9 (C=O aldehyde), 200.8 (C=O ketone), 111.5, 87.6, 80.2, 39.9, 35.9, 28.2, 27.9, 26.1, 21.1; MS (CI, (NH3)) *m/z* 230 ($M+NH4^+$, 46%), 213 (MH^+, 100); HRMS (CI, (NH3)) $C_{11}H_{17}O_4$ *m/z* Calc. 213.1127 Found 213.1127.

4-(^{t}butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-ol[72](**138**)



Imidazole (0.18g, 1.36mmol) and ^{t}butyldimethylsilylchloride (0.115g, 0.75mmol) was added to a stirred solution of the diol (**136**) (0.15g, 0.68mmol) in DMF (6ml). Tlc (4:1 petrol:ether) showed consumption of starting material after 20h so the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford 0.218g (97.1%) of the desired compound (**138**) after purification by flash column chromatography (10:1 petrol:ether). ν_{max}($CDCl_3$ solution) 3408 (OH), 2934, 2888, 2864, 1470, 1374, 1254cm^{-1}; δ(^{1}H)(400MHz) 3.90-3.86 (2H, m, C$\underline{H}_2$OSi), 3.84 (1H, br, O$\underline{H}$), 3.66 (1H, t, J = 10.8Hz, C$\underline{H}$C$\underline{H}_2$OSi), 3.57 (1H, m, C$\underline{H}$OH), 1.76-1.32 (8H, m, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CHOH), 1.42 (3H, s, C$\underline{H}_3$CCH$_3$), 1.35 (3H, s, CH3CC$\underline{H}_3$), 0.93 (9H, s, Si$^t\underline{Bu}$), 0.08 (6H, s, Si(C$\underline{H}_3$)$_2$); δ(^{13}C)(100MHz) 107.8, 83.1, 82.3, 72.0, 60.6, 45.2, 29.1, 28.5, 26.7, 25.8, 20.7, 19.2, 18.3, -5.6 (($\underline{C}$H$_3$)Si(CH$_3$)), -5.7 ((CH$_3$)Si($\underline{C}$H$_3$)); MS (CI, (NH3)) *m/z* 331 (MH$^+$, 2%), 273 (M$^+$-^{t}Bu, 100); HRMS (CI, (NH3)) $C_{17}H_{35}O_4Si$ *m/z* Calc. 331.2304; Found 331.2304.

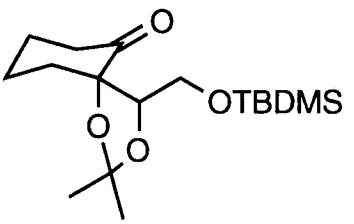
6-Acetoxy-4-(^{t}butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decane[56] (**139**)



To a stirred solution of alcohol (**138**) (0.05g, 0.13mmol) in pyridine (1ml) was added acetic anhydride (0.02ml, 0.19mmol) and DMAP (0.002g, 0.013mmol) and

stirring was continued for 40h (tlc 4:1 petrol:ether). The reaction was quenched with sat. NH_4Cl, extracted with ether, washed with $CuSO_4$ solution to remove pyridine, dried ($MgSO_4$) and concentrated to afford 0.028g (62.6%) of the acetylated product (**139**) after purification by flash column chromatography (30:1 petrol:ether). m.p. 79°C; ν_{max}($CDCl_3$ solution) 2958, 2932, 2860, 1734 (C=O ester), 1372, 1245cm^{-1}; δ(^1H)(400MHz) 4.76 (1H, m, C<u>H</u>OC(O)CH_3), 3.97-3.70 (3H, m, C<u>H</u>$_2$OSi, C<u>H</u>C<u>H</u>$_2$OSi), 2.07 (3H, s, OC(O)C<u>H</u>$_3$), 1.82-1.80 (2H, m, C<u>H</u>$_2$CHOC(O)CH_3), 1.61-1.35 (6H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CHOC(O)CH_3), 1.43 (3H, s, C<u>H</u>$_3$CCH_3), 1.35 (3H, s, CH3CC<u>H</u>$_3$), 0.90 (9H, s, Si^t<u>Bu</u>), 0.07 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ(^{13}C)(100MHz) 169.9 (C=O ester), 108.0, 83.4, 80.1, 75.3, 63.2, 28.8, 28.1, 27.1, 26.8, 26.0, 21.4, 20.6, 19.9, 18.5, -5.1 ((<u>C</u>H$_3$)Si(CH$_3$)), -5.72 ((CH$_3$)Si(<u>C</u>H$_3$)); MS (CI, (NH3)) *m/z* 315 (M^+-^{t}Bu, 40%), 255 (MH^+-(CH$_3$)$_2$^{t}BuSiO, 100); HRMS (CI, (NH3)) $C_{19}H_{35}O_5Si$ m/z Calc. 373.2410; Found 373.2410.

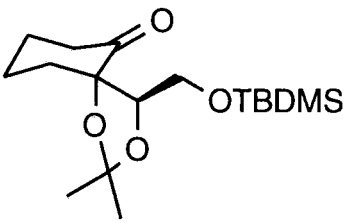
<u>4-(t-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-one</u>[35] <u>(**61**)</u>



Dimethyl sulphoxide (0.05ml, 0.79mmol) in DCM (8ml) was added dropwise, *via* cannula, to a solution of oxalyl chloride (0.04ml, 0.40mmol) in DCM (4ml) at -78°C. After stirring for a further 10min, a solution of the alcohol (**138**) (0.10g, 0.33mmol) in DCM (3ml) was added. The solution was stirred for a further 50min before triethylamine (0.24ml, 1.66mmol) was added and the reaction allowed to warm to room temperature. The resulting mixture was diluted with DCM and washed with 2M HCl, sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated to afford 0.074g (68.9%) of the desired ketone (**61**) as a waxy solid

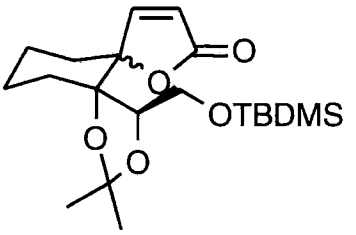
and 0.01g (13.4%) recovered starting material (**138**) obtained after purification by flash column chromatography (30:1 petrol:ether).

4-(ᵗbutyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-one[69] (**61**)



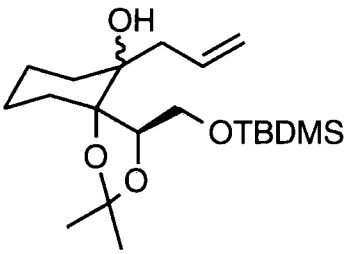
To a solution of alcohol (**138**) (0.160g, 0.41mmol) in DCM (4ml) was added 4Å molecular seives (0.25g), NMO (0.074g, 0.61mmol) and TPAP (0.014g, 0.041mmol). The mixture was allowed to stir for 50h after which it was filtered through a pad of celite, washed with DCM and concentrated to afford 0.054g (34.5%) desired product (**61**) and 0.09g (64.3%) recovered starting material (**138**) after purification by flash column chromatography (30:1 petrol:ether). Data for (**61**): m.p. 39-40°C; ν_{max}($CDCl_3$ solution) 2951, 2930, 2857, 1719 (C=O ketone), 1372, 1255cm^{-1}; $\delta(^1H)$(400MHz) 4.66 (1H, t, J = 6Hz, C<u>H</u>CH_2OSi), 3.70 (2H, d, J = 6Hz, C<u>H</u>$_2$OSi), 2.87 (1H, dt, J_1 = 20Hz, J_2 = 6Hz, HC<u>H</u>C=O) 2.39-2.34 1H, m, <u>H</u>CHC=O) 2.19-1.90 (3H, m, HC<u>H</u>CH_2C=O, C<u>H</u>$_2$COC$(CH_3)_2$), 1.72-1.58 (3H, m, C<u>H</u>$_2$(H)C<u>H</u>CH_2C=O), 1.43 (3H, s, C<u>H</u>$_3$CCH_3), 1.24 (3H, s, CH3CC<u>H</u>$_3$), 0.87 (9H, s, Si^t<u>Bu</u>), 0.07 (3H, s, (C<u>H</u>$_3$)Si(CH_3)) 0.07 (3H, s, (CH_3)Si(C<u>H</u>$_3$); $\delta(^{13}C)$(100MHz) 210.3 (C=O ketone), 108.78, 85.5, 76.1, 61.7, 39.6, 34.2, 28.5, 27.7, 28.0, 25.8, 21.0, 18.2, , -5.4 ((<u>C</u>H_3)Si(CH_3)), -5.4 ((CH_3)Si(<u>C</u>H_3)); MS (CI, (NH3)) *m/z* 329 (MH^+, 55%), 271 (M^+-^{t}Bu, 100); HRMS (CI, (NH3)) $C_{17}H_{33}O_4Si$ *m/z* Calc. 329.2148; Found 329.2148.

Attempted Preparation of 1-(^{t}Butyldimethylsilyloxymethyl)-2,2-dimethyl-5"-oxodispiro[perhydro[1,3]dioxolane-4,1'-cyclohexane-2',2"-(5"-H-furan)]-5-ane[39] (**140**)



To a stirred solution of 3-(*para*-toylsulphonyl)propionic acid (**63**) (0.73g, 3.22mmol) in THF (20ml) was slowly added butyl lithium (4.19ml, 6.70mmol) at -78°C. The resulting yellow solution was stirred for 1h whereupon a solution of ketone (**63**) (0.8g, 2.68mmol) in THF (8ml) was cooled to -78°C and added *via* cannula to the reaction mixture. The resulting solution was allowed to warm to -40°C and stirred for 30h before trifluoroacetic anhydride (1.05ml, 7.5mmol) was added and the mixture warmed to -30°C for 4h. The mixture was quenched with sat. $NaHCO_3$, extracted with ether, dried ($MgSO_4$) and concentrated to afford only ketone starting material (**61**) after purification by flash column chromatography (30:1 petrol:ether).

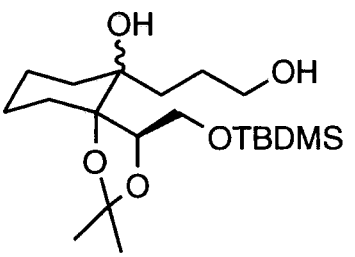
6-allyl-4-(^{t}butyl-dimethylsilanoxymethyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-ol[57] (**142**)



To a stirred solution of ketone (**61**) (0.10g, 0.30mmol) in ether (3ml) at -78°C was slowly added allylmagnesium bromide (0.44ml, 0.37mmol). After 1h (tlc 10:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (30:1 petrol:ether) to afford the desired

product as a 1.3:1 mixture of separable isomers (**142**) (0.108g, 97.1%). **Major isomer (142a):** m.p. 44°C; ν_{max}($CDCl_3$ solution) 3419, 2981, 2933, 2859, 1640, 1380, 1369, 1074, 1216cm^{-1}; δ(^{1}H)(400MHz) 5.95 (1H, m, C<u>H</u>=CH_2), 5.06 (2H, m, CH=C<u>H</u>$_2$), 4.24 (1H, m, C<u>H</u>CH_2OSi), 3.82 (1H, m, HC<u>H</u>CH=CH_2), 3.69-3.64 (2H, m, C<u>H</u>$_2$OSi), 2.42-2.40 (2H, m, <u>H</u>CHC(OH)(H)C<u>H</u>CH=CH_2), 1.80-1.20 (7H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$(<u>H</u>)CHCOH), 1.41 (3H, s, C<u>H</u>$_3$CCH_3), 1.37 (3H, s, CH_3CC<u>H</u>$_3$), 0.88 (9H, s, Si^t<u>Bu</u>), 0.13 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ(^{13}C)(100MHz) 135.0 (<u>C</u>H=CH_2), 117.3 (CH=<u>C</u>H$_2$), 107.3, 85.4, 76.6, 71.8, 60.7, 41.3, 33.2, 28.6, 27.1, 26.7, 25.8, 20.6, 20.3, 18.2, 1.0, -5.4 ((<u>C</u>H$_3$)Si(<u>C</u>H$_3$)); MS (CI, (NH_3)) *m/z* 371 (MH^+, 18%), 277 (MH^+-$(CH_3)_2$^{t}BuSiO, 100); HRMS (EI) $C_{20}H_{38}OSi$ *m/z* Calc. 370.2539; Found 370.2539. **Minor isomer (142b):** m.p. 42°C; ν_{max}($CDCl_3$ solution) 3480, 2983, 2934, 2859, 1640, 1378, 1369, 1258, 1086cm^{-1}; δ(^{1}H)(400MHz) 5.95 (1H, m, C<u>H</u>=CH_2), 5.06 (2H, m, CH=C<u>H</u>$_2$), 4.35 (1H, m, C<u>H</u>CH_2OSi), 3.76 (2H, m, C<u>H</u>$_2$OSi), 3.69-3.64 (2H, m, C<u>H</u>$_2$CH=CH_2), 2.23 (3H, m, C<u>H</u>$_2$CH=CH_2,HC<u>H</u>COH), 1.82-1.20 (7H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$(<u>H</u>)CHCOH), 1.43 (3H, s, C<u>H</u>$_3$CCH_3), 1.40 (3H, s, CH_3CC<u>H</u>$_3$), 0.89 (9H, s, Si^t<u>Bu</u>), 0.07 (3H, s, C<u>H</u>$_3$Si(CH_3), 0.06 (3H, s, CH_3Si(C<u>H</u>$_3$); δ(^{13}C)(100MHz) 133.9 (<u>C</u>H=CH_2), 117.5 (CH=<u>C</u>H$_2$), 107.1, 86.5, 78.1, 74.5, 63.0, 37.3, 34.6, 29.1, 28.9, 26.9, 25.9, 22.5, 20.5, 1.0, -5.2 ((<u>C</u>H$_3$)Si(CH_3)), -5.3 ((CH_3)Si(<u>C</u>H$_3$)); MS (CI, (NH_3)) *m/z* 371 (MH^+, 123%), 277 (MH^+-(CH3)$_2$^{t}BuSiO, 100); HRMS (EI) $C_{20}H_{38}OSi$ *m/z* Calc. 370.2539; Found 370.2539.

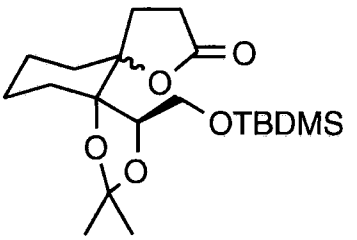
<u>4-(t-butyldimethylsilyloxymethyl)-6-(3-hydroxypropyl)-2,2-dimethyl-1,3-dioxa-spiro<4.5>decan-6-ol (**143a**)</u>



Borane.THF complex (0.14ml, 0.14mmol) was added dropwise to a stirred, cooled (0°C) solution of alkene (**142a**) (0.048g, 0.13mmol) in THF (1ml). The reaction was then stirred at room temperature for 2.5h when tlc (4:1 petrol: ether) indicated that the alkene (**142a**) had been consumed. The mixture was then cooled to 0°C and 3M NaOH (0.05ml, 0.14mmol) then hydrogen peroxide (0.06ml, 0.48mmol) were added dropwise such that the reaction temperature did not exceed 35°C. On completion of the addition, the reaction was heated at reflux for 1h, cooled to room temperature, quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford 0.032g (63.2%) of the desired product (**143a**) after purification by flash column chromatography (4:1 petrol:ether). **Major isomer (143a):** ν_{max}($CDCl_3$ solution) 3392, 2952, 2860, 1255, 1216, 1077, 840cm^{-1}; $\delta(^1H)$(400MHz) 4.28 (1H, dd, J_1 = 6.4Hz, J_2 = 4Hz, C<u>H</u>CH_2OSi), 3.77-3.58 (4H, m, C<u>H</u>$_2$OSi, C(OH)CH_2CH_2C<u>H</u>$_2$OH), 2.80 (1H, br, O<u>H</u>), 2.45 (1H, br, C(O<u>H</u>)$(CH_2)_3OH$), 1.90 (1H, m, HC<u>H</u>C(OH)$(CH_2)_3OH$), 1.76-1.10 (11H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C(<u>H</u>)HCC<u>H</u>$_2$C<u>H</u>$_2CH_2OH$), 1.43 (3H, s, C<u>H</u>$_3CCH_3$), 1.38 (3H, s, CH_3CC<u>H</u>$_3$), 0.88 (9H, s, Si^t<u>Bu</u>), 0.07 (6H, s, Si(C<u>H</u>$_3$)$_2$); $\delta(^{13}C)$(100MHz) 107.1, 85.5, 78.3, 72.8, 63.4, 63.1, 33.9, 29.1, 29.0, 28.8, 26.9, 26.2, 26.0, 22.7, 20.5, 18.4, -5.1 ((<u>C</u>H_3)Si(CH_3)), -5.3 ((CH_3)Si(<u>C</u>H_3)); MS (CI, (NH_3)) *m/z* 331 (MH^+-$(CH_2)_3OH$, 26%), 313 (MH^+-H_2O, 45), 199 (MH^+-(CH3)$_2$^{t}BuSiO, $(CH_2)_3OH$, 100); HRMS (EI) $C_{20}H_{40}O_5Si$ *m/z* Calc. 388.2645; Found 388.2645. In a similar manner (**142b**) gave the minor isomer (**143b**). **Minor isomer (143b):** ν_{max}($CDCl_3$ solution) 3415, 2937, 2859, 1248, 1075, 1124, 837cm^{-1}; $\delta(^1H)$(400MHz) 4.29 (1H, dd, J_1 = 9.6Hz, J_2 = 4Hz, C<u>H</u>CH_2OSi), 4.30-3.52 (4H, m, C<u>H</u>$_2$OSi, C(OH)CH_2CH_2C<u>H</u>$_2$OH), 4.10 (1H, br, O<u>H</u>), 3.25 (1H, br, C(O<u>H</u>)$(CH_2)_3$OH), 1.98-1.36 (12H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CC<u>H</u>$_2$C<u>H</u>$_2CH_2OH$), 1.41 (3H, s, C<u>H</u>$_3CCH_3$), 1.36 (3H, s, CH_3CC<u>H</u>$_3$), 0.92 (9H, s, Si^t<u>Bu</u>), 0.13 (6H, s, Si(C<u>H</u>$_3$)$_2$); $\delta(^{13}C)$(100MHz) 107.1, 85.5, 78.3, 72.8, 63.4, 63.1, 33.9, 29.1, 29.0, 28.8, 26.9, 26.2, 26.0, 22.7, 20.5, 18.4, -5.1 ((<u>C</u>H_3)Si(CH_3)), -5.3 ((CH_3)Si(<u>C</u>H_3)); MS (CI, (NH_3)) *m/z* 331 (MH^+-

$(CH_2)_3OH$, 24%), 313 (MH^+-H_2O, 100), 199 (MH^+-$(CH3)_2{}^tBuSiO$, $(CH_2)_3OH$, 56); HRMS (CI) $C_{20}H_{40}O_5Si$ *m/z* Calc. 388.2645; Found 388.2645.

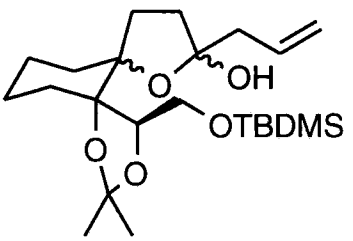
4-(^{t}butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecan-8-one[74] (**141**)



To a stirred solution of diol (**143a**) (0.035g, 0.09mmol) was added pyridinium chlorochromate (0.03g, 0.14mmol) and alumina (0.15g) after which stirring was continued for 12h whereupon pyridinium chlorochromate (0.03g, 0.14mmol) was again added. After a further 4h the reaction mixture was filtered through a pad of celite, the organic solution was then washed with water, dried ($MgSO_4$) and concentrated to afford 0.028g (79.9%) of the desired product (**141a**) after purification by flash column chromatography (4:1 petrol:ether). **Major isomer (141a):** m.p. 64°C; ν_{max}($CDCl_3$ solution) 2990, 2935, 2858, 1768 (C=O lactone), 1251, 1463, 1158, 1018cm^{-1}; δ(^{1}H)(400MHz) 4.15 (1H, m, C<u>H</u>CH_2OSi), 3.88 (2H, m, C<u>H</u>$_2$OSi), 2.58 (3H, m, HC<u>H</u>C<u>H</u>$_2$C=O), 2.0-1.90 (1H, m, <u>H</u>CHCH_2C=O), 1.90-1.80 (1H, m, HC<u>H</u>COC$(CH_3)_2$), 1.78-1.45 (7H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C(<u>H</u>)HCOC$(CH_3)_2$), 1.42 (3H, s, C<u>H</u>$_3$CCH_3), 1.34 (3H, s, CH_3CC<u>H</u>$_3$), 0.89 (9H, s, Si^t<u>Bu</u>), 0.07 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ(^{13}C)(100MHz) 176.6 (C=O lactone), 107.6, 87.3, 83.8, 79.8, 62.7, 36.1, 30.0, 29.2, 29.0, 28.8, 26.9, 25.9, 21.2, 20.7, 18.4, -5.3 ((<u>C</u>H_3)Si(CH_3)), -5.3 ((CH_3)Si(<u>C</u>H_3)); MS (CI, (NH_3)) *m/z* 402 (M+NH4$^+$, 82%), 253 (M^+-$(CH3)_2{}^tBuSiO$, 100); HRMS (CI) $C_{20}H_{40}NO_5Si$ *m/z* Calc. 385.2410; Found 385.2410. In a similar manner (**143b**) gave the minor isomer (**141b**). **Minor isomer (141b):** m.p. 66-67°C; ν_{max}($CDCl_3$ solution) 2996, 2956, 2930, 2894, 2858, 1767 (C=O lactone), 1465, 1252, 1158, 1020cm^{-1}; δ(^{1}H)(400MHz) 4.07 (1H, dd, J_1 = 6.8 Hz, J_2 = 6Hz,

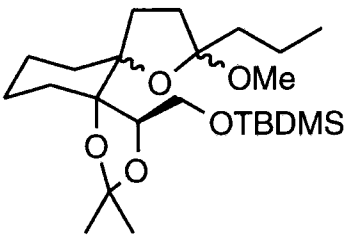
C<u>H</u>CH$_2$OSi), 3.81 (1H, dd, J_1 = 12Hz, J_2 = 6Hz, HC<u>H</u>OSi), 3.71 (1H, dd, J_1 = 12Hz, J_2 = 6.8Hz, <u>H</u>CHOSi), 2.55-2.43 (3H, m, HC<u>H</u>C<u>H</u>$_2$C=O), 2.12-1.94 (1H, m, <u>H</u>CHCH$_2$C=O), 1.90-1.82 (1H, m, HC<u>H</u>COC(CH$_3$)$_2$), 1.81-1.37 (7H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C(<u>H</u>)HCOC(CH$_3$)$_2$), 1.34 (3H, s, C<u>H</u>$_3$CCH$_3$), 1.27 (3H, s, CH$_3$CC<u>H</u>$_3$), 0.82 (9H, s, Si^t<u>Bu</u>), 0.06 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ(^{13}C)(100MHz) 176.5 (C=O lactone), 107.6, 87.3, 83.8, 65.9, 62.8, 36.1, 30.0, 29.2, 29.0, 28.9, 26.9, 25.9, 21.2, 20.7, 18.4, -5.3 ((<u>C</u>H$_3$)Si(CH$_3$)), -5.3 ((CH$_3$)Si(<u>C</u>H$_3$)); MS (CI, (NH$_3$)) *m/z* 402 (M+NH4$^+$, 21%), 253 (M$^+$-(CH3)$_2$^{t}BuSi, 100); HRMS (CI) C$_{20}$H$_{40}$NO$_5$Si *m/z* Calc. 385.2410; Found 385.2410; Analysis Found: C, 62.13%; H, 9.38%. C$_{20}$H$_{36}$O$_5$Si requires C, 62.46%; H, 9.43%.

<u>8-Allyl-4-(^{t}butylbimethylsilyloxymethyl)-2,2-dimethyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecan-8-ol (**144a**)</u>



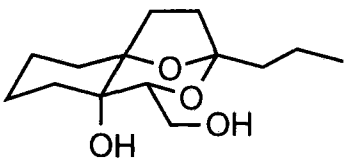
To a stirred solution of lactone (**141a**) (0.034g, 0.09mmol) in ether (0.5ml) at -78°C was slowly added allylmagnesium bromide (0.11ml, 0.086mmol). After 0.5h (tlc 2:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (3:1 petrol:ether) to afford 0.037g (95.6%) of the desired product (**144a**) as a 1.3:1 mixture of unseparable isomers.

4-(^{t}butylbimethylsilyloxymethyl)-8-methoxy-2,2-dimethyl-8-propyl-1,3,7-trioxa-dispiro<4.0.4.4>tetradecane (**158a**)



The alkene (**144a**) (0.058g, 0.14mmol) was dissolved in methanol (1ml) and added, *via* cannula, to a suspension of palladium hydroxide (0.001g, 0.0014mmol) in methanol (1ml). The mixture was degassed and stirred vigorously for 2h under hydrogen. On completion of the reaction (tlc 4:1 petrol:ether) the reaction mixture was filtered through a pad of celite, washed with methanol and concentrated to afford a yellow liquid which was purified by flash column chromatography (2:1 petrol:ether) to afford 0.057g (94.2%) of the methyl acetal (**158a**) as a colourless oil.

6-Hydroxy-9-propyl-8,12-dioxatricyclo<7.2.1.0>dodec-7-yl-1-methanol[28] (**157**)



To a stirred solution of propyl lactol (**158a**) (0.052, 0.12mmol) in methanol was added 12M HCl (0.06ml, 0.72mmol) at 0°C and the reaction mixture allowed to warm to room temperature. This was then heated to reflux for 12h whereupon the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (2:1 petrol:ether) to afford 0.011g (36.9%) of the desired product (**157**) as a white solid. m.p. 79°C; ν_{max}($CDCl_3$ solution) 2958, 2932, 2844, 1676, 1596, 1211, 1190, 1077cm^{-1}; δ(^{1}H)(400MHz) 4.29 (1H, dd, J_1 = 5.9Hz, J_2 = 3.0Hz, C<u>H</u>OCCH_2CH_2CH_3), 3.50 (2H, m, C<u>H</u>$_2$OH), 2.07 (1H, m, -OCC(H)<u>H</u>CH_2C-), 1.93 (2H, m, -OCC(H)HC(<u>H</u>)<u>H</u>C-), 1.68 (6H, m, O<u>H</u>, O<u>H</u>,

-OCC(H)HCH$_2$C-, CH$_2$CH$_2$CH$_3$, CH$_2$C(H)HCOH), 1.53-1.42 (9H, m, CH$_2$CH$_2$CH$_2$C(H)HCOH, CH$_2$CH$_3$), 0.93 (3H, t, J = 5.9Hz, CH$_3$); δ(^{13}C)(100MHz) 108, 83.5, 78.3, 69.1, 63.1, 39.5, 33.4, 33.1, 24.8, 21.1, 20.3, 16.7, 14.2; MS (CI, (NH_3)) *m/z* 257 (MH^+, 100%), 239 (MH^+-H_2O, 100); HRMS (CI) $C_{14}H_{25}O_4$*m/z* Calc. 257.1753; Found 257.1753.

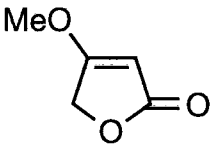
3Methoxybut-2-enoate[75] (**161**)

To a stirred solution of ethyl acetoacetate (**160**) (6.5g, 50mmol) and freshly distilled timethyl orthoformate (5.3g, 50mmol) in methanol (5ml) was added 12M HCl (0.03ml, 0.36mmol). The mixture was immediately distilled through an efficient fractionating column (lit. bpt 188-193°C) to form ethyl 3-methoxybut-2-enoate (**161**) (7.2g, 100%). This was subsequently used without further purification.

Ethyl 4-bromo-3-methoxybut-2-enoate[75] (**162**)

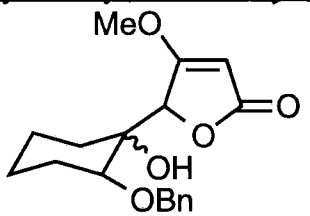
Ethyl 3-methoxybut-2-enoate (**161**) (7.2g, 43mmol) was heated to 100-115°C And was vigorously stirred while *N*-bromosuccinimide (7.5g, 43mmol) was added in small portions, the temperature during the addition being kept at 100°C. When addition was complete, the mixture was cooled to 70-80°C and vigorously stirred while water (12.5ml, 12.5mmol) was added. The aqueous layer was separated and the organic later was washed with water, dried ($MgSO_4$) filtered and distilled (lit. bpt 134-139/30mmHg) to give the desired bromide (**162**) (8.9g, 95.5%).

Methyl tetronate[75] (**159**)



A mixture of the bromide (**162**) (8.9g, 41mmol), anhydrous zinc bromide (0.035g, 0.15mmol) and dry *p*-xylene (7ml) was heated at reflux for 8h, after which the solvent was removed under reduced pressure. A 2:8 (v:v) mixture of chloroform and ether (29ml) was added to the residue and the mixture was well swirled, decanted and set aside for 18h between -20-0°C. Methyl tetronate (0.7g, 15.0%), was seperated as white crystals. The filtrate was evaporated under reduced pressure and a second crop of methyl tetronate was obtained using ether/petrol as recrystallising solvent. m.p. 67°C; ν_{max}($CDCl_3$ solution) 3154, 3134, 2984, 2942, 2872, 1785, 1745, 1636, 1243, 1056cm^{-1}; δ(^{1}H)(400MHz) 5.12 (1H, s, C=C<u>H</u>C=O), 4.64 (2H, s, C<u>H</u>$_2$COC=O), 3.91 (3H, s, OC<u>H</u>$_3$); δ(^{13}C)(100MHz) 180.3 (C=O), 173.3 (<u>C</u>=CHC=O), 88.8 (C=<u>C</u>HC=O), 67.7 (H$_2$<u>C</u>OC=O), 59.4 (O<u>C</u>H$_3$); MS (EI) *m/z* 114 (M^+, 70%), 69 (M^+-CO_2H, 100).

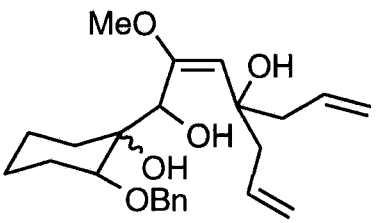
5-(1-Hydroxy-2-benzyloxy-cyclohexyl)-4-methoxy-5H-furan-2-one[75] (**163**)



To a stirred solution of butyl lithium (1.1ml, 1.76mmol) in THF (10ml) at -78°C was added a cooled solution of tetronate (**159**) and the mixture stirred for 4h before the addition of 2-benzyloxycyclohexanone (**48**) (0.294g, 1.44mmol) in THF (2ml) at -78°C. The mixture allowed to warm to room temperature and after 12h (tlc 6:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (6:1 petrol:ether) to afford the desired product (**163**) (0.242g, 53.9%) existing as a 1.3:1 mixture of isomers. **Major isomer:** ν_{max}($CDCl_3$ solution) 3154, 3132, 3032, 2941, 2864,

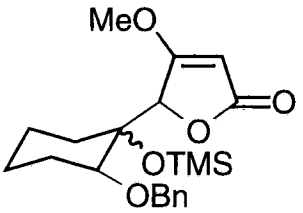
1794, 1749, 1626, 1244, 1053cm^{-1}; δ(^{1}H)(400MHz) 7.34 (5H, m, $C_6\underline{H}_5$), 5.12 (1H, s, C=C$\underline{H}$C=O), 5.06 (1H, s, $\underline{H}$COC=O), 4.66 & 4.55 (1H each, AB system, J = 11.2Hz, OC$\underline{H}_2C_6H_5$), 3.89 (3H, s, OC$\underline{H}_3$), 3.69 (1H, m, C$\underline{H}$OC$H_2C_6H_5$), 2.56 (1H, br, O$\underline{H}$), 1.92-1.26 (8H, m, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CHOC$H_2C_6H_5$); δ(^{13}C)(100MHz) 182.1 (C=O), 172.3 (C=CHC=O), 138.1 (Ar), 128.4 (Ar), 127.9 (Ar), 127.8 (Ar), 90.1 (C=CHC=O), 79.7, 78.2, 74.5, 71.3 (H_2COC=O), 59.7 (OCH_3), 28.1, 26.0, 23.5, 20.0; MS (CI, (NH_3)) *m/z* 319 (MH^+, 7%), 253 (MH^+-$(CH_2)_4$CH(OH)CH(OC$H_2C_6H_5$)-, 100); HRMS (CI) $C_{18}H_{23}O_5$ *m/z* Calc. 319.1545; Found 319.1545. **Minor isomer:** ν_{max}($CDCl_3$ solution) 3562, 2943, 2864, 1746, 1625, 1354, 1243cm^{-1}; δ(^{1}H)(400MHz) 7.38-7.23 (5H, m, $C_6\underline{H}_5$), 4.81 (1H, s, C$\underline{H}$C=O), 4.50 (1H, s, C$\underline{H}$COH), 4.41 & 4.30 (1H each, AB system, J_1 = 10.8Hz, OC$\underline{H}_2C_6H_5$), 3.45 (1H, m, C$\underline{H}$OC$H_2C_6H_5$), 3.24 (3H, s, OC$\underline{H}_3$), 2.94 (1H, br, O$\underline{H}$), 2.09-1.12 (8H, m, (C$\underline{H}_2$)$_4$COH); (^{13}C)(400MHz) 182.9 (C=O), 172.5 (C=CHC=O), 137.9 (Ar), 128.3 (Ar), 128.1 (Ar), 127.8 (Ar), 87 (C=CHC=O), 81.6, 76.2, 76.1, 70.4 (H_2COC=O), 58.8 (OCH_3), 33.9, 26.0, 23.4, 20.2; MS (CI, (NH_3)) *m/z* 336 ($M+NH_4^+$, 38%), 319 (MH^+, 87), 222 ($M+NH_4^+$-CH_2OC(O)CH=C(OCH_3)-), 132 ($M+NH_4^+$-$(CH_2)_4$CH(OH)CH(OC$H_2C_6H_5$)-, 100); HRMS (CI) $C_{18}H_{23}O_5$ *m/z* Calc. 319.1545; Found 319.1545.

Attempted Allylation of Tetronate (**163**) (**165**)



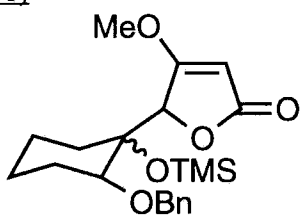
To a stirred solution of tetronate (**153**) (0.10g, 0.33mmol) in ether (5ml) at -78°C was slowly added allylmagnesium bromide (0.40ml, 0.40mmol). After 4h (tlc 10:1 petrol:ether) the reaction was quenched with sat. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (10:1 petrol:ether) to afford a mixture of compounds including di-allylated products.

Attempted Preparation of 5-(1-Trimethylsilyloxy-2-benzyloxy-cyclohexyl)-4-methoxy-5H-furan-2-one[58] (**166**)



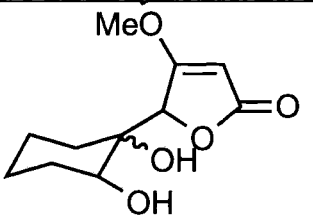
To a solution of alcohol (**163**) (0.09g, 0.29mmol) in THF (3ml) was added triethylamine (0.05ml, 0.35mmol) and trimethylsilyl triflate (0.07ml, 0.35mmol) at 0°C. The mixture was then allowed to warm to room temperature and followed by tlc (2:1 petrol:ethyl acetate). After 2h the mixture was quenched with water, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated to afford 0.01g of an alkene (**167**) upon flash column chromatography (2:1 petrol:ethyl acetate).

Attempted Preparation of 5-(1-Trimethylsilyloxy-2-benzyloxy-cyclohexyl)-4-methoxy-5H-furan-2-one (**166**)



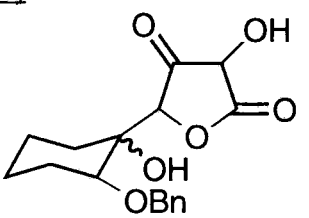
To a solution of alcohol (**163**) (0.12g, 0.37mmol) in THF (3ml) was added triethylamine (0.05ml, 0.40mmol) and trimethylsilyl chloride (0.07ml, 0.59mmol) at 0°C. The mixture was then allowed to warm to room temperature and followed by tlc (2:1 petrol:ethyl acetate). There was no reaction after 4h so the mixture was quenched with water, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated to afford 0.09g (73.2%) recovered starting material (**163**) upon flash column chromatography (2:1 petrol:ethyl acetate).

5-(1,2-dihydroxy-cyclohexyl)-4-methoxy-5H-furan-2-one (**168**)



The tetronate (**163**) (0.05g, 0.15mmol) was dissolved in methanol (1ml) and added, *via* cannula, to a suspension of palladium hydroxide (0.002g, 0.03mmol) in methanol (1ml). The mixture was degassed and stirred vigorously for 2h under hydrogen. The mixture was filtered through a pad of celite, washed with methanol and concentrated to afford a yellow liquid which was purified by flash column chromatography (ethyl acetate) to afford the diol (**168**) (0.029g, 84.8%) as a waxy solid. **Major isomer:** m.p. 156°C; ν_{max}(KBr disc) 3531 (OH), 3431 (OH), 2939, 2855, 1724 (C=O), 1619 (C=C) cm^{-1}; $\delta(^1H)$(400MHz) 5.10 (1H, s, C=C<u>H</u>C=O), 4.89 (1H, s, <u>H</u>COC=O), 3.90 (3H, s, OC<u>H</u>$_3$), 3.64 (1H, m, C<u>H</u>OH), 2.70 (1H, br, HOCCOC=O), 2.13 (1H, br d, J_1 = 6.8Hz, <u>H</u>OCHC(OH)C(H)OC=O), 1.82-1.04 (8H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$COH); $\delta(^{13}C)$(100MHz) 181.3 (C=O), 171.9 (<u>C</u>=CHC=O), 89.5 (C=<u>C</u>HC=O), 82.4, 74.5, 70.3 (H<u>C</u>OC=O), 59.6 (O<u>C</u>H$_3$), 31.3, 30.4, 23.8, 19.8; MS (EI) *m/z* 229 (MH^+, 13%), 115 (MH^+-$(CH_2)_4$C(H(OH)CH(OH)-, 100); HRMS (EI) $C_{11}H_{17}O_5$*m/z* Calc. 229.1076; Found 229.1076.

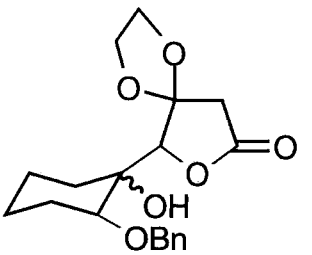
Attempted Preparation of (**170**)



A catalytic amount of osmium(IV) oxide (0.03ml, 0.03mmol), water (0.03ml, 0.03mmol) and NMO (0.05g, 0.41mmol) was added to a solution of tetronate (**163**) in ^{t}butanol (1ml). The mixture was stirred at 30°C for 16h however no reaction was shown to have taken place (tlc 2:1 petrol:ethyl acetate) so excess sodium metabisufite was added and the mixture stirred for 0.5h. The slurry was

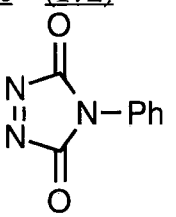
filtered through a pad of celite and concentrated to afford a yellow oil which was purified by flash column chromatography to afford 0.07g (82.8%) recovered starting material (**163**).

Attempted Preparation of (**171**)



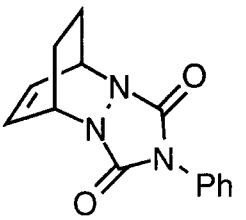
PTSA (3mg, 0.02mmol) was added to a mixture of tetronate (**163**) (0.05g, 0.16mmol) and ethylene glycol (0.02g, 0.31mmol) in benzene (2ml). The mixture was heated to reflux for 27h however no reaction occurred (tlc 2:1 petrol:ethyl acetate) and the reaction was quenched with sat. $NaHCO_3$, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated to afford only recovered starting material (**163**).

4-Phenyl-1,2,4-triazoline-3,5-dione[77] (**172**)



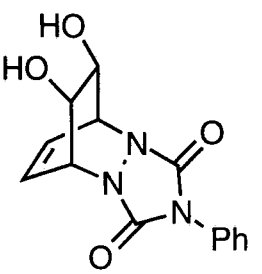
Gaseous nitrogen tetroxide was passed through a narrow tube to a cold (0°C) slurry of 4-phenyl urazole (**173**) (1.0g, 8.54mmol) and anhydrous sodium sulphate (16.0g, 113mmol) in DCM (50ml) until all the urazole had dissolved. The solution was maintained at 0°C during the reaction then it was filtered, washed with DCM and concentrated to afford 0.99g, 95.6% desired product (**172**) which was used without further purification. ν_{max} (KBr disc) 2945, 2940, 1738 (C=O); $\delta(^1H)$(400MHz) 7.51-7.38 (6H, m, C_6H_5); $\delta(^{13}C)$(100MHz) 157.7 (C=O), 129.9 (Ar), 129.5 (Ar), 129.4 (Ar), 123.9 (Ar).

4-Phenyl-2,4,6-triaza-tricyclo<5.2.2.0^{2,6}>undec-8-ene-3,5-dione[76] (**174**)



To a solution of 1,4-cyclohexadiene (0.14g, 1.7mmol) in DCM (1ml) at -78°C was added a cooled solution of triazolinone (**172**) (0.15g, 0.86mmol) in DCM (5ml). Almost immediately a colour change from deep red to yellow was observed, whereupon the mixture was concentrated to afford 0.18g (82.1%) desired product (**174**) after recrystallisation from ethyl acetate/petrol. m.p. 177-179°C; ν_{max}(KBr disc) 2958, 2928, 2856, 1764 (C=O), 1705 (C=C), 1497, 1410, 1261cm^{-1}; δ(^{1}H)(400MHz) 7.44-7.34 (5H, m, C_6H_5), 6.51 (2H, m, CH=CH), 4.96 (2H, m, 2CHN), 2.21 (2H, m, HCHHCH), 1.61 (2H, m, HCHHCH); δ(^{13}C)(100MHz) 171.0 (C=O), 160.8 (C=O), 136.7 (Ar), 128.6 (Ar), 128.2 (Ar), 122.6 (Ar), 118.0, 113.8, 89.9, 59.2, 25.5, 24.7; MS (CI, (NH_3)) *m/z* 273 (M+NH4$^+$, 96%), 256 (MH$^+$, 100); HRMS (CI) $C_{14}H_{14}N_3O_2$*m/z* Calc. 256.1086; Found 256.1086.; Analysis Found: C, 65.69%; H, 5.20%; N, 16.54%. C14H13N3O2 requires C, 65.87%; H, 5.13%; N, 16.46%.

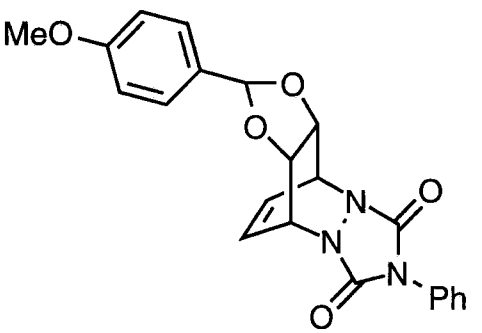
10,11-Dihydroxy-4-phenyl-2,4,6-triaza-tricyclo<5.2.2.0^{2,6}>undec-8-ene-3,5-dione[76] (**175**)



To a stirred solution of *cis*-cyclohexadiene diol (**42**) (0.55ml, 0.89mmol) in DCM (1ml) was added the triazolinone (**172**) (0.23g, 1.33mmol) in DCM (5ml) at -40°C. The reaction was monitored by nmr and after 2h the mixture was concentrated to afford 0.058g (22.6%) desired diol (**175**) as a white solid after purification by flash column chromatography (neat ethyl acetate). m.p. 228°C;

ν_{max}(KBr disc) 3276 (OH), 1768, 1704, 1610, 1496, 1413, 1278cm^{-1}; δ(^{1}H)(400MHz) 7.49-7.37 (5H, m, $C_6\underline{H}_5$), 6.51 (2H, m, C<u>H</u>=C<u>H</u>), 5.30 (2H, m, 2<u>H</u>CN), 4.77 (2H, m, 2C<u>H</u>OH), 3.78 (2H, br, 2O<u>H</u>); δ(^{13}C)(100MHz) 170.3 (C=O), 154.3 (C=O), 131.7, 130.3 (Ar), 129.0 (Ar), 128.1 (Ar), 126.0 (Ar), 61.5, 55.9; MS (EI) *m/z* 287 (M^+, 16%), 227 (M^+-$(CH_2OH)_2$, 100); HRMS (EI $C_{14}H_{13}N_3O_4$ *m/z* Calc. 287.0910; Found 287.0910.

<u>10-(4-methoxyphenyl)-4-phenyl-9,11-dioxa-2,4,6-triazatetracyclo<5.5.2.0^{2,6}.0^{8,12}>tetradec-13-ene-3,5-dione</u>[76,78] <u>(**180**)</u>



To a solution of *para*-anisaldehyde dimethyl acetal (0.89g, 4.89mmol) and *cis*-cyclohexadiene diol (**42**) (0.55ml, 0.89mmol) in deuterated chloroform (0.6ml) was added *para*-toluene sulphonic acid (0.017g, 0.089mol) at -78°C. The mixture was allowed to warm to -40°C wherupon aliquots were removed and quenched with $NaHCO_3$ then analysed by NMR. After 1.5h the reaction had gone to completion and $NaHCO_3$ (0.015g, 0.17mmol) was added before the addition of the triazolinone (**172**) (0.23g, 1.33mmol) in DCM (5ml) at -40°C. Again the reaction was monitored by nmr and after a further 2h the mixture was concentrated to afford (0.217g, 60.2%) of a mixture of isomers (1.3:1) after recrystallisation from ethyl acetate/petrol. **Major isomer:** m.p. 207-209°C; ν_{max}(KBr disc) 2966, 2940, 2896, 1772 (C=O), 1716 (C=C), 1406, 1176, 1139cm^{-1}; δ(^{1}H)(400MHz) 7.45- 7.24 (5H, m, C_6H_5), 7.33 (2H, d, J = 8.8Hz, **Ar**), 6.88 (2H, d, J = 8.8Hz, **Ar**), 6.53 (2H, t, J = 3.6Hz, C<u>H</u>=C<u>H</u>), 5.76 (1H, s, ArC<u>H</u>(O)O), 5.27 (2H, m, 2C<u>H</u>N), 4.70 (2H, m, 2C<u>H</u>OC), 3.79 (3H, s, $OC\underline{H}_3$); δ(^{13}C)(100MHz) 161.0 (C=O), 155.6 (C=O), 131.1, 130.1, 129.2, 128.7, 127.4,

126.8, 125.5, 113.8, 105.6, 74.7, 74.0, 55.3, 52.2; MS (CI, (NH_3)) *m/z* 423 (M+NH4$^+$, 23%), 406 (MH^+, 11), 137 (MH^+-$(CH_3)_2C(O)O$, 100); HRMS (CI) $C_{22}H_{24}N_4O_5$*m/z* Calc. 423.1668; Found 423.1668.; Analysis Found: C, 64.99%; H, 4.73%; N, 10.37%. $C_{22}H_{19}N_3O_5$ requires C, 65.18%; H, 4.72%; N, 10.36%.

Appendix
Requirements for the Board of Studies

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix listing:-

i. all research colloquia, seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student;

ii. lectures organised by Durham University Chemical Society;

iii. details of the postgraduate induction course; and

iv. all research conferences attended and papers presented by the author during the period when research for the thesis was carried out.

Colloquia, Lectures and Seminars From Invited Speakers

1993-1996

September 13 Prof. Dr. A. D. Schlüter, Freie Universität Berlin, Germany*
Synthesis and Characterisation of Molecular Rods and Ribbons.

September 13 Prof. K. J. Wynne, Office of Naval Research, Washington, U.S.A.
Polymer Surface Design for Minimal Adhesion

September 14 Prof. J. M. DeSimone, University of North Carolina, Chapel Hill, U.S.A.
Homogeneous and Heterogeneous Polymerisations in Enviromentally Responsible Carbon Dioxide.

September 28 Prof. H. Ila., North Eastern University, India*
Synthetic Strategies for Cyclopentanoids via OxoKetene Dithiacetals.

October 4 Prof. F. J. Feher , University of California at Irvine
Bridging the Gap between Surfaces and Solution with Sessilquioxanes.

October 14 Dr. P. Hubberstey, University of Nottingham*
Alkali Metals: Alchemist's Nightmare, Biochemist's Puzzle and Technologist's Dream.

October 20 Dr. P. Quayle , Unversity of Manchester*
Aspects of Aqueous Romp Chemistry.

October 23 Prof. R. Adams , University of S. Carolina*
The Chemistry of Metal Carbonyl Cluster Complexes Containing Platinum and Iron, Ruthenium or Osmium and the Development of a Cluster Based Alkyne Hydrogenating Catalyst.

October 27 Dr. R. A. L. Jones , Cavendish Laboratory*
'Perambulating Polymers'.

November 10 Prof. M. N. R. Ashfold , University of Bristol
High-Resolution Photofragment Translational Spectroscopy: A New Way to Watch Photodissociation.

November 17 Dr. A. Parker , Laser Support Facility
Applications of Time Resolved Resonance Raman Spectroscopy to Chemical and Biochemical Problems.

November 24 Dr. P. G. Bruce , University of St. Andrews*
Synthesis and Applications of Inorganic Materials.

December 1 Prof. M. A. McKervey , Queens University, Belfast*
Functionlised Calixerenes.

December 8 Prof. O. Meth-Cohen, Sunderland University*
Friedel's Folly Revisited.

December 16 Prof. R. F. Hudson, University of Kent
Close Encounters of the Second Kind.

1994

January 26 Prof. J. Evans , University of Southhampton*
Shining Light on Catalysts.

February 2 Dr. A. Masters , University of Manchester*
Modelling Water Without Using Pair Potentials.

February 9 Prof. D. Young , University of Sussex*
Chemical and Biological Studies on the Coenzyme Tetrahydrofolic Acid.

February 16 Prof. K. H. Theopold, University of Delaware, U.S.A
Paramagnetic Chromium Alkyls: Synthesis and Reactivity.

February 23 Prof. P. M. Maitlis , University of Sheffield*
Why Rodium in Homogenous Catalysis.

March 2 Dr. C. Hunter , University of Sheffield*
Non Covalent Interactions between Aromatic Molecules.

March 9 Prof. F. Wilkinson, Loughborough University of Technology
Nanosecond and Picosecond Laser Flash Photolysis.

March 10 Prof. S.V. Ley, University of Cambridge*
New Methods for Organic Synthesis.

March 25 Dr. J. Dilworth, University of Essex
Technetium and Rhenium Compounds with Applications as Imaging Agents.

April 28 Prof. R. J. Gillespie, McMaster University, Canada*
The Molecular Structure of some Metal Fluorides and OxoFluorides: Apparent Exceptions to the VSEPR Model.

May 12 Prof. D. A. Humphreys, McMaster University, Canada
Bringing Knowledge to Life

October 5 Prof. N. L. Owen, Brigham Young University, Utah, USA
Determining Molecular Structure - the INADEQUATE NMR way

October 19 Prof. N. Bartlett, University of California*
Some Aspects of Ag(II) and Ag(III) Chemistry

November 2 Dr P. G. Edwards, University of Wales, Cardiff*
The Manipulation of Electronic and Structural Diversity in Metal Complexes - New Ligands

November 3 Prof. B. F. G. Johnson, Edinburgh University*
Arene - Metal Clusters - DUCS Lecture

November 9 Dr J. P. S. Badyal, University of Durham
Chemistry at Surfaces, A Demonstration Lecture

November 9 Dr G. Hogarth, University College, London*
New Vistas in Metal Imido Chemistry

November 10 Dr M. Block, Zeneca Pharmaceuticals, Macclesfield*
Large Scale Manufacture of the Thromboxane Antagonist Synthase Inhibitor ZD 1542

November 16 Prof. M. Page, University of Huddersfield*
Four Membered Rings and b-Lactamase

November 23 Dr J. M. J. Williams, University of Loughborough*
New Approaches to Asymmetric Catalysis

December 7 Prof. D. Briggs, ICI and University of Durham
Surface Mass Spectrometry

1995

January 11 Prof. P. Parsons, University of Reading*
Applications of Tandem Reactions in Organic Synthesis

January 18 Dr G. Rumbles, Imperial College, London
Real or Imaginary 3rd Order non-Linear Optical Materials

January 25 Dr D. A. Roberts, Zeneca Pharmaceuticals*
The Design and Synthesis of Inhibitors of the Renin-Angiotensin System

February 1 Dr T. Cosgrove, Bristol University
Polymers do it at Interfaces

February 8 Dr D. O'Hare, Oxford University
Synthesis and Solid State Properties of Poly-, Oligo- and Multidecker Metallocenes

February 22 Prof. E. Schaumann, University of Clausthal*
Silicon and Sulphur Mediated Ring-opening Reactions of Epoxide

March 1 Dr M. Rosseinsky, Oxford University
Fullerene Intercalation Chemistry

October 11 Prof. P. Lugar, Frei Univ Berlin, FRG
Low Temperature Crystallography

October 13 Prof. R. Schmultzer, Univ Braunschwieg, FRG
Calixarene-Phosphorus Chemistry: A New Dimension in Phosphorus Chemistry

October 18 Prof. A. Alexakis, Univ. Pierre et Marie Curie, Paris*
Synthetic and Analytical Uses of Chiral Diamines

October 25 Dr.D.Martin Davies, University of Northumbria*
Chemical reactions in organised systems.

November 1 Prof. W. Motherwell, UCL London*
New Reactions for Organic Synthesis

November 3 Dr B. Langlois, University Claude Bernard-Lyon*
Radical Anionic and Psuedo Cationic Trifluoromethylation

November 8 Dr. D. Craig, Imperial College, London*
New Stategies for the Assembly of Heterocyclic Systems

November 15 Dr Andrea Sella, UCL, London
Chemistry of Lanthanides with Polypyrazoylborate Ligands

November 17 Prof. David Bergbreiter, Texas A&M, USA
Design of Smart Catalysts, Substrates and Surfaces from Simple Polymers

November 22 Prof. I Soutar, Lancaster University
A Water of Glass? Luminescence Studies of Water-Soluble Polymers.

November 29 Prof. Dennis Tuck, University of Windsor, Ontario, Canada
New Indium Coordination Chemistry

December 8 Professor M.T. Reetz, Max Planck Institut, Mulheim*
Perkin Regional Meeting

1996

January 10 Dr Bill Henderson, Waikato University, NZ*
Electrospray Mass Spectrometry - a new sporting technique

January 17 Prof. J. W. Emsley , Southampton University
Liquid Crystals: More than Meets the Eye

January 24 Dr Alan Armstrong, Nottingham Univesity*
Alkene Oxidation and Natural Product Synthesis

January 31 Dr J. Penfold, Rutherford Appleton Laboratory,
Soft Soap and Surfaces

February 7 Dr R.B. Moody, Exeter University*
Nitrosations, Nitrations and Oxidations with Nitrous Acid

February 12 Dr Paul Pringle, University of Bristol
Catalytic Self-Replication of Phosphines on Platinum(O)

February 14 Dr J. Rohr, Univ Gottingen, FRG*
Goals and Aspects of Biosynthetic Studies on Low Molecular Weight Natural Products

February 21 Dr C R Pulham , Univ. Edinburgh
Heavy Metal Hydrides - an exploration of the chemistry of stannanes and plumbanes

February 28 Prof. E. W. Randall, Queen Mary & Westfield College
New Perspectives in NMR Imaging

March 6 Dr Richard Whitby, Univ of Southampton*
New approaches to chiral catalysts: Induction of planar and metal centred asymmetry

March 7 Dr D.S. Wright, University of Cambridge
Synthetic Applications of Me_2N-p-Block Metal Reagents

March 12 RSC Endowed Lecture - Prof. V. Balzani, Univ of Bologna
Supramolecular Photochemistry

March 13 Prof. Dave Garner, Manchester University
Mushrooming in Chemistry

April 30 Dr L.D.Pettit, Chairman, IUPAC Commission of Equilibrium Data
pH-metric studies using very small quantities of uncertain purity

Invited specially for the graduate training programme.
* Those attended by the author.

First Year Induction Courses

This course consists of a series of one hour lectures on the services available in the department.

Departmental Organisation -	Dr. E.J.F. Ross
Safety Matters -	Dr. G.M. Brooke
Electrical Appliances -	Mr. B.T. Barker
Chromatography and Microanalysis -	Mr. T.F. Holmes
Absorptiometry and Inorganic Analysis -	Mr. R. Coult
Library Facilities -	Mr. R.B. Woodward
Mass Spectroscopy -	Dr. M. Jones
Nuclear Magnetic Resonance Spectroscopy -	Dr. R.S. Matthews
Glass-blowing Techniques -	Mr. R. Hart and Mr. G. Haswell

Research Conferences Attended

December 1993	Modern Aspects of Stereochemistry Sheffield University
December 19934	Modern Aspects of Stereochemistry Sheffield University
September 1995	8th RSC-SCI Medicinal Chemistry Symposium Cambridge.
July 1996	BOSS-6 Gent, Belgium.

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