Studies towards the first synthesis of Tetronothiodin

Additional Information:

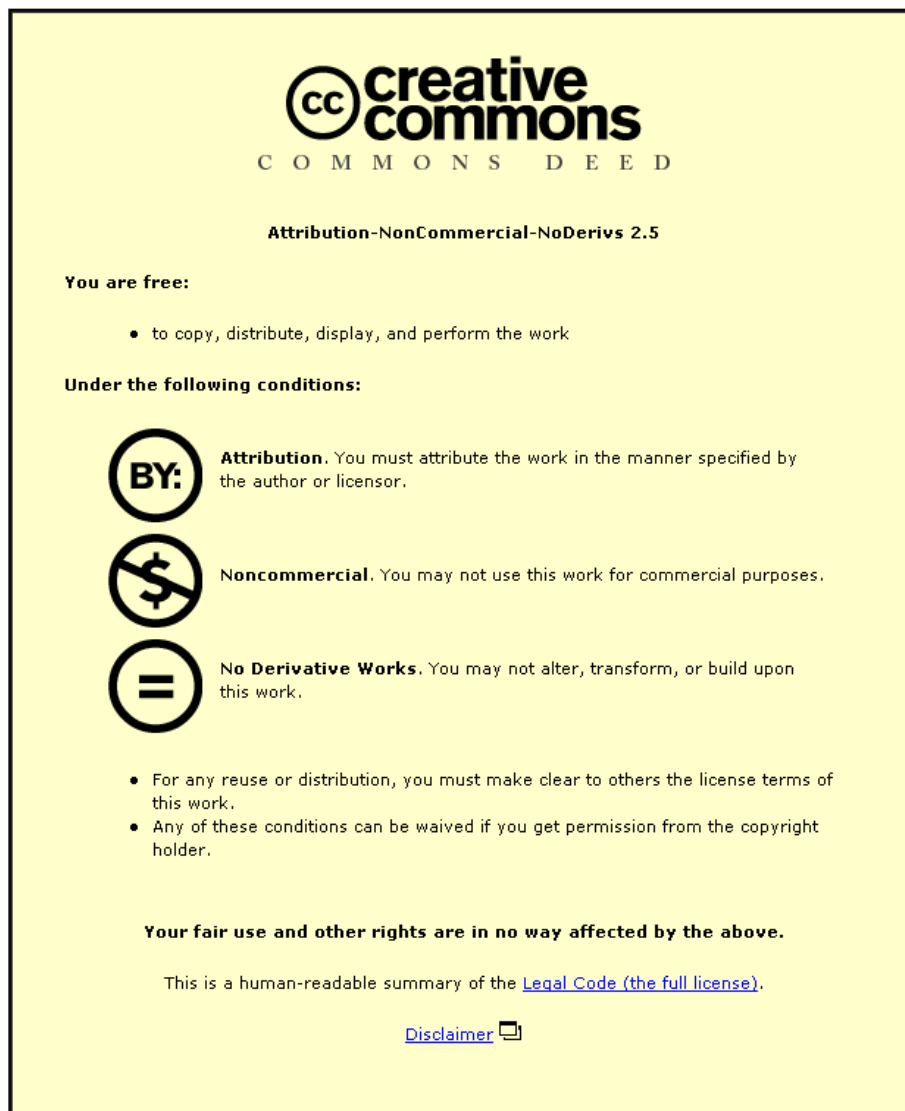# Studies towards the first synthesis of Tetronothiodin

By

Olivier Dubert

A doctoral thesis

Submitted in partial fulfilment of the requirements

For the award of

Doctor of Philosophy of Loughborough University

22th December 2005

Abstract

In our studies towards the synthesis of tetronothiodin, we completed the synthesis of **195**, a precursor of the oxaspirobyciclic unit of tetronothiodin.

The synthesis was achieved in an eight step strategy and afforded the α-hydroxy lactone **195** as a diasteroisomeric mixture with **194** in a 5.7% overall yield.
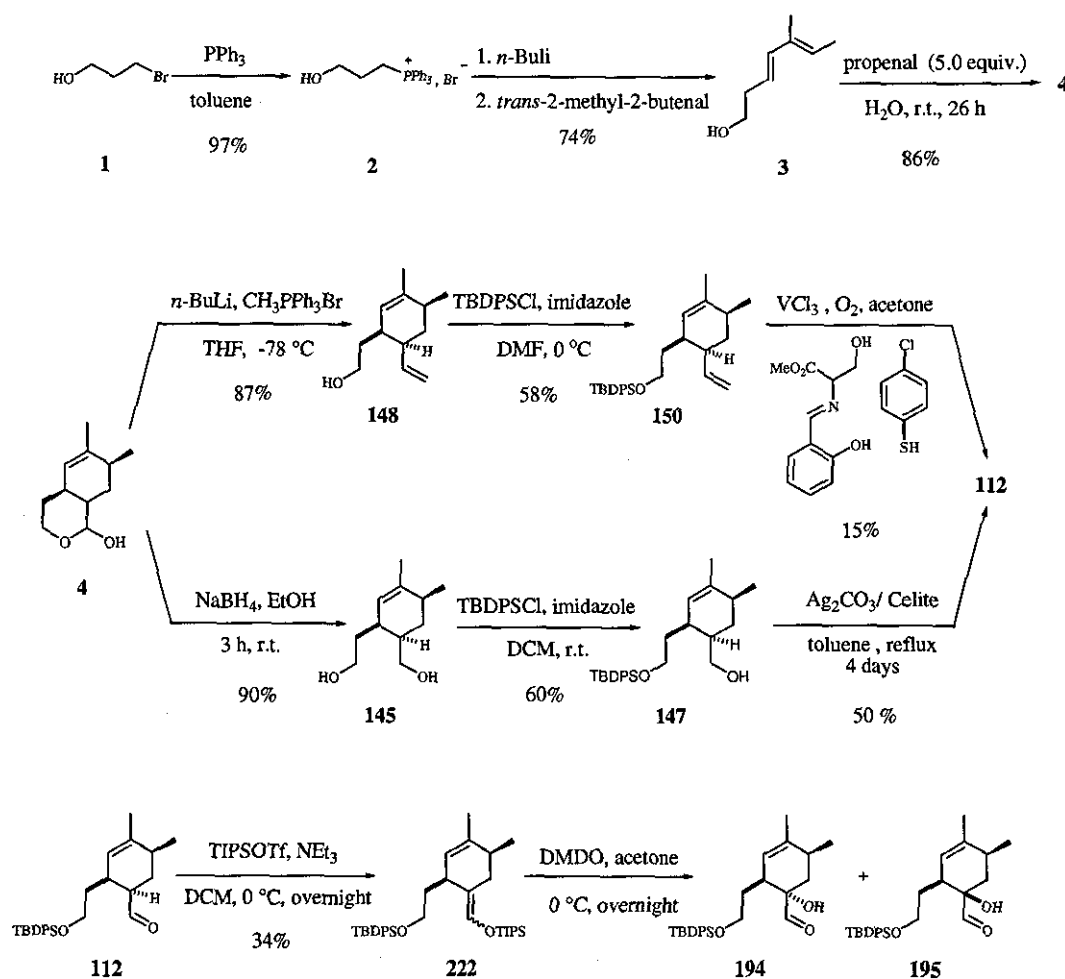
Chapter 1: provides a report of the biological effects of tetronothiodin and a survey of a selection of previous syntheses of oxaspirobyciclic units.

Chapter 2: states the progress and the shortfalls encountered during my three years of research.

Chapter 3: provides experimental data for our studies.

Acknowledgements

Abbreviations

Ac	Acetyl
acac	acetylacetonate
AP	anterior pituitary
aq.	aqueous
Asp	aspartic acid
BHT	butylated hydroxy toluene (2,6-di-*t*-butyl-4-methylphenol)
Bn	benzyl
Boc	tertiary butyloxycarbonyl (CO-*t*-C_4H_9)
Bp	boiling point
br	broad
Bt_2cGMP	dibutyryl cyclic Guanosine Monophosphate
t-Bu	tertiary butyl
n-Buli	normal butyl lithium
Bz	benzoyl
Cat.	catalytic
Cbz	carboxybenzyl (BnO-C=O)
CCK	cholecystokinin
CCK-8 or CCK-8S	cholecystokinin-sulphurated octapeptide
CCK-8NS	cholecystokinin-desulphurated octapeptide
$CDCl_3$	deuterio chloroform
CNS	central nervous system
COSY	correlation spectroscopy (NMR)
CSA	camphorsulfonic acid
CSF	cerebrospinal fluid
°C	degree Celsius
d	doublet
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
dd	double doublet
ddd	double double doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	diastereoisomeric excess
DIBAL (DIBAH)	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one)
DMDO	dimethyl dioxirane

DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dt	double triplet
E	entgegen (opposite, trans)
e.e.	enantiomeric excess
EI	electron impact (MS)
equiv.	equivalent
Et	ethyl
FAB	fast atom bombardment (MS)
F.S.	Frémy's Salt (KO$_3$S)2NO
GABA	γ-aminobutyric acid
Gly	glycine
G-4	tetragastrin
h	hour
HBT	hydroxybenzotriazole
HMBC	heteronuclear multiple bond correlation (NMR)
HMDS	hexamethyldisilazide
HOMO	highest occupied molecular orbital
HMPA	hexamethylphosphorictriamide
HPLC	high performance liquid chromatography
HSAB	hard-soft-acid-base
5-HT	serotonine
Hünig's Base	diisopropylethylamine
IBX	1-hydroxy-1,2-benziodoxol-3-one-1-oxide
IC$_{50}$	inhibition concentration of 50% of the specific binding
^{125}I-CCK	^{125}I-labelled Bolton Hunter cholecystokinin octapeptide
Im	imidazole
IMDA	intramolecular Diels-Alder
IPN	interpendecular nucleus
IR	infrared
iPr	*iso*-propyl
J	coupling constant (NMR)
Leu	leucine
LiAlH$_4$ (LAH)	lithium aluminum hydride
LiCA	lithium N-isopropylcyclohexylamide
LDA	lithium diisopropylamide

LHMDS (LiN(TMS)$_2$)	lithium hexamethyldisilazide
liq.	liquide
Lit.	literature
LSPD	long-range selective proton-decoupling
LUMO	lowest unoccupied molecular orbital
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Meerwein's Salt	trimethyloxonium fluoroborate
MEM	methoxyethoxymethyl (CH$_3$OCH$_2$CH$_2$O-CH$_2$-)
Met	methionine
Mp	melting point
MS	mass spectrum
Ms	methanesulfonyl (Mesyl, CH$_3$SO$_2$-)
MOM	methoxymethyl (CH$_3$OCH$_2$-)
MoOPD	oxodiperoxymolybdenum(1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone)hexamethylphosphoramide (MoO$_5$-DMPU-HMPA)
MoOPH	oxodiperoxymolybdenum(pyridine)hexamethyl phosphoramide (MoO$_5$-Py-HMPA)
MTM	methylthiomethyl (CH$_3$-S-CH$_2$-)
NBS	*N*-bromosuccinimide
Nle	norleucine
NMO	*N*-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
nOe	nuclear overhauser effect (NMR)
NTS	nucleus tractus solitarius
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Phe	parts per million
Ph	phenyl
Piv	pivaloyl
ppm	phenylalanine
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
Py	pyridine
q	quartet
r.t.	room temperature
s	singlet

SARS	structure-affinity relationship studies
TBAF	tetra-n-butylammonium fluoride
TBDMS	tertiary butyldimethylsilyl
TBDPS	tertiary butyldiphenylsilyl
TBHP	tertiary butylhydroperoxide
TCCA	3,5-trichloro-2,4,6-triazinetrione trichloroisocyanuric acid
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
Tf	triflate (CF_3SO_2)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-n-propylammonium perruthenate
Trp	tryptophan
Trityl	triphenylmethyl
Ts	tosyl (p-$CH_3C_6H_4SO_2$)
Tyr	tyrosine
UV	ultraviolet spectroscopy
Z	zusammen (together, cis)

Chapter 1

Introduction

1. Introduction

Cholecystokinin **1** is a 33-amino acid intestinal peptide hormone that was discovered in the 1920's, purified in the 1960's, and was isolated as a gastrin-like material from brain tissue in 1975 by Vanderhaegen *et al.*[1]

Lys-Ala-Pro-Ser-Gly-Arg-Val-Ser-Met-Ile-Lys-Asn-Leu-Gln-Ser-Leu-Asp-Pro-Ser-His-Arg-Ile-Ser-Asp-Arg-Asp-Tyr(SO₃H)-Met-Gly-Trp-Met-Asp-Phe-NH₂

CCK-33

1

CCK-33 **1** is a linear polypeptide hormone closely related to gastrin.[2] Both CCK and gastrin have a common terminal peptide amide sequence, but exhibit different biological effects on their target tissues. CCK is found in the mammalian intestinal tract, where it acts as a peripheral hormone, and in the central nervous system where it is the most abundant peptide, and plays the role of a central neurotransmitter or neuromodulator.

1.1. Various types of CCK peptides

The two predominant naturally occurring molecular forms of CCK peptides are CCK-58 and the sulphurated octapeptide (CCK-8S) **2** produced by the 115-amino acid preprocholecystokinin.[3]

CCK-26-33 or CCK-8

2

1
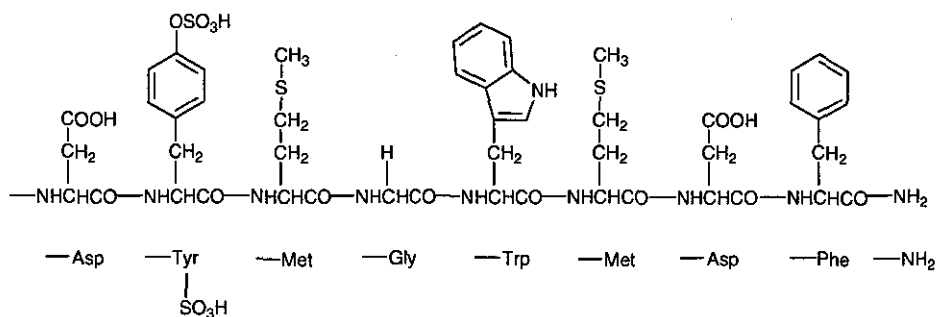
They are found in the periphery (throughout the digestive tract and in the small intestine, with high concentration in the duodenum) with, to a lesser extent, CCK-33, the biosynthetic precursor, and CCK-4 which is identical to tetragastrin (G-4) **3**, the minimal peptide sequence exhibiting a high affinity for CCK receptor binding sites.[4]

Trp-Met-Asp-Phe-NH$_2$

Tetragastrin or CCK-4

3

Most gastrin-like activity in the brain is due to CCK-8 in sulphurated (CCK-8S) and desulphurated (CCK-8NS) forms. Other molecular forms of CCK, which have the –COOH terminal penta-peptide sequence of gastrin in common, have also been identified including CCK-5, CCK-21, and CCK-12. A shorter peptide, caerulein **4**, sharing seven of the eight amino acid residues of CCK-8 has been isolated from the skin of the Australian Hylide frog, *Hyla Caerulea*, by Anatasi.[4]

Pyr-Gln-Asp-Tyr(SO$_3$H)-Trp-Gly-Trp-Met-Asp-Phe-NH$_2$

Caerulein

4

CCK-39 and CCK-59 are also found. Like CCK-8 and CCK-33, these correspond to peptides produced by cleavage of the arginine residue.

1.2. CCK as a Peripheral Hormone

CCK is an adrenohypophyseal hormone (i.e. it is secreted by the endocrine cells of the anterior pituitary gland (AP) called "mucosal epithelial cells"), and is regulated by hypothalamic hormones. CCK is released into the bloodstream, by which it is

transported to the duodenum, where it exerts its effects by selective binding to specific protein molecules known as CCK receptors.[5]

1.2.1. Effect on pancreatic releasing enzymes

Older literature refers to cholecystokinin as "pancreozymin". This name comes from the fact that CCK stimulates delivery of digestive enzymes from the pancreas into the duodenum. The pancreatic enzymes are large proteins containing around twenty amino acids. They can be divided into three major groups, critical to efficient digestion:

The proteases, which cause the bulk of protein digestion,

The pancreatic lipases, recently used as a target for management of obesity,

The amylases, the major dietary carbohydrate for many species found in starch, a storage form of glucose in plants.

The secretion of these enzymes, with the action of associated bicarbonate, contributes to the transformations of nutrients into energy.

These enzymes together have the capacity to reduce virtually all digestible macromolecules (proteins, polysaccharides and triglycerides) into forms that are capable of being absorbed, for example, amino acids, monosaccharides and fatty acids.

1.2.2. Effect on Bile Release

Cholescystokinin also provokes the contraction of the gallbladder: in fact, the name cholecystokinin (from the ancient Greek "gallbladder movement") was given to describe this effect, leading to the delivery of bile into the small intestine. Bile contains bile acids (derivatives of cholesterol), which are critical for digestion

and absorption of fats and fat-soluble vitamins. Also, many waste products are eliminated from the body by secretion into bile and elimination in faeces.

1.2.3. Interdependence of CCK and digestive secretions

Full biological activity such as gallbladder contraction, gut motility and pancreas secretion is retained by the C-terminal sulphurated octapeptide (CCK-8S).[4] Both pancreatic enzymes and bile flow lead to digestion and absorption of the molecules that stimulate cholecystokinin secretion. When absorption is completed, cholecystokinin secretion ceases, stopping the release of bile and pancreatic enzymes.

1.3. CCK as a Central Neurotransmitter or Neuromodulator

Like many substances used as peripheral hormones, cholecystokinin is also produced by neurons. It is released into the synapse by the synaptic vesicles located in the axon of a neuron, crossing this gap to the receptor located on the dendrite of the next neuron, and therefore acting as a neurotransmitter.[6,7] CCK also appears to act as a neuromodulator, modulating the activity of other hormones, and neuropeptides such as dopamine, serotonin (5-HT),[8] endogenous opioid, and γ-aminobutyric acid (GABA).[9]

CCK appears to be the most abundant neuropeptide in the central nervous system (including cerebral cortex, hippocampus, basal ganglia[10-12] and spinal cord[13]) where it is found predominantly in two forms: CCK-8 (around 80%) and CCK-4.[1,14-16]

1.3.1. Agonists and Antagonists

Specific protein molecules, known as receptors, are usually located within the cell membrane, and respond to endogenous chemicals or drugs. Chemicals that bind to receptors, and in turn activate them, are called agonists. These agonists initiate changes in cell function, producing a response, which can cause various effects. The potency of agonists depends upon two functions: the affinity for the receptor, which is the tendency to bind to a receptor and form an agonist-receptor complex; and the efficacy or the ability, once bound, to initiate changes in the receptor which leads to a response.

However, some chemicals prevent or reverse the actions of neurotransmitters by keeping them from binding to receptors. These chemicals are known as antagonists. There are two types of antagonists: the indirect antagonists such as cocaine or amphetamine, which produce their effects by changing the flow of neurotransmitters, and the direct antagonists which combine with receptors, yet fail to activate them. Direct antagonists and agonists find their efficiency by their ability to bind to a specific receptor.

Initially, agonists and direct antagonists are attracted to receptors by relatively long-range electrostatic forces. Once there, their affinity for the receptor will depend on the "closeness of fit" and the number of chemical bonds that can be formed between the two molecules. The bonds formed are usually non-covalent (for example, hydrogen bonds and Van der Waals attractions). But, irreversible antagonists bind to receptors with strong covalent bonds, in contrast to competitive antagonists that bind reversibly to receptors.

1.3.2. Heterogeneity of CCK receptors

The existence of two distinct CCK receptor types in peripheral and central tissues has been suggested by a study on rats and guinea pigs, by Innis and Snyder,[17]showing that pancreatic and brain CCK receptors differed markedly by their affinity for CCK-8 and CCK-4. Peripherally circulating CCK does not cross the blood-brain barrier, suggesting that peripheral and central CCK represents two distinct functional pools.[18]

This hypothesis was demonstrated by determination of the molecular mass of both types of receptors, their differential affinities for various agonists and antagonists, and by radioligand binding studies. These latter techniques involve competitive binding experiments carried out in order to measure the binding of a single concentration of labelled drug (the radioligand) in the presence of a range of concentrations of unlabeled ligand.[19] The concentration of unlabeled drugs that blocks 50% of the specific binding of the radioligand IC_{50} (Inhibition Concentration of 50% of the specific binding) represents the reference value used to show the affinity of a drug for a receptor. It can validate the expected potency of a drug, determine whether a drug binds to a receptor, or determine receptors number and affinity.[20]

Thus, two receptor subtypes, CCK_A and CCK_B, have been identified. This nomenclature was intended to reflect their localisation: A for Alimentary and B for Brain.[17]

This was an oversimplification. Instead, the techniques of receptor autoradiography[21] and homogenate binding allowed the localisation of the two subpopulations of CCK receptors to be more accurate.[22-25]

Both of the receptor types are present in the brain and in gastric mucosa, even if one is in a minority. Consequently, the nomenclature had to be modified. CCK_A became CCK_1 and CCK_B was changed to CCK_2. Little information is available on

the molecular structures of these receptors: so far limited only to their amino acid sequences.[26] The elucidation of their secondary and tertiary structures by means of X-ray or NMR spectroscopy still awaits the availability of sufficient quantities of purified proteins and crystallised samples.

1.3.3. CCK type 1 receptor

The CCK_1 receptor is the predominant peripheral CCK receptor. It is present in gastric smooth muscle cells and gallbladder[2] and regulates most of the gastrointestinal apparatus by mediating pancreatic enzyme secretion, gallbladder contraction, gastric emptying and intestinal motility, as described above.[27]

The CCK_1 receptor is also found in the brain, but only in discrete regions which possess a relatively porous blood-brain barrier, and therefore represent brain sites opened to peripherally release circulating CCK. These regions mainly include the dorsomedial hypothalamus, the IPN (Interpendecular Nucleus),[28] the AP (Anterior Pituitary), where a chemosensitive trigger zone is found[29] and the NTS (Nucleus Tractus Solitarius) where afferents (vessels and nerves) enter the brain.[30] This central reception of peripherically circulating CCK hormones by CCK_1 receptors could imply that they are involved in inhibitory actions on food intake.

It is important to mention that these localisations are not only found for humans, but differences in the distribution of central CCK binding sites also occur in other species.[31]

CCK_1 receptor subtype binds only with the CCK forms presenting the intact terminal heptapeptide that is required for the full nanomolar affinity between the receptor and the agonist.[32] Because of this specificity, the type 1 receptor can differentiate between circulating CCK, gastrin, and other CCK fragments, as it does in the pancreas for example.[23]

1.3.4. Type 2 CCK receptor

In contrast with the CCK_1 receptor, the CCK_2 receptor is the CCK receptor prevalently present in the central nervous system with a high density. It is diffusely distributed in the brain including regions such as ventromedial hypothalamus, nucleus accumbens, cortex, hippocampus, and the area of the limbic system and basal ganglia where it plays different role associated with its location.[2,33] In these non-porous regions, the type 2 receptor is protected from circulating CCK and gastrin by the blood-brain barrier and is responsive to central neurotransmitter CCK only.

In the periphery, CCK_2 receptors are rare. They have similar structural and pharmacological receptor profiles than the gastrin receptors and in consequence, can regulate gastrin effects.[34]

Contrary to the CCK_1 receptor subtype, the CCK_2 receptor is relatively non-specific.[21] It binds with various forms of CCK: CCK-8 and also its desulphurated form (CCK-8NS), pentagastrin and CCK-4 the smallest active form of CCK whereas the type 1 CCK receptor will exhibit a high degree of selectivity for the sulphurated form of the octapepetide.[17,21] This aspect allowed differentiating the two types of receptors and their role in the pathologies discussed in the following section.

1.4. Therapeutic applications

The precise physiological function of cholecystokinin remains to be elucidated and is most intriguing.

Diseases related to CCK can result from either its deficient or excessive secretion. CCK deficiency has been described in humans as a part of autoimmune

polyglandular syndrome, and is manifested as a malabsorption syndrome clinically similar to pancreatic exocrine insufficiency.[35]

Excessive production of CCK, or highly efficient assimilation by the receptors within the human brain, may play a part in several syndromes such as certain types of anxiety, panic attacks[36] and schizophrenia[37], nociception, and aberration in feeding behaviour.[35]

1.4.1. Role of CCK in nociception (perception of the pain)

CCK is found in CNS regions associated with pain modulation and opioid analgesia. In this regard, studies have established that CCK receptors are functional modulators of the opioidergic system with a tonic antiopioid effect in nociceptive pathways, and that CCK antagonists potentiate opioid analgesia and may also have intrinsic analgesic activity.[38,39] This observation could lead to pharmacological applications in the treatment of pain. For instance, CCK antagonists may be useful as adjuvants to morphine induced analgesia in the treatment of pain and for preventing the development of opioid tolerance in patients receiving repeated injections of morphine for chronic pain. The action of endogenous CCK at CCK_2 receptors opposes the action of endogenous opioids at opioid receptors.

When morphine is administered, its opioid agonist action overcomes the effect of endogenous CCK, and analgesia results. This balance can be shifted by injecting an exogenous CCK antagonist, which opposes the action of morphine and decreases pain thresholds.[40]

1.4.2. Role of CCK in psychotic behaviours

Patients with schizophrenia produce more dopamine than is normal. Clinical studies have also revealed that they show altered human cerebrospinal fluid (CSF)

levels of CCK. In addition, CCK and dopamine coexist in a subpopulation of meso-limbic neurons.[41] Dopaminergic agents have been proven to alter the number of CCK brain binding sites, and CCK administration has been shown to increase dopamine binding sites in the brain.[35]

These observations may reveal an interaction between dopamine and CCK. It is even thought that CCK_2 receptors may potentiate dopamine-mediated motivational mechanisms which are driving exploratory behaviour.[42] CCK might therefore be used as a neuroleptic and antipsychotic agent. However, no clinically useful drugs have been yet reported, to our knowledge.

1.4.3. Role of CCK in anxiety

1.4.3.1. Action of CCK

The known interaction of CCK with neurotransmitters implicated in anxiety states, such as GABA, 5-HT and norepinephrine, support the potential role of CCK in mediation of anxiety.[9] In the same way, CCK-4 mainly, but also CCK-8 and pentagastrin, have panicogenic and anxiogenic effects similar to CO_2 effects.[43,44] On the basis of the accumulating evidence of abnormal CCK function in panic disorder, CSF and lymphocyte[45] studies present a lower concentration of CCK-8S in panic disorder patients than in normal comparison subjects. The decrease in CCK-8 concentration reflects a compensatory increased CCK-4 activity (*in vitro* studies in rodents have shown that pretreatment of cell preparations with CCK-4 prevent CCK-8 induced neuronal firing). [46]

This fact has been confirmed by the panic-like attack resulting from the intravenous administration of selective CCK_2 receptor agonists CCK-4 and pentagastrin, which can cross the blood-brain barrier to act centrally through

excitation of deep cortical and hippocampal neurons, of the amygdala, and possibly other areas related to anxiety. [45,47]

1.4.3.2. Treatments with CCK antagonists

Panic-inducing agents can be effectively prevented by pre-treatment with a CCK_2 receptor antagonist.[48] The efficiency of CCK_2 receptor antagonists in anxiolytic activity was revealed by several standard anxiety tests such as "the mouse light/dark compartment test" (the preference for the dark side of the box observed in the mice, is suppressed by the injection of the selective CCK_2 antagonists), or "the rat elevated plus-maze test" (the time spent by the mice in the open arms of the elevated plus-maze is increased by the injection of the selective CCK_2 antagonists).[2,49] In contrast, CCK-8S, an agonist of CCK_1 receptor, induced intestinal symptoms but did not induce apparent anxiety. These experiments suggest that CCK_2 receptor is the only CCK receptor involved in the process of anxiety.

However, the role of CCK_1 in anxiety is not so clear. Controversial results were obtained with L-365,031 5; a pattern for CCK_1 receptor antagonists, which was mostly found to be inactive in the rodent tests of anxiety but which showed anxiolytic profiles in some other cases where CCK_2 antagonists were inefficient.[50]
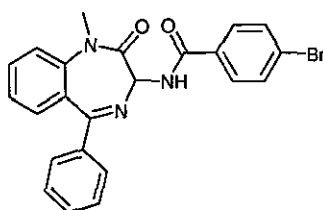
L-365,031

5

In addition, devazepide **6**, another selective CCK_1 receptor, which was inactive in most of the studies, blocked brain CCK_1 receptors at excess doses.[51] Other behavioural studies have reported devazepide to be active at very low doses in the rodent tests. However, its effect was not dose-related and it was only active at one of the doses tested.[50]
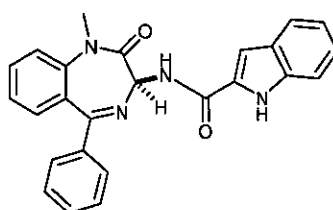
devazepide
(L-364,718 or MK-329)

6

To conclude, interpretation is difficult but it seems that both CCK_2 and CCK_1 receptors may be involved in the expression of distinct forms of anxiety or panic in humans.

1.4.4. Role of CCK on feeding behaviour

The possibility that bulimia might be associated with anxiety and not with core symptoms of eating disorder was exposed after CSF studies giving the same results with patients affected by bulimia nervosa as by anxiety.[8,52] Researches on implications of CCK in the processes of eating disorders were subsequently carried out. CCK abnormalities were encountered in bulimia and anorexia nervosa.[8,53,54] Injection of cholecystokinin into the ventricles of the brain induces satiety in laboratory animals.[55-57] CCK appeared to play a role, through both peripheral and central mechanisms, in stimulating cessation of feeding following food intake in a larger number of animal species and in obese humans.[58,59]

The idea of a link between eating disorder and anxiety was supported by the fact that patients with bulimia exhibit high anxiety, and the inhibitory action of CCK-8 on food intake is dependent on intact function of central serotonin, a neurotransmitter also involved in satiety as well as anxiety.

Consequently, experiments, involving starving rats were carried out. The antisatiety effects of both type 1 (devazepide **6** and proglumide **10**) and type 2 (L-365,260 **17**) receptor antagonists were demonstrated (see section 1.5.2.2 and section 1.5.2.3).[60,61]

1.4.5. Limits of the therapy

One major problem of this type of therapy remains in the drug addiction. Sometimes, cells adapt to previous drug exposure. For example, long-term treatment with CCK antagonists could increase the number of CCK receptors. This would happen as the nervous system tries to make up for less stimulation of the receptors by CCK itself. Likewise, the receptors themselves could become more sensitive to CCK. Both cases are examples of a process called "sensitisation".

Tolerance, the opposite process, could also affect the therapy. Indeed, the nervous system will attempt to maintain homeostasis. By this process, it keeps a constant level of cell activity in spite of major changes in receptor stimulation due to the presence of foreign chemicals. In its attempt to keep the body in a state of equilibrium, the nervous system could defeat the strategy.

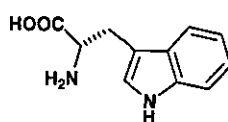### 1.5. CCK receptor antagonists

The CCK field of research has been widened because of the diversity of structure types that are known to be antagonists. Comprehensive structure-affinity

relationship studies (SARS) between antagonists and receptors revealed regions of the antagonist molecules which induced modulation of physiochemical properties, and often resulted in improved CCK receptor affinity and selectivity.

Antagonists range from peptides to cyclic nucleotides and benzodiazepines and have been classified into several main groups described below.[49]

1.5.1. Peptides and pseudopeptide analogues

The major naturally occurring molecular forms of CCK are polypeptides. Therefore, peptides which can act as CCK antagonists have been developed. Their synthesis was based on the deletion or modification of phenylalanine at the carboxy-terminal of CCK, and three rules had to be respected: the sequences synthesised could not be smaller than a tetrapeptide, which represents the smallest required sequence for recognition by CCK_2 receptors; the presence of a terminal amide, which is an important determinant of the inhibitory potency of the antagonist, was essential; and the presence of L-tryptophan **7** residue, important for binding to central and peripheral CCK receptors is also necessary.

L-tryptophan

7

1.5.1.1. Peptides

Deletion of the phenylalanine carboxy-terminal from CCK produces an antagonist: CBz-Tyr(SO$_3$H)-Met-Gly-Trp-Met-Asp-NH$_2$ (CBz-CCK-27-32-NH$_2$), which is the most potent peptide CCK receptor antagonist described to date. It is approximately 30 times more potent than dibutyryl cyclic guanosine monophosphate (Bt$_2$cGMP) (see section 1.5.2.1). But with an IC$_{50}$ of binding of

^{125}I-CCK in guinea pig pancreatic acini of about 3μM, it does not compete with the potency of CCK-8 (IC$_{50}$≈1nM).[62]

Similarly, antagonists based on the modification of the partial C-terminal sequence of CCK have been investigated and Boc-Tyr(SO$_3$H)-Met-Gly-Trp-Met-X-Phe-NH$_2$ (where X is an amino acid) were found to be highly potent antagonists of the gastrin receptor.[63]

Unfortunately, peptides and modified peptides show rapid *in vivo* degradation by proteases. Enzyme-resisting and potent pseudopeptide analogues of CCK are therefore interesting synthetic targets.

1.5.1.2. Pseudopeptide analogues

In vivo, degradative activity cleaves peptides at specific peptide bonds. Thus, it has been necessary to turn to the novel field of peptidomimetics to design pseudopeptide compounds which are used for their biological activity, but are resistant to degradation *in vivo*.

Pseudopeptide analogues have been obtained by modifying the backbone of CCK or gastrin. Sequential replacement of each of the amide linkages in a CCK-4 analogue (Boc-Trp-Leu-Asp-Phe-NH$_2$) was investigated.
Peptide bonds, between leucine and aspartic acid, and between aspartic acid and phenylalanine, were replaced by CH$_2$NH bonds (schematised as ψ[CH$_2$-NH]). The two resulting pseudopeptides, Boc-Trp-Leuψ[CH$_2$-NH]-Asp-Phe-NH$_2$ and Boc-Trp-Leu-Aspψ[CH$_2$-NH]-Phe-NH$_2$, were found to act as antagonists of pentagastrin-stimulated acid secretion.[64]

Similarly, antagonists from CCK-8 were synthesised by replacing the peptide bond between norleucine and glycine by a ketomethylene bond (ψ[CO-CH$_2$]). Thus,

Boc-Tyr(SO₃H)-Nleψ[CO-CH₂]-Gly-Trp-Nle-Asp-Phe-NH₂ was found to be a very potent inhibitor of the binding of radiolabeled CCK-8 to rat pancreas ($IC_{50} \approx 5nM$) and mouse brain ($IC_{50} \approx 0.7nM$).[64]

Unfortunately, very few peptidal and pseudopeptidal analogues were obtained, primarily due to the limitations inherent in the peptide structure itself. In addition, they show a poor oral bioavailability, partial agonist actions, and a lack of specificity.

1.5.2. Non-peptidal analogues

In contrast, non-peptidal analogues offer possible solutions, as they can be orally effective, metabolically stable, and can present a high affinity for CCK receptors. At least ten chemical classes of CCK non-peptide antagonists have been described.

1.5.2.1. Derivatives of nucleotides

Very limited studies have been focused on nucleotides; only on the pancreatic acini and ileum of the guinea pig. Guanyl nucleotides such as Bt₂cGMP **8** have been shown to be the best CCK antagonists of this group.[65,66] This group is unfortunately not highly potent.
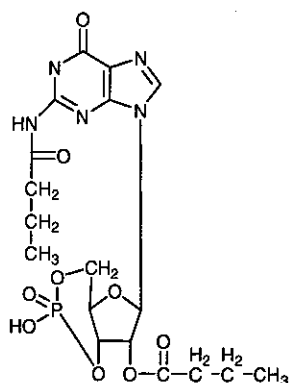
Bt$_2$cGMP

8

Nevertheless, cyclic nucleotides provide mechanistic insights.

In the case of a nucleotide, one possibility has been suggested by Miller,[67] that cyclic nucleotides are indirect antagonists, and combine with CCK to prevent or interfere with binding of the peptide to its receptor. This idea was confirmed by Gaudreau *et al.* The data obtained during their experiments suggest that the binding of the radioligands to CCK receptor sites is regulated by guanyl nucleotides.[68]

1.5.2.2. Derivatives of amino acids

Several amino acid derivatives were reported to act as CCK antagonists but with poor binding affinity for the receptors. Attention was, however, focused on two compounds: *p*-chlorobenzoyl-L-tryptophan (benzotript) **9**, a glutaramic acid derivative and benzoyl-DL-glutamic acid dipropylamide (proglumide) **10**, a derivative of tryptophan, the first gastrin/CCK antagonist used for the treatment of ulcers.[69]
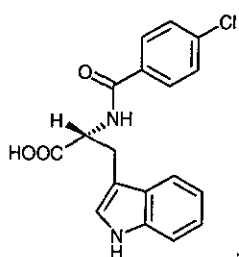
Benzotript   Proglumide
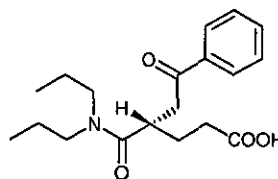
9   10

However, they feature poor potency and selectivity compared to the antagonists examined previously (Table 1).[62]
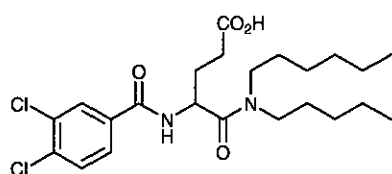
Table 1: Inhibition of [^{125}I]CCK-33 binding to CCK receptors in rat pancreas and brain

Antagonist	IC$_{50}$ (µM) rat pancreas CCK$_1$	IC$_{50}$ (µM) rat brain CCK$_2$	CCK$_1$/CCK$_2$
CBz-CCK-27-32-NH$_2$	3.5 ± 0.4	6.8 ± 0.8	0.51
Bt$_2$cGMP	87 ± 11	1600 ± 300	0.05
Benzotript	102 ± 18	84 ± 13	1.21
Proglumide	600 ± 58	875 ± 125	0.69

In consequence, studies towards the synthesis of new compounds such as glutamaric acid derivatives have been achieved. Surprisingly, the conclusions showed that neither tryptophan nor its various derivatives, in terms of their abilities to function as CCK receptor antagonists, depend on the stereospecificity of the tryptophan moiety.[27] In contrast, it appears that potency was increased with increased hydrophobicity of the *N*-acyl moiety.[70] *N*-carbobenzoxy-tryptophan was the most potent of the compounds tested.

In the same way, glutaramic acid analogues such as lorglumide (CR 1409) **11** and loxiglumide **8** proved to have a potent antagonistic effect on gallbladder CCK$_1$

receptors.[71] For example, lorglumide **12** is 7000 times more potent than proglumide in displacing binding to CCK_1 receptors on pancreatic acini (Table 2).[2]

Lorglumide
(CR 1409)

11
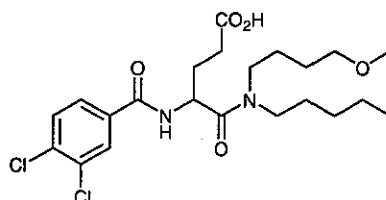
Loxiglumide

12

Table 2: Inhibition of $[^{125}I]CCK$-33 binding to CCK receptors in rat pancreas and mouse cortex[72]

Antagonist	IC_{50} (nM) rat pancreas CCK_1	IC_{50} (nM) mouse cortex CCK_2	CCK_1/CCK_2
Devazepide	0.19 ± 0.01	31.7 ± 5.0	0.006
CR 1409	7.1 ± 0.5	>1000	<0.007

Chemical manipulations of its structure, which found its CCK-antagonist activity, partially because of its R form, led to CR 2194 **13**.[73] CR 2194 is the most potent CCK_2 antagonist among this class of chemicals.
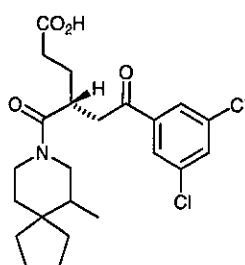
CR 2194

13

However, the inhibitory potency of these classes of CCK receptors is relatively low, and this may limit their applications in *in vivo* systems.

1.5.2.3. Benzodiazepines

The selectivity of benzodiazepines has been confirmed for the cloned human CCK_1 and CCK_2 receptors. The benzodiazepines are chemicals used as active ingredients in mind-affecting drugs such as valium. They provide anxiolytic action, ataxia, and sedative effects exerted through specific recognition sites on the GABA receptor complex.

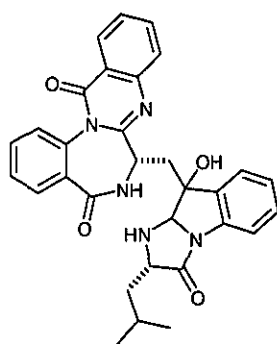In 1985, a fermentation product of *Aspergillus alliaceus* called asperlicin 14 was found to be the first effective nonpeptidal ligand CCK antagonist, possessing a better potency than the most widely used antagonists proglumide and benzotript ($IC_{50} \approx 1\,\mu M$, binding of $[^{125}I]CCK-33$ in rat pancreas).

Asperlicin

14

Presenting poor water solubility, and a lack of oral bioavailability, asperlicin was not effective pharmacologically and could not be used as a potential therapeutic agent. Attempts have subsequently been made to improve its physical properties.

Design of potent, orally effective benzodiazepines fusing the elements of diazepam 15 and D-tryptophan 16 was undertaken (Figure 1).[74]

diazepam

15

D-tryptophan

16

potent benzodiazepine pattern
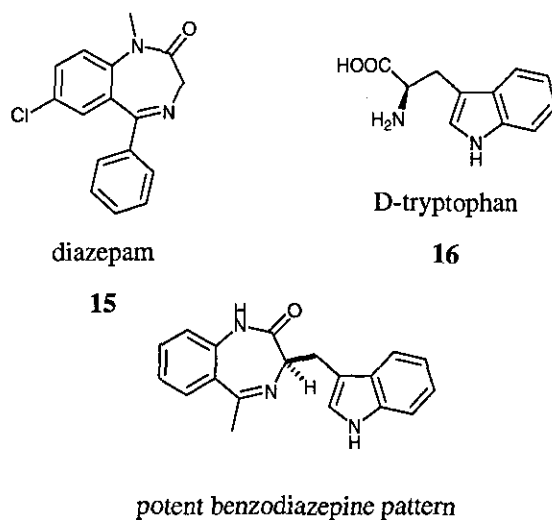
Figure 1

First generation compounds, devazepide (also known as L-364,718 or MK-329) **6**[75] and L-365,260 **17**[76] are respective selective antagonists of CCK_1 and CCK_2, confirming and extending the original findings.
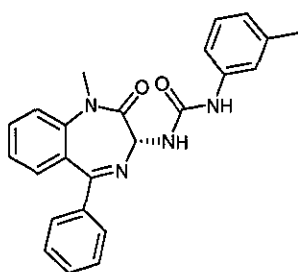
L-365,260

17

Their high affinity permitted a much clearer differentiation between the two classes of CCK-receptors.[77] Nevertheless, the low aqueous solubility of their crystalline form (0.002 mg.mL^{-1} at pH=7.4) required the benzodiazepine structures to be improved. The development of selective CCK_1 receptor antagonists has not been significant, except for IQM-95,333 **18** (from a series of 1, 3-dioxoperhydropyrido [1, 2-c] pyrimidine derivatives); devazepide **6**, is the

commonly used pattern of CCK_1 receptor antagonists. In contrary, L-365,260 **5** has been replaced by more recently developed antagonists. YM-022 **19** is an example of this evolution, exhibiting superior affinity and selectivity among benzodiazepine CCK_2 receptor antagonists (Table 3).

IQM-95,333

18

YM-022

19
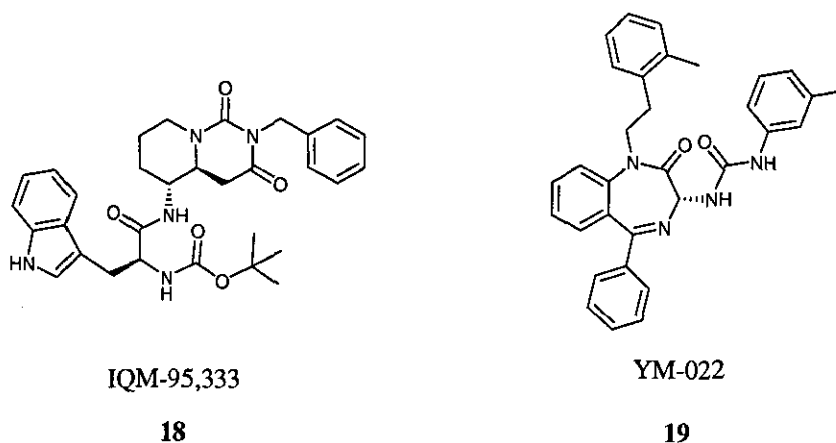
Table 3: Estimated binding affinities for the cloned human CCK_1 and CCK_2 receptors[78]

Antagonist	IC_{50} (nM) CCK_1	IC_{50} (nM) CCK_2	CCK_1/CCK_2
L-365,260	589	12.6	47
YM022	316	0.05	6000

SARS revealed regions of the molecule which permitted improvement, CCK_2 receptor affinity and selectivity.

A second-generation of benzodiazepines incorporating basic or acidic solubilising functionalities (sometimes 10 times more soluble than L-365,260 **17**) has thus been obtained. Compounds which incorporate an aminotetrazole unit attached to the phenylurea moiety of L-365,260 **17** were designed and synthesised such as L-738,425 **20**, most selective CCK_2 reported so far (CCK_1/CCK_2, 37000) and L-736,380 **21** showing an extremely high affinity due to the fact that it is very lipophilic (IC_{50}=0.054nM, binding of $[^{125}I]$CCK-8S in guinea pig cortical membranes).[79]
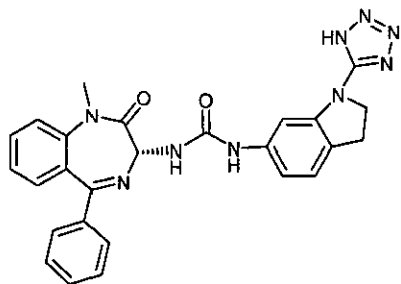
L-738,425

20
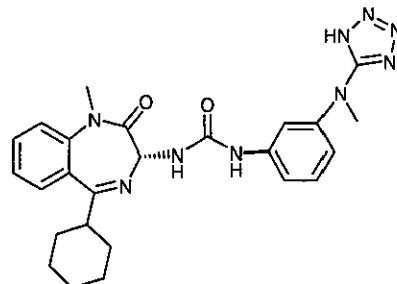
L-736,380

21

The real problem with these compounds is the tolerance developed to many of their behavioural effects following long-term administration.[9]

1.5.2.4. Dipeptoids

The synthesis of dipeptoids (derived from a non-contiguous dipeptide fragment of CCK) would be predicted to have a more improved side-effect profile in man than benzodiazepines. Indeed, CI-988 **22** is an orally active compound which can be defined as anxioselective: it produces anxiolytic-like actions in several animal models of anxiety and does not appear to possess the adverse properties associated with benzodiazepines (like ataxia or myorelaxant effects).[80]
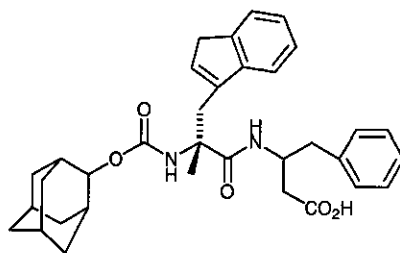
CI-988

22

Table 4: Inhibition of $[^{125}I]$BH CCK-8S binding to CCK receptors in guinea pig pancreas and cortex[81]

Antagonist	IC$_{50}$ (nM) g. pig pancreas CCK$_1$	IC$_{50}$ (nM) g. pig cortex CCK$_2$	CCK$_1$/CCK$_2$
L-365,260	86 ± 29	8.1 ± 1.6	11
CI-988	490 ± 170	0.65 ± 0.03	754

Here again, the stereochemistry of the compounds influences their behaviour. For instance, PD 135666 is a selective CCK$_2$ receptor antagonist (IC$_{50}$=0.1nM, binding of $[^{125}I]$CCK-8S in mouse cerebral cortex), whereas its enantiomer PD 140548, shows a selectivity for the type 1 receptor (CCK$_1$ IC$_{50}$=2.8nM, binding of $[^{125}I]$CCK-8S in rat pancreas; CCK$_2$ IC$_{50}$=260nM, binding of $[^{125}I]$CCK-8S in rat pancreas) (Table 5).[82]

Table 5: Inhibition of $[^{125}I]$BH CCK-8S binding to CCK receptors in rat pancreas and mouse cortex[82]

Antagonist	IC$_{50}$ (nM) rat pancreas CCK$_1$	IC$_{50}$ (nM) Mouse cortex CCK$_2$	CCK$_1$/CCK$_2$
PD 135666	26 ± 10	0.15 ± 0.06	170
PD 140548	2.8 ± 2.3	260 ± 50	0.01

1.5.2.5. Other groups of CCK antagonists

Likewise, but less significantly, quinazolinones **23** (based on the observation that asperlicin **14** contains a 3-phenyl-4-(3H)-quizanolinone nucleus), diphenylpyrazolidinones, ureidoacetamides, even hybrid CCK antagonists such as A-64,718 **24**, (prepared by coupling lorglumide **11** and devazepide **6**) (Scheme 1)[83] may serve as potent non-peptidal chemical classes of CCK receptor antagonists.

functionalised quinazolinone

23

lorglumide

11

devazepide

12

A-64,718

24

Scheme 1
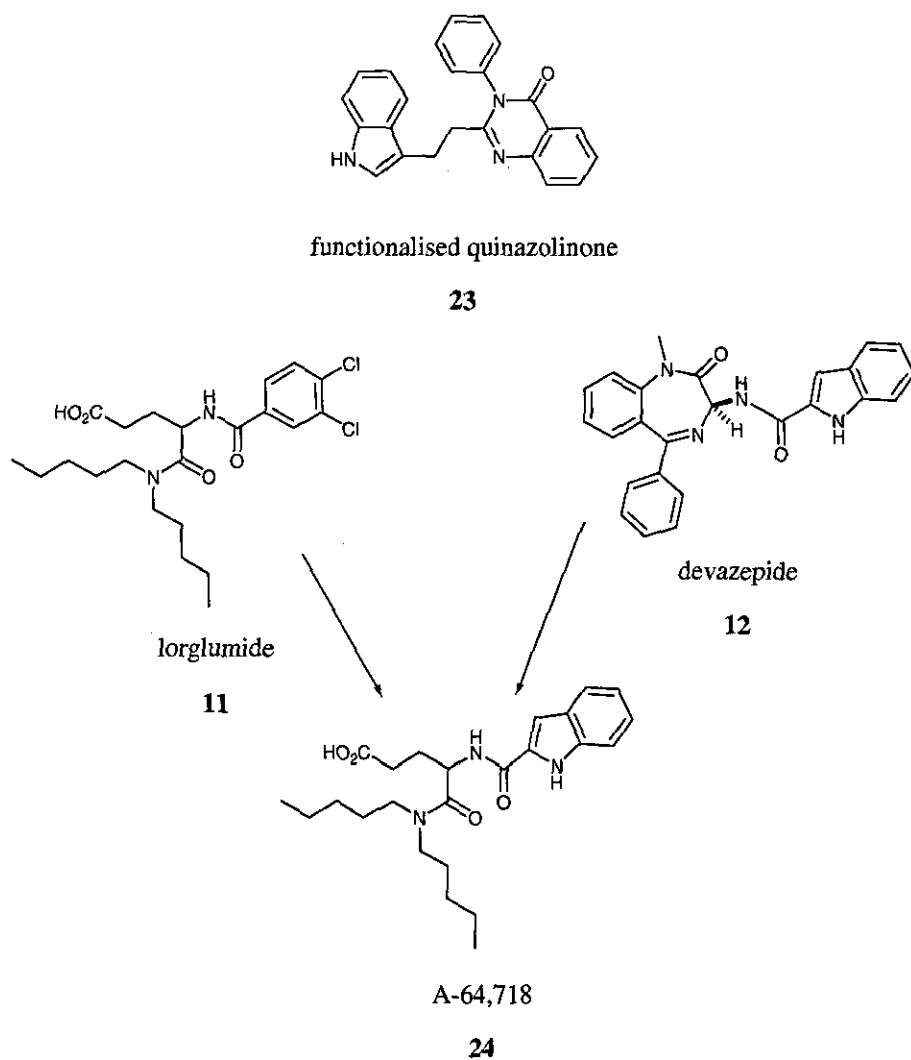
1.6. General remarks about tetronothiodin

Finally, looking forward to structurally unique and specific new receptor antagonists, tetronothiodin **26** was discovered through a screening process. The screening process involved microbial metabolites being screened through binding assays. In 1992, a binding assay method, involving rat cerebral cortex membranes as receptors and ^{125}I-labelled Bolton Hunter CCK-8 as the radioligand, found a novel CCK_2 receptor antagonist called tetronothiodin. The screening process

discovered tetronothiodin from the culture broth of *Streptomyces* sp. NR0489, a bacterium which produces a quantity of various enzymes and metabolites.[84-88] Like other natural products produced by *Streptomyces* sp. including anthramycin **25**,[89] tetronothiodin **26** was isolated through a procedure that first used fermentation of the strain NR0489.
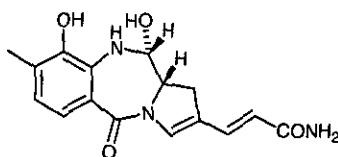
anthramycin

25

After a cultivation period of ten days, centrifugation is carried out to give the growth supernatant, and its pH was adjusted to allow column chromatography. Concentrating under reduced pressure, further re-extraction of aqueous layers and column chromatography gave an active organic compound. Final purification was achieved using reverse-phase preparative HPLC to give **26** as pale brown powder.[87]
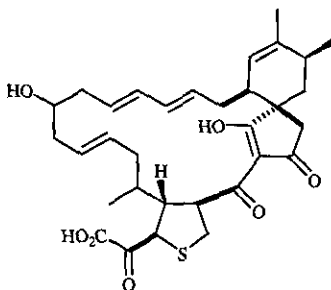
26

1.6.1. Biological activity of tetronothiodin

The inhibitory activities of tetronothiodin against the binding of $[^{125}I]$-CCK-8 to CCK_1 and CCK_2 receptors were tested. The test procedure involved incubation of test samples at 23 °C with $[^{125}I]$-CCK-8 of either pancreatic membranes (containing CCK_1 receptors) or cerebral cortex membranes (containing CCK_2 receptors), both of which are in a buffer and bovine serum albumin solution. After the samples reached equilibrium, they were filtered and the radioactivity was counted.

Tetronothiodin **26** was shown to inhibit the binding of $[^{125}I]$-CCK-8 to CCK_2 receptors on rat cerebral cortex membranes in a concentration dependent manner. The affinity of **26** to CCK_2 receptors was shown to be three to four times greater than known potent and selective CCK_2 receptor antagonists, and only three times less potent than the natural ligand CCK-8. Tetronothiodin did not, however, inhibit the binding of $[^{125}I]$-CCK-8 to CCK_1 receptors on rat pancreatic membranes. The ratio of affinity for CCK_2 to CCK_1 receptors of tetronothiodin was more than 27000; it is thus a highly selective binding inhibitor for CCK_2 receptors, with selectivity much greater than most known antagonists (Table 6).

Table 6: Inhibition of $[^{125}I]$CCK-8 binding to CCK receptors in rat pancreas and cortex[90]

Antagonist	IC_{50} (μM) rat pancreas CCK_1	IC_{50} (μM) rat cortex CCK_2	CCK_1/CCK_2
Tetronothiodin	›100000	3.6 ± 0.33	›30000
L-365,260	2700 ± 130	8.1 ± 0.90	300
Asperlicin	1100 ± 200	›10000	‹0.1
Devazepide	0.51 ± 0.18	320 ± 50	0.002
Proglumide	50 ± 12	640 ± 150	0.08
Loxiglumide	140 ± 33	4600 ± 780	0.03

The results were further corroborated by tests on GH3 cells from rat anterior pituitary gland (cells considered as "pro-vitamins" that secrete the two pituitary polypeptide hormones, prolactin and growth hormone), which contain CCK_2 receptors. Tests with the same GH3 cells demonstrated that intracellular Ca^{2+} (known to control fundamental neuronal functions such as neurotransmitter release) was increased in a concentration-dependent manner and that tetronothiodin **26** inhibited this increase in the same dependent manner.

1.6.2. Structural elucidation

The isolation procedure of tetronothiodin **26**, which involved extraction with ethyl acetate at pH=2 and back extraction with water at pH=7.5, indicated its acidic nature. Tetronothiodin **26** was found to be soluble in methanol, tetrahydrofuran, dimethylsulfoxyde and alkaline water but insoluble in ether, chloroform, hexane and water. The free form of tetronothiodin was unstable in solution; it gradually decomposed during NMR experiments over two weeks in DMSO-d6 or CD_3OD. Its alkaline metal salts were stable for at least five months under the same experimental conditions. The molecular formula of tetronothiodin was found to be $C_{31}O_8H_{38}S$ based on positive-ion FAB-MS (m/z 593 (M^+)).and negative-ion high resolution FAB-MS data (596.2237, calculated for M-H, $C_{31}O_8H_{37}S$ - 569.2210). This molecular formula was further supported by qualitative analysis for sulphur and analyses of the ^1H NMR and the ^{13}C NMR spectra, which shows 31 carbon signals.[89]

Structural elucidation was mainly carried out based on the NMR data obtained with the potassium salt of tetronothiodin in D_2O because all the carbon signals were observed in this solvent, compared to the use of DMSO-d$_6$, which hides two carbon signals (Figure 2).
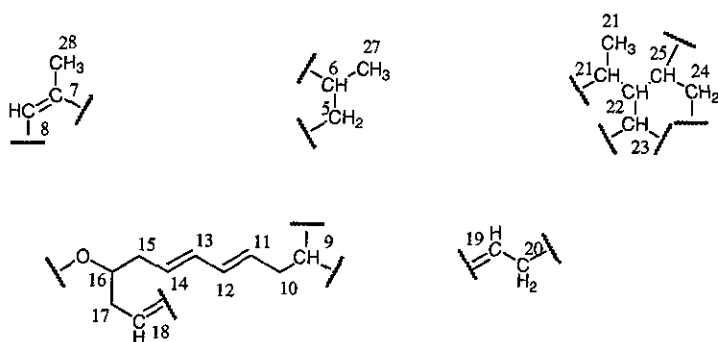
Figure 2

Interpretation of the ^{1}H-^{1}H COSY spectra shows allylic coupling between H-8 and the methyl protons H-28 connecting the olefinic carbon C-8 and the quaternary carbon C-7. The fragments shown in Figure 2 and the remaining quaternary carbons, C-3, C-4, C-26 and C-30, were connected to form the partial structure based on the analysis of the ^{13}C-^{1}H long-range couplings (shown by the arrows in Figure 3) obtained by HMBC experiments (Figure 3).[84,87]

Figure 3

E-stereochemistry was determined in all three double bonds in the macrocycle from the large coupling constant (*J* 15 *Hz*) associated with these olefinic proton signals. A hydroxyl proton was located at C-16 through a spin-spin coupling experiment with H-16 in DMSO-d$_6$.

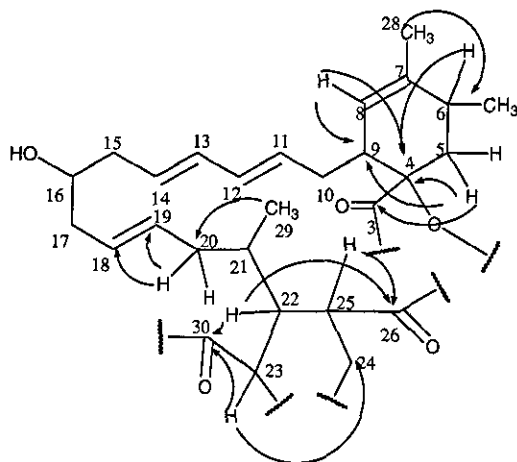Comparisons of the ^{13}C NMR spectral data with a carolic acid derivative **27**[91] shown in Figure 4, suggested the presence of an α-acetyl tetronic acid.[92] The suggestion was confirmed by UV, and IR spectroscopy. IR indicated the presence of a γ-lactone with a clearly separated band at 1760 cm^{-1} as well as absorption bands at 3000-2300 and 1728, suggesting a carboxylic acid. The UV spectrum in methanol indicated absorption maxima at 233 and 273 nm, which were attributed to an α-acetyltetronic acid functionality.

The carbon signals assigned at C-1, C-2, C-23 and C-26 all correspond to a tetronic acid moiety in tetronothiodin. This moiety was deemed to be attached to the cyclohexene ring at C-4 because of the [13]C-^{1}H long-range coupling between H-5a and C-3 (Figure 4).
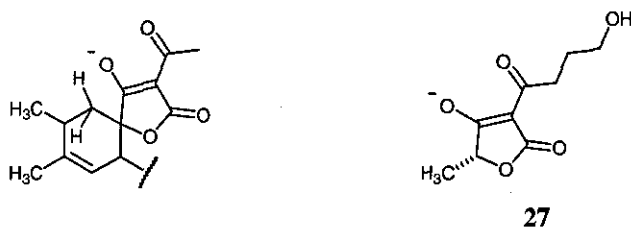
Figure 4

[13]C-^{1}H long-range coupling was observed between H-23 and C-24, suggesting the linkage of C-23 and C-24 through a heteroatom or quaternary carbon even though protons H-23 and H-24 were not coupled. This suggested either a sulfur atom or keto function inserted between C-23 and C-24. The cyclopentanone was eliminated as the possible structure through ^{13}C chemical shift and structural analysis of the reduced derivative. It was therefore reasonable to assume a sulfur atom between the two carbons, forming a tetrahydrothiophene ring. Comparisons with position 5 in dimethyl(2α,3β,4α)-2-(trimethylsilyl)tetrahydrothiophene-3,4-dicarboxylate **28**,[93] by chemical shift data further corroborated this structure (Figure 5).

Figure 5

Confirmation of the tetrahydrothiophene unit left two possible structures **A** and **B** for tetronothiodin (Figure 6).
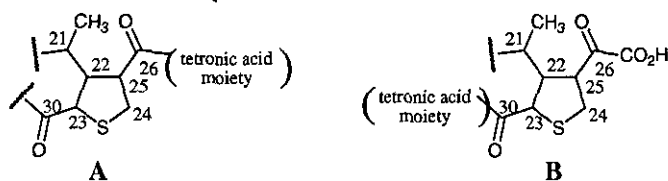
Figure 6

Allocation of the only remaining carboxylic function to either the C-26 or C-30 position was achieved through reduction of tetronothiodin by sodium borohydride to give the epimeric alcohols **29a** and **29b**. The newly observed proton signal was assigned to H-30 by ^{1}H-^{1}H COSY experiments and shown to be spin-coupled only to H-23. This established the structure to be represented by **A** in Figure 6 and the gross structure to be established as **26** (Figure 7).
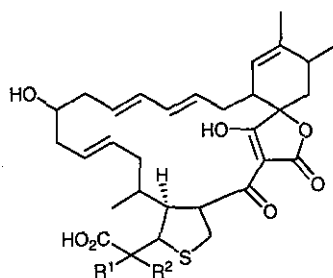
26: R^1 = R^2 = C=O
29a, 29b: R^1 = H, R^2 = OH

Figure 7

31

1.6.3. Stereochemistry

The relative stereochemistry for the six of the eight stereocentres has been determined through a series of nOe and long-range selective proton experiments (LSPD) carried out on the sodium salt of tetronothiodin in DMSO-d_6 (Figure 8).

A nOe between H-9 and H-5b indicated the *cis* relationship between these protons. A small coupling constant (J 2 Hz) between H-9 and H-8 was determined by homodecoupling, supporting the pseudoaxial orientation of H-9. The *cis* relationship between C-27 and H-5a was determined by a strong nOe between H-5a and H-27 and a weak nOe between H-5b and H-27. The coupling constant between C-3 and proton signals H-5b and H-9 was determined to be less than 4 Hz using a long-range coupling experiment with a double irradiation technique. The coupling constant between an axial proton and axial carbon would be large due to a *trans* relationship, thus these small coupling constants indicated a *cis* relationship between C-3 and H-5b or H-9.[87]
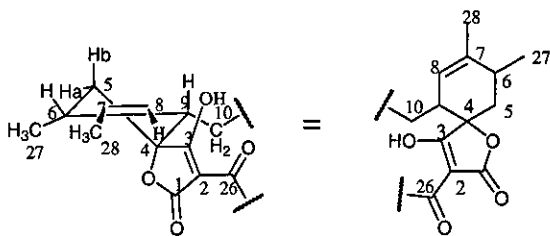

Figure 8

The *cis* relationship between H-23 and H-25 was established by the nOe between these protons for the tetrahydrothiophene ring (Figure 8).

Treatment of the free acid of tetronothiodin in CD_3OH resulted in the complete disappearance of the active H-25. Treatment of this sample with methanol recovered tetronothiodin without epimerisation at C-25 as revealed by the ^{1}H NMR

spectrum. This then showed that only one stable configuration exists in solution, and thus the less hindered more thermodynamically stable *trans* relationship was assigned to the substituents C-22 and C-25, giving the partial structure shown (Figure 9).[87]
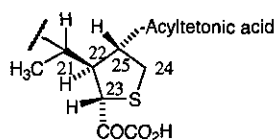
Figure 9

The stereochemistry for six of the eight stereocentres has thus been determined based on detailed spectroscopic analysis, although it is not supported by X-ray crystallography.

The stereochemical arrangement of the hydroxyl and methyl group at positions 16 and 21 respectively in the macrocyclic ring is currently unknown. Tetronothiodin **26** is depicted as shown above, with two stereocentres unassigned.
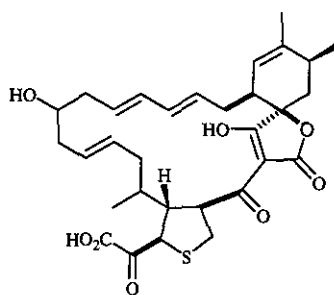
26

1.7. Synthesis

Our synthetic approach is based around a flexible and convergent route, with the target molecule disconnected into three units; the oxaspirobicyclic unit **30**, the

tetrahydrothiophene **31**, and the unsaturated macrocycle framework **32** (Figure 10).
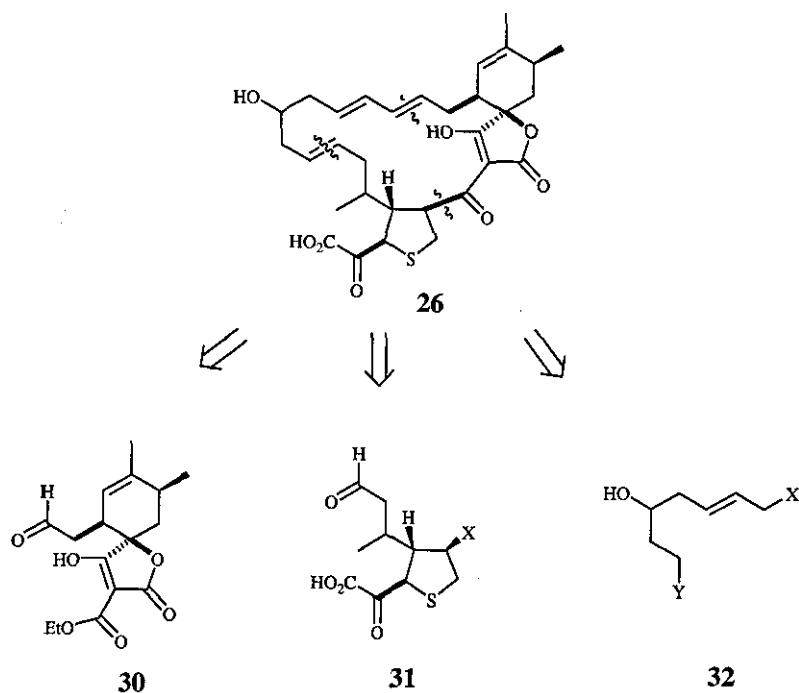
Figure 10

The synthetic plan involves a three stage construction of the oxaspirobicycle moiety, perhaps the most challenging feature of the molecule, and our aim in this thesis. This will be followed by preparation of the linking alkenol chain and macrocyclisation, and finally construction of the tetrahydrothiophene unit which is already under elaboration in our laboratories.

There have been several different attempts to synthesise an oxaspirobycycle unit of structurally related antibiotics in terms of a macrocyclic molecule containing an α-acyltetronic acid.

1.7.1. Analogous spirocycles in other natural products

The structure of tetronothiodin is related to a number of other natural products which contain analogous upper *exo*-spirotetronate fragments. In this section, we will be focusing specifically on investigations leading to the synthesis of these spirotetronate substructures.

1.7.1.1. Aglycones of antitumor antibiotics

Chlorothricolide **33**, the aglycone of the chlorothricins, was one of the first compounds of the family isolated from *Streptomyces antibiocus* in 1969. These compounds inhibit pyruvate carboxylase (the enzyme that catalyse the irreversible carboxylation of pyruvate into oxaloacetate in the process of energy generation) and are active against Gram-positive bacteria.[94]
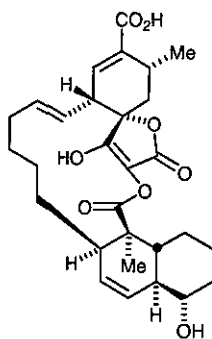
Chlorothricolide

33

Kijanolide **34** is the aglycone of kijanimicins, which are the major components of a complex of antibiotics produced by *Antinomadura kijania* SCC1256. It shows antitumor activity.[95]
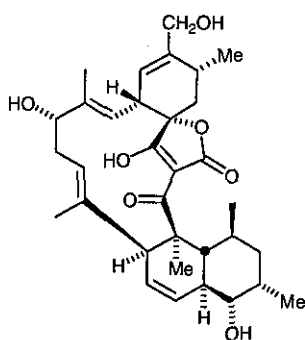
Kijanolide

34

Tetronolide **35** is the aglycone of tetrocarcins (A, B, C, E1, E2, F and F-1), which are isolated from the culture broth of *Micromonospora chalcea* KY 11091. These complex glycosides show activity against several types of tumours such as Ehrlich carcinoma,[96] and show specific inhibitory activity towards Bcl-2 functions (genes that encode the protein that blocks the apoptotic death of some cells).[97]
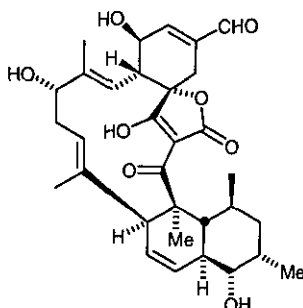
Tetronolide

35

Finally, PA-46101 A **36** is an anti-bacterial agent isolated from the culture broth of a streptomycete.[98]

R = disaccharide
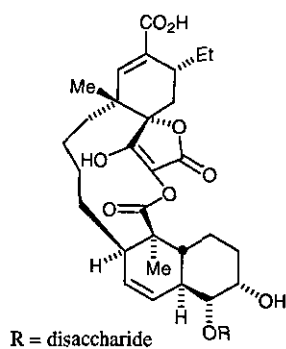
PA-46101 A

36

1.7.1.2. Quartromicins

The quartromicins **37** are a family of antibiotics first isolated from *Amycolatopsis orientalis* Q247-8 in 1991. They possess antiviral activities against some types of herpes, influenza and human immunodeficiency virus. The quartromicins possess four spirotetronic acid units. Quartromicins A_1, A_3, D_1 and D_3 are symmetrical, dimeric structures, in which the spirotetronic acid subunits at opposite corners of the structure are identical. Two of the subunits contain α-galactopyranosyl residues connected to C-26 and C-26'. The other type of spirotetronate is referred to *agalacto* fragments. The remaining A_2 and D_2 quartromicins differ from the C_2 symmetric members in that the two *agalacto* fragments have different oxidation states for C(8) and C(8') (Figure 11).

Figure 11
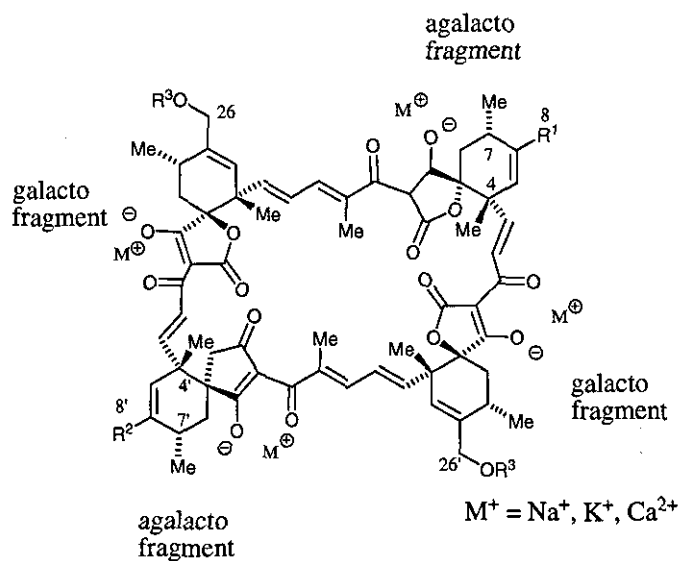
Quartromicin	R^1	R^2	R^3
A_1	CHO	CHO	α-D-galactosyl
D_1	CHO	CHO	H
A_2	CHO	CH_2OH	α-D-galactosyl
D_2	CHO	CH_2OH	H
A_3	CH_2OH	CH_2OH	α-D-galactosyl
D_3	CH_2OH	CH_2OH	H

Since the structure elucidation of these two families in 1980, they have attracted considerable synthetic interest. In this section, some synthetic routes used for forming some of these fragments are discussed.

1.7.2. Strategy of synthesis for the exo-spirotetronate units

1.7.2.1. The Bimolecular Diels-Alder approch

1.7.2.1.1. Initial attempts

The Diels-Alder reaction has been used from the very first synthesis of the upper fragment of kijanolide described by Yoshii *et al.*[99] This synthesis was also based on the treatment of ketone **43** with six equivalents of ethynylcerium dichloride **44**. The bulkiness of cerium favoured equatorial attack to produce the acetylenic carbinol **45** (Scheme 2).
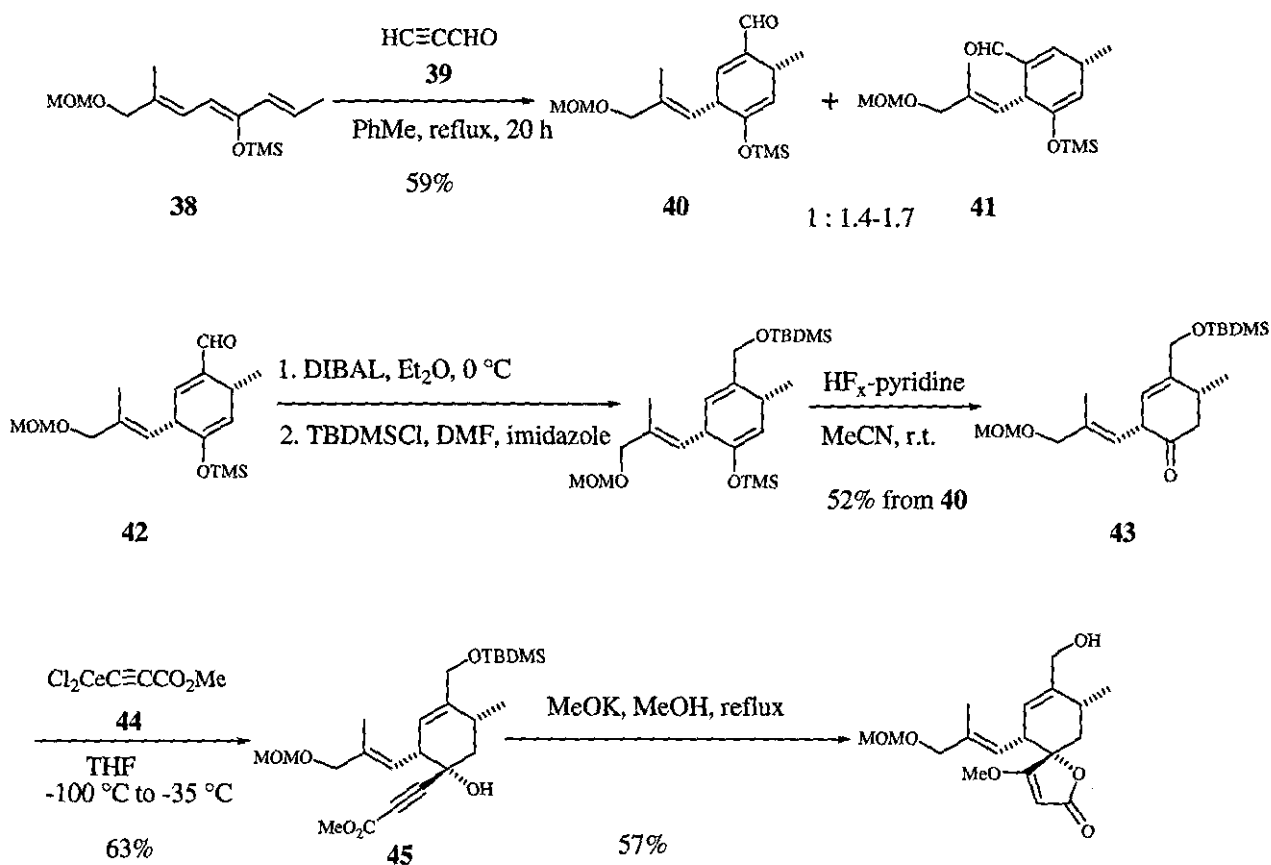
Scheme 2

By cycloaddition of the triene **38** with propargyl aldehyde **39** only a mixture of regioisomeric cycloadducts **40** and **41** was obtained. The yield was reasonable but the diastereoisomeric ratio was poor. This method was obviously unsatisfactory, and consequently, another route (described in the same publication) involving the cycloaddition of triene **46** and 5-methylenetetronate **47** was performed by the same group (Scheme 3).[99]
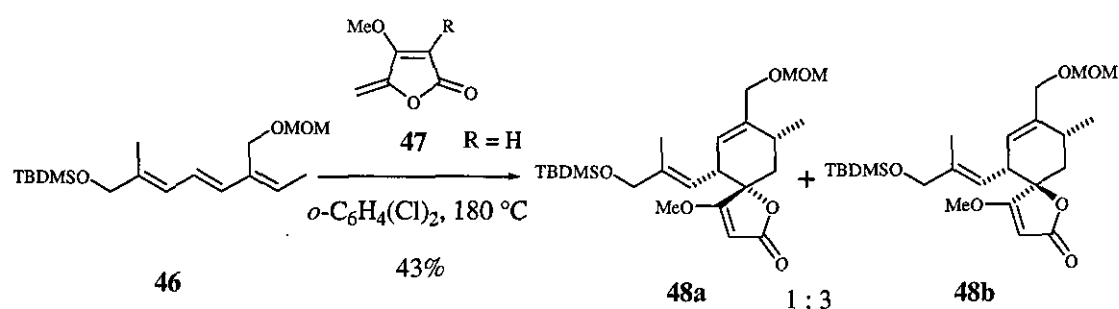
Scheme 3

A mixture of diastereoisomeric adducts **48a** and **48b** in a 1:3 ratio was obtained, unfortunately a yield of only 43% resulted from this method.

Several dienophiles derived from (γ-methylene)tetronate **47** were used in another of the first syntheses of Chlorothricolide. The best result was obtained with **49** (R = 2,4-$Cl_2C_6H_3CO_2$), a ratio of 61:24:15 of three isomeric adducts **50a**, **50b** and **51**, respectively *endo*, *exo* and a regioisomer were obtained (Scheme 4).[100]
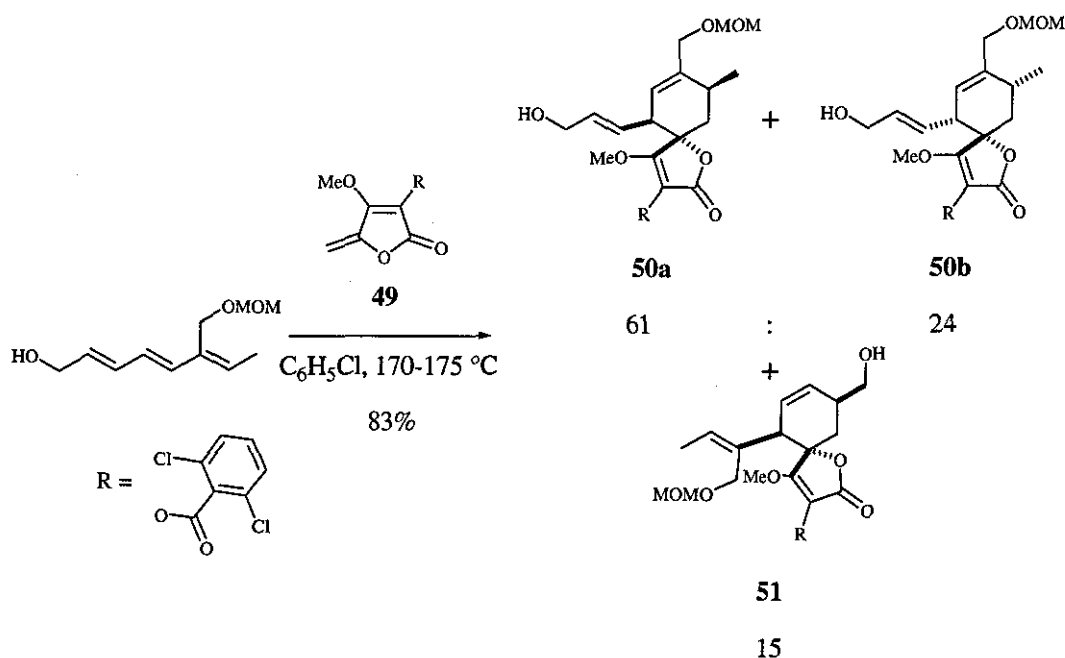
Scheme 4

Attempted synthesis by the Page group

One of the initial proposals for the synthesis in the Page group included a Diels-Alder reaction of the hydroxydiene **52** with nitroethylene **53**, followed by a Nef reaction to yield to the substituted cyclohexenone **55** (Scheme 5).[101]
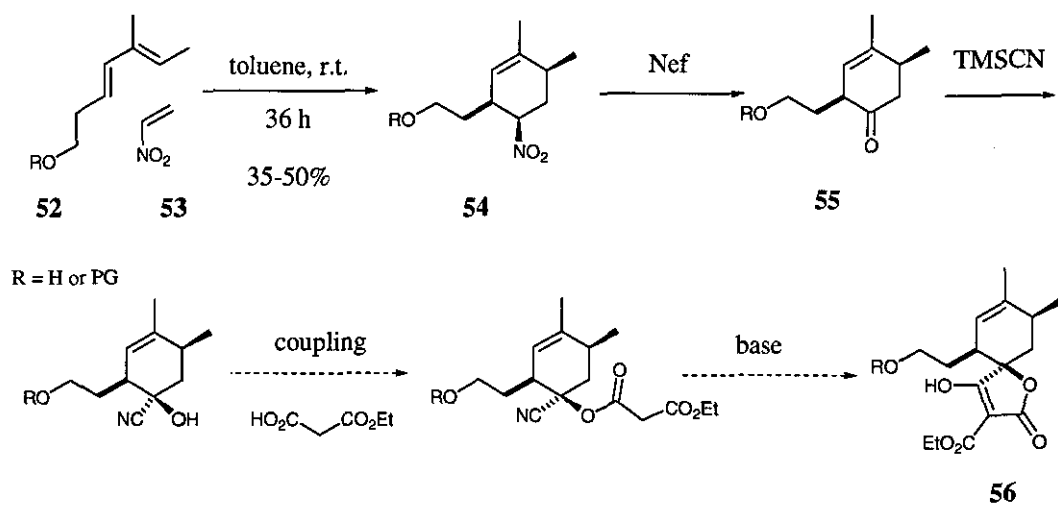
Scheme 5

The Nef reaction was more difficult to perform than it was originally anticipated, and the complete lack of any of the desired product suggested a failure to form the nitronate anion, necessary for subsequent transformation to the keto group. The difficulty thus came probably in the deprotonation of **54**. Changing the procedure gave decomposition of the starting material, and the anion, if formed, was very unstable.

Alternatively, another route leading to the ketone **55** involving a Pummerer rearrangement was planned.[101] The use of phenyl vinyl sulfoxide as dienophile was envisaged, to give the Diels-Alder product **57** in Scheme 6.
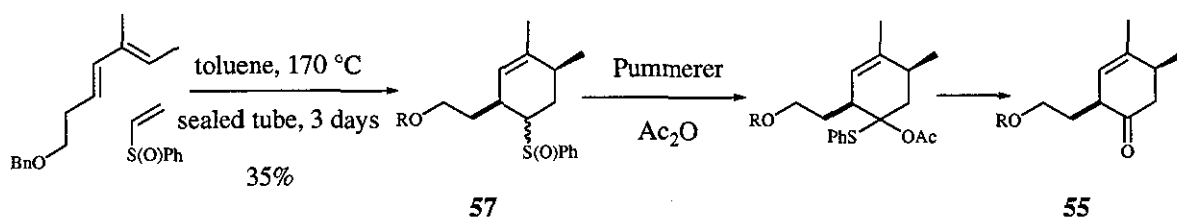
Scheme 6

The subsequent Pummerer reaction failed and the ketone **55** could not be prepared.[101]

1.7.2.1.2. Indirect approaches

Synthesis of the *exo*-spirotetronate **63** proved to be quite challenging. Indeed, direct Diels-Alder constructions of intermediates such as **62** are complicated by the fact the carbomethoxyl substituent is *trans* to the C-20 side chain (kijanolide numbering system), a stereoarrangement which requires an *exo*-mode of cycloaddition. The development of indirect approaches has been introduced: since a direct Diels-Alder route to the *exo*-Diels-Alder adduct **60** has not yet been devised, the use of the readily available *endo* product **59** was developed by Roush *et al.*[102,103] and introduced by Marshall and Xie.[104]

Marshall and Xie used this strategy in the scheme below (Scheme 7).[104]
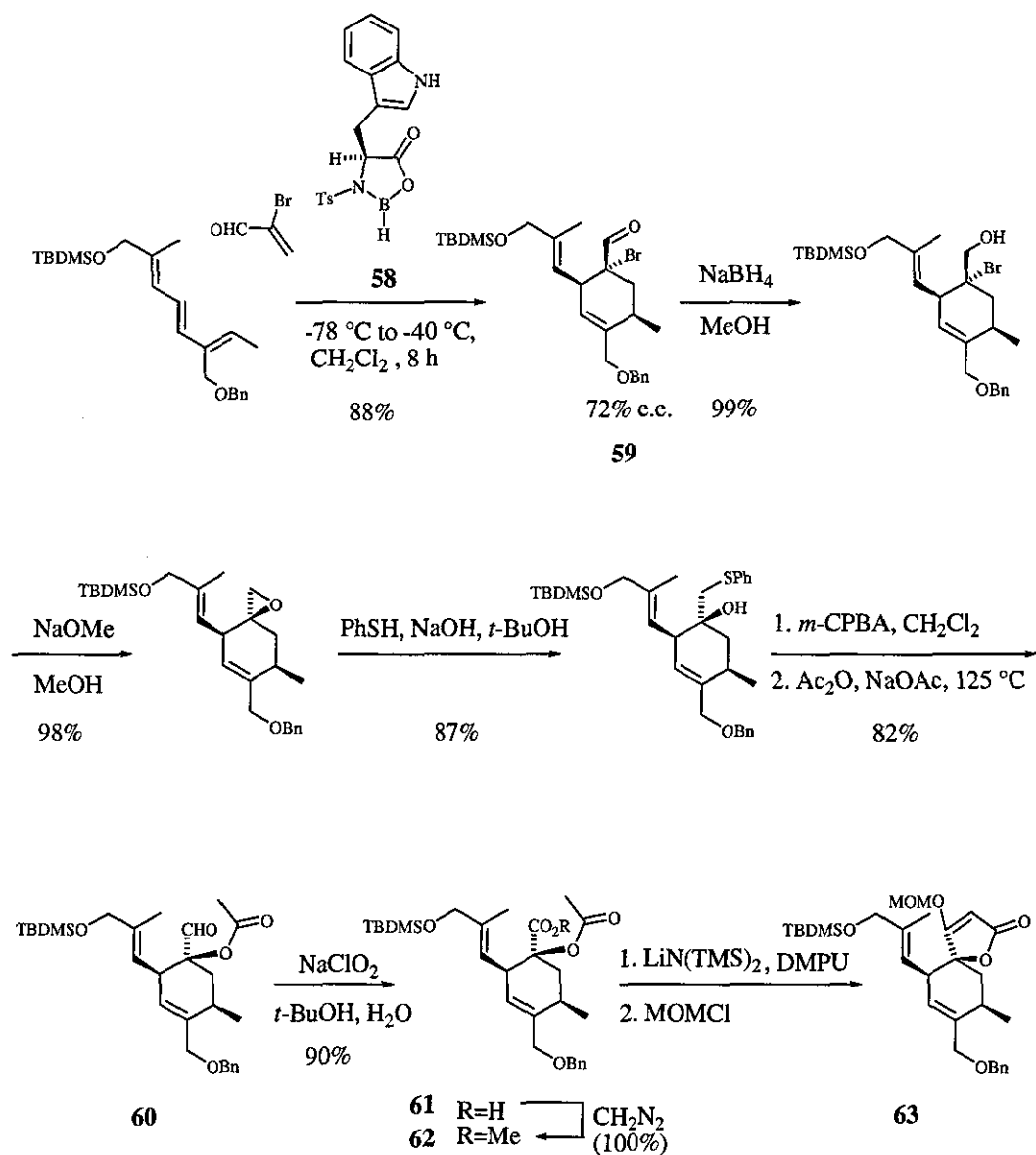
Scheme 7

The oxazaborolidine **58** reported by Corey and Loh[105] gave exclusively the *endo* product **59** with an enantiomeric excess of 72%. Inversion of the very hindered α-bromoaldehyde stereocentre of compound **59** allowed access to the *exo*-Diels-Alder adduct **60** but at the cost of several extra steps. Oxidation of **60** gave **61**,

which was esterified with diazomethane to give product **62**. Completion of the synthesis was effected through the Dieckmann cyclisation of **62** by treatment with LiN(TMS)$_2$, using DMPU as the cosolvent.

A similar route was proposed by Roush *et al.* in their synthesis of the *exo*-spirotetronate that corresponds to the *agalacto* fragment of quartromicins A$_3$ and D$_3$. The Diels-Alder reaction, employing dichloromethylaluminium **65** as a catalyst, provided 96% yield of a 96:4 mixture of *endo* and *exo*-cycloadducts **66a** and **66b** (Scheme 8).[102]

| 66a | : | 66b |
| 96 | : | 4 |
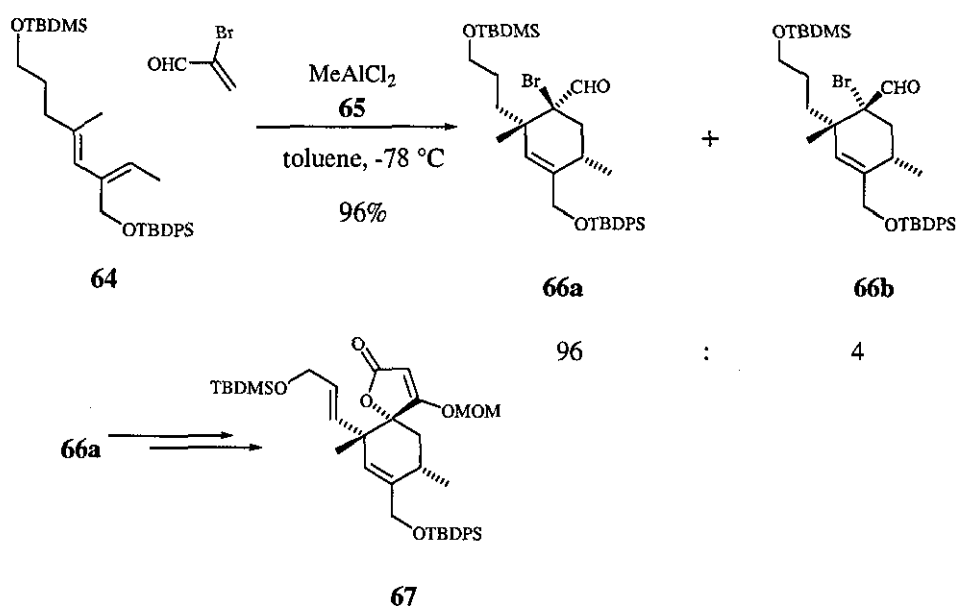
Scheme 8

The *exo*-spirotetronate **67** targeted was then synthesised from **66a**, with excellent diastereoselectivity, by following a similar sequence to the one proposed in Scheme 5.

Roush *et al.* have improved the diastereoselective Diels-Alder reaction of the acyclic tetrasubstituted diene **64** in a third generation synthesis of **67**.[103] The enantioselective preparation of this fragment was thus achieved to avoid

production of diastereoisomers in the coupling reaction affording the quartromicins.

Like the former route, the synthesis started with a MeAlCl$_2$-promoted Diels-Alder reaction, where *exo*-cycloadduct **69** was obtained with 7:1 diastereoselectivity by using the *N*-acryloyl sultam **68** (Scheme 9).
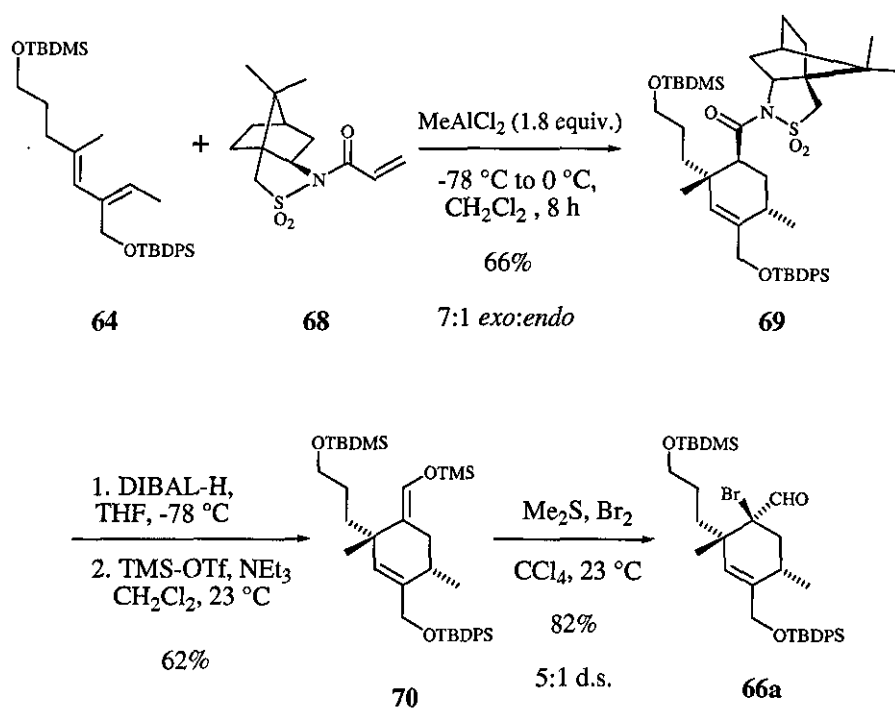
Scheme 9

Compound **69** was transformed into its derived aldehyde, which was treated with trimethyl silyl triflate and triethylamine to provide the enol silane **70**. Bromination of **70** with bromodimethylsulfonium bromide gave a separable 5:1 mixture of the *endo*-bromide **66a** and its *exo*-diastereoisomer in 82% yield.

In addition to the two syntheses described above, Roush et *al.* also developed a second generation synthesis to afford the *iso-exo* tetronate **67**.[102] This strategy was based on the control of the stereochemistry of early intermediates.

The C-5 α-acetoxy ester stereocentre in **74** was expected to be introduced stereoselectively by an enantioselective hydroxylation of the ester enolate (Scheme 10).[106]
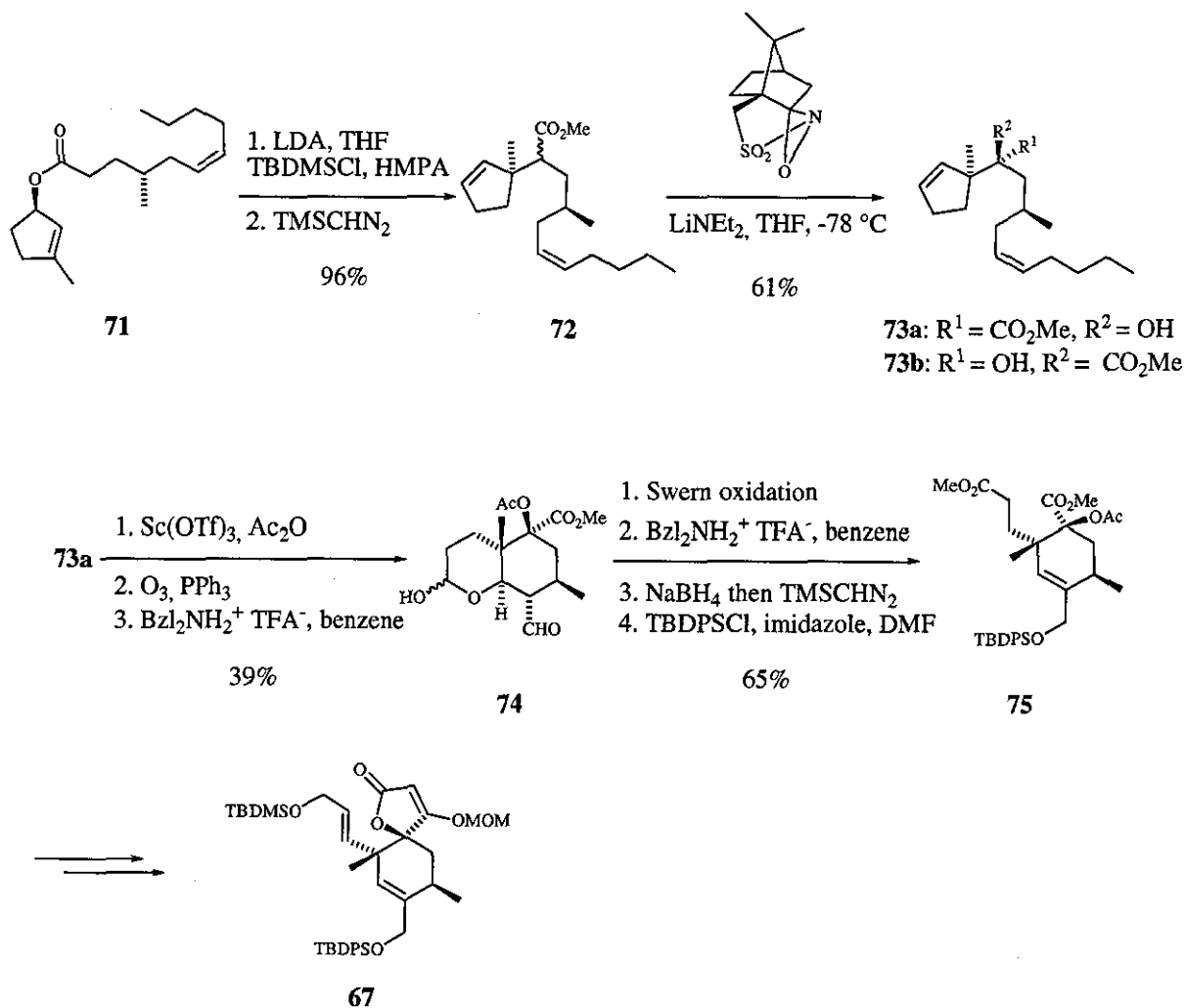
Scheme 10

A 1:1 mixture of diastereoisomers **72** was obtained by subsequent Claisen rearrangement of **71** followed by esterification of the carboxylic acids with TMSCHN$_2$. Unfortunately, the α-hydroxylation of the mixture of diastereoisomers **72** was non-stereoselective and provided a 1:1 mixture of the diastereoisomeric α-hydroxy esters **73**, from which the desired isomer **73a** was isolated

chromatographically. Several reactions provided the product **75**, the precursor of **67**, which had already been synthesised in the previous examples.

1.7.2.2. Utilisation of the chiral dienophiles (R)-76 and (R)-77

The biggest success in the synthesis of the *exo*-spirotetronates was the highly *exo*-selective Diels-Alder reactions of trienes with chiral dienophiles (R)-**76** and (R)-**77** mainly used by Roush and different coworkers.[107-113] The sterically demanding C_6H_{11} and *tert*-butyl substituents offer exceptional diastereofacial selectivity for the Diels-Alder reaction (Figure 12).

76: R = C_6H_{11}
77: R = C_4H_9

re face
(sterically shielded)

si face
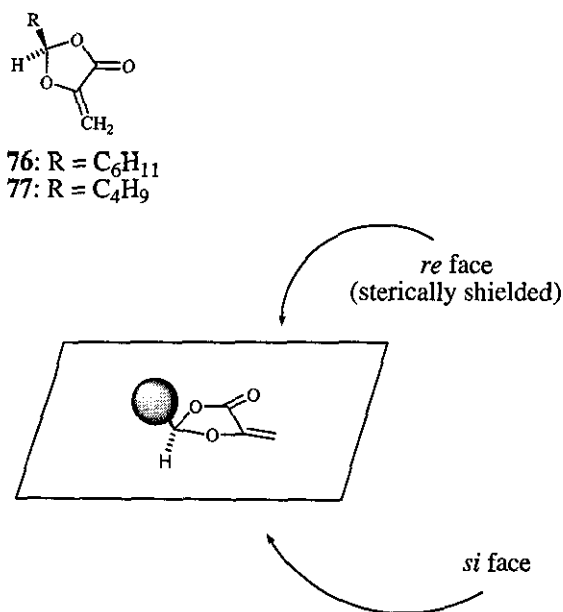
Figure 12

This class of dienophile also exhibits a tendency to undergo highly *exo*, rather than *endo*, Diels-Alder selectivity.

This apparently strange phenomenon has been explained by Berson.[114] He found that, for cyclopentadiene with methyl acrylate and related compounds, the

permanent dipole moment obtained in the case of the *endo* transition state is greater than in the case of the *exo* transition state. It follows that the dipole moments in *exo* transition state **78a**, leading to **79a**, would largely cancel out; the *endo* transition state **78b**, leading to **79b**, would contain a larger permanent dipole moment, and thus be higher in energy and disfavourable (Scheme 11).[114]
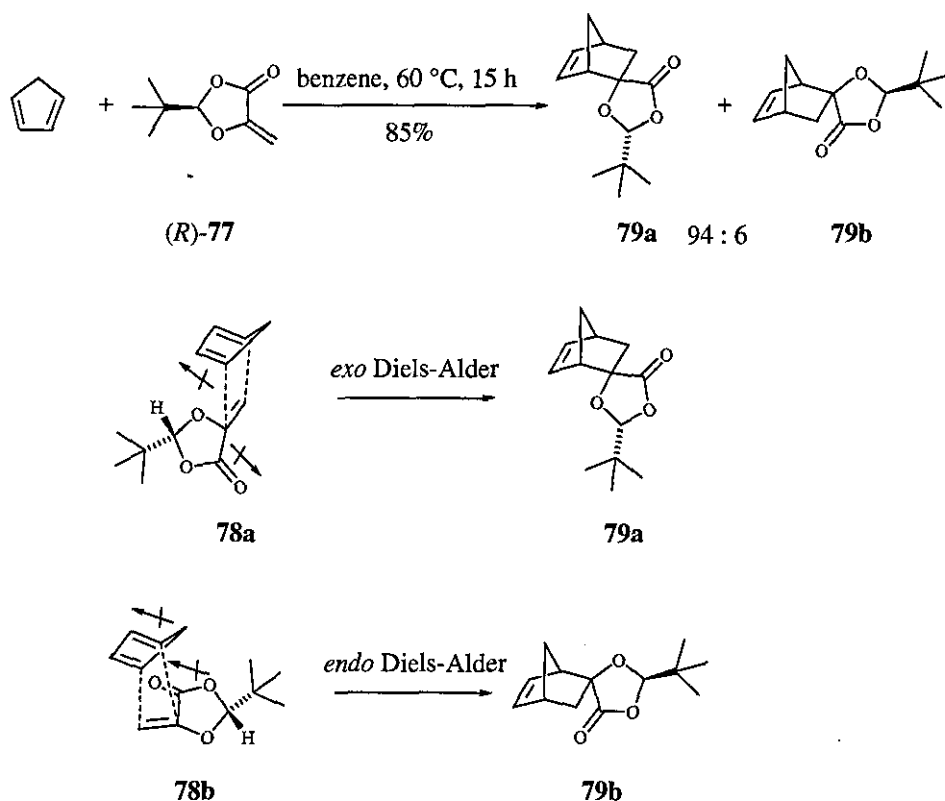
Scheme 11

Mattay *et al.* confirmed this hypothesis by observing a similar preference for *exo* cyclisation in a Diels-Alder reaction involving the (*S*)-isomer of **77** to give **80a** and **80b** (Scheme 12).[115]

(S)-77   80a   80b

                                      96.5   :   3.5
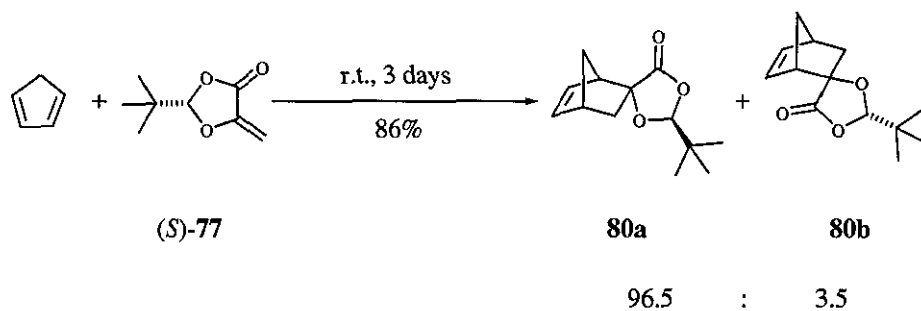
Scheme 12

Roush and Brown achieved the first highly diastereo- and enantioselective synthesis of the spirotetronate substructure of kijanolide by using this method.[107] The Diels-Alder reaction of **81** and the non racemic dienophile (R)-**77** provided a 13-14:1 mixture of the desire *exo*-cycloadduct **82a** and the *endo* isomer **82b** (Scheme 13).[107]
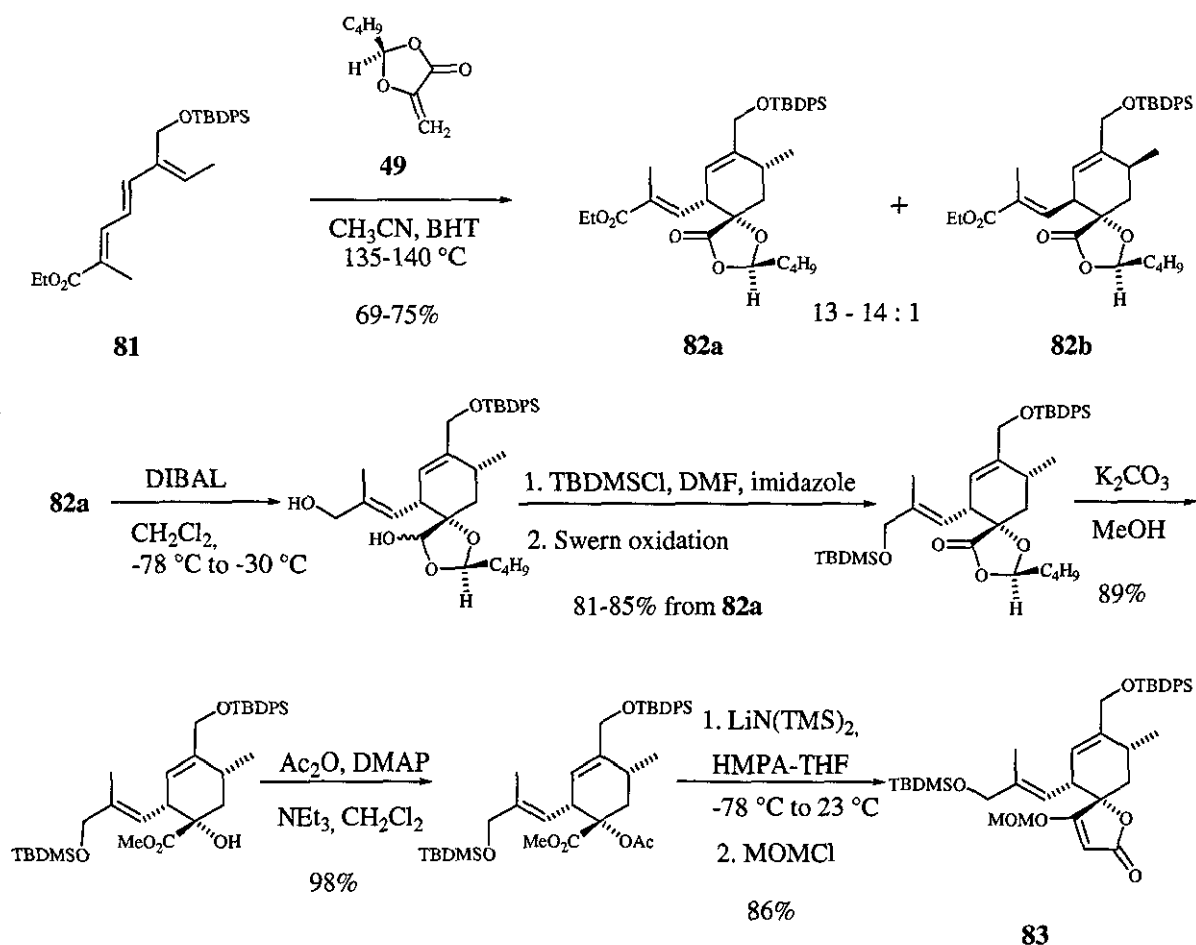
Scheme 13

Several reactions gave the product **83** from **82a**. The significance of this synthesis lies in the selectivity obtained during the Diels-Alder reaction by using (*R*)-**77**. Therefore, (*R*)-**77** was used in the synthesis of the top half spirotetronate subunits of tetronolide[108,109] and chlorothricolide,[110,111] showing similar results to these reported in Table 7.
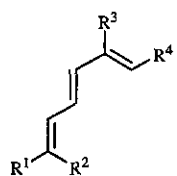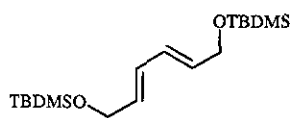
84   **85**

Table 7: highly selective Diels-Alder reactions using chiral dienophiles (R)-**76** and (R)-**77**.

Diene	Dienophile	Yield (%)	Ratio *endo : exo*	Ref
84, R^1=CO_2Me, R^2=H, R^3=$CH_2OTBDMS$, R^4=Me	(R)-**77**	64 – 70 ⎮ 84	15 : 1 ⎮ 6 : 1	110 ⎮ 111
84, R^1=CO_2Et, R^2=Me, R^3=$CH_2OTBDMS$, R^4=Me	(R)-**77**	69 – 75	93 : 7	107
84, R^1=CO_2Me, R^2=Me, R^3=H, R^4= $CH_2OTBDMS$	(R)-**77**	72	93 : 7	108,109
84 R^1=$(CH_2)_5OTBDMS$, R^2=H, R^3=$CH_2OTBDMS$, R^4=Me	(R)-**77**	78	14 : 1	110,111
85	(R)-**76**	46	7 : 1	112

To conclude the retrospective of different routes leading to the *exo*-spirotetronates, the enantioselective total synthesis of (-)-Chlorothricolide has been completed using a route involving the tandem inter- and intramolecular Diels-Alder reaction of polyene **86** and the chiral dienophile (R)-**77**. This reaction, which establishes seven asymmetric centres in a single operation, raises questions about regio- and diastereoselectivity. Taking into account all possible *endo*, *exo*, diastereofacial and regiochemical possibilities afforded by the diene-dienophile combinations, there are ninety-six distinct double Diels-Alder adducts that could be produced.

Fortunately, the (C-2)-(C-3) dienophile is the most activated of the three dienophiles of **86** and results shown in Table 7 prove that the rates of Diels-Alder reactions of dienophiles (R)-**77** and (R)-**76** with acyclic dienes (like **84**) are considerably lower than the corresponding reaction with conjugated trienes. On this basis, the (C-8)-(C-11) diene is unlikely to react. It is also possible that the intramolecular reaction is much faster and takes place first. This would imply that (C-8)-(C-11) diene is no longer available since it has already reacted. In addition, (R)-**77** proceeds with high *exo*, regio and diastereofacial selectivity (Scheme 14).[112,113]

86

77

toluene,
120 °C, 20 h, BHT

87a + **87b** + isomers

40-45%   25-20%

(R)-**77**, Cl₂C=CHCl,
125 °C, 28-36 h, BHT

58%

87a

1. K₂CO₃, MeOH
2. DCC, DMAP

MeO₂C—O—

91%

88

1. LiN(TMS)₂, THF,
   -78 °C to 0 °C;
   then MOMCl, HMPA

2. Pd(PPh₃)₄, THF
   dimedone

88%

89

BOP-Cl, NEt₃

toluene, 100 °C

50%

1. TEA·HF, CH₃CN, 50 °C
2. MnO₂, CH₂Cl₂

3. NaClO₂, NaH₂PO₄, t-BuOH, CH₃CN
4. EtSH, BF₃·Et₂O, CH₂Cl₂

68%

(-)-chlorotricolide

Scheme 14

53

The tandem Diels-Alder reactions provided the targeted double cycloadduct **87** in 40-45% yield, 19% of other cycloadduct isomers and 25-20% of the IMDA adduct **87b**. Compound **87b** was recycled by treatment with additional (*R*)-**77**. The overall yield reached 55-59%.

As described above, Dieckmann closure of the spirotetronate was accomplished by treatment of **88** with LiN(TMS)$_2$ followed by the addition of MOMCl to give **89**. The total synthesis proceeds the 20 steps in approximately 2% yield, and is still the only reported synthesis of (-)-chlorothricolide.

Attempted synthesis by the Page group

The aptitude of (*R*)-**77** to undergo highly *exo*-selective and highly stereofacial selective Diels-Alder reactions inspired a modified synthesis to yield the spirotetronic acid part of tetronothiodin (Scheme 15).[116]
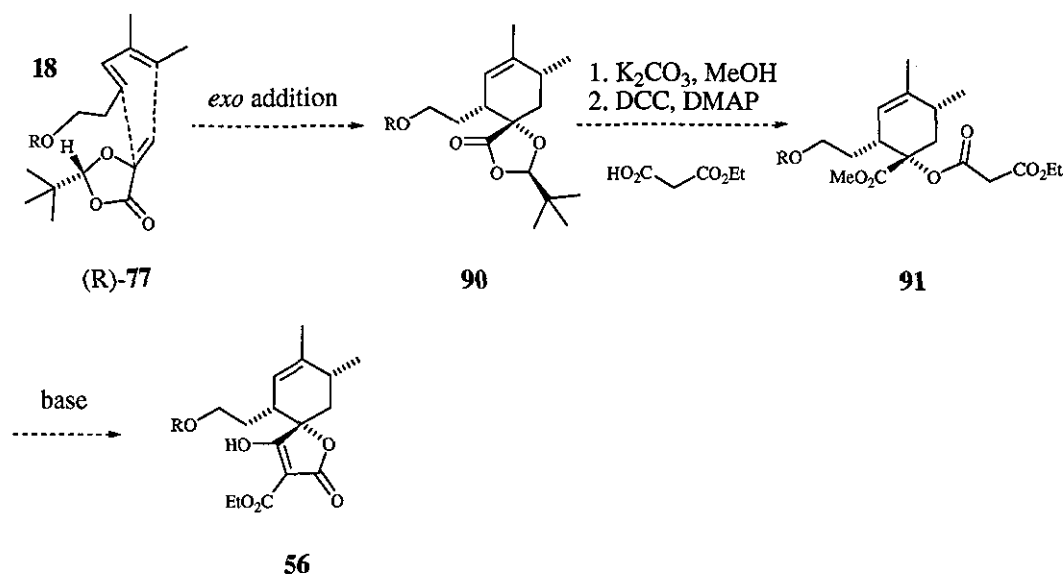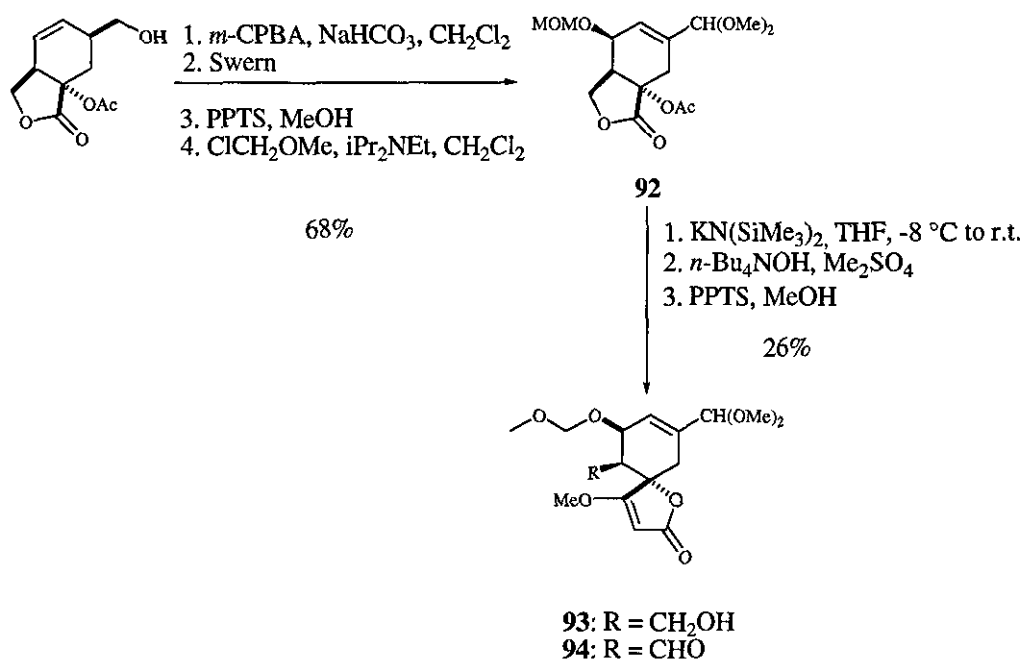

Scheme 15

Unfortunately, the Diels-Alder reaction did not proceed as planned, despite testing of many different reaction conditions. The main problem was the instability of the

precursors. In the case of the dienes, this was perhaps due to the size of the molecules, and the ease with which some dienes may polymerise. In the case of the dienophile, dioxolane rings may have been unstable under certain conditions used, such as the presence of Lewis acid. This pathway to the oxaspirobicyclic unit was consequently discontinued.

1.7.2.3. Atypical routes leading to the spirotetronate unit

1.7.2.3.1. The attempted Intamolecular Claisen reaction

In the studies towards the first synthesis of the upper fragment of tetronolide, Yoshii *et al.* proposed an unusual route to the elaboration of the *exo*-spirotetronate subunit. The key step was an intamolecular Claisen condensation of the α-acetoxy-γ-lactone **92** (Scheme 16).[117]

1. *m*-CPBA, NaHCO$_3$, CH$_2$Cl$_2$
2. Swern

3. PPTS, MeOH
4. ClCH$_2$OMe, iPr$_2$NEt, CH$_2$Cl$_2$

68%

92

1. KN(SiMe$_3$)$_2$, THF, -8 °C to r.t.
2. *n*-Bu$_4$NOH, Me$_2$SO$_4$
3. PPTS, MeOH

26%

93: R = CH$_2$OH
94: R = CHO

Scheme 16

The attempted oxidation of **93** to the aldehyde **94**, the aldehyde being required for elongation of the side chain, resulted in concomitant loss of the MOM group, presumably by β-elimination. The synthesis was not carried on further by this route.

### 1.7.2.3.2. The attempted Schmidt spiroannulation reaction

Another method proposed by Yoshii was based on two key steps: a Schmidt spiroannelation and a selective regio- and diastereoselective dihydroxylation. Schmidt spiroannulation of **95** gave **97** by using the β-dichlorocerium derivative of methyl *trans*-β-methoxyacrylate **96**. The choice of this organocerium compound allowed a better yield than a Grignard or a lithium reagent, because of its low basicity which prevents enolisation.[118] The remaining task was solved by a selective regio- and diastereoselective dihydroxylation of the *endo* double bond of **99** to give **100**. Finally, the diol **100** was first converted to the bis-methoxymethyl ether, and then treated with methanolic potassium carbonate to afford γ-methoxymethoxy-α,β-unsaturated aldehyde **101** (Scheme 17).[119]
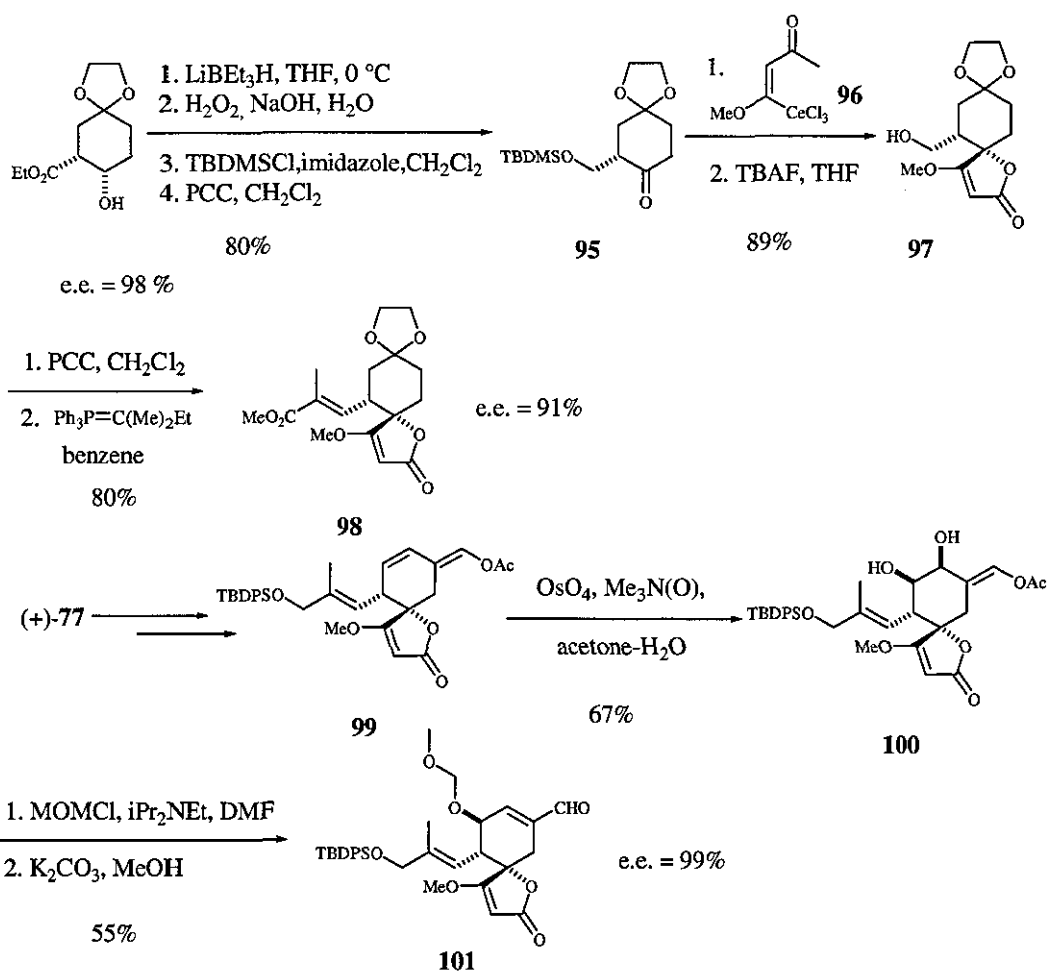
Scheme 17

1.7.2.3.3. The attempted Intramolecular Diels-Alder (IMDA) reaction

The synthesis using an IMDA reaction of compound **102** was developed. This route is unfortunately lengthier and suffers from poor diastereoselectivity owing to competitive olefin isomerisation, which led to three cycloadducts **103a**, **103b** and **103c**. Only a 13% yield of **103c** was obtained, which was the second most abundant product (Scheme 18).[120]

57
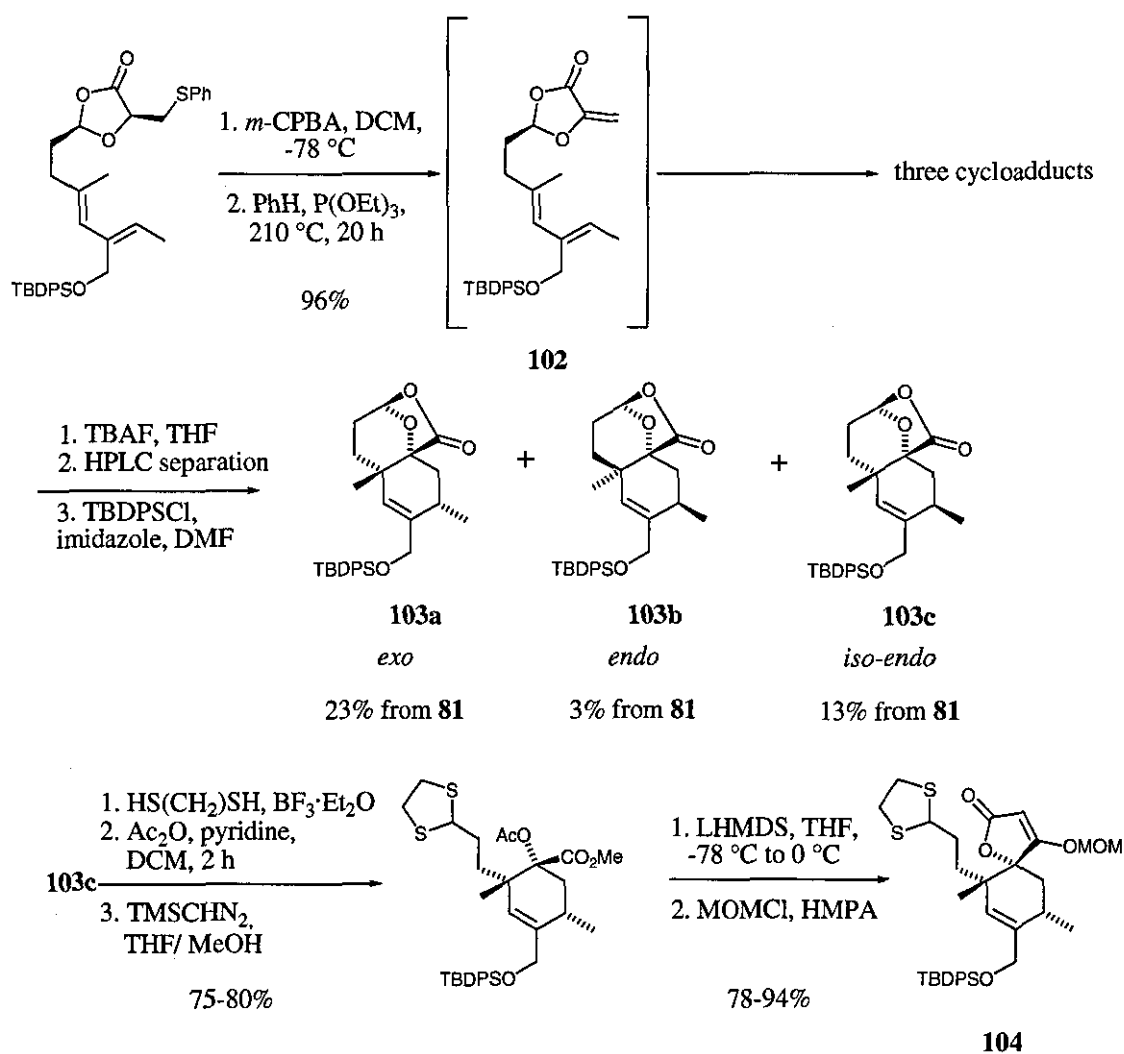
Scheme 18

**104** was obtained after five more steps from compound **103c**. This route was too inefficient for use in a total synthesis of the quartromicins, both in terms of chemical yield and stereoselectivity.

Attempted synthesis by the Page group

Nevertheless, the IMDA reaction has been considered by the Page group,[116] because it has advantages of being able to accelerate the rate of reaction compared

to the intermolecular Diels-Alder reaction. IMDA reactions also prevent regiochemical problems due to ring constraints (*vide supra*).[121] The process was improved in the group by Hindley, Batchelor and Vahedi to give the two synthetic plans (Schemes 19 and 20).[101,116,122]

The Nef and Pummerer routes to generate a carbonyl group at the *pro*-spiro position as in ketone **55** was replaced by the coupling of the hydroxydiene **111** with diphenylchlorovinyl silane **105** followed by an efficient IMDA outlined by Sieburth *et al.* to give **107** (Scheme 19).[123]
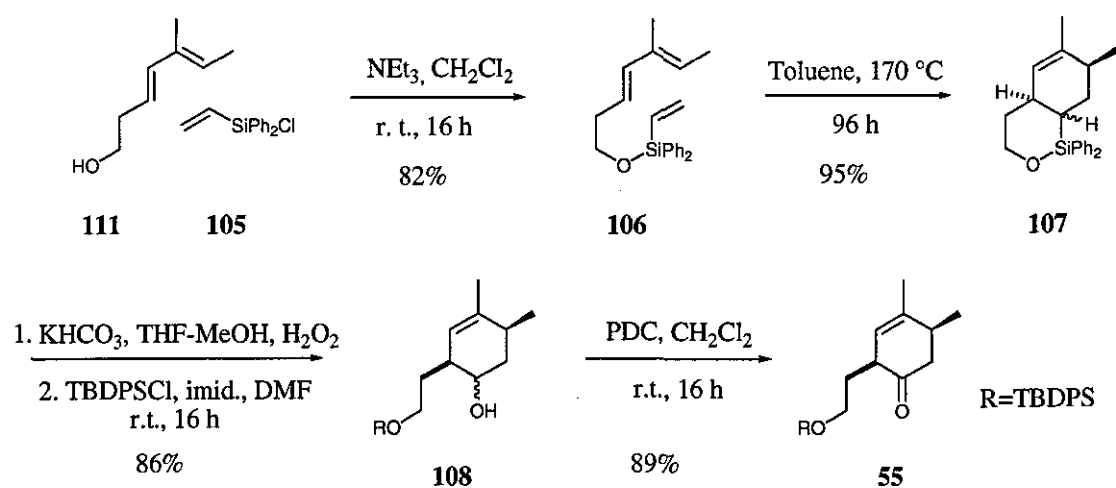
Scheme 19

The intramolecular Diels-Alder reaction of triene **106** gave **107** in a 95% yield. **107** firstly underwent a Tamao-type oxidation followed by the protection of the primary alcohol, and finally oxidation of **108** with PCC gave **55** in 59.6% overall yield.

Cyanohydrin formation from **55** proved to be poorly stereoselective, and other methods of functionalisation were low yielding. In addition this route was rather lengthy, and the group subsequently found a more efficient approach.

59

This synthetic approach involves the stereoselective synthesis of oxaspirobicyclic **116** as a diastereoisomeric precursor of **30** (Scheme 20).

Research conducted has established much of the chemistry of this promising, rapid route to the oxaspirobicyclic tetronic acid moiety **116**. In initial racemic studies, it has been found the Diels–Alder cycloaddition between diene **111** and acrolein to be the key in constructing the cyclohexene ring suitably functionalised for conversion to the target spirocycle **30**. The previous researchers have shown that this Diels–Alder reaction proceeds efficiently in water with a high degree of regio and stereoselectivity. PDC oxidation product **113** was isolated as the only isomer observed. The conversion of **113** to **116** was effected by the formation of α-hydroxy lactone **114**, followed by acylation to give **115** and final Dieckmann cyclisation with concomitant lactone ring opening. α-Hydroxylation of **113** with (1S)-(+)-(camphorsulfonyl)oxaziridine afforded **114**, which was identified by single-crystal X-ray crystallography.

The stereochemistry of the compounds was established through ^{1}H NMR analysis. Thus the stereostructural assignment for the diene **111** was based on the coupling constant value between H-3 and H-4 (J_{3-4}= 18 Hz), which is consistent with the E stereoisomer. Also, the stereochemical assignment of lactol **112** based on the small coupling constant between H-4 and H-8 (J_{4-8}= 4.5 Hz), which is consistent with the *cis* configuration (Scheme 20).
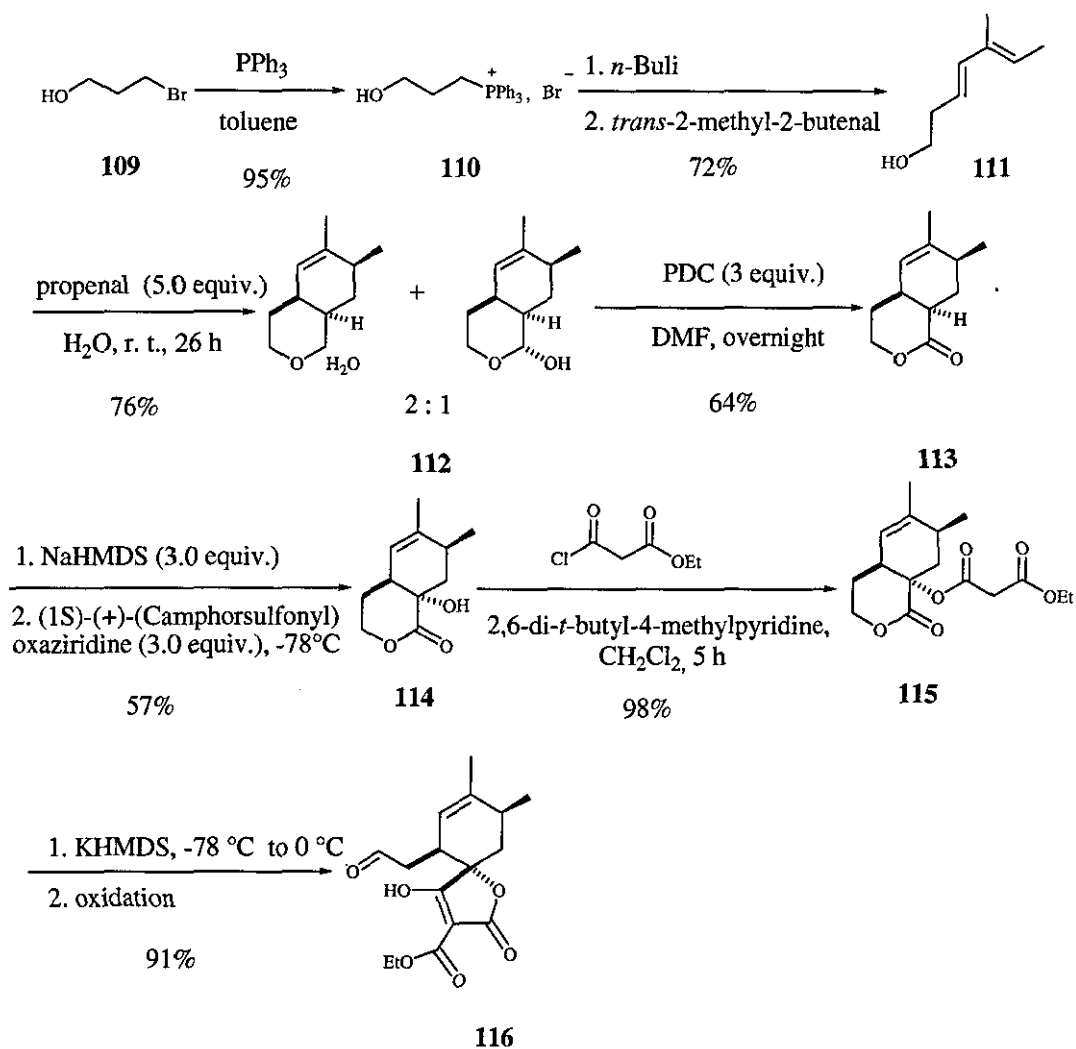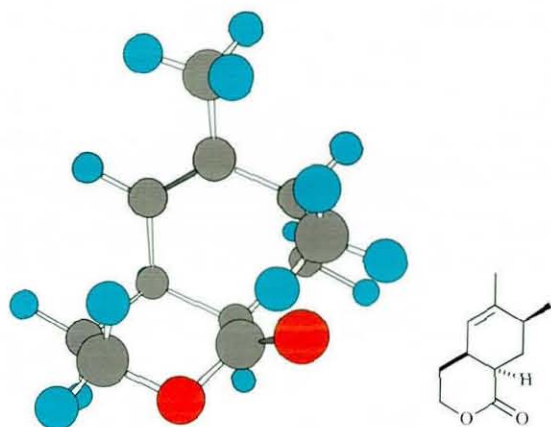
Scheme 20

This route has led to spirocycle **116**, which is a diastereoisomer of the target **30**.

30
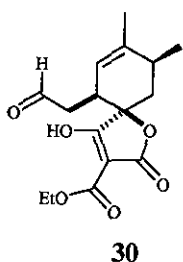
This stereochemical outcome is the result of the α-hydroxylation occurring exclusively from the least hindered face of the enolate of **113**. Access to the upper face is clearly hindered by the two methyl groups (Figure 13).

113

Figure 13

1.8. References

(1) Vanderhaegen, J.-J.; Signeau, J. C.; Gepts, W. *Nature* **1975**, *257*, 604.

(2) Woodruff, G. N.; Hugues, J. *Annu. Rev. Pharmacol. Toxicol.* **1991**, *31*, 469.

(3) Deschesnes, R. J.; Lorenz, L. J.; Haun, R. S.; Roos, B. A.; Collier, K. J.; Dixon, J. E. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 726.

(4) Van Dijk, A.; Richards, J. G.; Trzeciak, A.; Gillessen, D.; Mohler, H. *J. Neurosci.* **1984**, *4*, 1021.

(5) Bowen, R.; Colorado State University; http://arbl.cvmbs.colostate.edu, 2000.

(6) Meyer, D. K.; Krauss, J. *Nature* **1983**, *301*, 338.

(7) Pinget, M.; Strauss, E.; Yalow, R. S. *Life Sci.* **1979**, *25*, 339.

(8) Lydiard, R. B.; Brewerton, T. D.; Fossey, M. D.; Laraia, M. T.; Stuart, G.; Beinfeld, M. C.; Ballenger, J. C. *Am. J. Psychiatry* **1993**, *150*, 1099.

(9) Harro, J.; Lang, A.; Vasar, E. *Eur. J. Pharmacol.* **1990**, *180*, 77.

(10) Dockray, G. J. *Nature* **1976**, *264*, 568.

(11) Emson, P. C.; Rehfeld, J. F.; Rossor, M. N. *J. Neurochem.* **1982**, *38*, 1177.

(12) Larsson, L. I.; Rehfeld, J. F. *Brain Res.* **1979**, *165*, 418.

(13) Skirboll, L. P.; Hokfelt, T.; Dockray, G. J.; Rehfeld, J. F.; Brownstein, M.; Cuello, A. *J. Neurosci.* **1983**, *3*, 1151.

(14) Crawley, J. N. *Ann. N. Y. Acad. Sci.* **1985**, *448*, 1.

(15) Innis, R. B.; Correa, F. M. A.; Uhl, G. R.; Schreider, B.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 521.

(16) Vanderhaegen, J.-J.; Lotstra, F.; Demey, J.; Gilles, C. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1190.

(17) Innis, R. B.; Snyder, S. H. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 6917.

(18) Passaro, E.; Debas, H.; Oldendorf, W.; Yamada, T. *Brain Res.* **1982**, *241*, 338.

(19) Motulsky, H. *The GraphPad Guide to Analyzing Binding Data*; GraphPad Software Inc.: San Diego (USA), 1996.

(20) Kenakin, T. *Pharmacologic analysis of drug-receptor interaction*; Raven Press, 1993.

(21) Moran, T. H.; Robinson, P. H.; Goldrich, M. S.; McHugh, P. R. *Brain Res.* **1986**, *362*, 175.

(22) Gaudreau, P.; Quirion, R.; St-Pierré, S.; Pert, C. B. *Eur. J. Pharmacol.* **1983**, *87*, 173.

(23) Sankaran, H.; Goldfine, I. D.; Deveney, C. W.; Wong, K. Y. *J. Biol. Chem.* **1980**, *255*, 1849.

(24) Smith, G. T.; Moran, T. H.; Coyle, J. T.; Kuhar, M. J.; O'Donahue, T. L.; McHugh, P. R. *Am. J. Physiol.* **1984**, *246*, R127.

(25) Zarbin, M. A.; Innis, R. B.; Wamsley, J. K.; Snyder, S. H.; Kuhar, M. J. *J. Neurosci.* **1983**, *3*, 877.

(26) Wank, S. A.; Pisegna, J. R.; De Weerth, A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 8691.

(27) Gardner, J. D.; Jensen, R. T. *Am. J. Physiol.* **1984**, *246*, G471.

(28) Hill, D. R.; Shaw, T. M.; Dourish, C. T.; Woodruff, G. N. *Brain Res.* **1988**, *454*, 101.

(29) Borrison, H. L. *Life Sci.* **1974**, *14*, 1807.

(30) Leslie, R. A.; Gwyn, D. G.; Hopkins, D. A. *Brain Res. Bull.* **1982**, *8*, 37.

(31) Hill, D. R.; Shaw, T. M.; Woodruff, G. N. *Neurosci. Lett.* **1987**, *79*, 286.

(32) Penke, B.; Hajnal, F.; Lonovics, J.; Holzinger, J.; Kadar, G.; Telegdy, T.; Rivier, J. *J. Med. Chem.* **1984**, *27*, 845.

(33) Hill, D. R.; Shaw, T. M.; Dourish, C. T.; Woodruff, G. N. *Brain Res.* **1990**, *454*, 101.

(34) Saito, A.; Sankaran, H.; Goldfine, I. D.; Williams, J. A. *Science* **1980**, *208*, 1155.

(35) Abelson, J. L. *J. Psychiat. Res.* **1995**, *29*, 389.

(36) Crawley, J. N.; Corwin, R. L. *Peptides* **1994**, *15*, 731.

(37) Nair, N. P. V.; Bloom, D. M.; Nestoros, J. M. *Proc. Neuro-Psychopharmacol. Biol. Psychiatry* **1982**, *6*, 509.

(38) O'Neill, M. F.; Dourish, C. T.; Tye, S. J.; Iversen, S. D. *Brain Res.* **1990**, *534*, 287.

(39) Homayoun, H.; Dehpour, A. R. *Pharmacol. Biochem. Behav.* **2004**, *78*, 209.

(40) Dourish, C. T.; O'Neill, M. F.; Coughlan, J.; Kitchener, S. J.; Hawley, D.; Iversen, S. D. *Eur. J. Pharmacol.* **1990**, *176*, 35.

(41) Hökfelt, T.; Rehfeld, J. G.; Skirboll, L. P.; Ivemark, B.; Goldstein, M.; Markey, K. *Nature* **1980**, *285*, 476.

(42) Crawley, J. N. *Trends. Pharmacol. Sci.* **1991**, *12*, 232.

(43) Hamon, M. *Trends. Pharmacol. Sci.* **1994**, *15*, 36.

(44) Papp, L. A.; Klein, D. F.; M., G. J. *Am. J. Psychiatry* **1993**, *150*, 1149.

(45) Brambilla, F.; Bellodi, L.; Perna, G.; Garberi, A.; Panerai, A.; Sacerdote, P. *Am. J. Psychiatry* **1993**, *150*, 1111.

(46) Lydiard, R. B.; Ballenger, J. C.; Laraia, M. T.; Fossey, M. D.; Beinfeld, M. C. *Am. J. Psychiatry* **1992**, *149*, 691.

(47) De Montigny, C. *Arch. Gen. Psychiatry* **1989**, *46*, 511.

(48) Bradwejn, J.; Koszycki, D.; Couetoux du Tretre, A.; Van Megen, H.; Den Boer, J.; Westenberg, H.; Annable, L. *Arch. Gen. Psychiatry* **1994**, *51*, 486.

(49) Ravard, S.; Dourish, C. T. *Trends. Pharmacol. Sci.* **1990**, *11*, 271.

(50) Ravard, S.; Dourish, C. T.; Iversen, S. D. *Br. J. Pharmacol.* **1990**, *101*, 576P.

(51) Boden, P.; Hill, R. G. *Br. J. Pharmacol.* **1988**, *84*, 286.

(52) Lydiard, R. B. *Clin. Chem.* **1994**, *40*, 315.

(53) Philipp, E.; Pirke, K. M.; Kellner, M. B.; Krieg, J. C. *Life Sci.* **1991**, *48*, 2443.

(54) Tamai, H.; Takemura, J.; Kobayashi, N.; Matsubayashi, S.; Matsukura, S.; Nakagawa, T. *Metabolism* **1993**, *42*, 581.

(55) Della-Fera, M. A.; Baile, C. A. *Science* **1979**, *206*, 471.

(56) Gibbs, J.; Young, R. C.; Smith, J. P. *J. Comp. Physiol. Psychol.* **1973**, *84*, 488.

(57) Moran, T. H.; McHugh, P. R. *Am. J. Physiol.* **1982**, *242*, R491.

(58) Shick, R. R.; Schusdziarra, V.; Yaksh, T. L.; Go, V. L. W. *Ann. N. Y. Acad. Sci.* **1994**, *713*, 242.

(59) Dhillo, W. S.; Bloom, S. R. *Hormones and Metabolic Res.* **2004**, *36*, 846.

(60) Collins, S.; Walker, D.; Forsyth, P.; Belbeck, L. *Life Sci.* **1983**, *32*, 2223.

(61) Dourish, C. T.; Rycroft, W.; Iversen, S. D. *Science* **1989**, *245*, 1509.

(62) Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schönberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science* **1985**, *230*, 177.

(63) Martinez, J.; Rodriguez, M.; Castro, B.; Bali, J.-P.; Laur, J. *J. Med. Chem.* **1986**, *29*, 2201.

(64) Mendre, C.; Rodriguez, M.; Gueudet, C.; Lignon, M.-F.; Galas, M.-C.; Laur, J.; Worms, P.; Martinez, J. *J. Biol. Chem.* **1988**, *263*, 10641.

(65) Peikin, S. R.; Costenbader, C. L.; Gardner, J. D. *J. Biol. Chem.* **1979**, *254*, 5321.

(66) Innis, R. B.; Snyder, S. H. *Eur. J. Pharmacol.* **1980**, *65*, 123.

(67) Miller, L. J.; Reilly, W. M.; Rosenzweig, S. A.; Jamieson, J. D.; Go, V. L. W. *Gastroenterology* **1983**, *84*, 1505.

(68) Gaudreau, P.; St-Pierre, S.; Pert, C. B.; Quirion, R. *Ann. N. Y. Acad. Sci.* **1985**, *448*, 198.

(69) Hanhe, W. F.; Jensen, R. T.; Lemp, G. F.; Gardner, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 6304.

(70) Jensen, R. T.; Jones, E. G.; Gardner, J. D. *Biochem. Biophys. Acta.* **1983**, *761*, 269.

(71) Maselli, M. A.; Piepoli, A. L.; Pezzolia, F.; Guerra, V.; Caruso, M. L.; Mennuni, L.; Lorusso, D.; Makovec, F. *Digestive Diseases and Sciences* **2001**, *46*, 2773.

(72) Hugues, J.; Boden, P.; Costall, B.; Domeney, A.; Kelly, E.; Horwell, D. C.; Hunter, J. C.; Pinnock, R. D.; Woodruff, G. N. *Neurobiology* **1990**, *87*, 6728.

(73) Makovec, F.; Peris, W.; Revel, L.; R., G.; Mennuni, L.; Rovati, L. C. *J. Med. Chem.* **1992**, *35*, 28.

(74) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918.

(75) Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Kunkel, K. A. *Mol. Pharmacol.* **1986**, *30*, 212.

(76) Lotti, V. J.; Chang, R. S. L. *Eur. J. Pharmacol.* **1989**, *162*, 273.

(77) Hill, D. R.; Woodruff, G. N. *Brain Res.* **1990**, *526*, 276.

(78) Dunlop, J. *Gen. Pharmac.* **1998**, *31*, 519.

(79) Castro, J. L.; Ball, R. G.; Broughton, H. B.; Russell, M. G. N.; Rathbone, D.; Watt, A. P.; Baker, R.; Chapman, K. L.; Fletcher, A. E.; Patel, S.; Smith,

A. J.; Marshall, G. R.; Ryecroft, W.; Matassa, V. G. *J. Med. Chem.* **1996**, *39*, 842.

(80) Singh, L.; Field, M. J.; Hugues, J.; Menzies, R.; Oles, R. J.; Vass, C. A.; Woodruff, G. N. *Br. J. Pharmacol.* **1991**, *104*, 239.

(81) Fossa, A. A.; DePasquale, M. J.; Morrone, J.; Zorn, S. H.; Bryce, D.; Lowe, J. A.; McLean, S. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 180.

(82) Singh, L.; Field, M. J.; Hill, D. R.; Horwell, D. C.; McKnight, A. T.; Roberts, E.; Tang, K. W.; Woodruff, G. N. *Eur. J. Pharmacol.* **1995**, *286*, 185.

(83) Kerwin, J. F.; Nadzan, A. M.; Kopecka, A.; Lin, C. W.; Miller, T.; Witte, D.; Burt, S. *J. Med. Chem.* **1989**, *32*, 742.

(84) Baber, N. S.; Dourish, C. T.; Hill, D. R. *Pain* **1989**, *39*, 307.

(85) Magnusson, D. S. K.; Sullivan, A. F.; Simmonet, G.; Roques, B. P.; Dickenson, A. H. *Neuropeptides* **1990**, *16*, 213.

(86) Ohtsuka, T.; Kudoh, T.; Shimma, N.; Kotaki, H.; Nakayama, N.; Itezono, Y.; Fusijaki, N.; Watanabe, J.; Yokose, K.; Seto, H. *J. Antibiotics* **1992**, *45*, 140.

(87) Ohtsuka, T.; Kotaki, H.; Nakayama, N.; Itezono, Y.; Shimma, N.; Kudoh, T.; Kuwahara, T.; Arisawa, M.; Yokose, K. *J. Antibiotics* **1993**, *46*, 1.

(88) Ohtsuka, T.; Kotaki, H.; Nakayama, N.; Itezono, Y.; Kuwahara, T.; Yokose, K. *J. Antibiotics* **1993**, *46*, 18.

(89) Kubota, K.; Sugaya, K.; Koizumi, Y.; Toda, M. *Brain Res.* **1989**, *485*, 62.

(90) Kuwahara, T.; Kudoh, T.; Nagase, H.; Takamiya, M.; Nakano, A.; Ohtsuka, T.; Yoshizaki, H.; Arisawa, M. *Eur. J. Biochem.* **1992**, *221*, 99.

(91) Jacobsen, J. P.; Reffstup, T.; Boll, P. M. *Acta Chem. Scand. Ser. B* **1977**, *31*, 505.

(92) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; Mc Phail, A. T.; Macfarlane, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 3940.

(93) Linderman, R. J.; Cutshall, N. S.; Becicka, B. T. *Tetrahedron Lett.* **1994**, *35*, 6639.

(94) Schindler, P. W.; Scrutton, M. C. *Eur. J. Biochem.* **1975**, *55*, 543.

(95) Bradner, W. T.; Claridge, C. A.; Huftalen, J. B. *J. Antibiotics* **1983**, *36*, 1078.

(96) Morimoto, M.; Fukiu, M.; Ohkubo, S.; Tamaori, T.; Tomita, F. *J. Antibiotics* **1982**, *35*, 1033.

(97) Kaneko, M.; Takayuki, N.; Uosaki, Y.; Hara, M.; Ikeda, S.; Kanda, Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 887.

(98) Matsumoto, M.; Kawamura, Y.; Yoshimura, Y.; Teriu, Y.; Nakai, H.; Yoshida, T.; Shoji, J. *J. Antibiotics* **1990**, *43*, 739.

(99) Takeda, K.; Yano, S. G.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135.

(100)   Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1989**, *30*, 2233.

(101)   Batchelor, K. J.; Loughborough University, 2001.

(102)   Roush, W. R.; Barda, D. A.; Limberakis, C.; Kunz, R. K. *Tetrahedron* **2002**, *58*, 6433.

(103)   Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543.
(104)   Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987.
(105)   Corey, E. J.; Loh, T. P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.
(106)   Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *38*, 8785.
(107)   Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151.
(108)   Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *33*, 6227.
(109)   Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708.
(110)   Roush, W. R.; Sciotti, R. J. *Tetrahedron Lett.* **1992**, *33*, 4691.
(111)   Roush, W. R.; Sciotti, R. J. *J. Org. Chem.* **1998**, *63*, 5473.
(112)   Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.
(113)   Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457.
(114)   Berson, J. A.; Hamlet, J.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.
(115)   Mattay, J.; Mertes, J.; Mass, G. *Chem. Ber.* **1989**, *122*, 327.
(116)   Hindley, S. J.; Loughborough University, 1998.
(117)   Takeda, K.; Kato, H.; Sasahara, H.; Yoshii, E. *Chem. Commun.* **1986**, 1197.
(118)   Inamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.
(119)   Matsuda, K.; Nomura, K.; Yoshii, E. *Chem. Commun.* **1989**, 221.
(120)   Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *38*, 8781.
(121)   March, J. *Advanced Organic Chemistry; Reactions; Mechanisms and Structures*; Wiley-Interscience Publication: New York, 1992.
(122)   Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, 1022.
(123)   Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279.

Chapter 2

Results and discussion

2. Results and Discussion

The proposed route plan would repeat the work previously achieved in the group until the formation of the lactone **5**. This route has led to spirocycle **8** (Scheme 1).
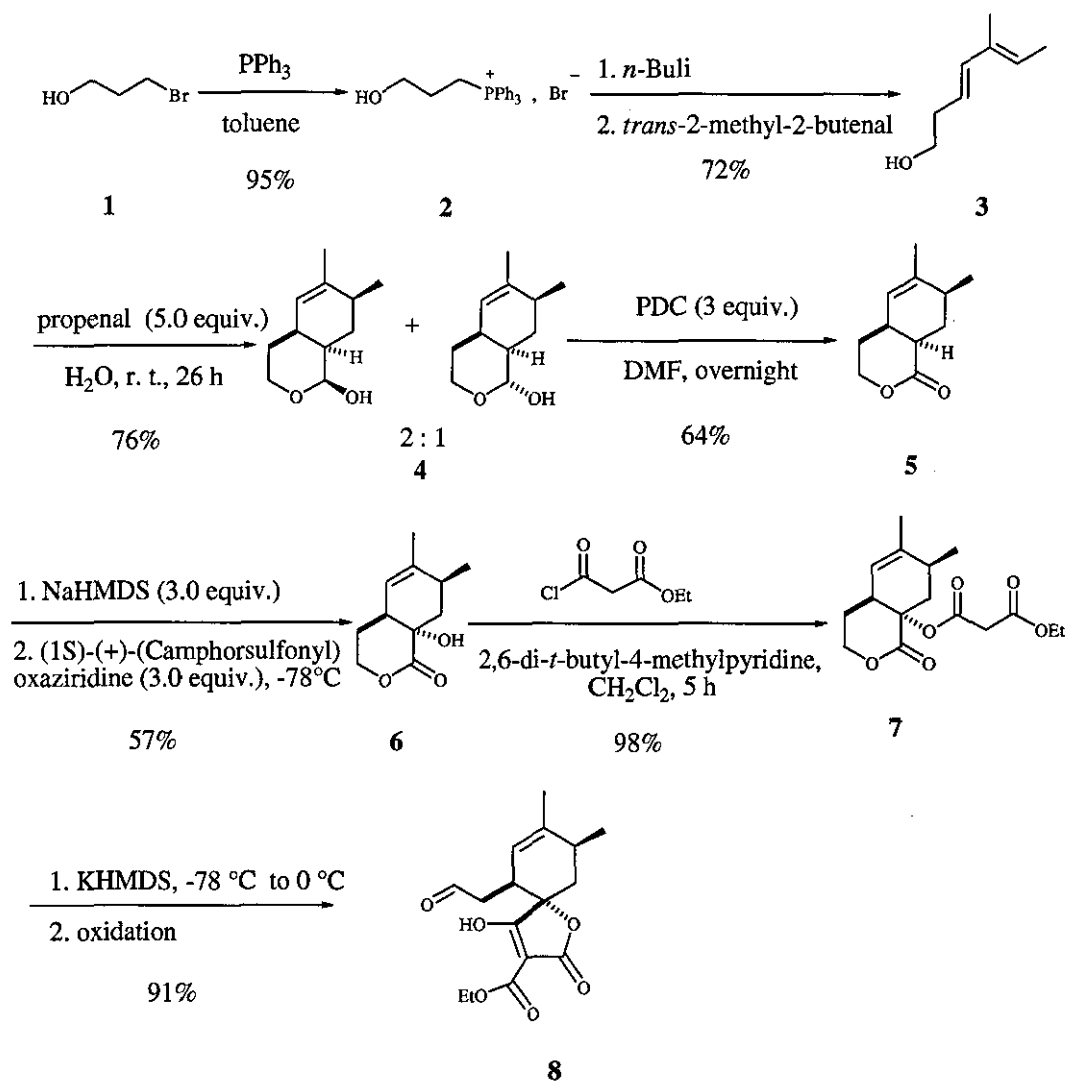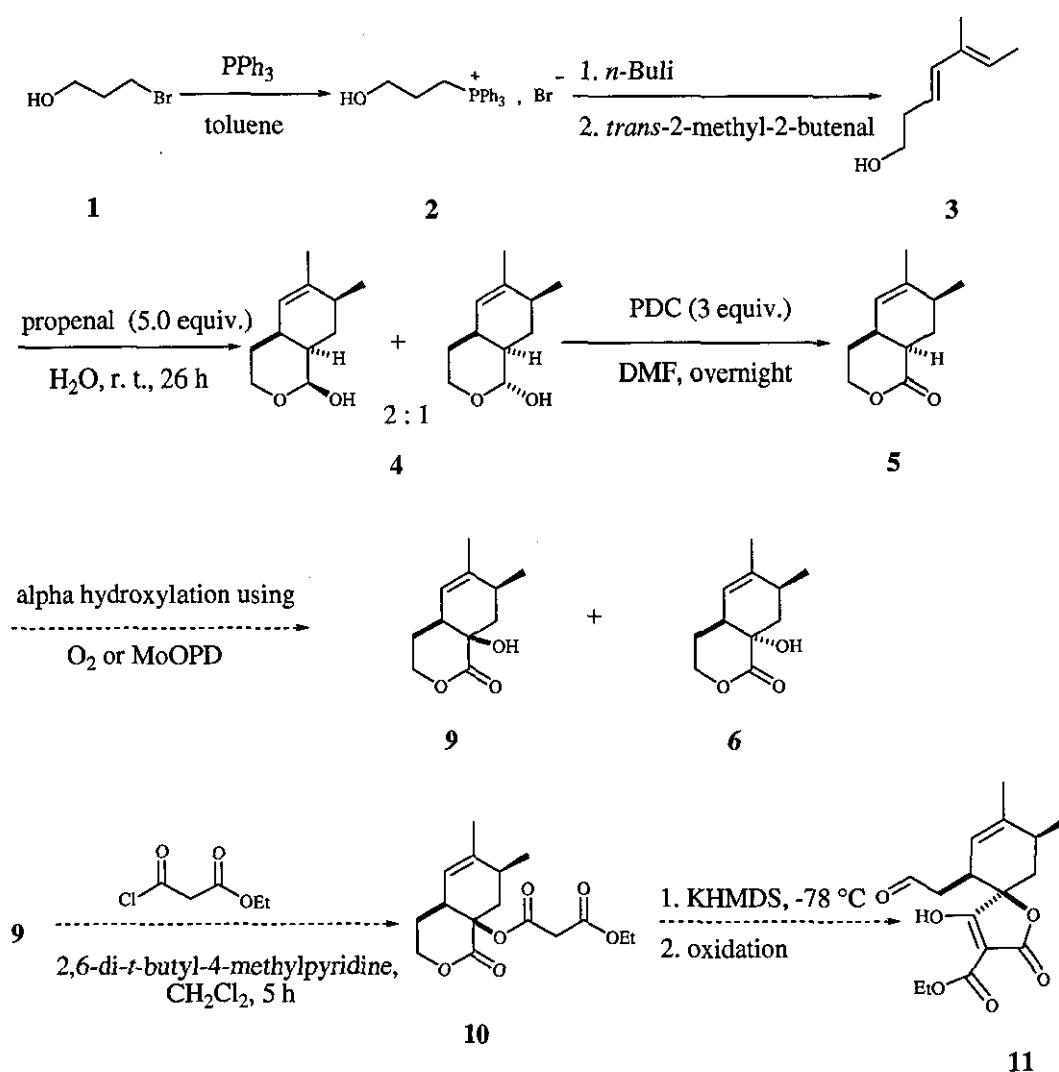

Scheme 1

Formation of the diene **3** would follow the synthesis of the Wittig salt **2**. Compound **3** would then undergo the Diels-Alder reaction leading to a mixture of diastereoisomers **4**. Compound **4** would afford the lactone **5** by oxidation, using PDC.

The key feature to this new route would be to modify the α-hydroxylation step. This would result in either compound **9** pure or a mixture of **9** and its diastereoisomer **6**.

Acylation of **9** would give **10** with the correct stereochemistry. The final Dieckmann cyclisation with concomitant lactone ring opening would afford the target compound **11**, which is a diastereoisomer of the target **8** (Scheme 2).
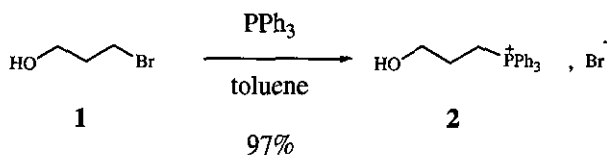

Scheme 2

2.1. Optimisation of the synthesis

We repeated the process up to the oxidation step giving the lactone **5**. This allowed us to raise the yield and to increase the scale by optimisation of the reactions conducted.

2.1.1. Synthesis of the Wittig salt 2

The synthesis of Wittig salt **2** has been scaled up from 25 g of bromo alcohol **1** to 100 g without any problems (Scheme 3).
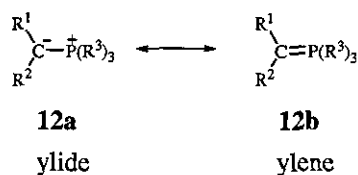

Scheme 3

2.1.2. Synthesis of the diene 3

2.1.2.1. The Wittig reaction

The Wittig reaction, first reported in 1953,[1] utilises a phosphonium ylide (or phosphorane) as nucleophilic entity. These ylides are usually stable but highly reactive. They can be represented by two resonance forms, ylide **12a** and ylene **12b** (Scheme 4).

Scheme 4

3

Their stability is partly due to the resonance between these two structures. However, NMR spectroscopic studies and theoretical calculations proved the dipolar structure of the ylide **12a** to be largely predominant. The carbanion electrons are delocalised towards the positively charged phosphorus, thereby increasing the stability of the charges.[2]

The reaction of a phosphonium ylide **12** with an aldehyde or a ketone **13** forms an olefin **14** in place of the carbonyl (Scheme 5).
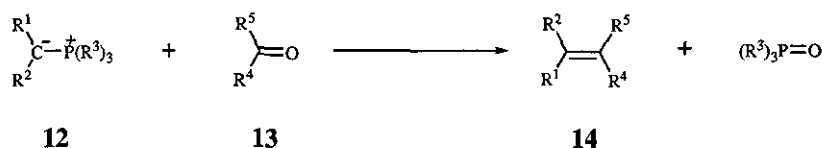
Scheme 5

The mechanism starts with addition of the nucleophilic carbon of the ylide **12** to the carbonyl group of **13**. The phosphonium ylide **12** is usually prepared by deprotonation of the corresponding phosphonium salt **15**. These entities are weak acids and a strong base must be used to deprotonate them to yield **12**.

Trialkylphenylphosphonium salts **15** are commonly used, obtained by the reaction of triphenylphosphine with alkyl halides **14**. Triaryl and trialkylphosphines are also encountered, but less frequently (Scheme 6).
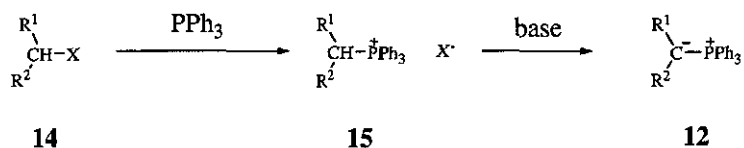

X = I, Br, Cl

Scheme 6

Phosphonium ylides bearing non-polar substituents, such as proton or alkyl and aryl groups, are unable to stabilise the negative charge and are highly reactive. They are called non stabilised ylides.

Salts containing electron-withdrawing groups at the α-position are much more acidic and can be transformed into ylides by using weaker bases. If the electron-withdrawing group is strong such as in β-ketophosphonium ylides or phosphonate ylides (Horner-Wadsworth-Emmons reaction),[3,4] the ylide is stabilised. Semi-stabilised ylides are obtained if the substituents are only weakly conjugating such as phenyl group. The resulting stabilised and semi-stabilised phosphonium ylides are less reactive towards carbonyl compounds and the reaction conditions must be more vigorous (Scheme 7).[5,6]
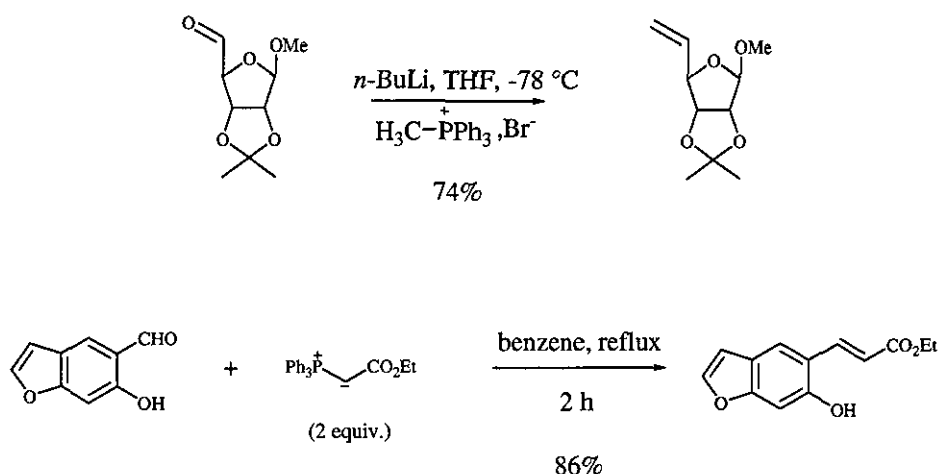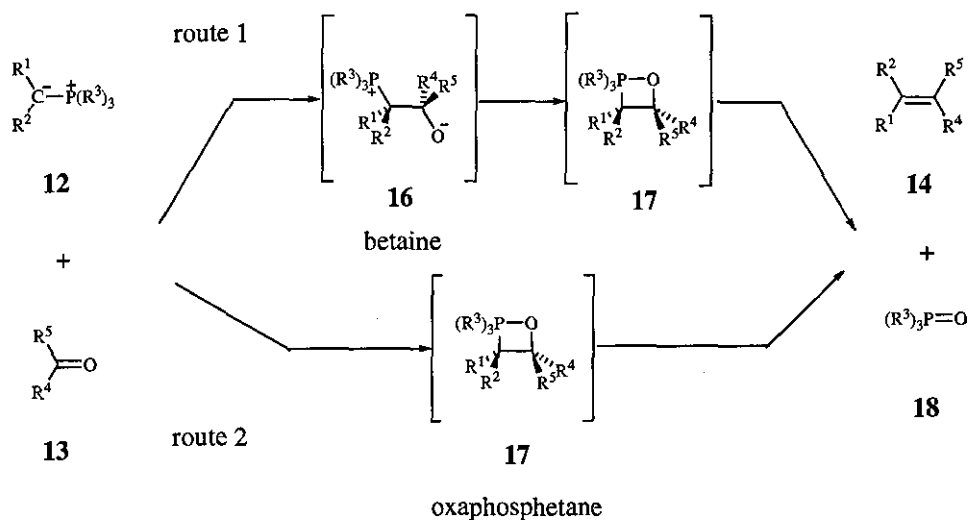

Scheme 7

Two mechanisms have been proposed for the reaction of the ylide with carbonyl groups.

The first stipulates the formation of an unstable zwitterionic intermediate called betaine **16** followed by its rapid cyclisation to a four-membered ring oxaphosphetane intermediate **17**. Elimination of the phosphine oxide **18** and formation of the alkene **14** complete the reaction.

In an alternative mechanism, the formation of betaine does not occur and the nucleophilic addition of **12** to **13** leads directly to the oxaphosphetane **17** (Scheme 8).[7]
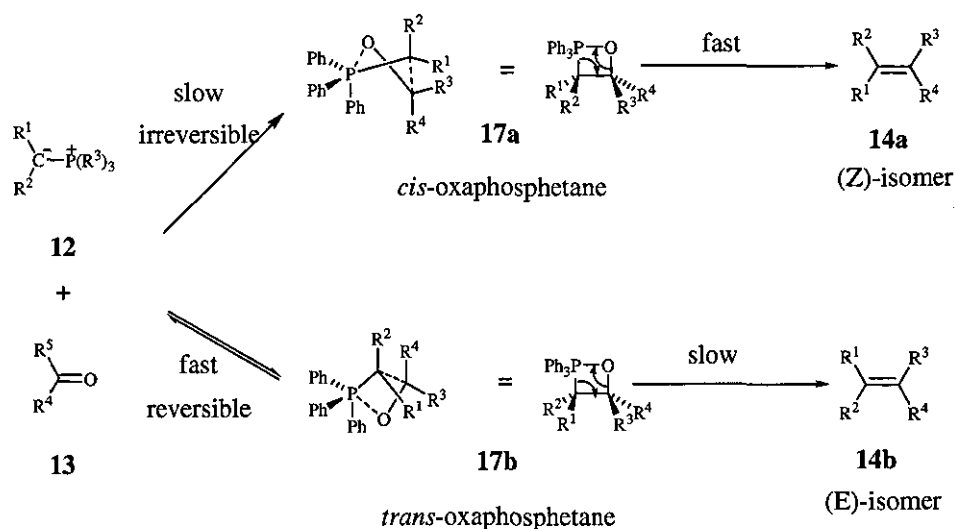

Scheme 8

Oxaphosphetane intermediates **17** have been observed by NMR spectroscopy at low temperature in the case of the reaction of non-stabilised ylides with aldehydes, but the existence of salt-free betaines still remains unclear because they are neither stable nor observable by available techniques.[8,9]

The simplest Wittig rationale accounts for high *cis*-selectivity. The process has the plane of the aldehyde tilted with respect to the ylide plane to minimise non-bonded interactions, and also has the C-O bond of the carbonyl and C-P bond of the ylide crossed to maintain reasonable C···C and P···O bonding distances.

However, there are variations in observed Wittig reaction stereochemistry which are attributed to dominant kinetic control. There is probably not a single mechanism for all Wittig reactions.

For the non-stabilised ylide, the first step is irreversible and kinetically controlled. The stereochemistry follows from the approach of the two reagents. This affords a predominant *cis*-disubstitued oxaphosphetane **17a** which quickly collapses in a stereospecifically *syn* manner to give primarily the (Z) alkene **14a**.

In contrast, with stabilised ylides, the first step is reversible and fast, leading to the most stable *trans*-oxaphosphetane **17b** (Scheme 9).[10-12]

R^1 bigger than R^2 and R^4 bigger than R^3

Scheme 9

The limiting geometries, **17a** puckered *cis*-selective and **17b** planar *trans*-selective have been presented, but there are intermediate cases due to interplay of 1,2 and 1,3 steric interactions which determine which diastereoisomeric oxaphosphetane will be favoured.[10,13,14]

The stereoselectivity depends not only on the structure of the ylide but also on the structure of the carbonyl substrate, the nature of the base used for the deprotonation of the phosphonium salt, the solvent and on the reaction conditions.

In a general pattern, reactions will favour Z-olefination if they involve non-stabilised ylides (especially if they are obtained by deprotonation by sodium bases rather than by corresponding lithio bases), aprotic solvents such as tetrahydrofuran, diethyl ether or dimethoxymethane and low temperature.[15]

2.1.2.2. Application of the Wittig reaction in the synthesis of 3

In this Wittig reaction, 3-hydroxypropyl phosphonium salt **2** reacted with the *trans*-isomer of 2-methyl-but-2-enal to afford the diene **3**. The stereostructural assignement for this diene, based on the coupling constant value between H-3 and H-4, was consistent with the E stereoisomer ($J_{3-4} = 15.6$ Hz) (Scheme 10).
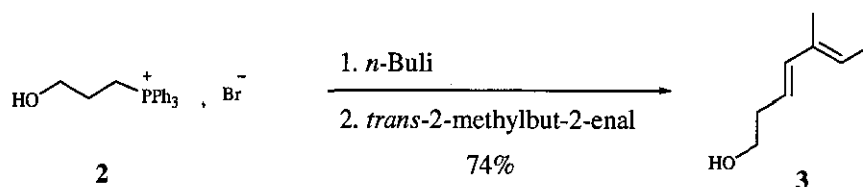
Scheme 10

While diene **3** is obtained as the product of the olefination in good yield, the triphenylphosphine oxide by-product, proved difficult to separate from **3**.

In order to avoid this problem, during work-up, an extract of the reaction mixture was poured into a solution of *tert*-butoxymethyl ether from which triphenylphosphine oxide precipitated. Subsequent purification of the crude product by Kügelrohr distillation was more successful than flash column chromatography. Indeed, the distillation was simpler and faster than chromatography and afforded increased yields. Finally, this step was scaled up four times which gave a slight increase in yields compared to previous results obtained in the group.

2.1.3. Synthesis of the lactol 4

2.1.3.1. The Diels-Alder reaction

The Diels-Alder reaction is the addition of an olefin to a diene leading to the formation of a cyclohexene unit, first reported in 1928 and developed by Diels and Alder.[16]

This pericyclic reaction involves four π-electrons of the diene and two π-electrons of the alkene (dienophile). It is a [4 + 2] cycloaddition, following the rule of aromatic resonance proposed by Hückel: $n_{e^-} = 4n + 2e^-$. Six electrons allow stabilisation by delocalisation of the transition state.

Experiments carried out on numerous substituted substrates have shown that the Diels-Alder cycloaddition can generate up to four new asymmetric centres controlled by a *syn*-suprafacial stereospecificy (Figure 1).[17]
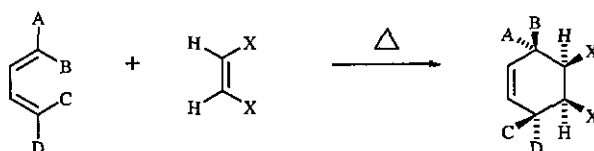

Figure 1

No loss of stereospecificity is observed indicating that a concerted reaction is occurring. Indeed, an intermediate would imply the formation of one bond before the other and the possibility of bond rotation, leading to the formation of **20** (Figure 2).
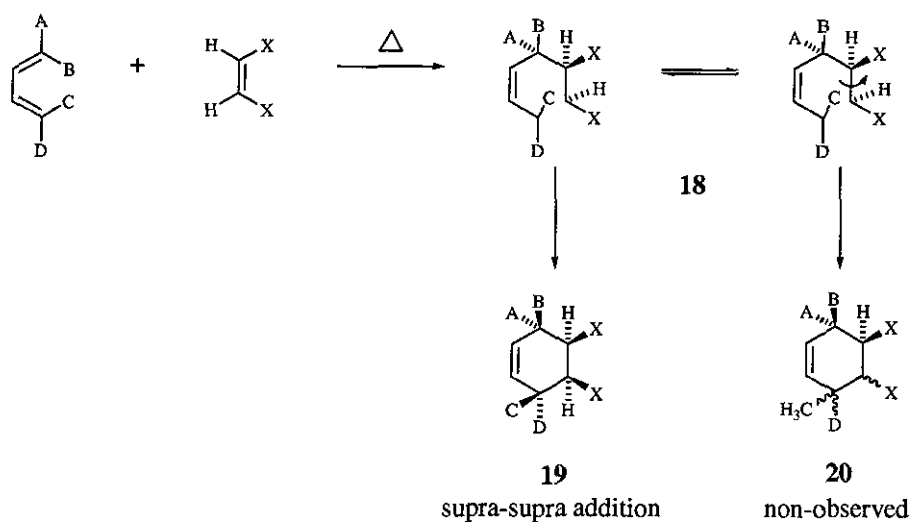
19
supra-supra addition

20
non-observed

Figure 2

The existence of intermediate **18** would suggest its formation to be so quick that the rotation would not have time to occur. Numerous theoretical analyses confirm the improbability of this hypothesis and the validity of the concerted process.[18]

2.1.3.2. The Alder *endo* rule

When there are one or more substituents in the olefin, two possible transition states can arise. When the substituents of the dienophile are directed towards the diene, the transition state is termed *endo* in opposition to the *exo* transition state (Figure 3).
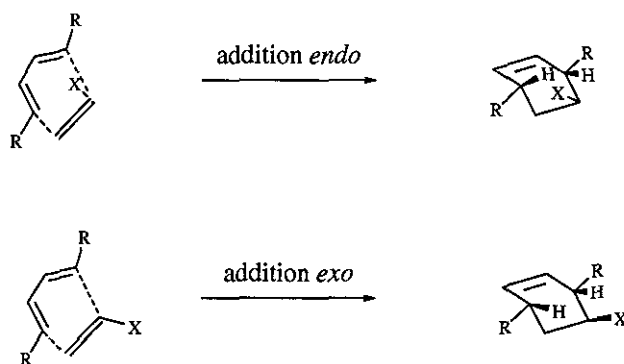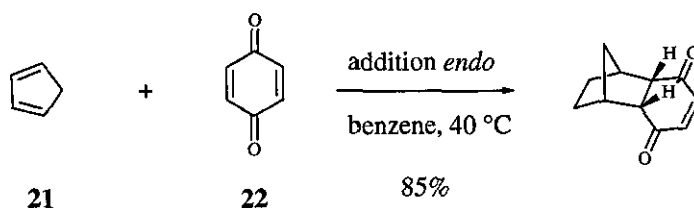

addition *endo*

addition *exo*

Figure 3

The *endo* system is obviously more hindered. Therefore, the *exo* transition state should be favoured. Nevertheless, the reaction usually adopts the *endo* configuration. The addition of benzoquinone **22** to cyclopentadiene **21** is a famous example of this fact (Scheme 11).[19]

21   **22**   *85%*

Scheme 11

Molecular orbital theory can be used to explain why the *endo* orientation is favoured. The orbitals involved in a Diels-Alder reaction are the Highest Occupied Molecular Orbital (HOMO) of the electron-rich diene and the Lowest Unoccupied Molecular Orbital (LUMO) of the electron-poor dienophile. The overlap of these two frontier orbitals is necessary to allow formation of the new bonds. The simplest system butadiene-ethene, illustrates this principle (Figure 4).[20]
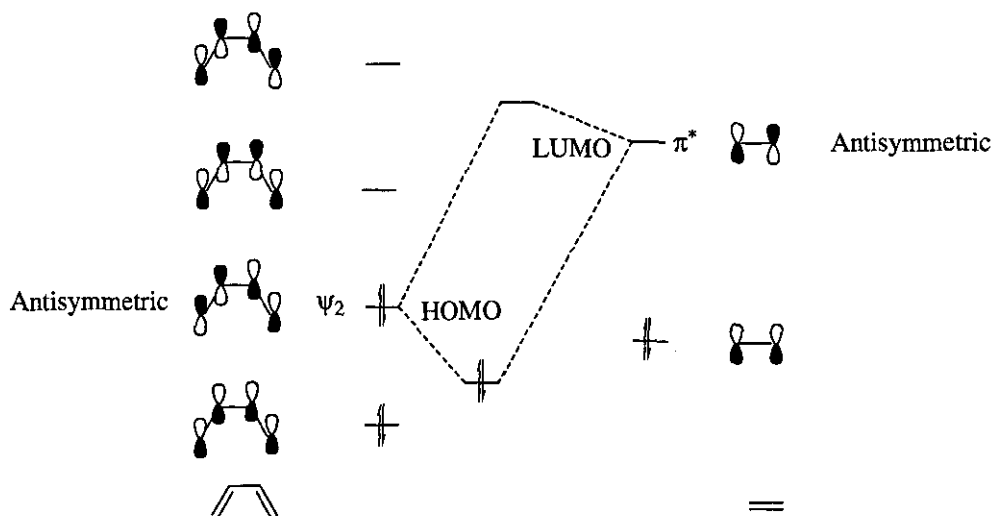

Figure 4

The closer the energy levels of the HOMO of the diene and the LUMO of the dienophile, the stronger the interaction between the frontier orbitals. Hence the cycloaddition is more favourable.

Secondary molecular orbital interactions between the substituent of the dienophile and the π-electrons of the diene, present in the *endo* transition state, enhance the overlap between the frontier orbitals and so the most stable transition state in the Diels-Alder reaction, the one which contains maximum orbital overlap, is the one leading to the *endo* product.[21]

In reversible Diels-Alder reactions, the *exo* stereoisomer is also found. The *endo*: *exo* ratio does not depend only on the secondary orbital overlap but also on steric effects, dipolar interactions, etc.

For example, reaction of cyclopentadiene with methyl acrylate gives 90% of the *endo* adduct **23a** in methanol and affords predominantly the *exo* adduct **23b**, which is the thermodynamically more stable product, with methyl methacrylate (Scheme 12).[22]


	23a	**23b**
	endo :	*exo*
R = H	90 %	10 %
R = CH$_3$	22 %	78 %
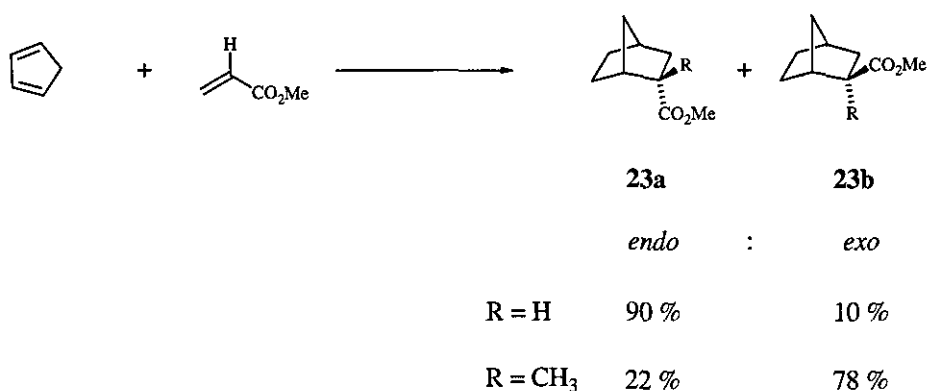
Scheme 12

### 2.1.3.3. Diene 3 is adapted for the Diels-Alder reaction

Substituents on both reactants can affect the outcome of the Diels-Alder reaction. Orbital theory states that electron-donating groups on the diene increase the energy of the HOMO and electron-withdrawing groups on the dienophile decrease the energy of the LUMO, thus improving the HOMO-LUMO overlap and enhancing the reaction rate.[23]

Consequently, the reaction is promoted by the inductive effect of alkyl groups, for example, at the C-1 and C-2 position in the diene, and by one or more electron withdrawing groups in the dienophile such as carbonyls and nitro groups (Scheme 13).

EDG = electron-donating group

EWG = electron-withdrawing group
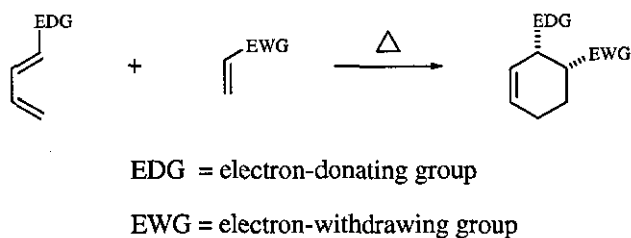
Scheme 13

The Diels-Alder reaction between diene **3** and acrolein fulfils the conditions described previously and the reaction afforded two diastereoisomers of lactol **4** in a 2:1 ratio (Scheme 14).


Propenal (5 equiv.)

H_2O, r.t., 26 h

86%

2 : 1

3

4
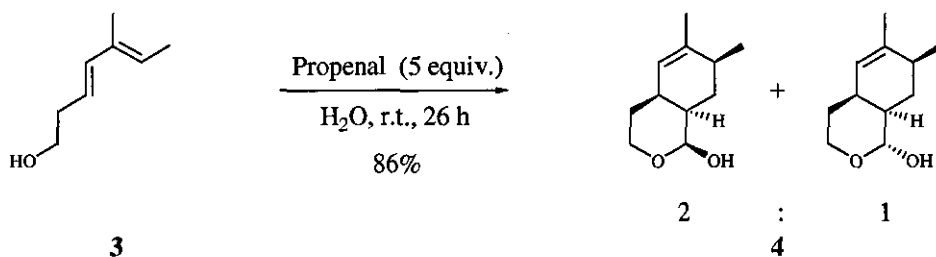
Scheme 14

2.1.3.4. Choice of the water as the solvent

The choice of solvent does not have a major effect on the reaction, because there are no ionic intermediates formed. However, in the 1980's, adding of water to the usual organic solvent was shown to promote the Diels-Alder reaction.

Lack of hydrophilic interactions between the reagents and the solvent causes a compressed transition state, resulting in improved reaction rate and selectivity (Scheme 15).[24,25]


	24a		24b	
	endo	:	exo	rate
isooctane	80%		20%	1
water	96%		4%	700
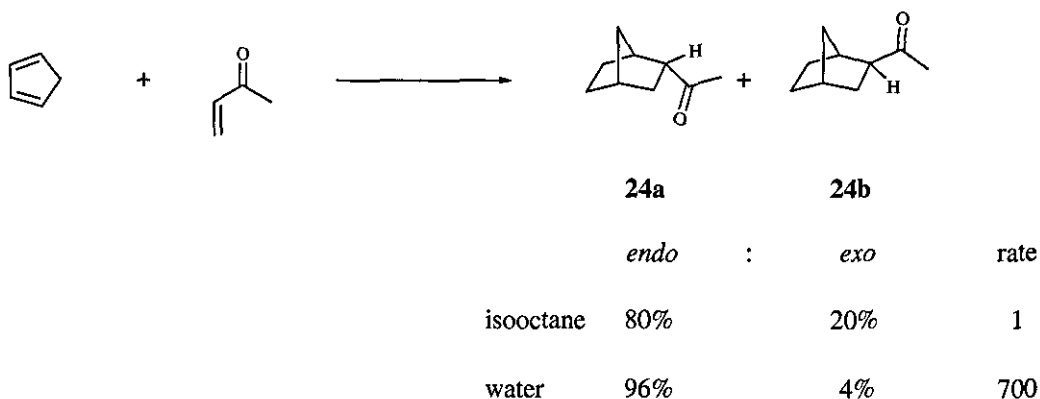
Scheme 15

2.1.3.5. Limitations of the reaction

Beyond 1g (7.9 mmol) of diene **3**, formation of lactol **4** was often prevented by polymerisation of the acrolein. Dilution of the reaction mixture, so decreasing the concentration of acrolein, had no effect on the problem. Therefore, in order to prevent this polymerisation, acrolein was distilled and kept with hydroquinone, refrigerated and protected from light. HPLC grade water was used as the solvent in order to prevent any polymer initiation due to the pH or the presence of ionic species. Acrolein was added dropwise using a syringe pump in order to avoid high concentration in the mixture, and the reaction flask was covered by tin foil so as to prevent radical polymer initiation due to the light. All these precautions allowed

the Diels-Alder reaction to be scaled up by a factor of fourteen, and afforded a slight increase in yield after purification of the crude product by Kügelrohr distillation.

2.1.4. Synthesis of the lactone 5

2.1.4.1. Problems linked to the oxidation
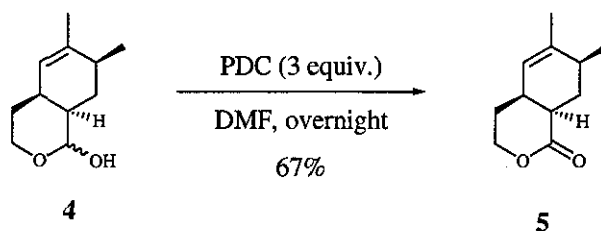
Scheme 16

The use of chromium (VI) in our synthesis has been introduced by Vahedi, a previous researcher of the group.[26]

Using pyridinium dichromate (PDC) creates considerable purification problems. Initially, this reaction was impossible to perform on a large scale because of this. Chromium forms sticky aggregates and thus prevents efficient extraction and reduces yields. Consequently, the work-up was difficult and hazardous in relation to the high toxicity of PDC.

2.1.4.2. Resolution of the problem

We decided to perform the Swern oxidation, which has the advantages of low cost and toxicity, and affords relatively clean carbonyl compounds which can sometimes be used without purification to give high yields of products (section 2.5.1.4.1.1.). Unfortunately, no significant results were obtained even at -40°C.

We next modified the work-up of the PDC oxidation. An increase in the yield and, more significantly, the scale of the reaction was afforded. A 67% yield was obtained from 13.2 mmol of **4** whereas a maximum scale of 4.3 mmol of **4** afforded a 64% yield with the previous work-up method.

The new technique was based on the trapping of the chromium which is soluble in ethanol followed by precipitation in ethyl acetate and absorption by a mix of silica gel-Celite® of the chromium salts in order to free the lactone **5**. The product was collected by filtration, and the waste chromium trapped in silica gel-Celite® was easily removed. The yield of the lactone **5** was increased by 5% and the oxidation step was achieved with three times more starting material.

2.1.5. Summary of the initial steps

The optimised results for the first steps, discussed above, are presented below (Scheme 17).
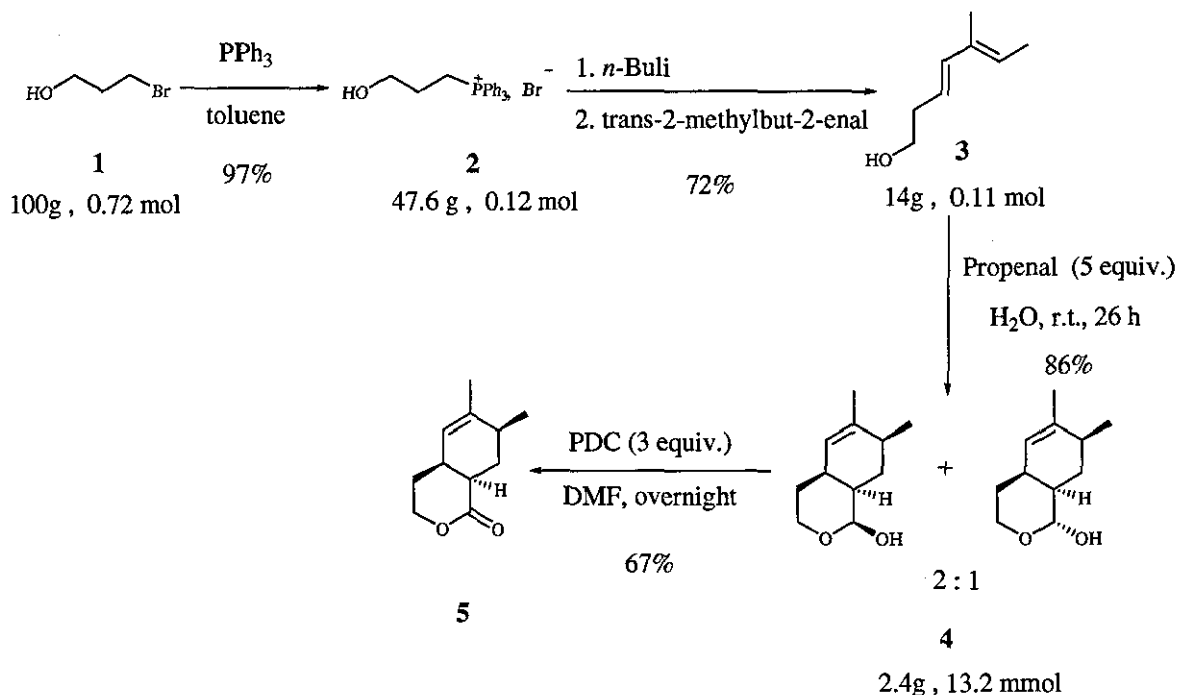
Scheme 17

2.2. α-Hydroxylation

Page group purpose was to synthesise one diastereoisomeric oxaspirobicyclic synthon in order to determine the absolute stereochemistry of tetronothiodin.

To this end, the α-hydroxylation, carried out by Vahedi, occurred exclusively from the least hindered face of the enolate of **5** (Scheme 18).
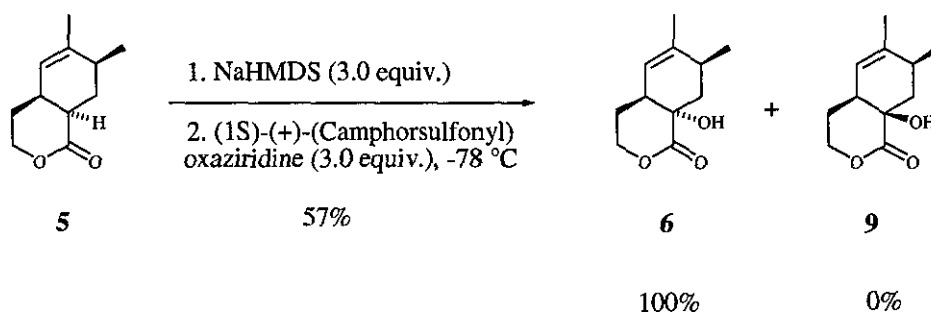

Scheme 18

This was due to steric factors already described but also to the choice of the hindered oxaziridine as the hydroxylation reactant.

2.2.1. Chiral oxaziridine oxidation

#### 2.2.1.1. Generality about oxaziridines

This method has been first investigated by Emmons[27] and Horner and Jurgens,[28] oxaziridines exhibit excellent reactivity for oxidation of a variety of substrates.

Sulfonyl oxaziridines **25** are heterocyclic compounds containing oxygen, nitrogen and carbon atoms in a three-membered ring, and a large *N*-sulfonyl group, conferring them an unusual reactivity.
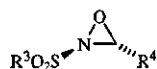
25

Thus, the driving force for oxygen transfer by the oxaziridine unit incorporates both the relief of the three-membered ring strain and the enthalpy associated with formation of strong C=N bond (Figure 5).
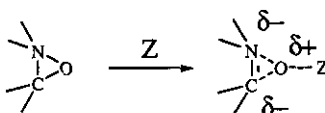

Z: nucleophilic substrate

Figure 5

The process is facilitated by the presence of the large N-sulfonyl group. Due to its powerfully electron-withdrawing effect, it is partly responsible for the highly electrophilic nature of the oxygen. Also, it shields the oxaziridine nitrogen atom from attack and stabilises any incipient charge in the transition state for sulfonimine displacement.[29]

Reaction of carbonyl enolates **26** with these reagents produces an α-hydroxy carbonyl product **27** by direct nucleophilic attack on the ring oxygen and subsequent β-elimination (Scheme 19).

26   **25**   **27**
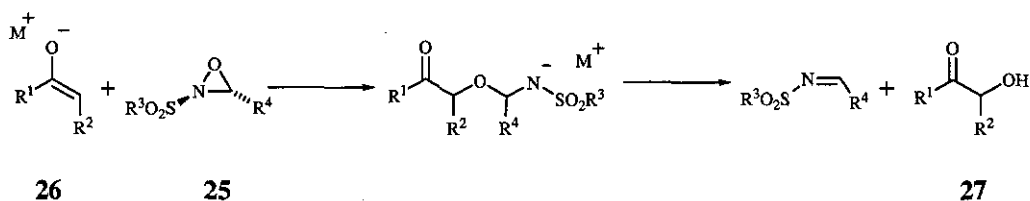
Scheme 19

2.2.1.2. Stereospecific oxidation

Camphorsulfonyl oxaziridine oxidation is commonly used for its reactivity and high stereoselectivity leading to a single diastereoisomer **6** due to the two methyl groups on the methylene bridge blocking the *exo* face of the C=N. The preparation of several diastereoisomerically pure oxaziridines **29** has been achieved by the Page group (Scheme 20).[30,31]
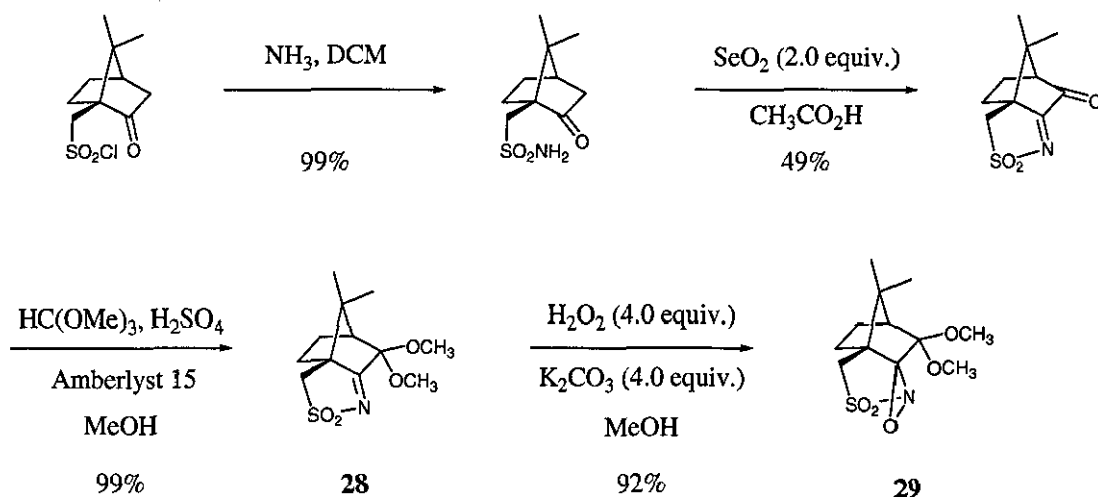
Scheme 20

This chiral oxaziridine afforded α-hydroxy carbonyl compounds in high optical purity through an open transition state, controlled by non-bonded steric interactions, which is responsible for the chiral recognition (Figure 6).[32,33]
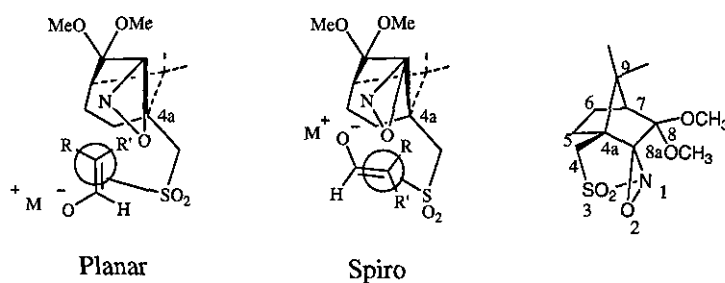

Planar   Spiro

Figure 6

Davis and Haque have suggested that the geometry of the planar open transition state is favoured over the spiro form because of the reduced non-bonded steric interactions between the largest enolate group O^-M^+ solvent aggregate complex and the bridgehead 5-4a bond in **29**.[32,33]

In addition, higher diastereoselectivity was obtained because of the presence of the 8-methoxy groups in **29.** When using NaHMDS, the sodium enolate was formed and improved the diastereoselectivity (because sodium is larger than lithium, it is capable of forming more covalent bonds with oxygen).[30]

Hydrogen peroxide treatment of dimethoxy ketal **28** in basic media produces diastereoisomerically pure oxaziridine **29** to be used in the α-oxidation of the lactone **5**. This resulted in the formation of the α-hydroxy lactone **6** (Scheme 20).

Transforming the stereospecificity of the reaction to stereoselectivity, allowing the formation of the desired α-hydroxylactone **9** is the focus of the next section.

2.2.2. Other α-hydroxylation methods

Many methods have been devised for the preparation of α-hydroxy carbonyl compounds. The most practical methods are also the simplest and involve direct enolate oxidation. A number were considered but were shown not to be adaptable to our substrate **5**. For instance, alkali metal based oxidants, such as potassium permanganate or potassium dichromate, would react with the olefin of the cyclohexene unit of **5**.[34] Methods based on peroxy acid reactions were rejected for similar reasons.[35]

Two methods, using molecular oxygen and Vedejs' reagent, molybdenum peroxide-pyridine-hexamethylphosphoramide (MoOPH), were explored.

These two methods often exhibit a poorer stereoselectivity than does use of oxaziridine reagents and, they can afford a mixture of stereoisomers.[36-39] Examples from the literature suggested that the desired diastereoisomer **9** might be obtained in a mixture with the most favourable diastereoisomer **6** already obtained. The synthesis of daunomycinone, a component of useful antitumor agents, is a good example of this.

Boeckman *et al.* carried out an α-hydroxylation by using LDA/O$_2$/ P(OEt)$_3$, which afforded a 1:1 ratio of both epimers **30a** and **30b** (Scheme 21).[38]

Scheme 21

Further, Swenton *et al.* used LiCA/MoOPH to accomplish a related α-hydroxylation and obtained a 2:3 ratio of epimers **31a** and **31b** (Scheme 22).[36]

Scheme 22

Unfortunately, these isolated examples cannot be considered as a pattern. Sometimes, more stereocontrolled introduction of a hydroxyl group is achieved

with these reagents. This is shown in the following example, where the lactone **32**, derived from (S)-glutamic acid, was used as a chiral template to construct acyclic polyols (e.g. **33a** and **33b**) with good stereochemical control (Scheme 23).[40]
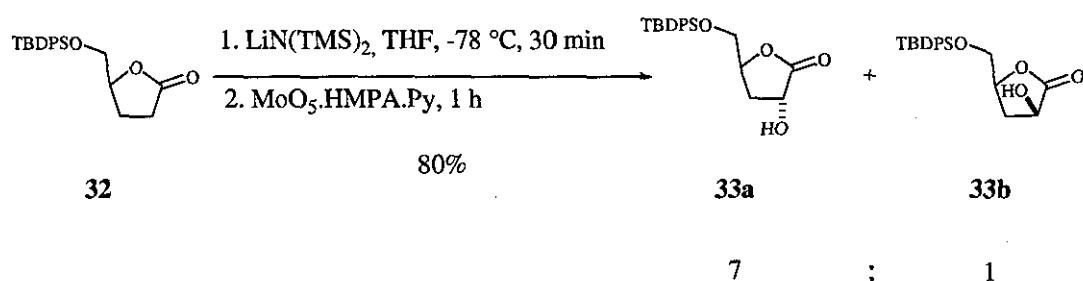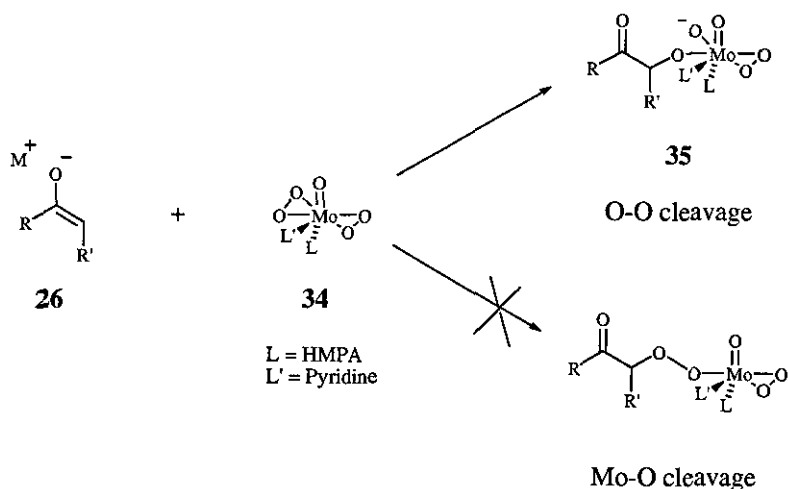
Scheme 23

Formation of diastereoisomeric mixtures in all these examples is an important point, which suggests that we may obtain the desired **9**, albeit as the minor component of a mixture.

2.2.2.1. α-Hydroxylation using Vedejs' reagent

The first enolate oxidation by reaction with molybdenum peroxy complexes was reported by Vedejs.[41]

α-Hydroxylation is obtained by nucleophilic attack by the enolate **26** at a peroxy oxygen atom. Two pathways are possible, but the lack of α-hydroperoxy products suggests that the mechanism involves only O-O cleavage and go through **35** (Scheme 24).

Scheme 24

The oxygenation has been shown to occur, in some cases, however using less than a stoichiometric amount of MoOPH. This indicates that both peroxy bridges can be available for the reaction. The ketone enolate is formed, and the reaction is carried out at low temperature (between -50 and -30 °C) in order to limit side reactions such as aldol condensation.

Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) **34** contains hexamethylphosphoramide (HMPA) which is a well known harmful carcinogen. Thus, an alternative reagent, MoOPD, was developed using 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU) **38** instead of HMPA, and can be used in the same way for the α-hydroxylation procedure.
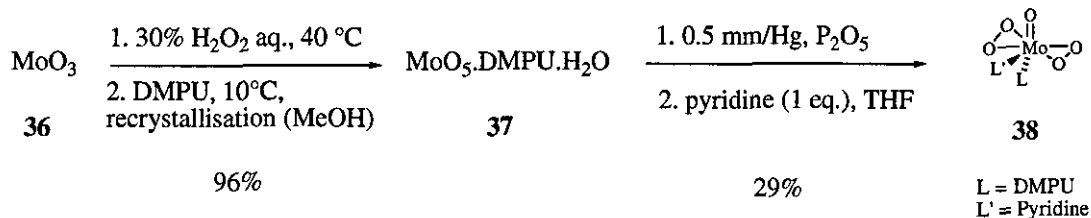

38
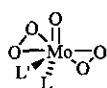
L = DMPU
L' = Pyridine

MoOPD and MoOPH have been compared as oxidants, and reactions involving them showed comparable yields.[42]

MoOPD commonly requires a longer reaction time (2.5 hours against 30 minutes for MoOPH), however, by which time by-products are unfortunately also produced. This lower reactivity is believed to be due to its lower solubility. Thus reaction times must be increased compared to MoOPH reactions.

Preparation of MoOPD **38** was achieved in our hands through reacting molybdenum (VI) oxide **36** with hydrogen peroxide followed by addition of DMPU. Dehydration of the pale yellow crystals of the recrystallised monohydrated **37**, under high vacuum and over P_2O_5, gave the very hygroscopic $MoO_5.DMPU$. This was transformed into MoOPD **38** by treatment with pyridine. An overall 28% yield of the yellow solid **38** was obtained (Scheme 25).[42,43]

| MoO_3 | 1. 30% H_2O_2 aq., 40 °C | $MoO_5.DMPU.H_2O$ | 1. 0.5 mm/Hg, P_2O_5 | |
| **36** | 2. DMPU, 10°C, recrystallisation (MeOH) | **37** | 2. pyridine (1 eq.), THF | **38** |
| | 96% | | 29% | L = DMPU
L' = Pyridine |

Scheme 25

A freshly prepared sample of MoOPD was used in each reaction because we were not able to store it without decomposition even in a refrigerator.

A large excess, up to ten equivalents of the molybdenum reagent, is often used accordingly to the literature.[44] However, using an excess of MoOPD did not show any improvement on the method we used, and subsequently only one equivalent of reagent was used.

Vedejs *et al.* have shown that aldol condensation can be minimised by inverse addition of the enolate to MoOPD.[45] No such differentiation was noticed by us in the oxidation of **5**, and the reaction gave a poor yield (14%). Only the unwanted α-hydroxy lactone **6** was obtained (Scheme 26).
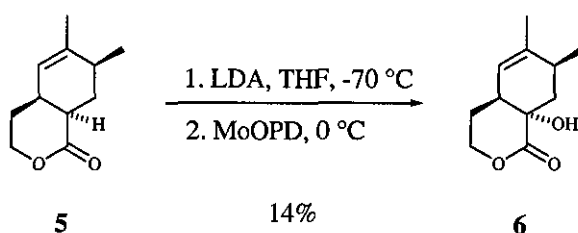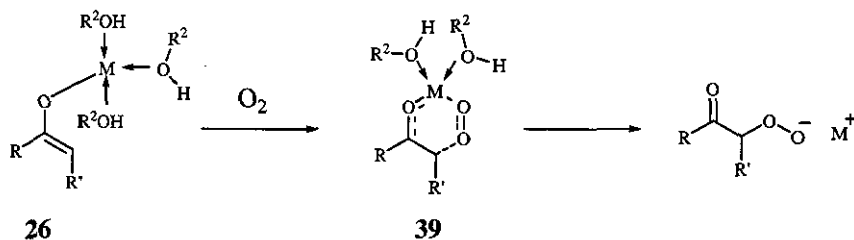

Scheme 26

Reaction with molecular oxygen was next investigated

2.2.2.2. α-Hydroxylation using molecular oxygen

For suitable substrates, the use of molecular oxygen as the source of a hydroxyl group remains the method of choice due to high yields.

First, molecular oxygen undergoes an electrophilic addition to the enolate **26** activated by counter-ion complexation via a six-membered transition state **39**. This step involves displacement of one of the solvent molecules by oxygen (Scheme 27).

Scheme 27

This fact is important for the choice of the solvent and its specific effect. Thus, *t*-butyl alcohol is normally chosen to be the solvent, because it is more easily displaced than primary and secondary alcohols, which show a greater tendency to form coordinate compounds.[46]

Alternatively, Russell has proposed a radical chain mechanism as a possible alternative oxidation pathway, involving single electron transfer from the enolate to the molecular oxygen, generating an α-keto radical **40**. This radical reacts with oxygen to give **41**. Finally, the hydroperoxide **43** is formed by transfer of the radical hydrogen from the ketone **42** to compound **41**, generating the radical species **40**. The process is then reinitiated (Scheme 28).[46]
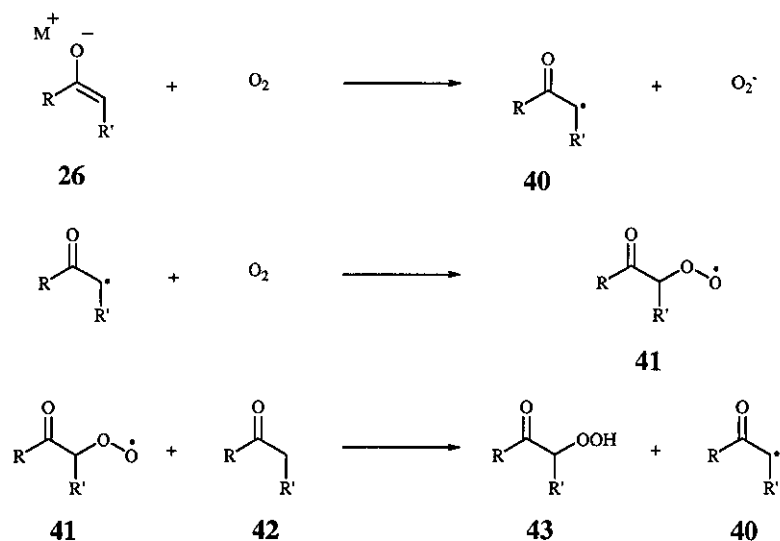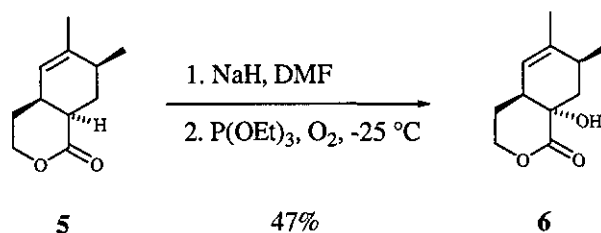

Scheme 28

The reduction of the hydroperoxide **43** is then accomplished with simultaneous oxidation of the triethyl phosphite **44** into triethyl phosphate **45**. This species is easily removed by washing with water. This oxidation-reduction reaction is believed to proceed by an ionic mechanism. Indeed, the reaction is not affected by the presence of trinitrobenzene, which is well known as an inhibitor of homolytic reactions (Scheme 29).[47]

Scheme 29

In the reaction with **5**, increasing the amount of base and triethyl phosphite, as indicated in the literature[38] did not improve the yield. This method was, however, much faster than MoOPD reaction.[48]

Unfortunately, this reaction also led to the exclusive formation of the unwanted isomer **6**. An average yield resulted from a messy reaction mixture where numerous by-products were formed, probably due to the high reactivity of oxygen radicals (Scheme 30).


1. NaH, DMF

2. P(OEt)$_3$, O$_2$, -25 °C

5   47%   **6**

Scheme 30

2.2.2.3. Explanation for the lack of efficiency of the above methods

The poor yields observed may result from a number of reactions:

- Reactions between carbonyls and oxygen can result from autoxidative cleavage of the carbon chain adjacent to the carbonyl group under basic conditions as shown in the following Scheme (Scheme 31).[49]
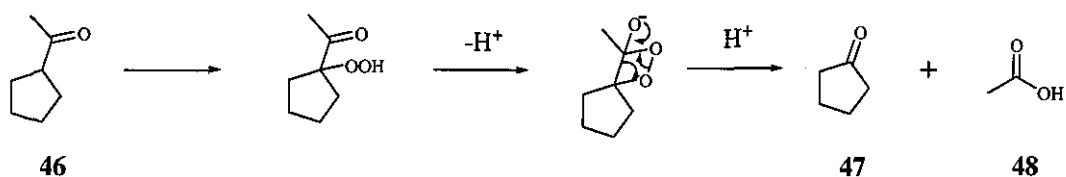
Scheme 31

In this example, the ketone **46** absorbs one equivalent of oxygen to give pentanone **47** and acetic acid **48**.

- Steric hindrance could be a reason for the loss of reactivity or the even no reactivity of these methods in our case.[50]

- The decomposition products of the intermediate α-hydroperoxy aldehyde can also pollute the reaction mixture, although this usually happens at higher temperatures.[51]

- Aldol condensation, most serious for relatively unhindered enolates, can occur by using MoOPD.[45]

In our case, the real problem however, was not linked to the yield but to the high stereoselectivity, presumably due to the steric conditions imposed by the the substrate **5**. The strategy to modify the stereocontrol in our approach thus had to be revised. The new pathway elaborated was based on an inversion of stereochemistry exemplified by Shi *et al.*[174]

2.3. Reactions attempted on the bicyclic unit

2.3.1. The *O*-acylation strategy

2.3.1.1. Description of the strategy

Initially we thought that a high degree of stereoselectivity might be available from a modified route to give target **11** in a highly stereoselective manner from **5** (Scheme 32).
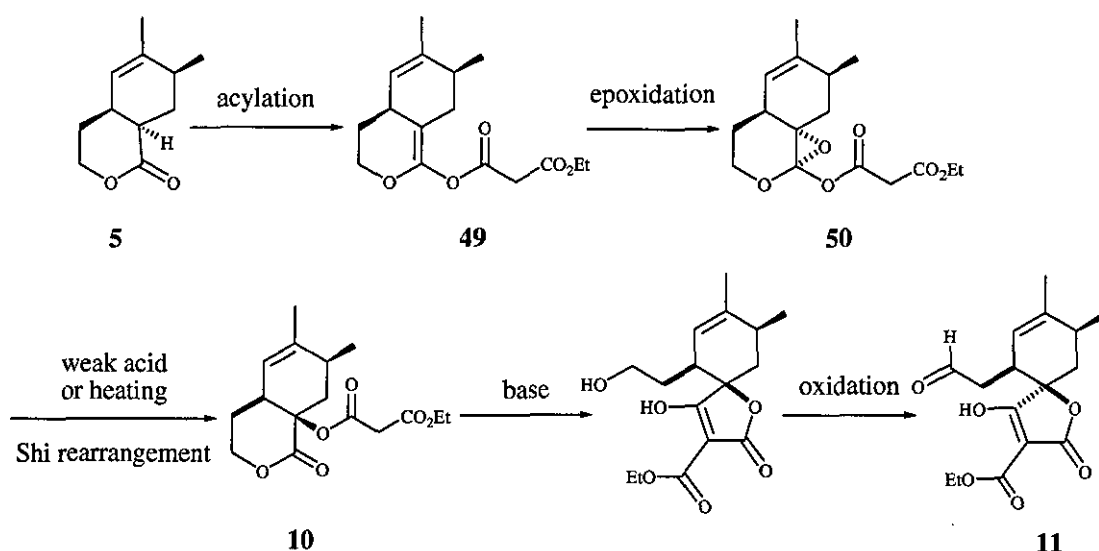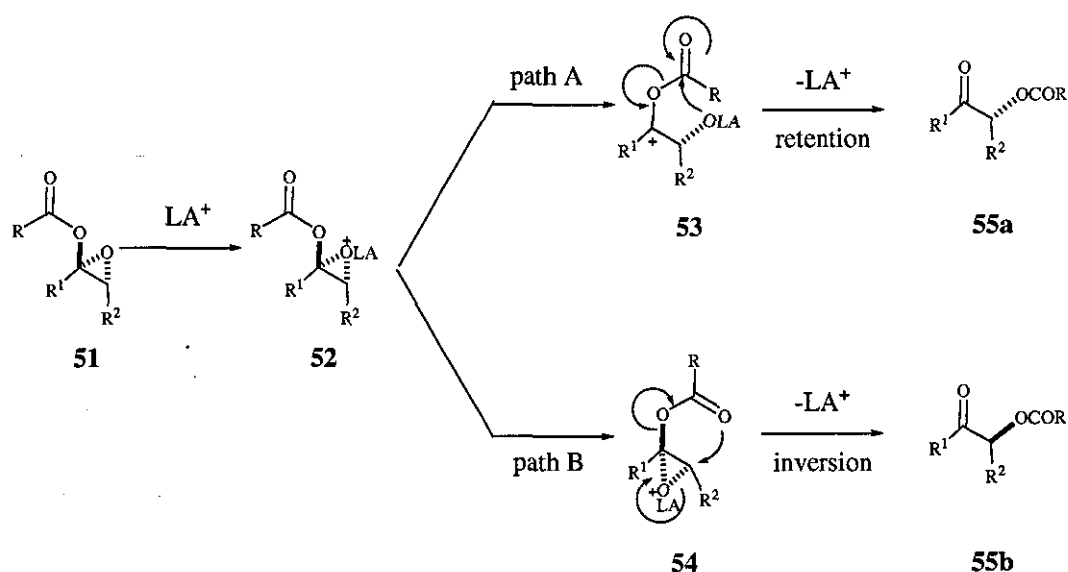

Scheme 32

The plan was to trap the enolate of **5** under *O*-acylation conditions to give **49**, which was predicted to be susceptible to highly stereofacially-selective epoxidation to give **50**. The key step of this process was the stereoselective rearrangement of this enol ester epoxide to give **10**, with inversion of configuration at the hydroxylated centre.

This plan was based on the discovery by Shi of a dual pathway allowing one to synthesise either enantiomer of an α-acyloxy ketone from a single enantiomer of

an enol epoxide by the choice of reaction conditions. Under acidic conditions, the rearrangement of the epoxide **51** occurs readily. Retention of configuration prevails when strong Lewis acid is used, whereas complete inversion is observed with a mild Lewis acid or simple heating (Scheme 33).[52]
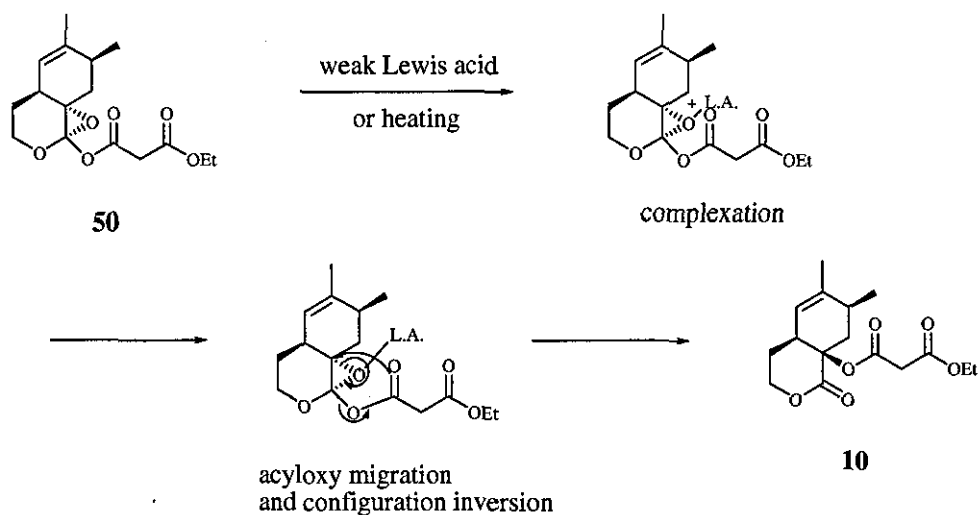

Scheme 33

In pathway A, the complexation of a strong acid to the epoxide oxygen of **51** leads to cleavage of C_1-O bond of **52** to form the intermediate carbocation **53**. Subsequent acyloxy migration with retention of configuration gives the acyloxy ketone **55a**.

In pathway B, the complexation of a weak acid to **51** weakens both epoxide bonds, facilitating acyloxy migration with inversion of configuration (**54**) to give the acyloxy ketone **55b**.

Applied to our own approach, such a rearrangement with inversion of configuration would provide the desired product **10** (Scheme 34).

Scheme 34

Successful completion of this stage of the work would thus provide the possibility to synthesise the diastereoisomeric oxaspirobicyclic synthon **9**, starting with *O*-acylation of the lactone **5**.

Compound **49** was therefore the next target for synthesis. It was expected to be obtained by a simple *O-acylation of the lactone* **5** *(Scheme 35).*
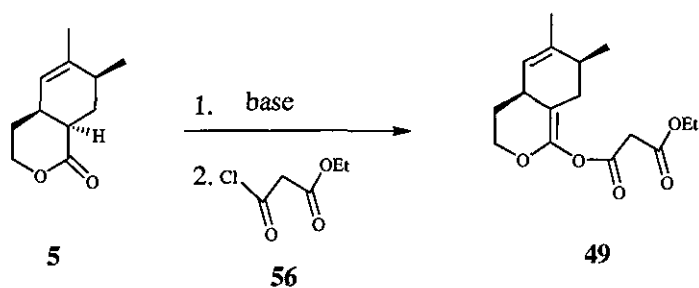
Scheme 35

2.3.1.2. Attempts under basic conditions

Reactions were carried out under the most favourable conditions for an *O*-acylation to take place. In this respect, the counter-ion of the base must be

dissociated from the oxygen anion created. Thus, potassium and sodium bases were used as priority.

For this reason also, dimethylformamide was chosen as a solvent due to its polarity and as it offers good solubility. It is an aprotic solvent, which prevents solvation, which would decrease the nucleophilicity of the anion, due to hydrogen bonding. Dimethylsulfoxide and THF/HMPA are also appropriate solvents but the hazards linked to THF/HMPA made this solvent less attractive.

Finally, according to the HSAB (Hard-Soft-Acid-Base) effect, O-acylation is favoured with electrophiles bearing hard leaving groups (tosylate, triflate or even anhydride), over these containing halogens.

Taking the aforementioned considerations into account, the lactone 5 was added to a base (potassium bis(trimethylsilyl)amine or potassium hydride (3 equiv.)) in dimethylformamide or tetrahydrofuran. The solution was stirred at 0 °C under a nitrogen atmosphere. Despite the fact that halide groups are not favoured in our case, the commercial availability of ethyl 3-chloro-3-oxopropanoate 56 persuaded us to use it. 56 was added to the enolate. All the reactions afforded only starting materials.

The lactone 5 and the propanoate 56 possess acidic protons Ha and Hb respectively (Scheme 36). Hb (pKa $\approx$13) is more acidic than Ha (pKa $\approx$20). It is therefore likely that the enolate formed did not attack the acyl chloride functionality, but deprotonated the propanoate 56. This acid-base reaction only gives starting materials (Scheme 36).

pKa (Ha) =20

base

56

pKa (Hb) =13

56

5

49

Starting material +

5
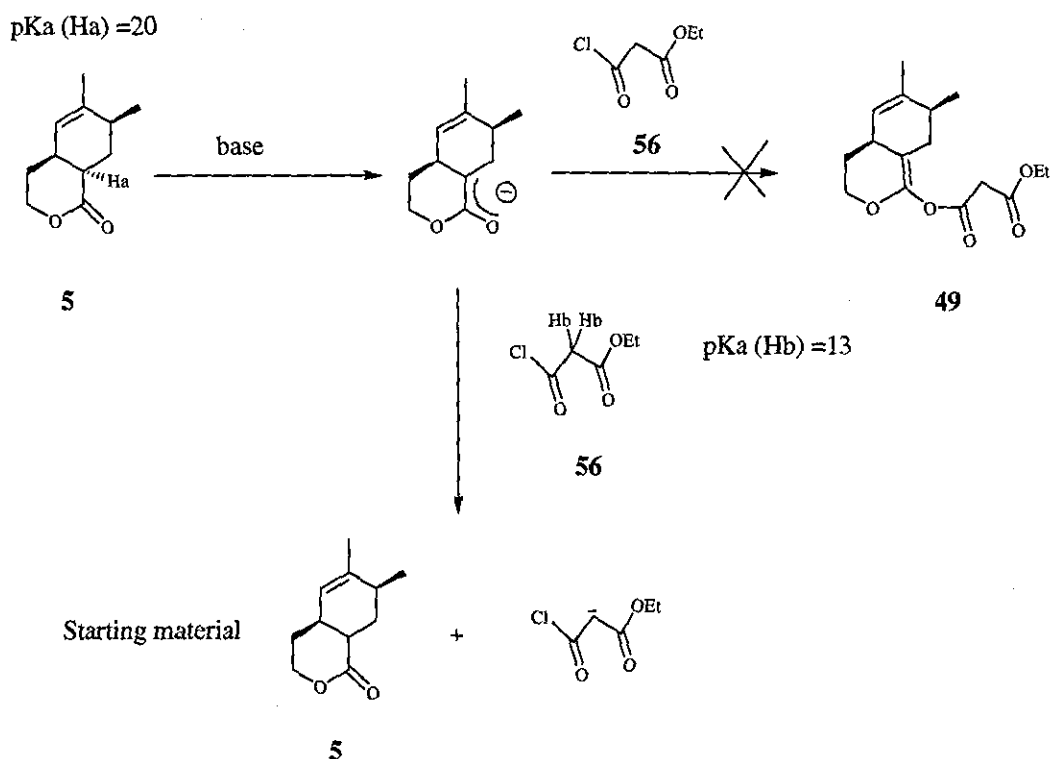
Scheme 36

The easiest way to prevent the acid-base reaction was to avoid using a compound containing an acidic proton. In this respect, three solutions were suggested: the use of acetyl chloride, which would give an acetoxy ester, the preparation of a ketene from the propanoate **56**, or the use of 4-methylidene oxetane-2-one. The second and third propositions would afford the desired compound, and were the first attempted (Scheme 37).

**56** + NEt₃ → Et₂O / 0 °C → **57** + **58**
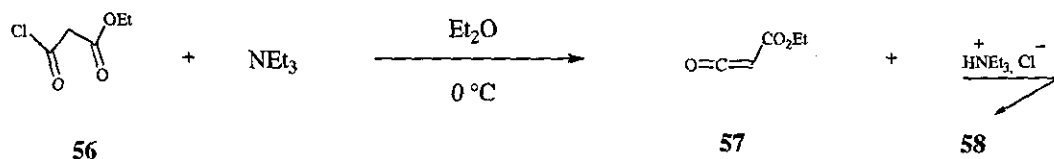
Scheme 37

The carboethoxyketene **57** was generated *in situ* by using three equivalents of triethylamine in diethyl ether at 0 °C, according to the experimental procedure

reported by Newman.[53] When the mixture was added to the potassium enolate of
5, a precipitate of triethylammonium salt **58** was formed and the IR spectrum of
the reaction mixture showed an absorption at 2120 cm^{-1} (ν C=C=O).[54] These two
facts support the formation of the ketene **57**. However, after work up, the NMR
spectra of the reaction mixture were complex, and the reaction was considered to
have failed (Scheme 38).

1. KHMDS

2. EtO$_2$C—C=O , Et$_2$O
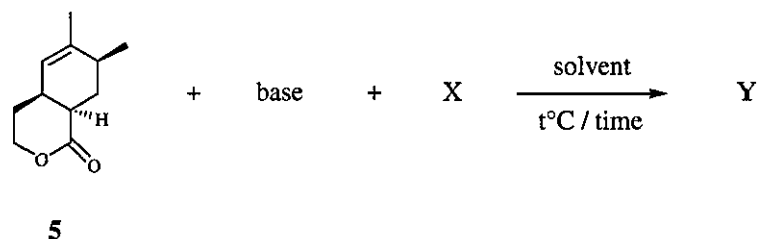
starting materials

5
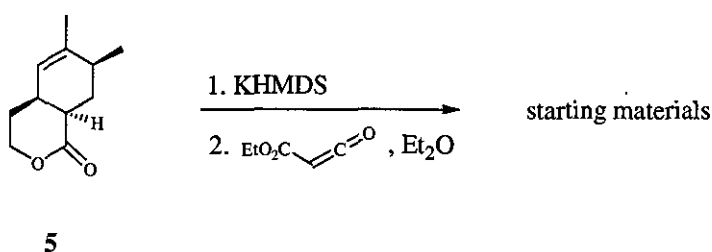
Scheme 38

4-Methylideneoxetane-2-one **60** is a compound which does not contain any acidic
protons. In the following example, the hindered tertiary alcohol **59** failed to be
acylated under a variety of conditions. However, reaction with diketene **60**, in the
presence of a catalytic amount of DMAP proceeded smoothly to afford the β-keto
ester **61** (Scheme 39).[55]

traditionnal methods

no reaction

59

60

DMAP $_{cat.,}$
THF, r.t.
88%

61
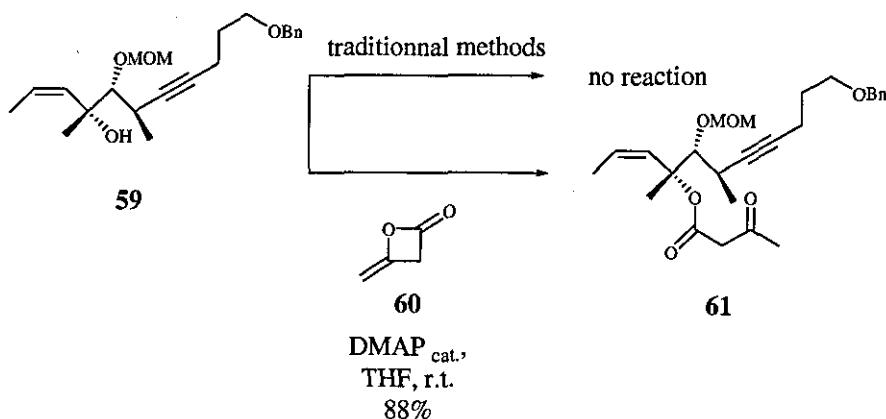
Scheme 39

These conditions were investigated with compound **5**, but again the reaction failed.

The *O*-acylation reaction planned was thus unsuccessful. Various protocols were examined. Numerous solvents, conditions, bases and electrophilic species were used but no significant positive results were obtained (Table 1).

5

Bases	X	Solvents	Temperatures	Times	Y
KHMDS 1.1 equiv.	ketene 1.3 equiv.	THF	-78 °C to r.t. 0 °C to r.t.	4 h	Complex mixture
DMAP Cat	**60** 1.5 equiv.	THF	r.t.	Overnight	Starting materials
Pyridine	Ac$_2$O	Pyridine/Ac$_2$O	110 °C	3 h	Decomposition
NEt$_3$ 3 equiv.	AcCl / DMAP 1.5 equiv.	DCM	r.t.	20 h	Starting materials
KH 1.1 equiv.	AcCl / DMAP 2 equiv.	DMF	0 °C	Overnight	Starting materials
NaH 3 equiv.	AcCl 1.2 equiv.	DMF	0 °C	Overnight	Complex mixture
NaHMDS 3 equiv.	AcCl 3 equiv.	THF	-78 °C	Overnight	Complex mixture
NaHMDS 3 equiv.	MeI 3 equiv.	THF	-78 °C	Overnight	Trace of C-alkylation

Table 1: Attempts to *O*-acylate **5**.

In some cases, a catalytic amount of 4-dimethylaminopyridine **62** was added. This formed a highly reactive 1-acylpyridinium intermediate **63**, which was expected to facilitate the reaction (Scheme 40).[56]


62   **63**
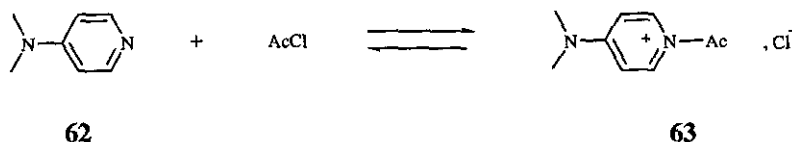
Scheme 40

No improvements were noticed. Only a reaction carried under conditions expected to induce a *C*-alkylation (sodium bis(trimethylsilyl)amine, tetrahydrofuran, overnight/ -78 °C), gave traces of the *C*-alkylated product, which could not be isolated. This fact suggests that the enolate was formed. Therefore, the problem would not be in the enolate formation but in the reaction itself. Nevertheless, this deduction is subject to caution because we did not obtain a high yield of *C*-alkylated material.

2.3.1.3. Attempts under acidic conditions

As a base-mediated route to reach the acetoxy ether was unsuccessful, acidic conditions were investigated. In this connection, Shi has reported a method using perchloric acid.[52] The oxopropanoate **56** (1.1 equiv.) was added to the lactone **5** in hexane or dichloromethane at room temperature. The reaction was performed in the presence of a catalytic amount of perchloric acid. Only starting materials were recovered (Scheme 41).
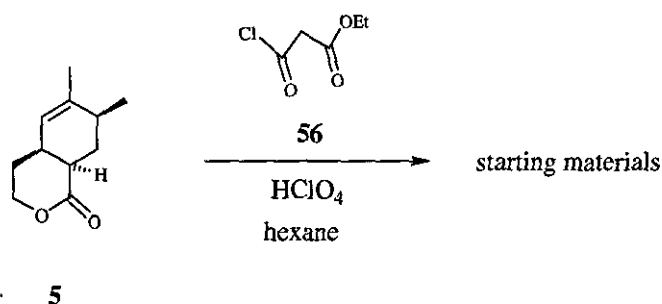
Scheme 41

Similarly, the lactone **5**, trimethyl orthoformate (2 equiv.) and a catalytic amount of *para*-toluene sulfonic acid were dissolved in methanol and set to reflux overnight. The desired product was not obtained (Scheme 42).
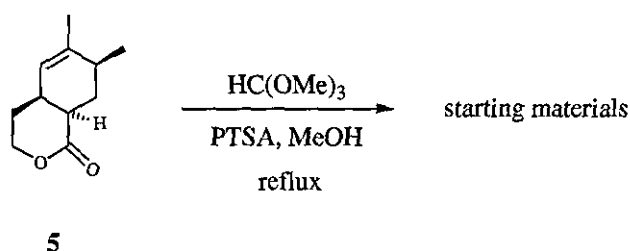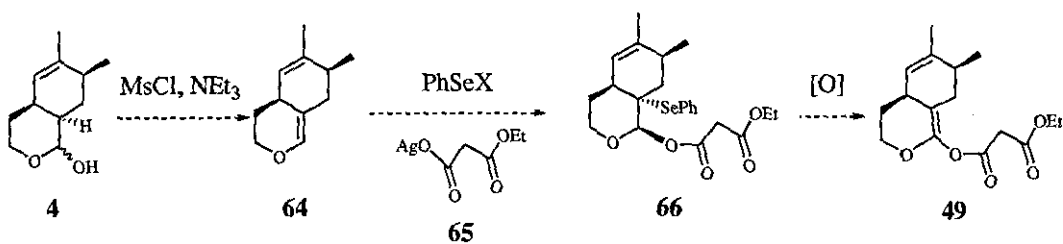

Scheme 42

2.3.1.4. A possible explanation

Both basic and acidic methods for *O*-acylation reaction were unsuccessful. We have synthesised (4aS,7S)-6,7-Dimethyl-4,4a,7,8-tetrahydro-3H-isochromene **64**. This compound is unstable and readily undergoes degradation or rearrangement (section 2.3.2.1.). Like **64**, enol ether **49** possesses an electron-rich double bond. It is possible that **49** was formed but subsequently underwent a rapid degradation process. Attempts to test for a hypothetical short-term formation of **49** by performing the reaction in deuteriated solvent in a NMR tube were not conclusive.

## 2.3.2. New routes based on the synthesis of the enol ether 64

Two new methods of attaining our objective were suggested and are discussed below. The first one was based on selenium chemistry (Scheme 43).

Scheme 43

The conversion of olefin **64** to the acyloxy selenide **66** using a phenylselenenyl chloride or bromide and **65**, followed by selenoxide elimination would provide the desired enol ether **49**.

The conversion of olefins to alkoxy selenides is *trans*-stereospecific, but the regioselectivity is usually poor with simple alkene substrates (Scheme 44).[57]

45 : 55
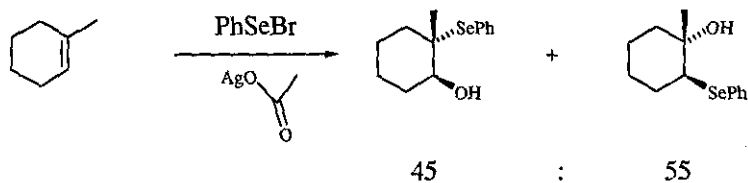
Scheme 44

In the case of enol ethers, however, the mesomeric effect controls the reaction, and the process is highly regioselective (Scheme 45).

67

R= Ac, SiMe₃...
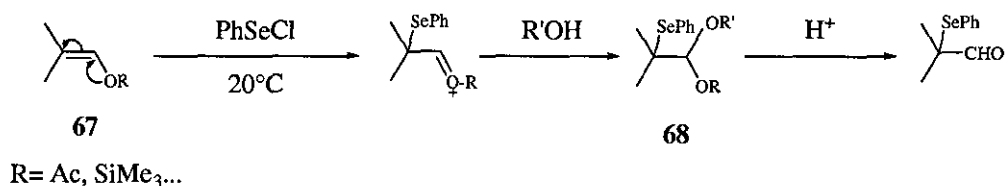
Scheme 45

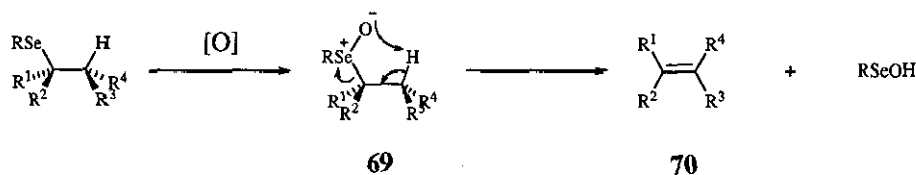The conversion of enol ether **67** to the acyloxy selenide **68** proves the efficiency of the method.

When there is a proton *cis* on the carbon atom alpha to the selenoxide in **69**, and when the product structure is not strained, *syn*-elimination occurs readily even below room temperature to give **70** (Scheme 46).[58]

69   **70**

Scheme 46

The selenoxide elimination, which affords the enol ether **49**, would follow this mechanism.

The second method was grounded on an epoxidation inversion procedure as the key step, inspired by the following sequence of reactions described during a synthesis of an analogue of inositol (Scheme 47).[59]
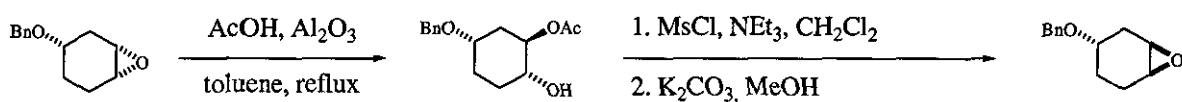
Scheme 47

Treatment of the epoxide **71** with acetic acid under alumina catalysis selectively gives the hydroxyl acetate **72**. Conversion to the corresponding mesylate, followed by treatment with potassium carbonate, resulted in acetate hydrolysis and subsequent ring closure to form the inverted epoxide **73**.

Corresponding cleavage of **74** by a masked hydroxyl nucleophile would be followed by conversion of the resulting alcohol to a suitable leaving group. Subsequent ring closure under basic conditions would lead to **75** on the way to the synthesis of **10**, without using the Shi rearrangement (Scheme 48).
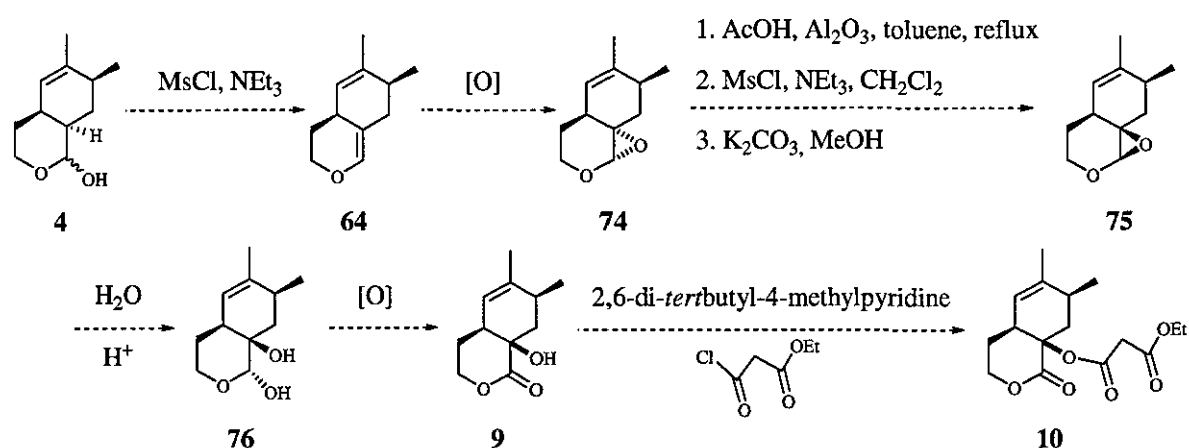
Scheme 48

Both epoxidation and selenation routes depended on the successful synthesis of the enol ether **64**.

### 2.3.2.1. Synthesis of enol ether 64

Mesylation of lactol **4** followed by base-induced elimination of the mesylate of the intermediate **77** gave the alkene **64** after overnight stirring and purification.

The problem of low yield due to the instability of this product had, however, still to be solved. Compound **64** was obtained in only 20% yield, whereas the

conversion was approximately 65%, established by NMR spectroscopy of the crude product. Therefore the low yield appeared to be linked with the purification process.

Flash column chromatography, even after treatment of silica gel by triethylamine, was not efficient. This method of purification was successfully replaced by Kügelrohr distillation of the product, and gave **64** in 63% yield (Scheme 49).
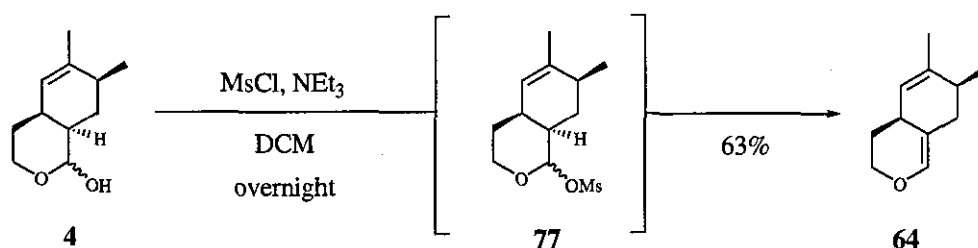
Scheme 49

When purified, the enol ether **64** had to be stored. Maximum precautions allowed this compound to be kept for two days in a refrigerator under nitrogen (the glassware was previously treated overnight by a solution of potassium hydroxide in isopropanol so as to avoid the acidic action of the glass). Afterwards the compound underwent degradation.

The two new routes were based on compound **64**, in which the double bond of the enol ether is activated by the vinylic oxygen of the ring. Further reactions would therefore involve this double bond, which is electronically enriched, rather than the other olefin, which is electron-poor.

2.3.2.2. The selenium route

The conversion of olefins to alkoxy or acyloxy selenides followed by selenoxide elimination provides a mild and efficient route to vinylic alcohols and enol ethers, and provided the impetus to test the following strategy (Scheme 50).[60,61]
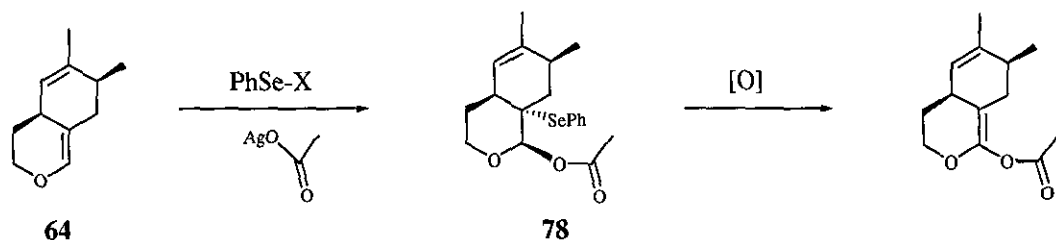
Scheme 50

Silver acetate was used to convert **64** to **78** instead of oxopropanoate **65** (Scheme 43) due to the problem associated with the presence of the two acidic protons described previously in Scheme 36. A silver salt was used because of its solubility in organic solvents, and because the conditions required were mild. Only one equivalent of phenylselenenyl chloride was used to guarantee that over-reaction with the less reactive olefin was prevented.

Two different procedures were investigated for the formation of the β-acetoxyalkyl selenide **78**. First, acetolysis in acetic acid of a β-chloroalkyl selenide **79** initially formed across the double bond of the enol ether was envisaged and secondly, the direct addition of acetoxyphenyl selenide **80** to the enol ether unit was proposed (Scheme 51).[57]
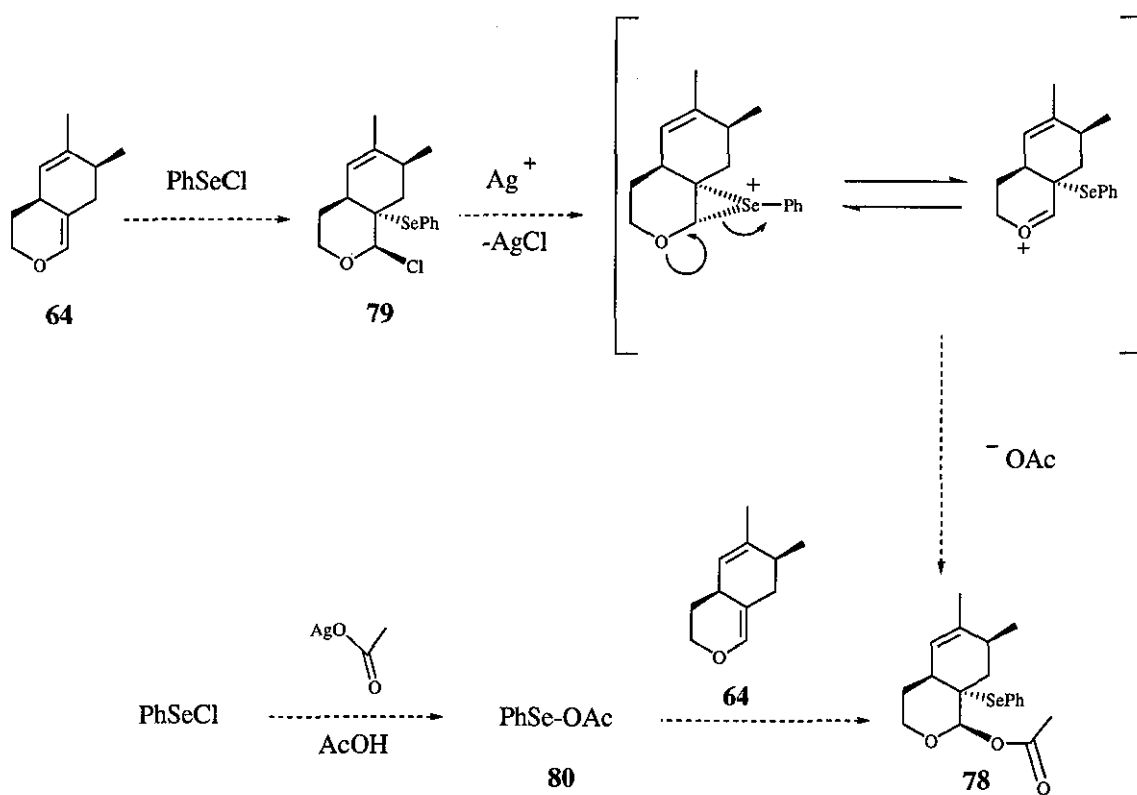
Scheme 51

Various reaction conditions were examined, and are described below. Unfortunately, all the different protocols gave complex mixtures, where acetoxy or hydroxy selenide could not be identified.

Several attempts were made following the procedure used by Perez and Beau in their synthesis of deoxyglycosides (Scheme 52).[62]
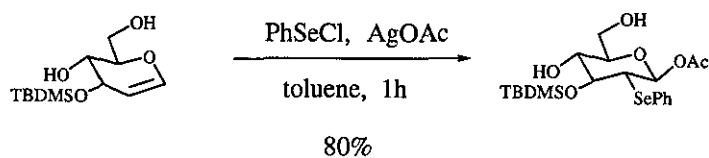
Scheme 52

A solution of olefin **64** (1.22 mmol) in dichloromethane was treated with phenylselenenyl chloride (1 equiv.). The reaction was stirred for 30 minutes before the addition of silver salt (1.5 equiv.). Instantaneously, a precipitate of silver chloride was formed and the solution passed from a yellowish to an orange colour, which seemed to indicate the success of the reaction. Unfortunately, after filtration of the precipitate and the evaporation of the solvent, a mixture of products was formed that was impossible to purify. Strangely, precipitation of the silver chloride did not appear upon exchanging dichloromethane for toluene, and the solution remained a yellow colour. Nevertheless, the starting material could not be retrieved and the reaction gave a mixture of products, perhaps due to the instability of **64**. The inverse addition of the olefin to phenylselenenyl chloride was also attempted, but without success (Scheme 53).[63]
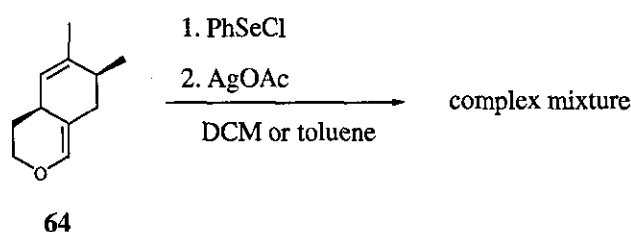
Scheme 53

The generation of phenylselenenyl acetate followed by addition to the enol ether was attempted using the following conditions (Scheme 54).[57]
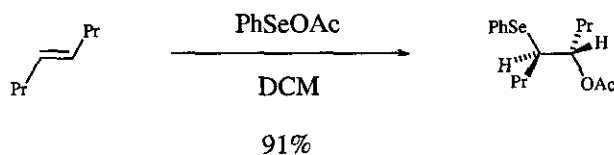
Scheme 54

Phenylselenenyl acetate was readily generated *in situ* by reacting phenylselenenyl chloride (1 equiv.) with silver acetate (1.5 equiv.) in acetic acid. An orange

precipitate of silver chloride was formed. After stirring for 30 minutes, the phenyl selenyl acetate was added to a solution of olefin **64** (1.22 mmol) in dichloromethane. The solution was allowed to stir overnight. The crude product mixture obtained was too complex to be exploited (Scheme 55).
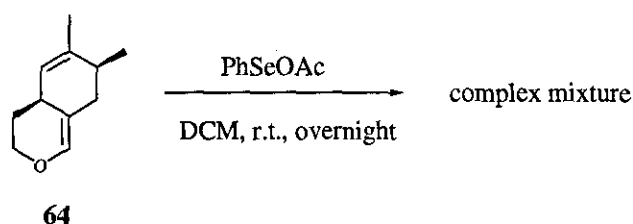
Scheme 55

A hybrid reaction was also attempted where the reactants were added simultaneously at low temperature in etheral solution according to the an example from the literature (Scheme 56).[57]
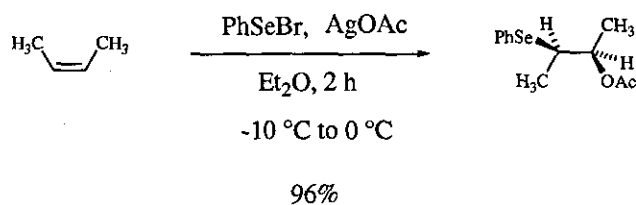
Scheme 56

Phenylselenenyl bromide (1 equiv.) was added to a cold solution (-10 °C) of olefin **64** (1.22 mmol), followed by an excess of silver acetate (1.2 equiv.) in 10 mL of diethyl ether. Here again a precipitate was formed, and after a night at room temperature, a mixture of products was obtained after filtration and solvent evaporation (Scheme 57).
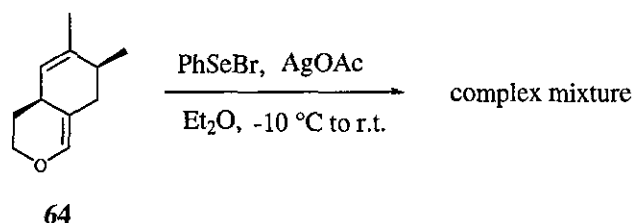
Scheme 57

The use of trifluoroacetoxy selenides **82** represented the last alternative method, where acetate is replaced by trifluoroacetate. Trifluoroacetate **81** is less basic than acetate, which prevents the following possible side reaction of elimination by deprotonation of the proton alpha to the selenenium ion (Scheme 58).
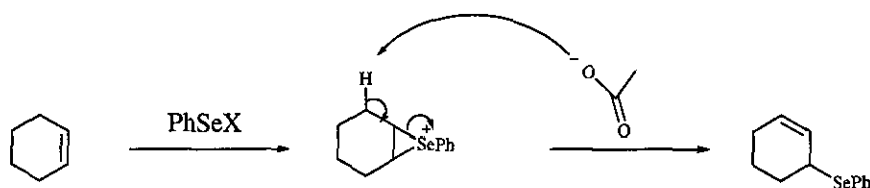
Scheme 58

Trifluoroacetate **81** is the nucleophile in the addition reaction and opens the transitory 1,2-episelenonium ion (Scheme 59).[64]
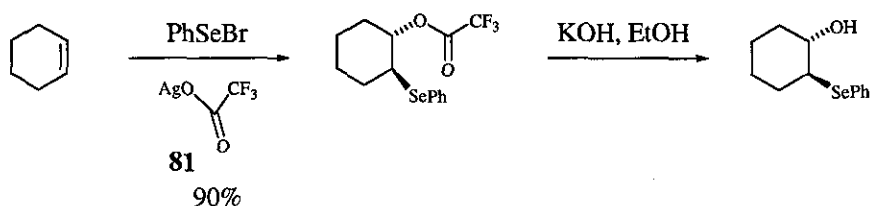
Scheme 59

Phenylselenenyl bromide (1 equiv.) was treated with silver trifluoroacetate (1 equiv.) in 10 mL of toluene. Instantaneously, a precipitate of silver bromide was formed and the solution passed from purple to orange, which indicated the formation of phenylselenenyl trifluoroacetate. Olefin **64** (1.22 mmol) was added to

the mixture and the solution was allowed to stir overnight. The precipitate was filtrated and the solvent was evaporated. The reaction afforded a complex mixture, as did the previous examples (Scheme 60).
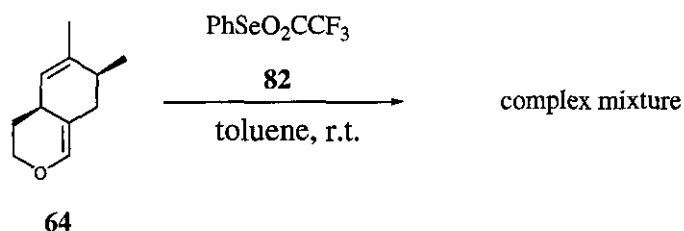
Scheme 60

The formation of numerous products in each of these procedures may have been due to the instability of substrate **64**, and perhaps the reactivity of the other olefin, was causing competition with the enol ether.

Also, the formation of by-products such as allylic derivatives has been described. It has been even shown that, in some cases, there is a strong preference for elimination in the direction that gives the allylic derivative **82** rather than the vinylic product **83** (Scheme 61).[65]

	82		**83**
X = OH	98.8	:	0.2
X = OAc	97	:	3
X = OMe	98	:	2
X = Cl	51	:	49
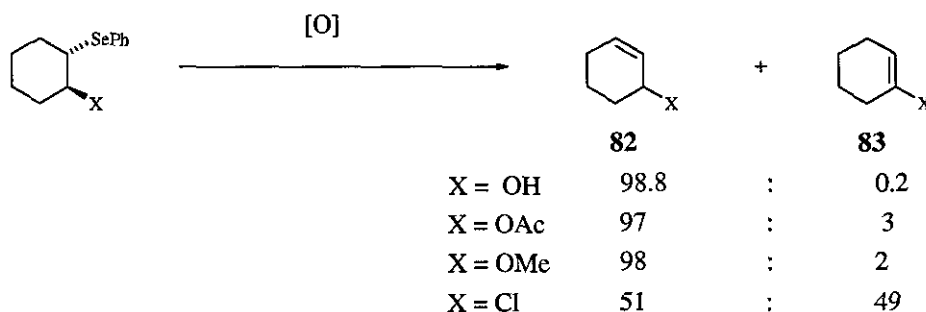
Scheme 61

Compound **66** possesses three protons alpha and *cis* to the selenium. In the best case, the desired compound **49** would have been synthesised, but potentially mixed

with two other compounds. As shown in Scheme 62, the allylic products **84** and **85** may be more favourable than **49** (Scheme 62).
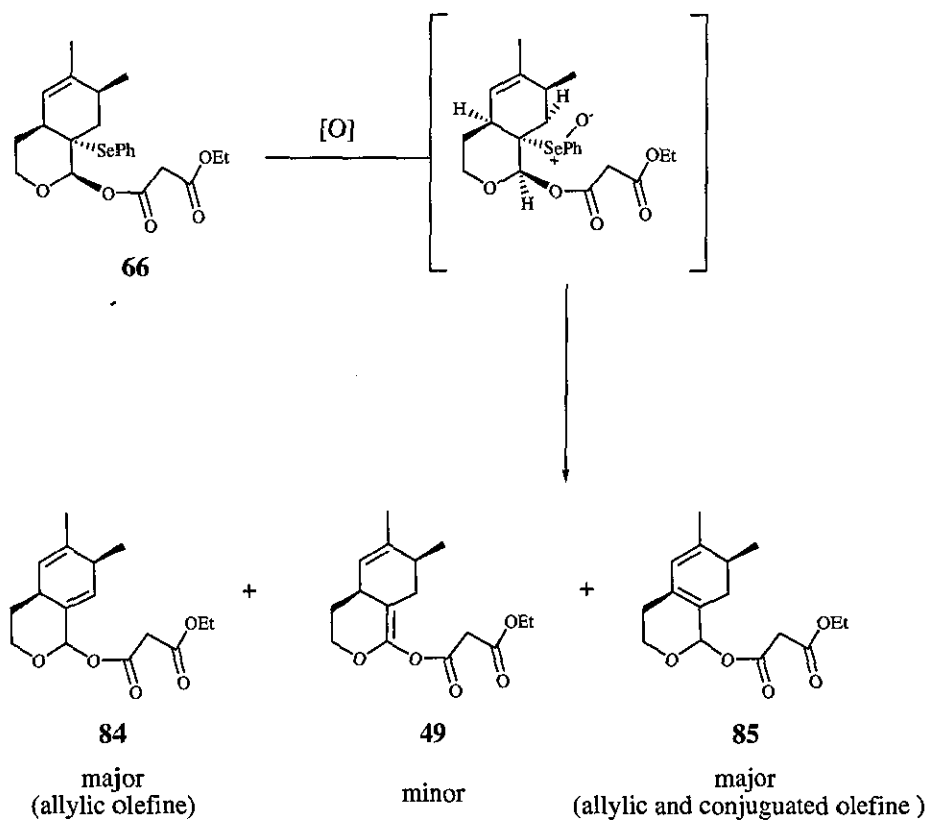
Scheme 62

2.3.2.3. The epoxidation route

This alternative strategy begins with the formation of **74** by simple epoxidation of the enol ether **64**. Classic epoxidation conditions proposed by Baker *et al.*[59] and Arbelo *et al.*[66] were repeated. However, we were unable to isolate **74** from the reaction mixtures. It is possible that the enol ether **64** was too unstable and decomposed or rearranged *in situ* before the epoxidation reaction could occurred (Scheme 63).
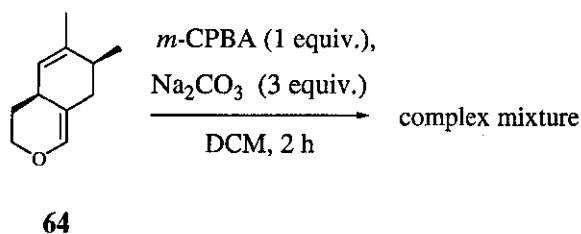
Scheme 63

As a model and to provide experience, an epoxidation was attempted on ethyl vinyl ether **86** using *meta*-chloroperbenzoic acid. Sodium carbonate was added to the reaction mixture in order to prevent the attack of the *m*-chlorobenzoic acid on the epoxide **87** formed. The mechanism of the epoxidation reaction is presented below (Scheme 64).[67]

"butterfly" transition state
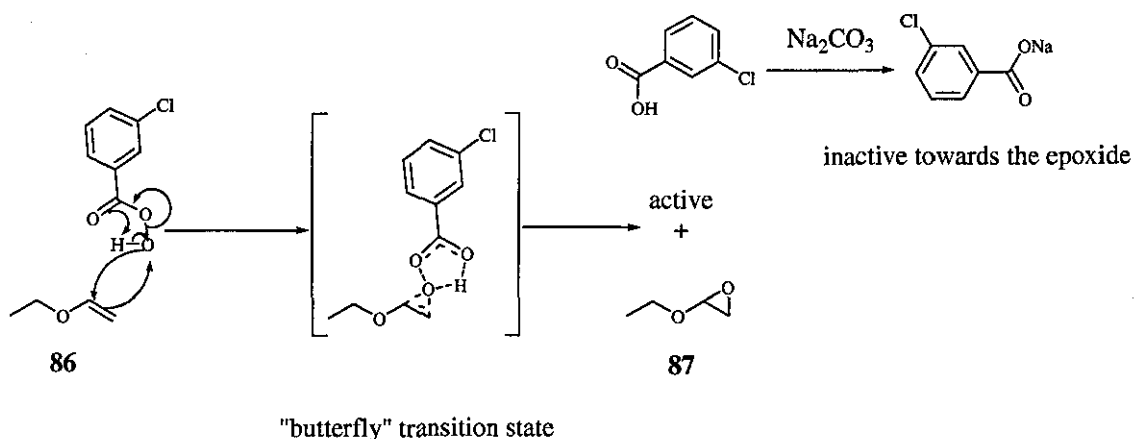
Scheme 64

The reaction was successful and we decided to continue the epoxidation chemistry by changing the strategy.

This strategy was abandoned and replaced with a new route shown in the next section. It was thought to be a more sensible approach to work with a ring opened isomer.

2.4. Working with an opened ring

Vahedi obtained the oxaspirobicycle unit **8** with the wrong stereochemistry. This stereochemistry was due to the cis-fused bicyclic unit where the access to the upper face was disfavoured in the enolate of **5** (Figure 7).

5
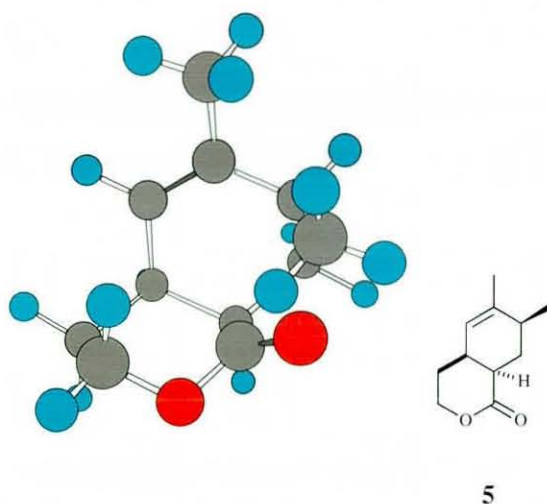
Figure 7

As the stereochemistry of the bicycle was causing the problem, we decided that it would be best to avoid its formation. The opened-ring would be functionalised first, as it would offer more accessibility and reactivity than the bicyclic unit, before ring closure.

2.4.1. Formation of a monocycle by different Diels-Alder reactions

2.4.1.1. Nef reaction

First, we decided to explore the Nef reaction which had been investigated by a previous researcher, but without success.[121]

2.4.1.1.1. Synthetic plan

This reaction was a key step of the synthetic plan towards the synthesis of the required spirotetronate **9** illustrated in Scheme 65.
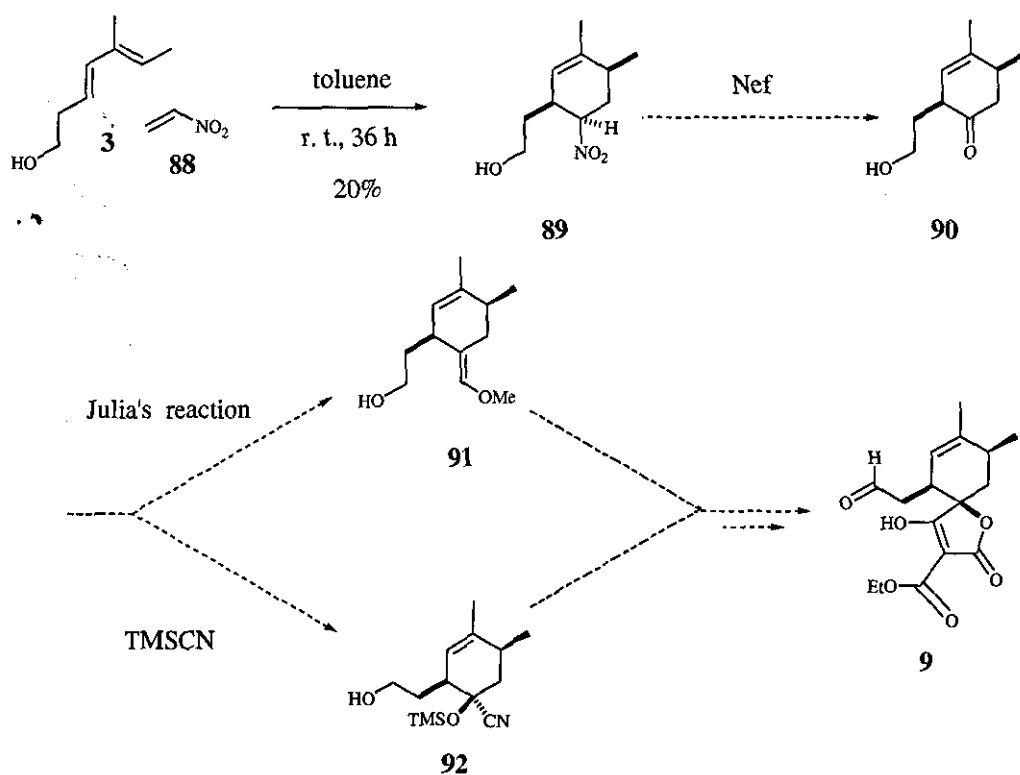
Scheme 65

First a Diels Alder reaction between **3** and nitroethylene **88** would give the formation of the cyclohexene ring with the nitro functionality **89**. The desired cyclohexenone **90** would then be obtained by converting the nitro group into a ketone. The Nef reaction is the conversion of a primary or a secondary nitroalkane **93** into the corresponding carbonyl compound **94**. Nef first reported the reaction in 1894 (Scheme 66).[68]
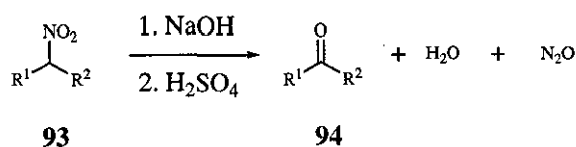
Scheme 66

A number of mechanisms have been proposed for the reaction. The simplest is illustrated below.[69] Thus, the initial reaction consists of the deprotonation by a strong base (usually sodium hydroxide) of the nitro compound **93** to give nitronate **95**. A succession of protonation-deprotonation processes, nucleophilic attack by water and loss of water lead finally to the carbonyl compound **94** (Scheme 67).
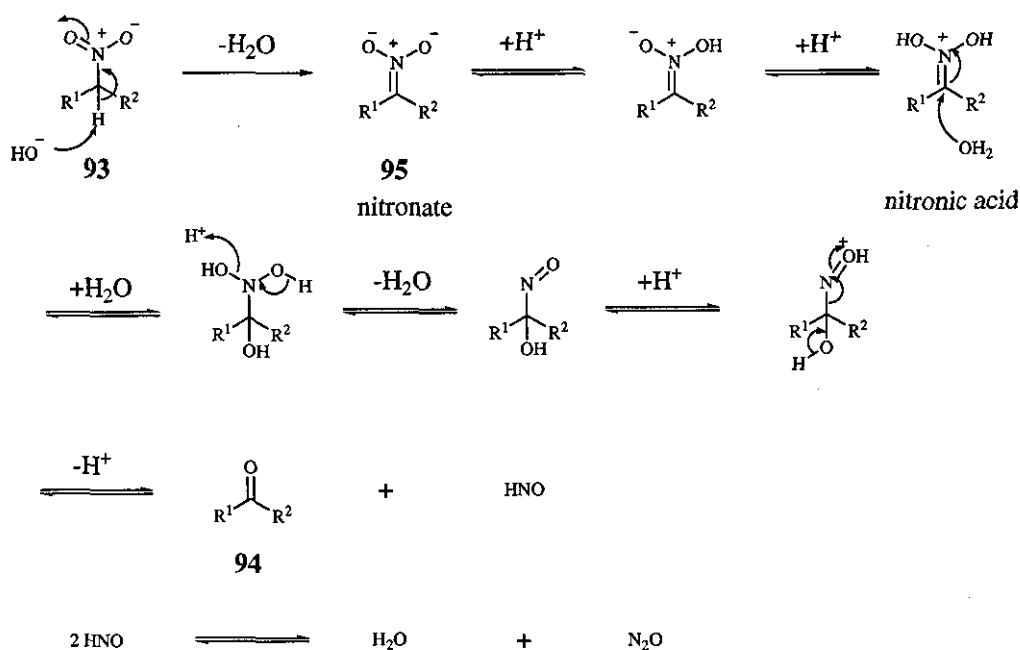
Scheme 67

It is important to mention that nitroalkanes are acidic by nature and form sodium salts. When a mineral acid is added, nitroalkanes are regenerated. However, the action is different when the sodium salts are added to an excess of acid. In this case, carbonyl compounds are formed with the evolution of nitrous acid.

2.4.1.1.2. Previous attempts on Nef reaction

Previous researchers have tested numerous alternative methods, some of which involve mild conditions.[70,71]

Many of these modern approaches utilised oxidising agents. Use of reagents such as oxone/potassium hydrogen persulfate,[72] MoOPH,[73] potassium permanganate[74,75] has been described in the literature. Oxidative cleavage of the nitronate by means of TMSCl/*m*-CPBA,[76] *tert*-butyl hydroperoxide/VO(acac)₂,[77] and TPAP/NMO[78-80] has been attempted by previous researchers of the Page group because they represent efficient methods which would not cause competing reaction of the olefin of the cyclohexene unit of **89** (Scheme 65). The selectivity of these methods towards the nitro functionality is shown below (Scheme 68).[76,77,80]
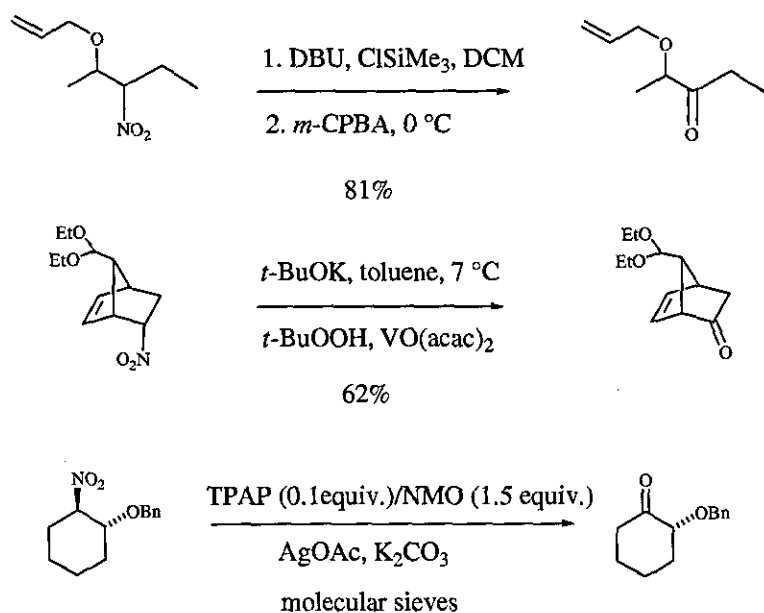
Scheme 68

These reactions are successful but prevent working with substrates bearing a free alcohol due to the concurrent alcohol oxidation. Indeed, these oxidising reagents are commonly used for the oxidation of sulphides to sulfones and alcohols to

53

carbonyl compounds. As depicted in Scheme 69, during the formation of **97** from **96**, the hydroxyl group was oxidised.[81]
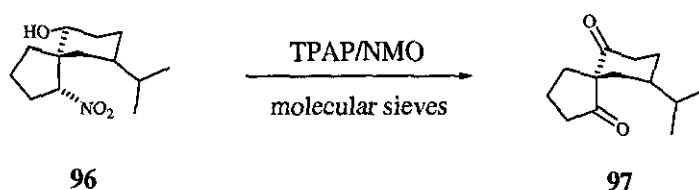
Scheme 69

Therefore the hydroxyl group of the nitro compound **89** had to be protected before such protocols could be attempted. All attempted oxidative cleavage reactions with benzyl-protected substrate **98**, carried out by Batchelor during his PhD, failed, and the starting material was recovered (Scheme 70).[71]
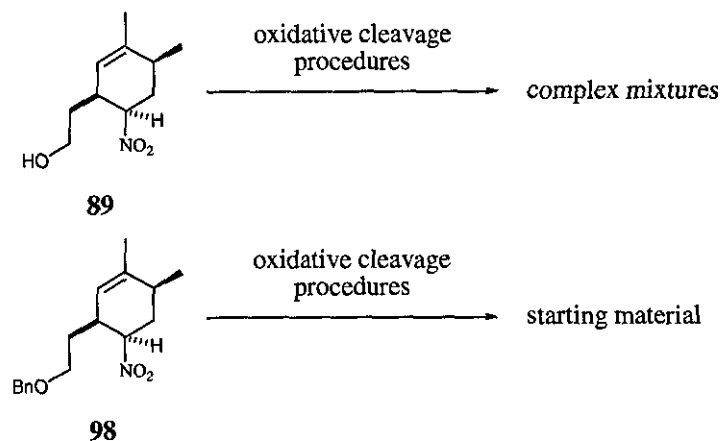
Scheme 70

The oxidative cleavage methodology was not successful, and so reductive cleavage methodology was attempted. Only few reagents convert nitro compounds into aldehydes or ketones by reductive processes. The most widely used reductive modified Nef reaction uses aqueous titanium chloride.[82-84] This reagent can be very acidic, and the reaction often uses an ammonium acetate or sodium acetate buffer to prevent any side reactions with sensitive compounds (Scheme 71).[82]

1. NaOCH$_3$, MeOH

2. TiCl$_3$, NH$_4$O$_2$CCH$_3$

61%
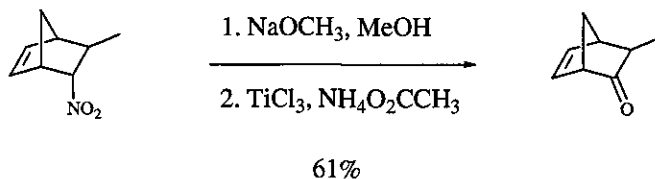
Scheme 71

Other reagents such as tin complexes in conjunction with sodium hydrogen sulphate[85] or vanadium (II) chloride[84] can also be used, but are less common.

The failure of the process persuaded previous researchers to seek another route to the carbonyl compound **90** (Scheme 72).[71]

TiCl$_3$, THF, r.t., 18 h

89   **90**
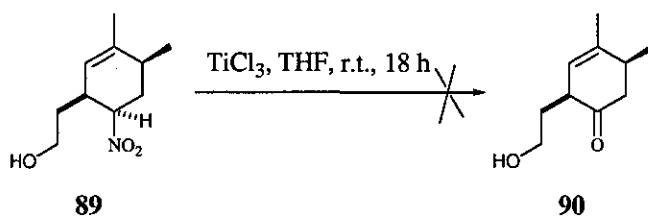
Scheme 72

2.4.1.1.3. New attempts

Extended work was carried out using the previous research[70,71] described in the previous section.

2.4.1.1.3.1. Attempts towards the synthesis of compound 90

The two steps presented in Schemes 73 and 74 had to be repeated. The formation of nitroethylene **88** showed to be more difficult than predicted. Whereas the previous researcher obtained a 57% yield, we managed to form only a poor 11% of nitroethylene **88** (Scheme 73).

phtalic anhydride (1.5 equiv.)

Kugelrohr equipement, 160 °C

11%
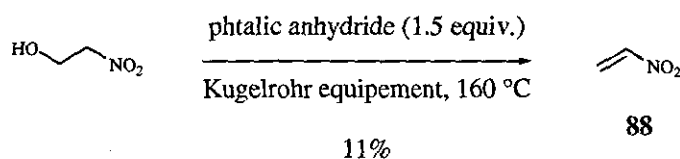
Scheme 73

Different attempts, including the use of the Kügelrohr equipment, were very disappointing. In the same way, the Diels-Alder reaction between the hydroxy diene **3** and nitroethylene **88** led to **89** in a 20% yield compared with the 64% obtained by Batchelor (Scheme 74).
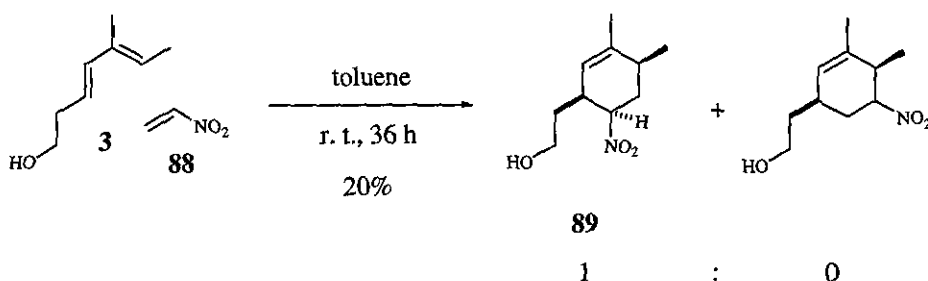
Scheme 74

The correct regioisomer **89** was exclusively afforded according to comparison with the data previously obtained and which fully characterised the product **89**. Postulating that maybe the protocols used previously for the next reaction were too mild, we decided to carry on the Nef reaction as it was originally described, following the general procedure proposed by Culford Bell et al.[86] Compound **89** was dissolved in a solution containing sodium hydroxide. Addition of sulphuric acid dropwise to the reaction mixture gave a complex mixture which could not be separated (Scheme 75).

1. NaOH
2. H$_2$SO$_4$
→ complex mixture

89
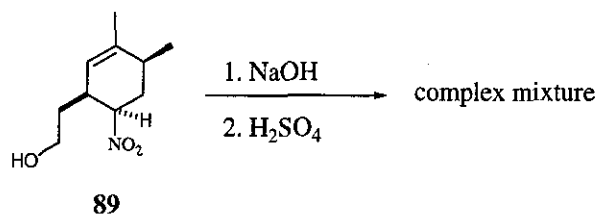
Scheme 75

This result may be explained by the fact that this procedure, using a base followed by sulphuric acid, is drastic and can produce a number of unwanted side reactions on sensitive substrates, as described by Pinnick.[82]

Nitronate **95** is highly reactive towards electrophiles at several sites because of the delocalisation of the negative charge. Addition of a proton to the α-carbon atom regenerates the nitro species **93** (Scheme 76).

95   **93**
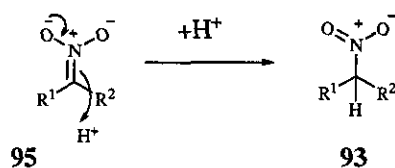
Scheme 76

Also, nitrite ion can behave as a good leaving group and can be eliminated upon treatment of **93** with base. Substrate **89** bears a secondary nitroalkane group, the formation of a pseudonitrole **99** may be favoured by slow addition of the nitronate to the acid (Scheme 77).

HNO$_2$ + H$^+$ ⇌ NO$^+$ + H$_2$O

95   **99**
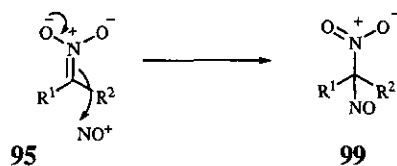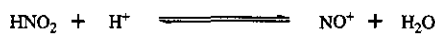
Scheme 77

57

A new methodology proposed by Ballini [84] was also explored.[87] This method consists on a one-step conversion of secondary nitro compounds into the corresponding carbonyl derivatives using DBU in acetonitrile.

Direct cleavage of the nitronate anion under basic conditions is a rather uncommon process that has only been observed on dry activated silica gel,[88] or when proton transfer is facilitated by a neighbouring group participation.[89]

Davis et al. have demonstrated that DBU in acetonitrile is not able to efficiently convert nitroethane into the corresponding nitronate.[90] The situation may be different when secondary nitroalkanes are used as substrates since they are slightly more acidic than the primary nitroalkanes. It is therefore possible that DBU is able to produce a complex **100** that behaves similarly to a protonated nitronic acid intermediate in the classical Nef reaction (Scheme 78).
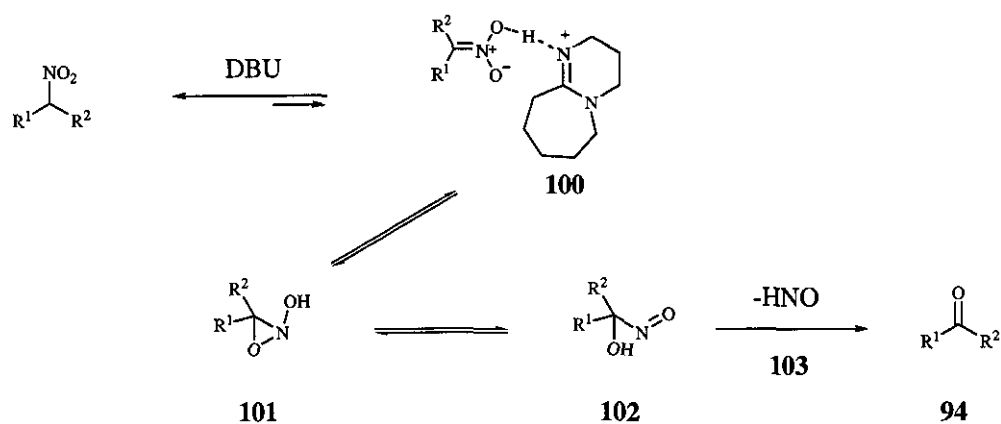
Scheme 78

An equilibrium is achieved between the complex **100**, the oxaziridine **101** and the hydroxynitroso derivative **102**. The last intermediate eliminates hyponitrous acid **103** affording the carbonyl derivative **94** as the final product.

This method offers usually good yields (54–80%) and preserves functionalities, whereas the previous methods did not. It was therefore possible to work with **89** without protecting the hydroxyl group and without risking the integrity of the olefin.

Treating one equivalent of nitro **89** with DBU (2 equiv.) in acetonitrile, and heating at 60 °C, the secondary nitro compound was not converted into the corresponding ketone **90**. Even after 5 days, only the starting material was recovered (Scheme 79).
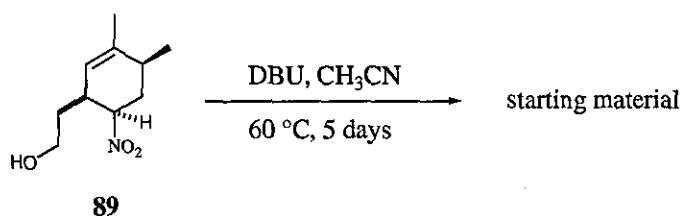
Scheme 79

The Nef reaction was not the main focus of this project. Therefore, the lack of a positive result coupled with the time limitations did not allow us to perform another procedure such as the innovative utilisation of activated basic silica gel previously mentioned.[88]

2.4.1.1.3.2. Julià's reaction
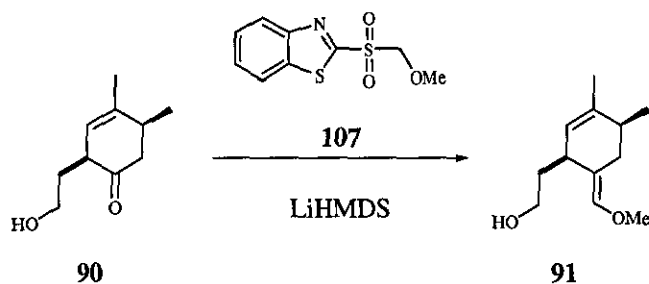
Scheme 80

Having planned for the success of the Nef reaction, we wished to explore the possibility of using α-alkoxyheteroaryl sulfone **107** in a Julià olefination reaction on ketone **90** to give **91** (Scheme 80), such as the reaction proposed by Charette *et al.* in their approaches to the formation of E,Z-dienes (Scheme 81).[91]

BT = BenzoThiazoyl

LiHMDS, DCM, 25 °C
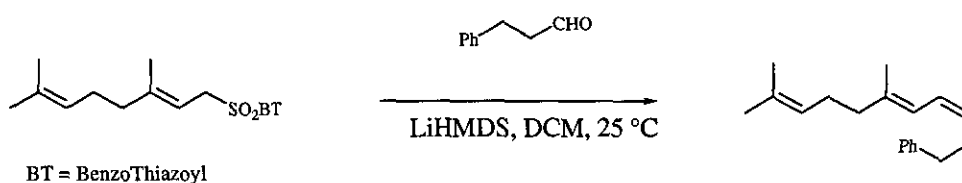
Scheme 81

This olefination reaction was first reported in 1991 by Julià *et al.* as a new connective one-pot synthesis of alkenes involving the reaction of lithiated benzothiazolyl sulfones with carbonyl compounds.[92] Julià olefination was chosen because it overcomes the problems linked to the formation of vinyl ethers through Wittig and Horner olefinations. These later methods can suffer from low yields, requiring a higher temperature in addition to the difficulty in removing phosphine oxide from the desired product. Also, alkoxymethyltriphenylphosphorane ylides are reportedly unstable and afford low yields of vinyl ethers with enolisable substrates.[93]

Sulfone **107** was prepared in two steps from commercially available reagents chloro(methoxy)methane **105** and 2-mercaptobenzothiazole **104** according to the procedure described by Berthelette *et al.* (Scheme 82).[94]

104   **106**   **107**

86%   61%
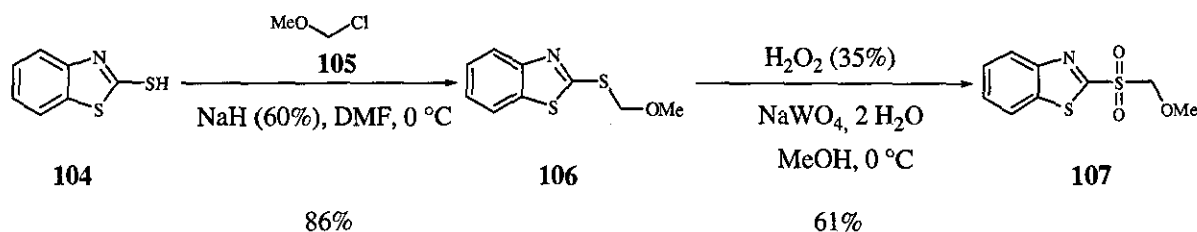
Scheme 82

The oxidation of sulphide **106** to sulfone **107** was carried out with hydrogen peroxide, the catalyst being tungsten in its higher oxidation state. This method was shown to give relatively good yields.[95]

Unfortunately, the synthesis of ketone **90** was not completed, and the formation of **107** found an application only later in our researches (section 2.5.3.4.).

2.4.1.2. Attempts to use 1-cyanovinyl acetate 253 in a Diels-Alder reaction

A Diels-Alder reaction involving 2-chloroacrylonitrile was accomplished by the previous researchers, but the conversion of the cycloadduct formed into the corresponding ketone was not achieved.[121]

The relative success of the cycloaddition led us to try another dienophile which can be used as a ketene equivalent: the 1-cyanovinyl acetate **108** in order to form **109**. The formation of the cyclohexenone **90** would then give a viable intermediate that could be converted to give the spirocycle as discussed earlier (Scheme 83).
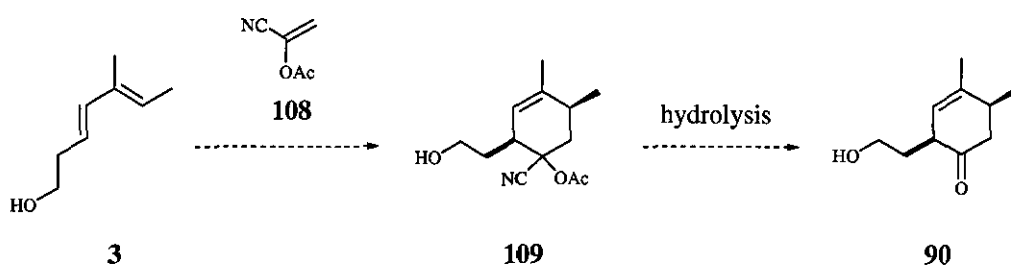
Scheme 83

The desired regiochemistry was afforded exclusively with 2-chloroacrylonitrile, suggesting that the compound **110** would not be formed in appreciable quantity with our very similar choice of dienophile (Scheme 84).
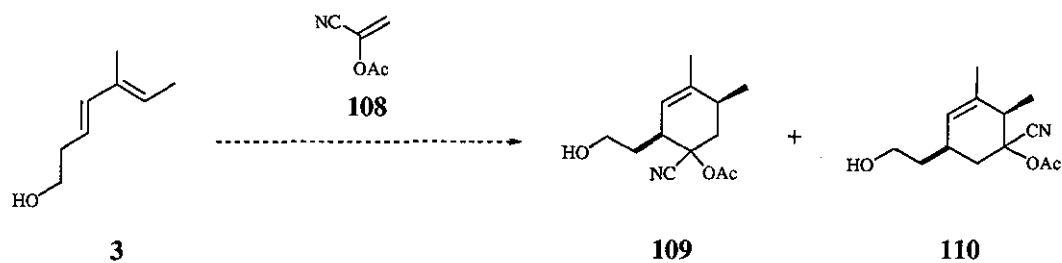
Scheme 84

The Diels-Alder reaction was carried out with heating, using toluene as the solvent. Attempts without solvents were also made (Scheme 85).
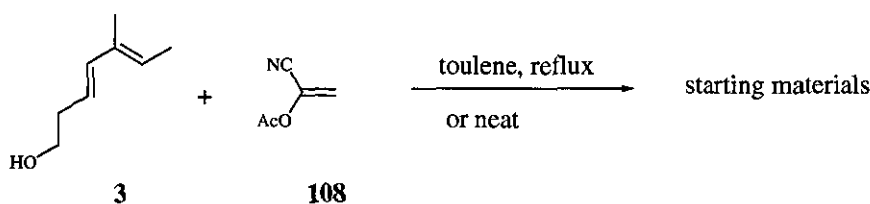
Scheme 85

Only starting materials were recovered, even after the addition of titanium chloride. This suggested the diene to be insufficiently reactive, requiring the most forceful of conditions. The stability of the dienophile in these high temperatures and pressures however proved problematic. Decomposition of materials occurred, even when the reaction was carried out in a sealed tube.

The failure of this route led to the following investigation.

2.4.1.3. Avoiding the ring closure

Two different routes were planned, based on the formation of the aldehydes **111** or **112**, leading to **9** as a precursor for **11**.

The first pathway is based on the Shi's rearrangement process. The synthesis would start with the formation of an acetoxy ester **113**, which would be consecutively oxidised to give the epoxide **114**. Shi's rearrangement followed by deprotection of the alcohol using TBAF would afford **115**, having the correct stereochemistry. Oxidation of the alcohol and treatment with potassium carbonate would result in acetate hydrolysis to give **9**. Three steps from **9** would then give the desired spirocycle **11** (Scheme 86).

111: R= TBDMS
112: R= TBDPS

113

114

115

9

11

Shi rearrangement:

114

acyloxy migration
and configuration inversion
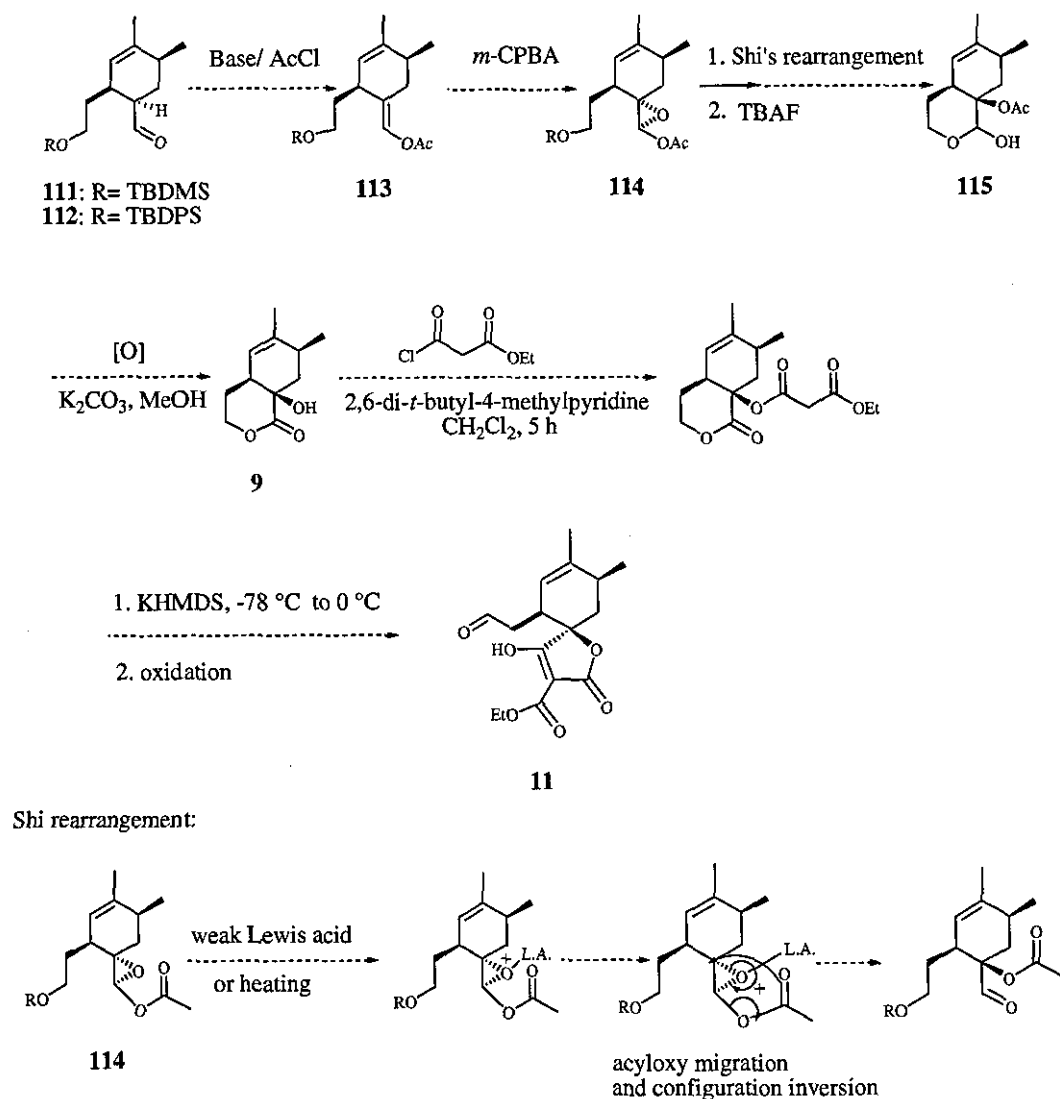
Scheme 86

The alternative is based on a chelated epoxidation using vanadyl bis(acetylacetonate)/ *t*-butyl hydroperoxyde of **91** to give **116**. Methoxy ether **91** would be first synthesised from **111** or **112** using a methylating agent such as methyl triflate followed by deprotection of the hydroxyl group. Acidic treatment of **116**, followed by oxidation of the alcohol, would give **9** having the correct stereochemistry. As in the previous example, three steps from **9** would afford the desired spirocycle **11** (Scheme 87).

111: R= TBDMS
112: R= TBDPS

91

116

9

11
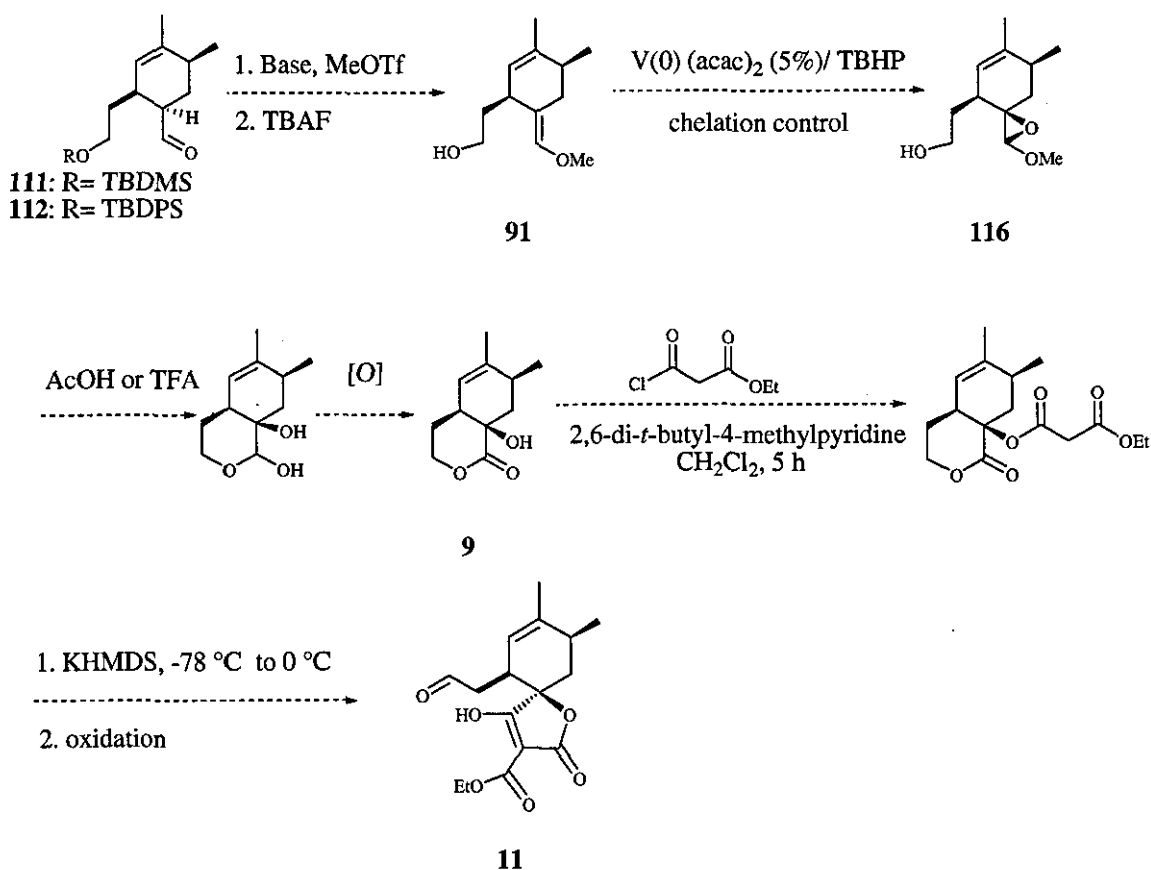
Scheme 87

Formation of the aldehydes **111** or **112**, which was attempted by protecting the alcohol of the hydroxy diene **3**, would prevent the ring closure to **4**. This would represent the first step of the new strategy presented in Schemes 86 and 87 (Scheme 88).
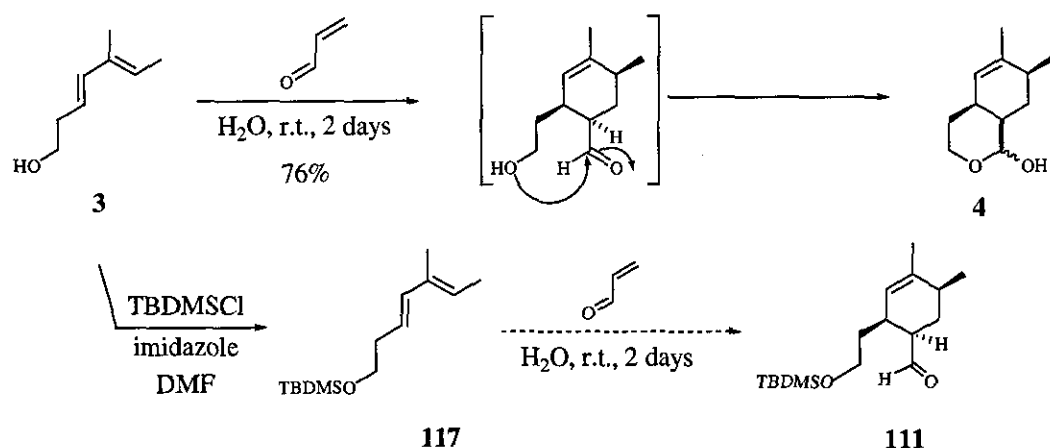
Scheme 88

The first step was to protect the primary alcohol of the compound **3** before trying the Diels-Alder reaction.

2.4.1.3.1. Protection of the hydroxyl in compound 3

Formation of silyl ethers, especially the more sterically demanding variants, is a standard method for protecting alcohols. The popular bulky *tert*-butyldimethylsilyl group was chosen to be the protecting group. This group is widely used and is stable except towards acid hydrolysis or in the presence of fluoride ions.[96] The protected product **256** was obtained in a 65% yield by using *tert*-butyl dimethylsilyl chloride (1.1 equiv.) and imidazole in large excess (3 equiv.) (Scheme 89).
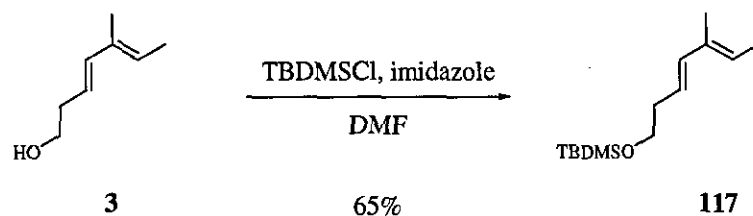
Scheme 89

The protection of the alcohol ensures that the formation of the hemiacetal **119**, obtained during the reaction between **3** and acrolein **118**, does not occur. Thus, the regiochemistry would not be fixed during the Diels-Alder reaction and both **111** and **120** would be produced (Scheme 90).

3	**119**	**4**
118	regiocontrol	single regioisomer formed

but:

117	**118**	**111**

and   +

117	**118**	**120**
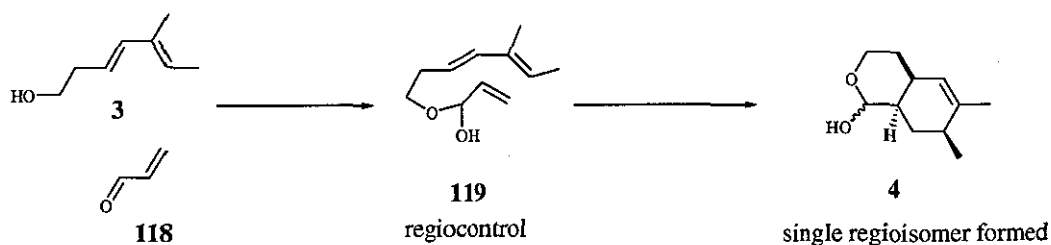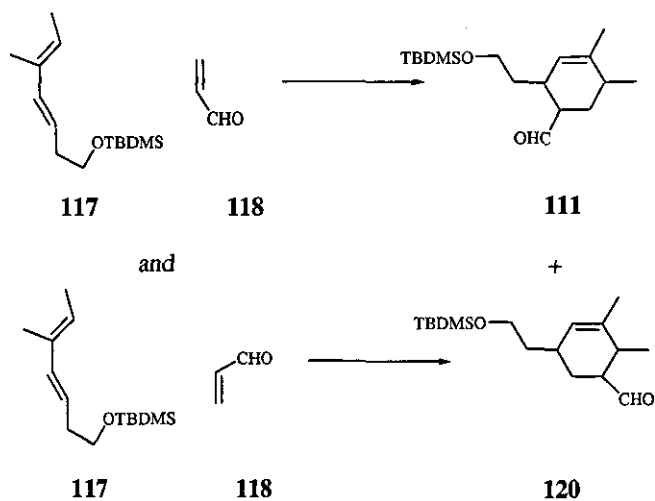
Scheme 90

2.4.1.3.2. The Diels-Alder reaction attempts

Water was maintained as the solvent in order to force the hydrophobic reactants into a compressed transition state (section 2.1.3.4.) Diels-Alder reactions were attempted but no cycloaddition occurred (Scheme 91).
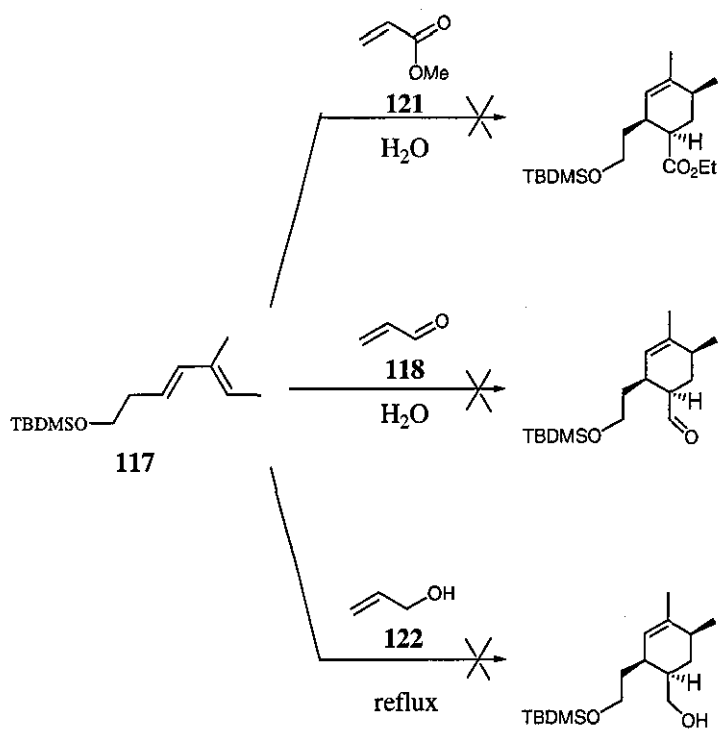
Scheme 91

Using acrolein **118** or even methyl acrylate **121** led to recovery of starting materials. Allyl alcohol **122** used as the solvent was also a failure. In consequence, we understood that the formation of the hemiacetal followed by oxonium ion formation represented a key requirement of the reaction.

2.4.2. Trapping the open chain isomer

Nevertheless, the open chain isomer **4a** exists in equilibrium with the ring-closed lactol **4** (Scheme 92).
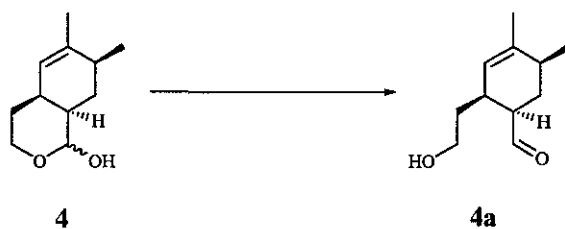
Scheme 92

Trapping the open chain isomer **4a** was our new target.

2.4.2.1. Ring opening by protection of the alcohol

Two examples of an opened ring lactol isomer trapping by protection of the alcohol were found in the literature (Scheme 93).

4
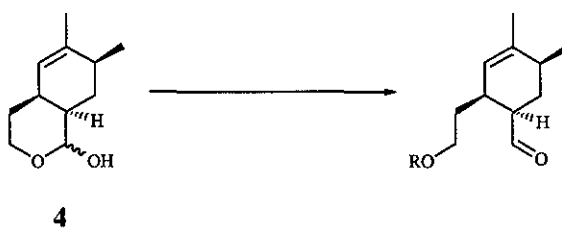
Scheme 93

2.4.2.1.1. Method used by Nicolaou

The first method was reported by Nicolaou, during studies towards the total synthesis of antibiotic X-14547A. It involved the treatment of a lactol **123** with *tert*-butyl dimethylsilyl chloride and imidazole (Scheme 94).[97]

123
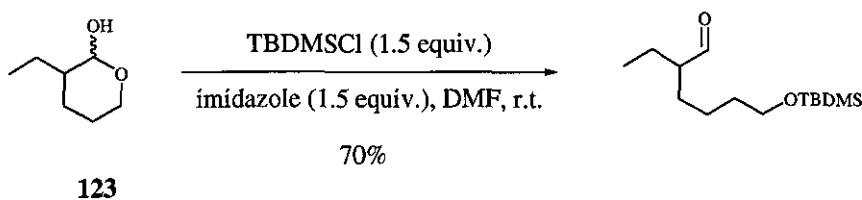
Scheme 94

The conditions used by Nicolaou were repeated, but the reaction furnished the lactol silyl ether **124** in 85% yield and not the silyl ether aldehyde **111** targeted. The expected faster reaction of the open-chain isomer did not occur even by reducing the temperature of the reaction (Scheme 95).
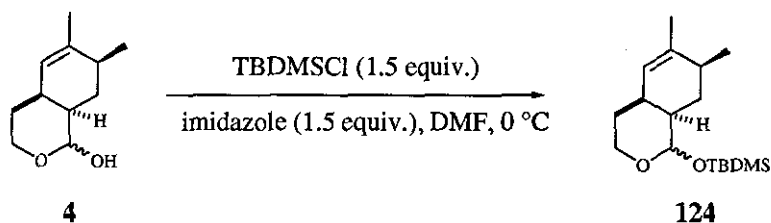
Scheme 95

2.4.2.1.2. Method used by Hatakeyama

The second method was reported by Hatakeyama *et al.* in their synthesis of (-)-pyrenophorin. The reaction of a lactol **125** with the phosphonoacetate **126** leads directly to formation of an aldehydophosphonoacetate **127** because the aldehydoalcohol **125a** can undergo the esterification reaction much faster than the lactol **125**, presumably due to steric reasons (Scheme 96).[98]
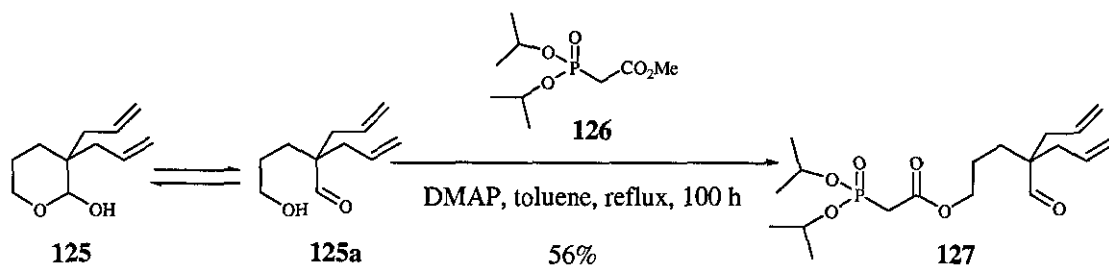
Scheme 96

The method was repeated several times on our substrate. Lactol **4** was allowed to react with **126** (1.2 equiv.) in the presence of a catalytic amount of 4-DMAP in refluxing toluene for 2 weeks. The evolution of the reaction was monitored by TLC, which indicated that no reaction had occurred even after two weeks (Scheme 97).
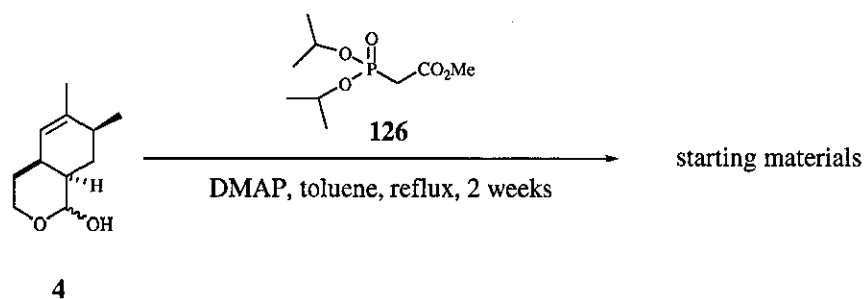
Scheme 97

2.4.2.2. Ring opening by reaction of the carbonyl group

As an alternative to protection of the hydroxyl group of the ring-opened hydroxy aldehyde, we decided to investigate reaction of the carbonyl group.

2.4.2.2.1. Thioacetalisation

Two routes, leading to open chain thioacetals **128** and **130** were envisaged (Scheme 98).
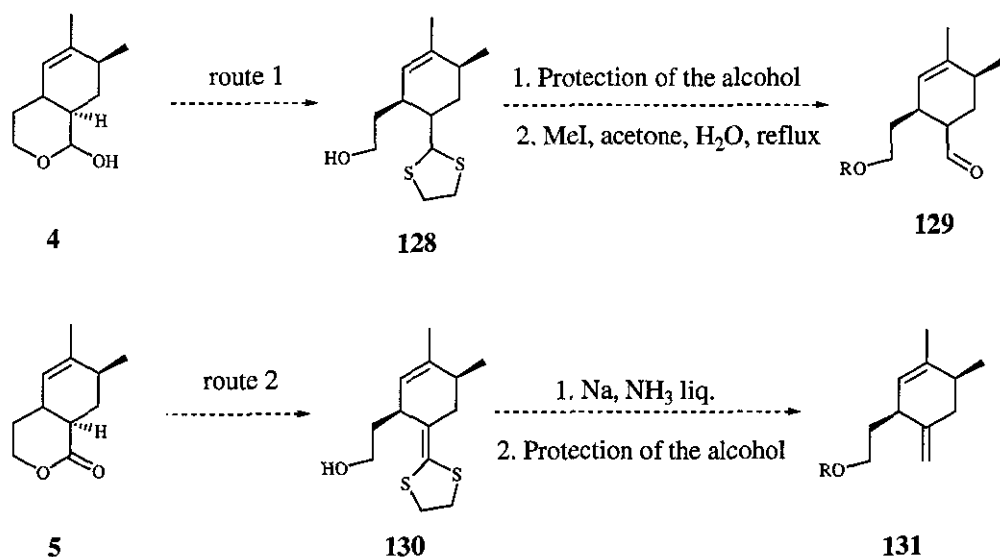
Scheme 98

Route 1 was inspired by Paquette and Fetizon. The thioacetal **128** would be converted into the parent aldehyde **129** for example by methyl iodide in moist acetone according to the mechanism shown in Scheme 99,[99,100] or by other thioacetal hydrolysis protocols.
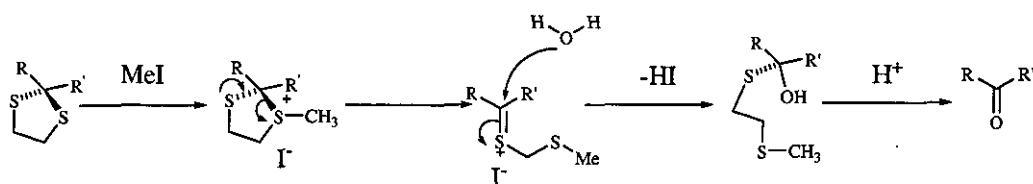
Scheme 99

Route 2 would afford compound **131** which could allow for a subsequent chelated epoxidation and deprotection to presumably afford a mix of **132** and **133**. Protection of the hydroxy group of the isolated **132**, followed by aqueous acidic treatment, would generate the dihydroxy compound **134**. The subsequent oxidation of the primary alcohol and deprotection of the protected hydroxy group would then give **9** (Scheme 100).
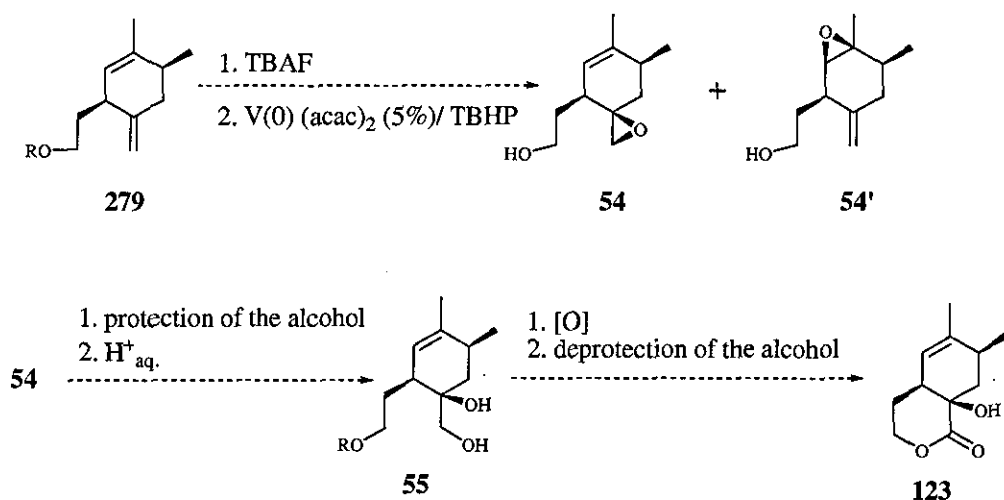
Scheme 100

Nevertheless, the deprotection in route 2 (Scheme 98) involves a Birch reaction to give compound **131**. This kind of reaction has not been reported in the literature. Also, this route requires the formation of lactone **5** from lactol **4**, therefore route 1 was shorter and was first investigated.

Dithiols were used because they are more likely to capture the masked aldehyde as a ring-opened thioacetal than diols, due to the stronger nucleophilicity of sulfur compared with oxygen.

A Lewis acid is usually used as the catalyst of the reaction. Most of the examples found in the literature use boron trifluoride etherate. Such protocol was related by Roush *et al.* in their synthesis of verrucarol, a natural product possessing a skeleton common to the trichlorotercene family of terpene antibiotics (Scheme 101).[101]

96%
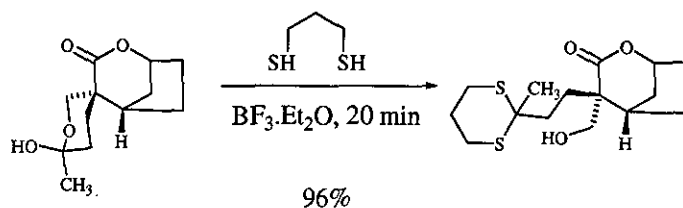
Scheme 101

These conditions proved to be ineffective for our substrate **4**, and led to recovery of the starting material. In order to improve the process, we envisaged that Lewis acids based upon titanium reagents, capable of forming covalent bonds with oxygen and with thiols, with which titanium generates octahedral complexes, would probably best suit our purpose.[102] Studies achieved by Paquette and Page[100] showed that such more forcing conditions are required in order to cleave the endocyclic carbon-oxygen bond of γ-lactols, frequently recalcitrant to ring opening (Scheme 102).[103,104]

BF$_3$·Et$_2$O	100	0	92 %
TiCl$_4$	0	100	85 %
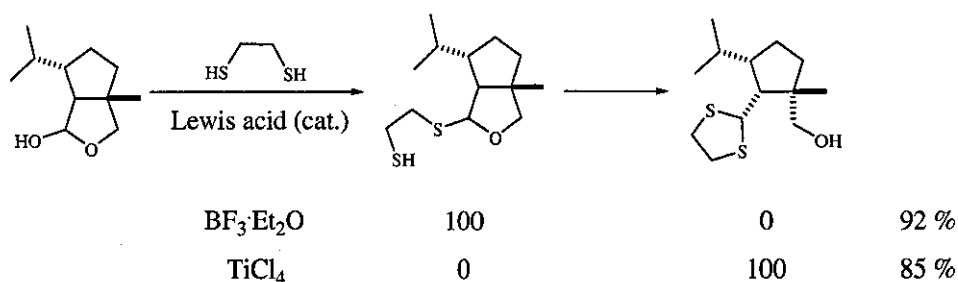
Scheme 102

Replacement of the Lewis acid, however, did not give any more results and no reaction was observed when using either boron trifluoride etherate or titanium tetrachloride (Scheme 103).
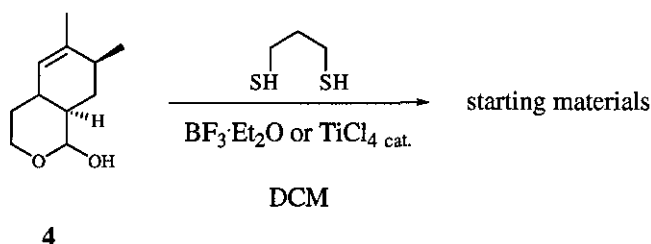
Scheme 103

In the example depicted in Scheme 102, ethanedithiol has been used. It is a better reactant than propanedithiol due to the kinetically-favoured formation of five-membered rings over six-membered rings as a result of entropic, enthalpic and

stereoelectronic factors.[105] A reaction involving ethanedithiol and titanium tetrachloride was therefore attempted. The lactol ring cleavage was unfortunately not obtained, and only the compound **135** was afforded. The reaction was attempted with hydrochloric acid (6M) at room temperature in place of titanium tetrachloride, as exemplified by Peng *et al.*,[106] but the same product **135** was obtained in similar yields (Scheme 104).
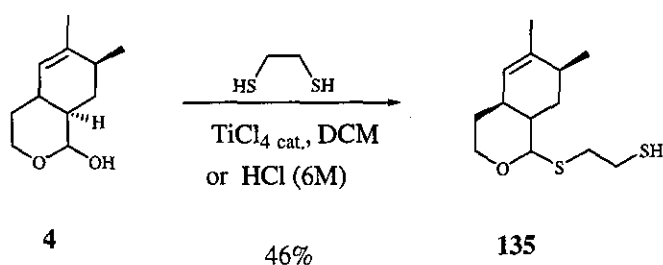
Scheme 104

The conversion of **135** to **128** was attempted by treating **135** with aluminium chloride. The reaction was carried out in dichloromethane or chloroform in compliance with the conditions used by Paquette, Page *et al.*[107] Even under *reflux in toluene (in order to increase the temperature of reaction), the ring opening did not occur.*

An alternative procedure was therefore considered: the formation of ketene dithioacetal **130** by reaction of lactone **5** with a *bis*-dimethylaluminium salt **136**, which is an activated derivative of alkanedithiol (Scheme 105).[108,109]
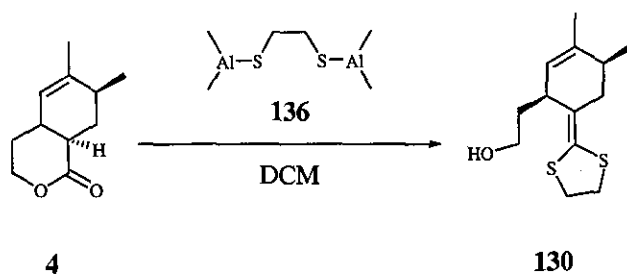
Scheme 105

The reaction between ethanedithiol **137** and trimethyl aluminium, reported by Corey,[110,111] affords the very reactive species **136** (Scheme 106).
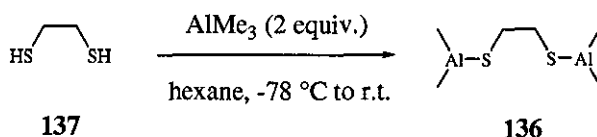
Scheme 106

Unfortunately, reaction of **136** with lactone **5** was unsuccessful and the scheme was discontinued.

2.4.2.2.2. Formation of an oxime

We next proposed ring-opening of lactol **4** by formation of the oxime **138** (Scheme 107).
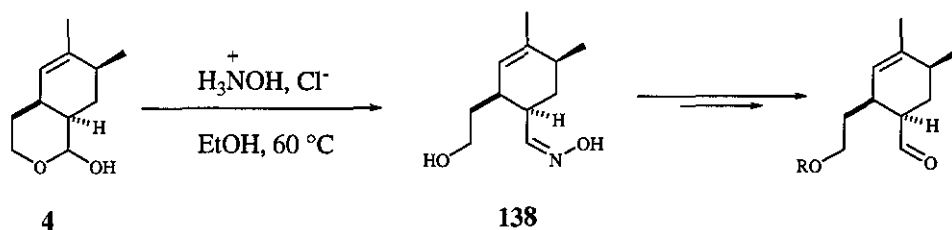
Scheme 107

Dorsey *et al.* used this pathway in their synthesis of glycosylamines (Scheme 108).[112]
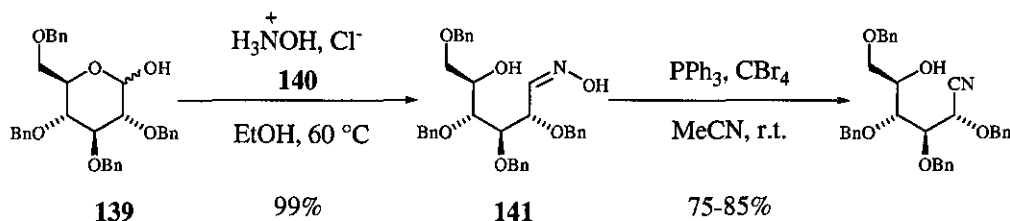
Scheme 108

The conversion of the tetra-*O*-benzylglucose **139** into the corresponding oxime **141** was almost quantitative. The dehydration under conditions described by Vasella was the next step.[113] The procedure of oxime giving nitrile was repeated on the lactol **4**.

The hydroxylamine hydrochloride salt **140** (1.6 equiv.) was added at 60 °C to a stirred solution of sodium in 96% aqueous ethanol, followed by addition of the substrate **4** (1.65 mmol). A complex mixture of products was formed. It seems that the substrate was decomposed. Less forcing conditions, avoiding the heating, still gave decomposition products (Scheme 109).
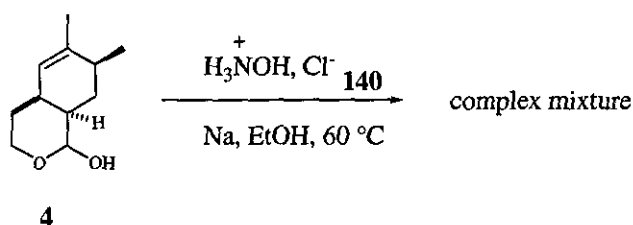
Scheme 109

Both aldehyde and alcohol had trapping failed. The next plan was based on nucleophilic attack of the carbonyl group by the phosphite **142** (Scheme 110).

2.4.2.2.3. Nucleophilic addition of a phosphite to the carbonyl
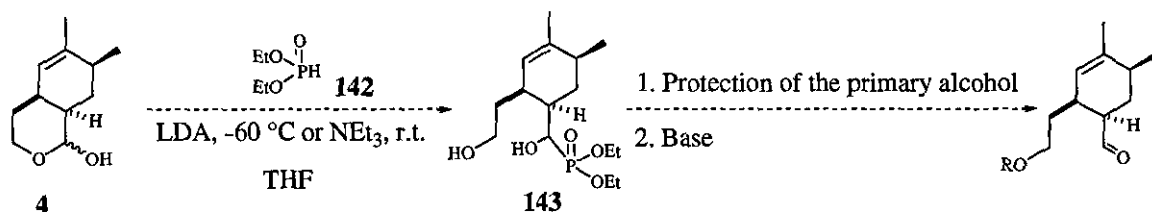
Scheme 110

The first step of the reaction sequence involves the addition of a phosphite **142** to a carbonyl group and is known as the Abramov reaction. Wróblewski *et al.* reported an efficient Abramov reaction procedure in their search for structural analogues of

76

paclitaxel, an important anti-cancer agent used for the treatment of various tumours (Scheme 111).[114]

Scheme 111

(EtO)$_2$P(O)H, NEt$_3$	65%	75	:	25
(EtO)$_2$P(O)H, LDA	90%	70	:	30
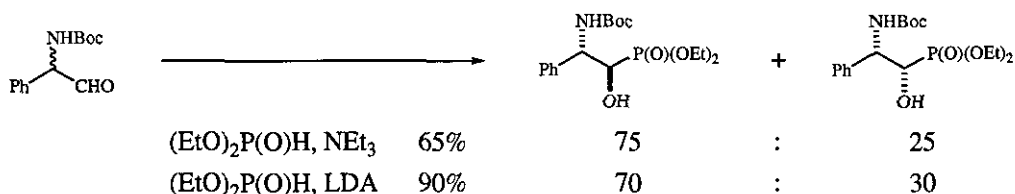
The coupling of diethyl phosphite and the aldehyde is usually carried out in the presence of triethylamine. Employing lithium diethyl phosphonate gave a drop of diastereoselectivity but afforded better yield, which is precisely our aim.

Both of these protocols were reported by Wróblewski *et al.* and tested on lactol 4.[115] The first procedure was to simply mix lactol 4, diethyl phosphite 142 ($\delta_P \approx$ 7.8 ppm) and triethylamine, which were stirred at room temperature for 24 hours.

The second protocol consisted of cooling a solution of lactol 4 in tetrahydrofuran to -78 °C and adding dropwise a solution of lithium diethyl phosphonate in tetrahydrofuran at -78 °C). The reactions were monitored by ^{31}P NMR spectroscopy. After one day the ^{31}P NMR spectroscopy disappointingly, revealed only the presence of the starting material 142 (δ_P = 7.8 ppm) (Scheme 112).
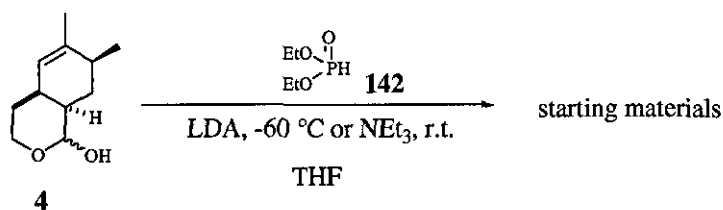
Scheme 112

The failure of the Abramov reaction led us to try a modified procedure, commonly known as the Pudovic reaction.

Diethyl phosphite **142** in dichloromethane was silylated with trimethylsilyl chloride in the presence of triethylamine at 0 °C to produce a nucleophilic phosphorus species, diethyl trimethylsilyl phosphite **144** (δ_P = 117.3 ppm) (Scheme 113).[116]
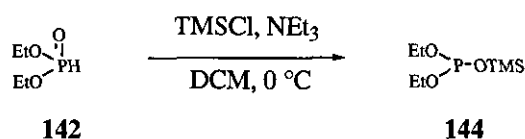
Scheme 113

144 was allowed to react overnight with lactol **4** (2.05 mmol, 0.7 equiv.) in refluxing dichloromethane.[117] ^{31}P NMR spectroscopy did not reveal anything else apart from the starting material **144** (Scheme 114).
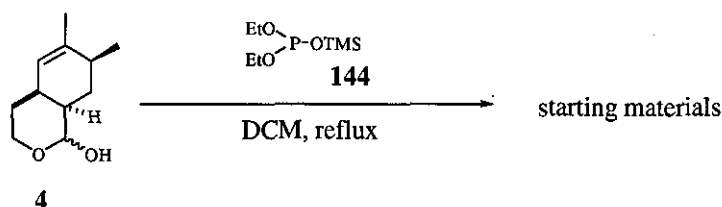
Scheme 114

This route was abandoned after the first step, as neither of the two protocols gave any promising results. The Wittig reaction was the last rraction on the carbonyl group attempted and showed more success as it as been reported in the next section.

2.5. Two new routes leading to intermediates 111 and 112

A new strategy, however, allowed the opened ring to be trapped. The open chain isomer could now finally be obtained using the two methods in Scheme 115,

leading to compounds **111** and **112** precursors of **9** (section 2.4.1.3.) (Scheme 115).
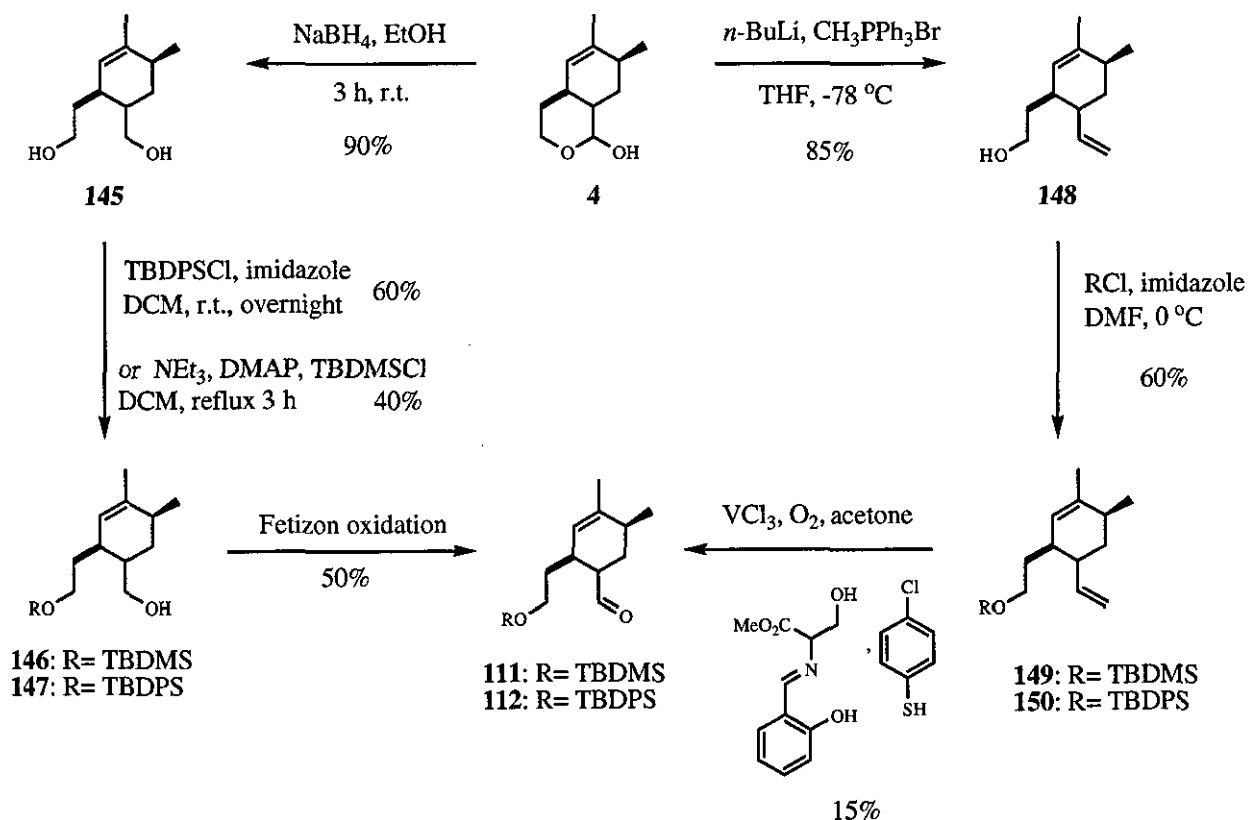
Scheme 115

Reduction of the open chain isomer of **4** allowed the formation of the diol **145**. Selective protection of one of the primary alcohols gave **146** or **147**. Finally, the *oxidation of these compounds gave respectively 111 or 112.*

Wittig reaction on the open chain isomer of **4** afforded compound **148**. The alcohol functionality was protected to give **149** or **150**. A selective oxidation of these compounds led to **111** or **112**.

2.5.1. Formation of 111 and 112 through route 1
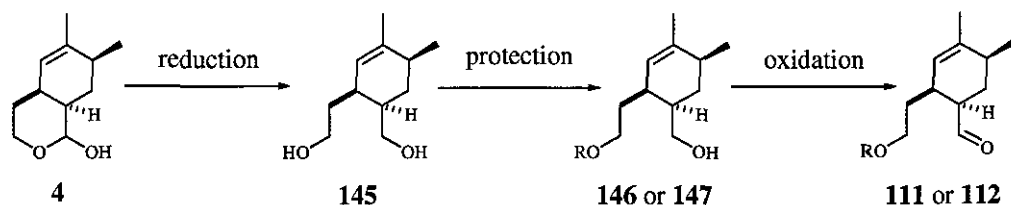
Scheme 116

2.5.1.1. Ring opening by simple reduction of 4

Ring opening of lactols by reduction has been reported in numerous literature examples using various conditions (Scheme 117).[118]
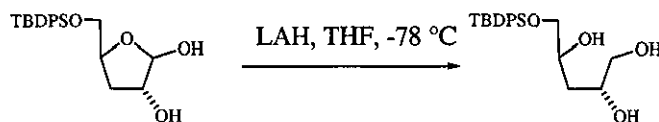
Scheme 117

The first route began with the reduction of the lactol **4**. Use of lithium aluminium hydride in tetrahydrofuran at 0 °C, could perform this task. However, the hazard linked to the use of this powerful reducing agent and the messy aqueous work-up using sodium potassium tartrate, was avoided by a reduction using sodium borohydride instead (Scheme 118).
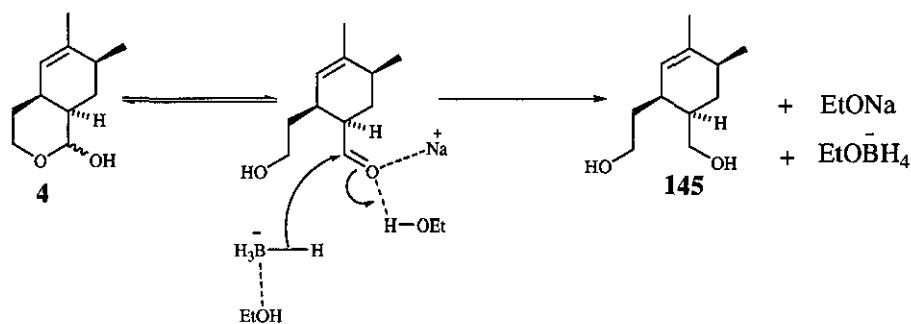
Scheme 118

This much weaker hydride donor allowed an easier procedure and work-up. The expected diol **145** was obtained with 90% yield after filtration though silica gel (Scheme 119).
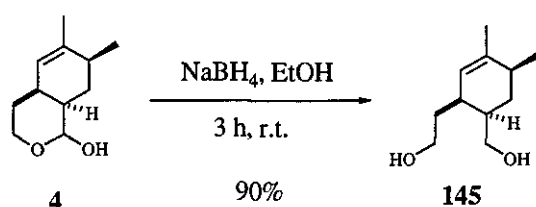
Scheme 119

2.5.1.2. Selective protection of the less hindered hydroxy group of 145
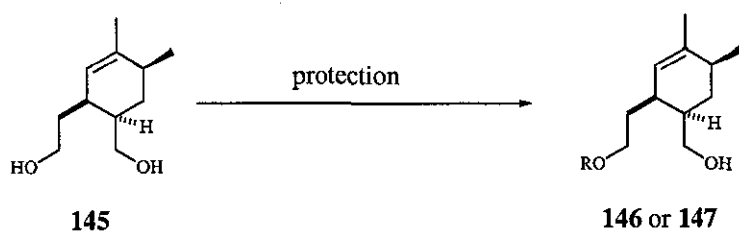
Scheme 120

The selective protection of one of the hydroxyl functionalities was essential in our strategy. The next step involved the oxidation of the least hindered alcohol closest to the ring. The other alcohol had to be protected first so it was not also oxidised (section 2.5.1.2.).

The selective protection of one hydroxyl group in the presence of another can often be readily achieved. This process, however, becomes more complicated if the hydroxyl groups are similar. The diol **145** indeed possesses two primary alcohols. Nevertheless, the particular hydroxyl group that we aimed to protect is

81

sterically more accessible and might be differentiated from the other hydroxyl group (Figure 8).

145
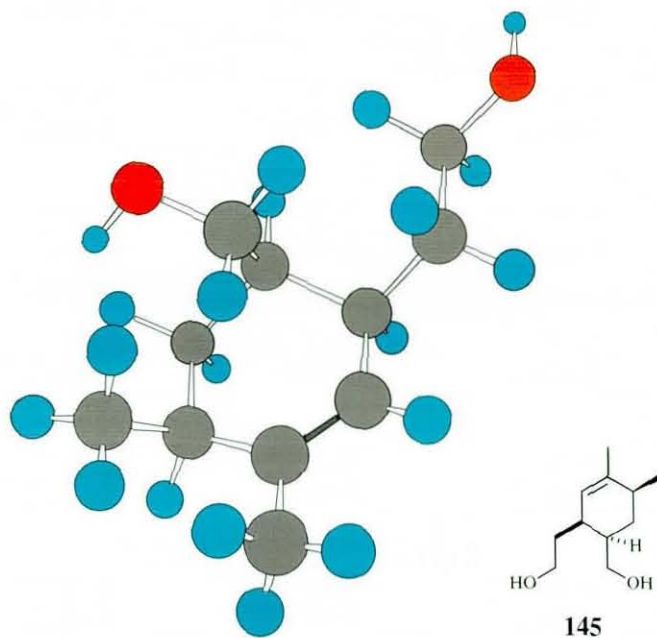
Figure 8

Only few methods are described in the literature, which are predominantly based on the use of silyl reagents. The O-alkylsilyl ether protective groups are stable under oxidative conditions and the desilylation does not affect other functionalities, such as alkenes or enol ethers, which is essential in order for us to complete the next steps.

Three methods had shown potential in the literature:

- Pearson *et al.* used *tert*-butyl dimethylsilyl ether as protecting group in the context of a synthesis of (-)-slaframine, a substance with potential beneficial effects on ruminant digestive functions (Scheme 121).[119]
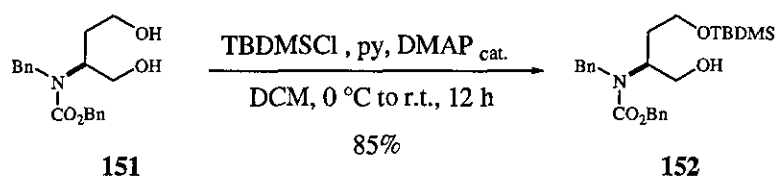
Scheme 121

Selective silylation of **151** leading to **152** occurs presumably because of the differing steric and electronic environments of the two hydroxyl groups.

As well as Pearson, Oestreich *et al.* achieved a regioselective silylation, using refluxing dichloromethane as solvent. Compound **153** led to **154** in a 76% yield (Scheme 122).[120]
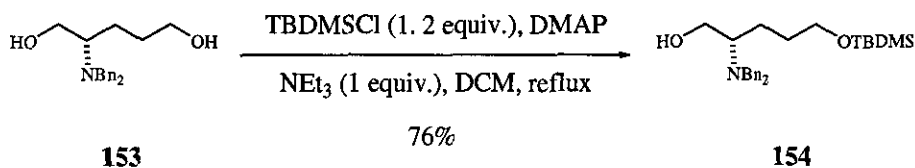
Scheme 122

We applied these reactions to the diol **145**.

Monoprotected diol **146** and diprotected diol **155** were obtained in a 2:1 ratio with similar yields. The second method, which uses triethylamine and dichloromethane under reflux, has the advantage of being much faster (only 3 hours, against 18 hours for the method used by Pearson) (Scheme 123).
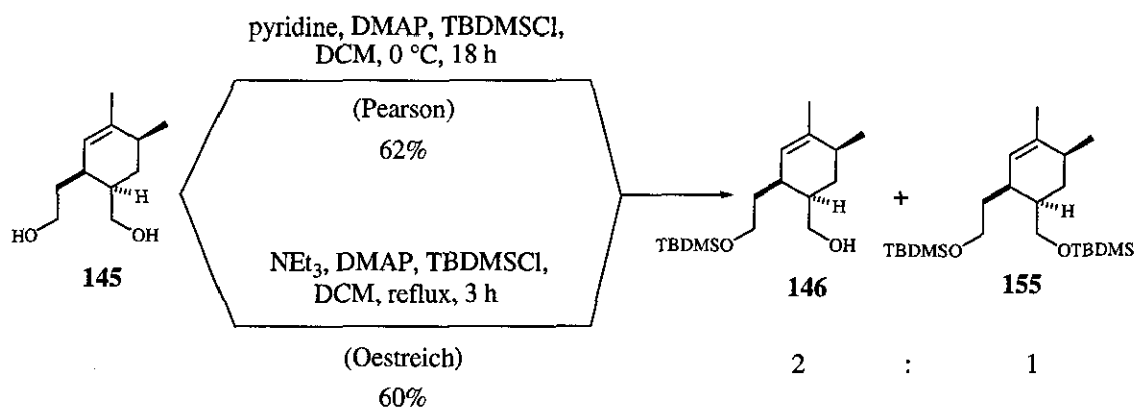
Scheme 123

We aimed to improve the degree of selectivity in this reaction. With this in mind, *tert*-butyl diphenylsilyl chloride proved it was the ideal reagent, as it allowed us to improve the regioselectivity of the silylation by following the protocol reported by Walton *et al.* (Scheme 124).[118]
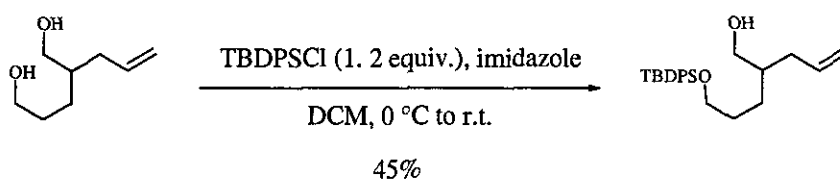
Scheme 124

This can be explained by considering that TBDPS is a larger silyl protective group than TBDMS. The steric repulsion effect is significantly increased and the regioselectivity will increase as well. Dilution, temperature and the rate of addition of *tert*-butyldiphenylsilyl chloride were optimised to give a final 3:1 ratio in favour of the monoprotected adduct **147** and 20% of recovered starting material. We obtained a 60% yield of **147** (Scheme 125).
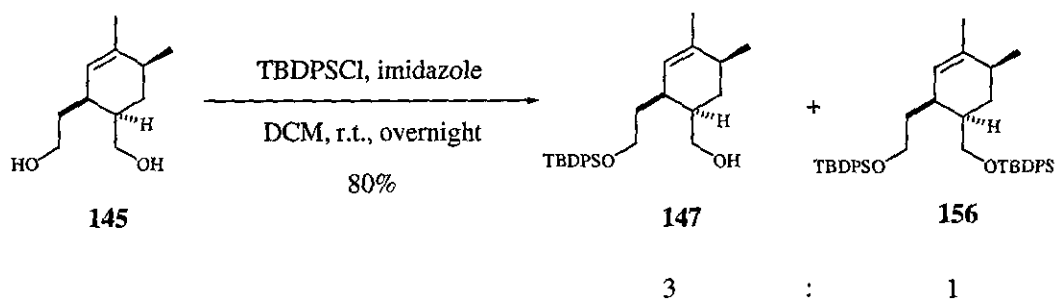
Scheme 125

Diol **145** was recovered efficiently by deprotecting compounds **155** and **156** using *tetra*-butyl ammonium fluoride (Scheme 126).

155: R=TBDMS 75%
156: R=TBDPS 82%
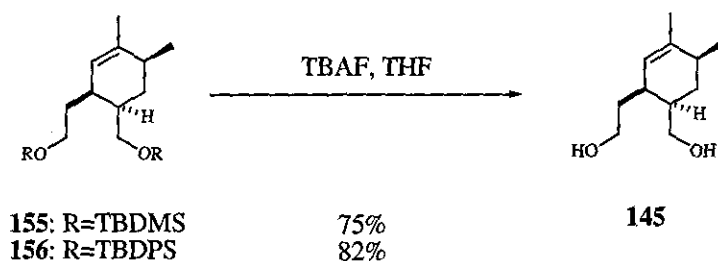
Scheme 126

2.5.1.3. Attempts to synthesise 131

As we proceeded with route 1, we ventured a shortcut in the synthesis of **9** (see Scheme 100). The first step of the strategy was to successfully synthesise **131** (Scheme 127).
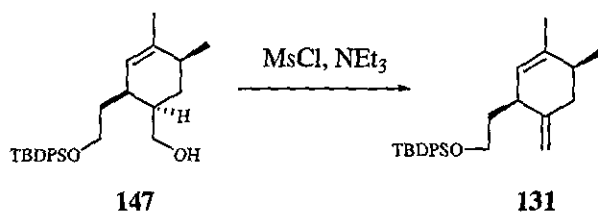
Scheme 127

The elimination reaction from **147** to **131** was carried out according to the reaction conditions used to synthesise **64** (section 2.3.2.1.). No reaction occurred when mesyl chloride followed by triethylamine was added to a solution of the alcohol **147** (Scheme 128).
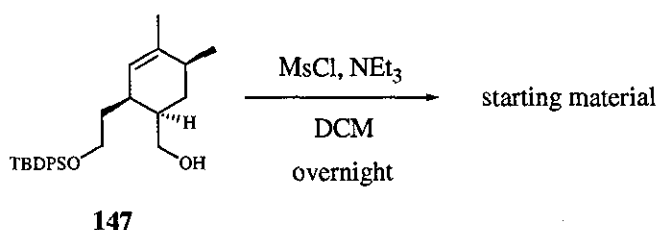
Scheme 128

After several unsuccessful attempts, the formation of **131** was abandoned in favour of the synthesis of **112**.

2.5.1.4. Oxidation to the carbonyl 112

The last step of route 1 was the oxidation of **147** to **112**.
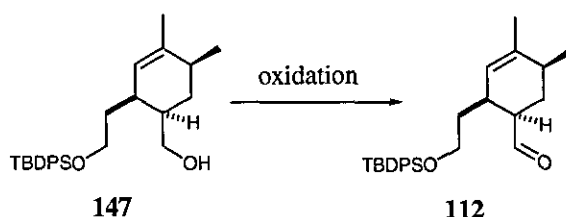
Scheme 129

Several different methods of oxidation, which will be described in the following section, were attempted. It was rather surprising to see that they led to only poor yields or even no reaction.

2.5.1.4.1. Oxidations using a stoichiometric amount or an excess of oxidant

2.5.1.4.1.1. Dimethyl sulfoxide oxidation procedures

The nucleophilic nature of the sulfinyl oxygen of sulfoxides has been used in the oxidation of primary and secondary alcohols into aldehydes and ketones with activated dimethyl sulfoxide.[121] Its use in the oxidation of primary alcohols to aldehydes has been particularly recognised. Pfitzner-Moffatt and Swern procedures were the two reactions attempted from the large variety of dimethyl sulfoxide oxidations. Oxysulfonium ylide **157** is the key intermediate of these procedures, as we report in the following section. It reacts intramolecularly to give the desired carbonyl product **158** (Scheme 130)

157   **158**
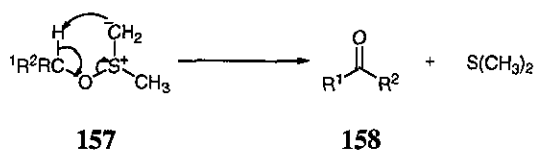
Scheme 130

The main advantage of Swern and Pfitzner-Moffatt procedures is the fact that they are carried out at low temperature (at -60 $^{\circ}$C and -78 $^{\circ}$C respectively). This allows one to minimise the formation of by-products, which consist mainly of methylthiomethyl (MTM) ethers **161**.

Formation of **160**, possible through dissociation of activated ylides **159** and subsequent alkylation of the alcohol, appears to be too slow to occur at low temperature (Scheme 131).[121]

159   **160**   **161**
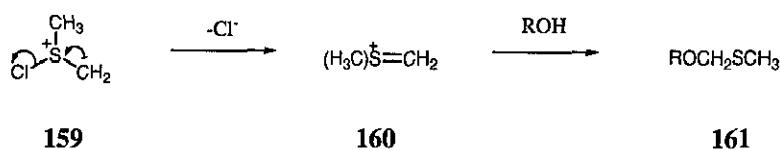
Scheme 131

This contrasts with other dimethyl sulfoxide oxidations, that use acetic anhydride,[122] pyridine/sulfur trioxide,[123] or phosphorus pentoxide,[124] which require higher temperatures and longer reaction times.

2.5.1.4.1.1.1. Swern oxidation

Swern oxidation was the first to be attempted. Two main reasons explain our choice. First, Swern oxidation, based on activation of dimethylsulfoxide by oxalyl chloride, has the advantage of low cost. Like activation with trifluoroacetic anhydride,[125] it usually gives better yields than other dimethyl sulfoxide oxidation procedures, and prevents the formation of trifluoroacetate.[126] Secondly, Swern oxidation affords relatively clean carbonyl compounds which can sometimes be used without purification to give high yields of products. Indeed, the side-products formed are carbon monoxide, carbon dioxide, dimethylsulfide and triethylamine hydrochloride. They are easily removed from the reaction mixture *in vacuo* (Scheme 132).
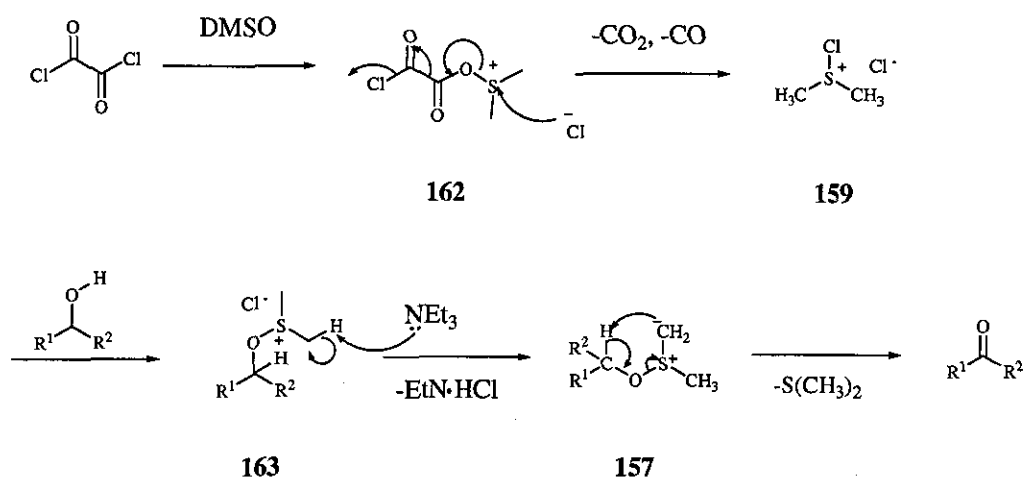
Scheme 132

The mechanism of Swern oxidation involves the formation of an initial adduct **162**, which collapses to a dimethylchlorosulfonium salt **159**. Reaction of **159** with

an alcohol at -78 °C produces the alkoxysulfonium ion **163**, which is converted into the product by reaction with an amine base to give ylide **157**, which undergoes a rearrangement. In our case, Swern oxidation gave no results at -78 °C, despite the fact that all reactants were distilled. The temperature of the reaction has been increased to -40 °C, the standard temperature for Swern oxidation, and triethylamine was replaced by diisopropylethylamine which, in some cases, allows the reaction to work. The reaction was still unsuccessful, and only starting material was recovered (Scheme 133).[127]

Scheme 133

2.5.1.4.1.1.2. Pfizner-Mofatt oxidation

The Pfizner-Mofatt reaction was then attempted. This choice may seem strange because it was the first reported reaction of this class of oxidation before the considerable improvements which led to the Swern oxidation. However, this reaction has been shown to be efficient in some cases where all other reactions of the same group have been unsuccessful.[121] The reaction requires the use of DCC **164**, which is by far the most used diimide. The large excess of DCC required leads to the biggest drawback of the procedure: the residue is difficult to remove during the work-up. The excess reagent can be converted by oxalic acid into the highly insoluble dicyclohexylurea, which is removed by filtration (Scheme 134).

Scheme 134

In this procedure, oxygen transfer occurs from DMSO to generate the dicyclohexylurea **165**. The reaction is completed by the intramolecular hydrogen transfer in **157** to give **158**. Unfortunately, the reaction did not occur in our case (Scheme 135).

Scheme 135
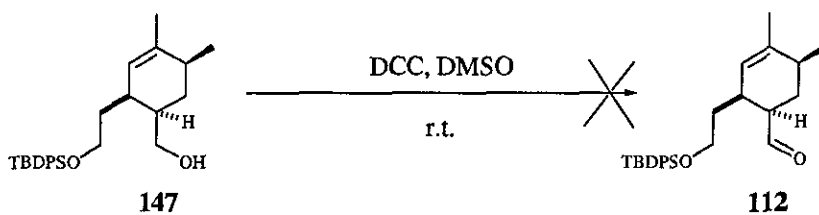
The cause of the ineffectiveness of these oxidations remains unknown, especially as we were working with a saturated primary alcohol. The high lability of the substrate or product may have caused this lack of success. As the dimethyl sulfoxide oxidations did not work, we next used the more vigorous conditions of chromium (VI) based reagents.

2.5.1.4.1.2. Oxidations using chromium (VI)

Comforted by its success (67% yield) in the oxidation of lactol **4** to lactone **5** (section 2.1.4.), we felt pyridinium dichromate (PDC) to be the reactant of choice.

Use of PDC or PCC (pyridinium chlorochromate) avoided the drastic or hazardous conditions of Jones, Sarett or Collins oxidations and their numerous drawbacks such as the labour to prepare the reagents, the tendency to overoxidise primary alcohols,[128]and the cost and problems of purification linked to the large excess of reagent used to achieve rapid reactions.

PDC   PCC

Figure 9

These chromium (VI) reagents are widely used and offer the advantages of commercial availability and effectiveness in near stoichiometric amounts. They oxidise alcohols to aldehydes and ketones when they are used as a suspension in methylene chloride or as a solution in N,N-dimethylformamide following the oxidation process presented in Figure 10.

R_2CHOH	+	Cr (VI) ⟶	R_2CHO	+	Cr (IV)
R_2CHOH	+	Cr (IV) ⟶	$R_2\dot{C}OH$	+	Cr (III)
$R_2\dot{C}OH$	+	Cr (VI) ⟶	R_2CHO	+	Cr (V)
R_2CHOH	+	Cr (V) ⟶	R_2CHO	+	Cr (III)

Figure 10

Both methylene chloride and *N,N*-dimethylformamide were tried as solvents for PDC and PCC reactions.

To prevent overoxidation at room temperature, association of PDC (0.7 equiv.) with acetic anhydride (3 equiv.) in DMF or DCM as co-solvent gave rise to a strong but mild, neutral oxidant.[129] Both conditions led to similar results. Dichloromethane was adopted because it is easy to remove *in vacuo* at the end of the reaction. These conditions afforded the aldehyde **112** in only 10% yield in the best attempt. The rest of the material was mostly some unreactive starting material (Scheme 136).
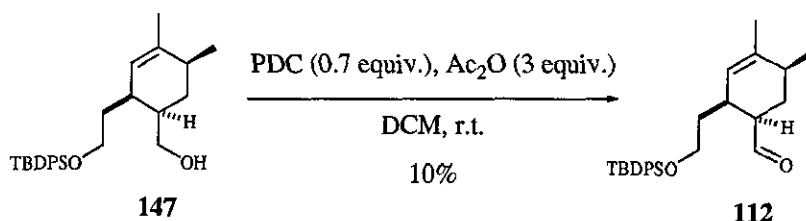
Scheme 136

PDC is much milder oxidizing agent than PCC, and is complementary to PCC for alcohols containing acid-sensitive groups. Nevertheless, PCC gave the aldehyde **112** without oxidizing the silyl-protected alcohol.

To achieve the reaction, the PCC suspension was buffered by the use of sodium acetate. We also added molecular sieves, known to give rate enhancement of the reaction, and this allowed us to work under less drastic conditions than the reflux in toluene.[130,131] The reaction did not occur in dichloromethane but afforded the aldehyde **112** in 8% yield when PCC was dissolved in DMF (Scheme 137).
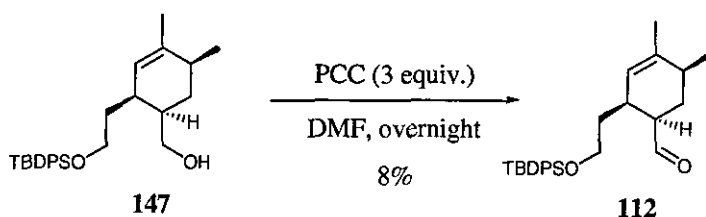
Scheme 137

After the disappointing result of the DMSO oxidation attempts, the more powerful chromium reagents PCC and PDC gave poor 8% and 10% yields. Problems inherent to the difficulties in product isolation because of the formation of insoluble chromium salts may have contributed to the poor yield of **112**, despite the improvements made in their elimination during the oxidation of **4** (section 2.1.4.). In addition, the moderately high cost of these reagents led us to try other oxidations.

2.5.1.4.1.3. Frémy's salt (F.S.) oxidation

Frémy's radical (potassium nitrosodisulfonate) **166** is a widely used reagent. It is particularly valuable for oxidizing phenols, naphthols or anilines to the corresponding quinones.[132-136] It is also known to be an oxidant for conversion of benzylic alcohols to aldehydes and of amino acids to α-keto acids.[137] The nitrosodisulfonate radical anion **167** is one of the most long lived nitroxyl radicals. This radical, purple in solution, is formed by virtually complete homolysis of its commercially available orange solid dimer **166**, called Frémy's salt which dissolves in polar solvents (Scheme 138).[138]

$$4 \text{ K}^+, [(O_3S)_2NO-ON(SO_3)_2]^{4-} \longrightarrow 2[\cdot ON(SO_3)_2]^{2-} + 4 \text{ K}^+$$

166 **167**

Scheme 138

Because of its radical character, Frémy's salt is a rather unstable compound. It was stored in a desiccator in the presence of ammonium carbonate to provide an ammoniacal atmosphere, limiting the hazards of spontaneous decomposition resulting in a violent explosion. The decomposition is dependent on the hydrogen ion concentration. Therefore, a control of the pH was necessary. To this end, a range of buffers (mainly sodium carbonate pH 10, phosphate buffer pH 7.2) was used in all our reactions. Unfortunately, even under the most favourable conditions, using a large excess of Frémy's salt (6 equiv.) and a reaction time of one week, no results were obtained and the starting material **4** was recovered. Addition in two batches of Frémy's salt did not affect the result. The process is shown in scheme 139. [136,137,139]

$$S\text{-}H \xrightleftharpoons{F.S.} S\cdot + HON(SO_3K)_2$$

$$\downarrow F.S.$$

S = substrate

$$S_{ox}$$
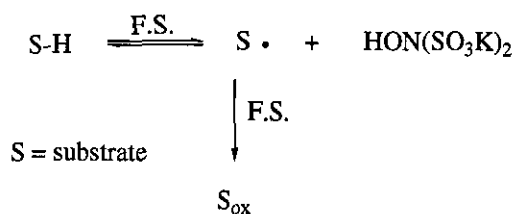
Scheme 139

Despite all our efforts, the oxidation did not occur (Scheme 140).
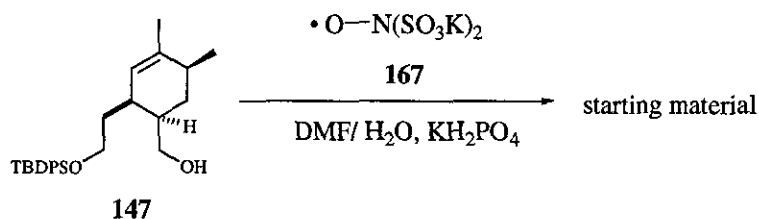
Scheme 140

2.5.1.4.1.4. Oxidation using hypervalent iodine (V) reagents

Our interest was next focused on hypervalent iodine (V) derivatives. Organic chemists are increasingly appreciating the oxidizing properties of such compounds because they are mild, they prevent from using possibly toxic or expensive metals, and they do not produce toxic or noxious by-products.

2.5.1.4.1.4.1. Oxidation with Dess Martin Periodinane

The most famous hypervalent iodine (V) reagent is the Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one) (DMP) **169**.
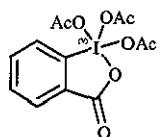
DMP

169

This method, involving DMP, has attracted particular attention because it has several advantages over other commonly employed oxidizing reagents, such as chromium (VI) and dimethylsulfoxide. It has found a wide acceptance for the selective oxidation of primary and secondary alcohols to carbonyl compounds.[140] It is also one of the mildest reagents available for the conversion of alcohols to carbonyls. It is used in nearly stoichiometric amounts and offers simple work-up. Thus it provides an alternative of great value. The mechanism is not fully understood but involves first an exchange of an acetate ligand on the iodine with the alcohol. The intermediate then collapses to form the carbonyl compound, a reduced iodine compound, and acetic acid.

This method gave good results on a large scale, and afforded 26% of carbonyl compound **111** and 30% of carbonyl compound **112** without any modification in the procedure. The rest of the material was mostly some unreactive starting material (Scheme 141).

| 146 | R = TBDMS | 26% | 111 |
| 147 | R = TBDPS | 30% | 112 |
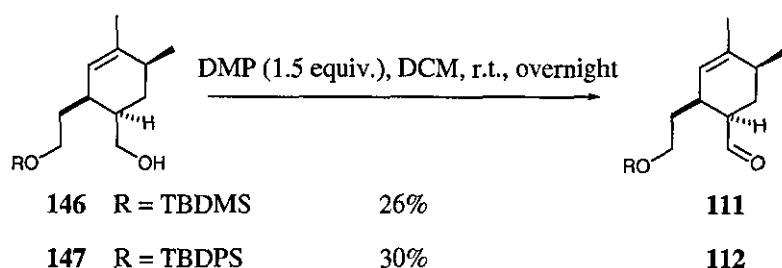
Scheme 141

The yield was improved by 5% and the scale by 6.8 times by using freshly prepared reagent (following a modified route associating the Ireland[141] and Schreiber[142] preparations of DMP). This preparation involves the formation of the IBX intermediate which can also be used as an oxidant.

2.5.1.4.1.4.2. Oxidation with IBX

In the same range of compounds derivate from *o*-iodoxybenzoic acid, 1-hydroxy-1,2-benziodoxol-3-one-1-oxide (IBX) **168** represents a new oxidizing reagent, inexpensive to prepare, easy to handle, which can tolerate moisture and water, and generally gives very good yields. This iodinane oxide is a direct precursor of DMP **169** (Scheme 142), and shares with it the fact that they oxidise primary alcohols to aldehydes without overoxidation to carboxylic acids.[140,143]

IBX   DMP

168   **169**
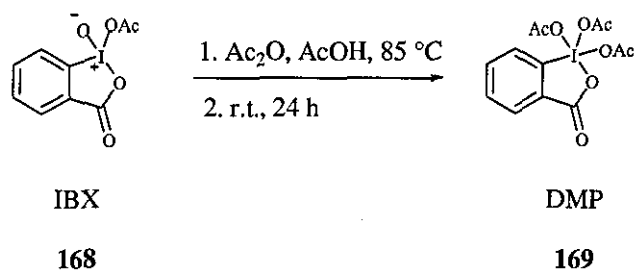
IBX and DMP are explosive when dried

Scheme 142

IBX is highly insoluble except in polar aprotic solvents as DMF or DMSO. It is then capable of oxidation at room temperature in few hours.[144] A possible mechanism for the oxidation of alcohols by IBX is based on a two-step reaction mechanism involving a fast pre-equilibrium step leading to an alkyloxyiodinane oxide **170**, the reactive intermediate, with concomitant release of a water molecule through a process of ligand exchange at iodine, followed by a rate determining step giving iodosobenzoic acid **171** as shown in Scheme 143.[140]

170

alkoxyiodinane oxide

171

IBA : iodosobenzoic acid
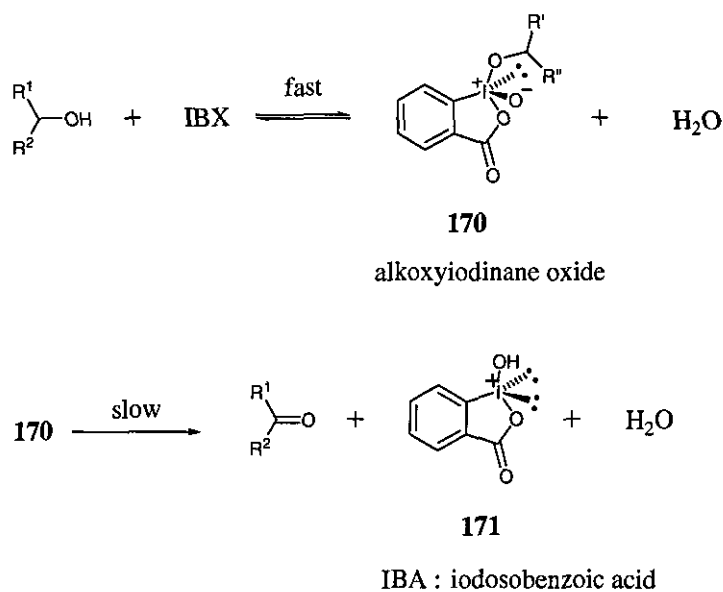
Scheme 143

IBX was found to be less reactive than DMP, and the best result, obtained by using DMSO as a solvent, afforded 11% of aldehyde **112** (Scheme 144).
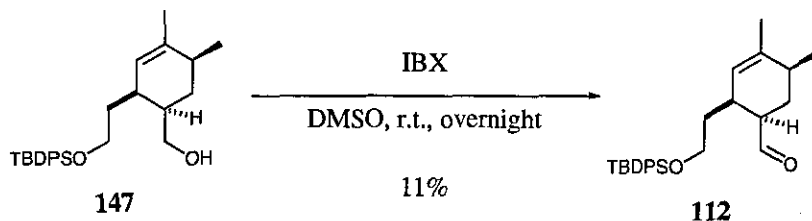
Scheme 144

This yield was obtained on 0.64 mmol of substrate **147**; as soon as we tried to scale–up the reaction, yields dropped significantly. IBX could thus not replace DMP oxidation.

2.5.1.4.1.5. Oxidation of alcohols by silver carbonate on Celite® (Fetizon reagent)

The advantages of this reagent lie in its selectivity, the mild conditions necessary to carry out the oxidation, and the ease with which the products can be isolated by simple filtration of the oxidising salt.[145,146] The reaction can be schematised as follows (Figure 11).

$$A + F_o \rightleftharpoons A\text{-}F_o \longrightarrow P\text{-}F_r \rightleftharpoons P + F_r$$
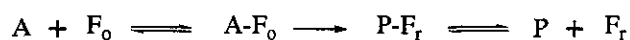
Figure 11

The letter A represents the free alcohol in solution, P a molecule of the product, and F_o and F_r the oxidised and reduced forms of the silver carbonate reagent. Consequently, A-F_o represents the adsorbed alcohol on the oxidised form of the reagent and P-F_r the adsorbed product on the reduced form of the reagent.

The mechanism postulated for this reaction is presented below (Scheme 145)
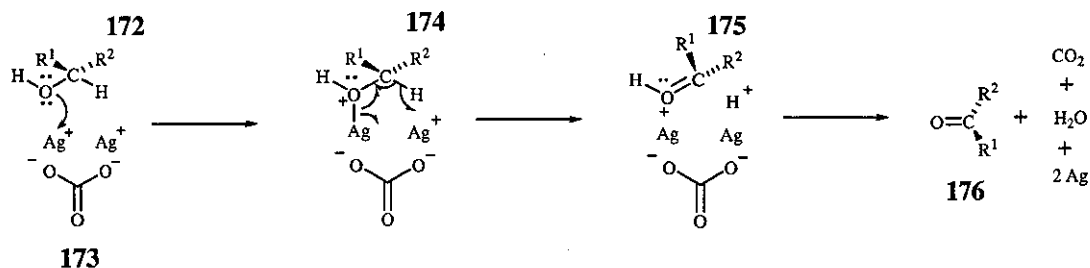
Scheme 145

After the reversible adsorption of the alcohol **172** on the surface of the oxidant support **173** the oxygen electrons form a bond with the silver ions to give **174**, and carbon-hydrogen bond is orientated so that the HCOH groups are coplanar and perpendicular to the silver carbonate/Celite® surface. A concerted shift of electrons then occurs to generate reduced silver atoms, hydrogen ions and a protonated carbonyl compound **175**. Finally, these species collapse to product **176** with the carbonate ion acting as a hydrogen ion acceptor, thereby generating carbonic acid which is immediately decomposed to carbon dioxide and water.

This method has been shown to oxidise the high molecular weight alcohols fastest because they show a better adsorption than lighter ones.

It has been postulated that an increase in temperature increases the rate of oxidation and desorption of the product from the salt, while leaving the concentration of chemisorbed alcohol virtually unaffected. Thus, we carried out the oxidation at reflux.

Fetizon's group reported the use of heptane or hexane as solvents.[146] Reaction under such conditions led to poor yields (<10%) in our case. The literature shows that benzene was also used.[145,147] In this instance, the solid surface is covered with benzene molecules which form π complexes with the silver ions in the reagent.

Consequently the alcohol must displace the benzene molecules from the adsorption sites before binding, which leads to longer reaction times.

In order to avoid using benzene because of its toxicity, toluene was chosen for our reactions. The choice of this solvent allowed us to improve considerably the yield of the oxidation, even though the reaction time was very long.

We also developed a modification to the preparation of the salt originally proposed by Fetizon.[147] The method used is responsible for increasing the number of active sites on the surface. The process of drying the salt was modified. The procedure was considerably improved by exchanging a three days pre-drying of the reagent under vacuum[146] for an elimination of the water over one night on a rotary-evaporator followed by a one hour reflux of the reagent in toluene using a Dean-Stark head to remove completely the water from the reaction mixture. The substrate was then added subsequently to the dry oxidant salt in toluene. Oxidation was achieved after four days and afforded a maximum 50% yield (Scheme 146).
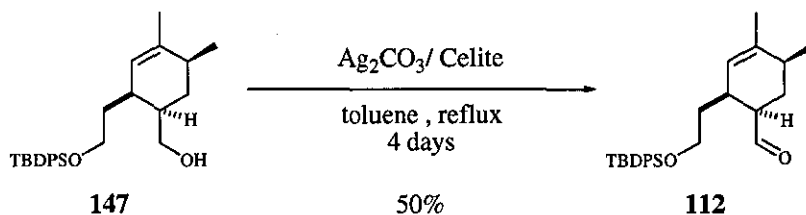
Scheme 146

The yields of the reaction were not reproductible and varied from 35 to 50%. Indeed, in this particular system, there are some important reaction parameters which are impossible to control.

To begin with, it is impossible to achieve absolute uniformity in the size and shape of the adsorbent particles. Such variations are known to affect significantly the course of heterogeneous reactions.[146]

Secondly, it has been established that the rate of agitation greatly influences the rate of oxidation.[146]

Finally, while we always utilised pre-dried silver carbonate/Celite® reagent by following the same procedure every time, there is no way of assessing quantitatively the amount of moisture which was retained by the samples in each case.

The yield of our product may have been limited by several other factors. First, all the groups undergoing bond change in **112** must adapt a coplanar configuration and be perpendicular to the plane of the solid surface of the oxidizing reagent. In this orientation, there could be interaction between the methyl group in C-4 and the solid surface of the oxidant. This observation could explain a loss of reactivity.

Moreover, the oxidation begins with the chemisorption of the hydroxyl group on surface the silver ions of the oxidant. Our molecule contains an olefin which, as another π electron system offering alternative mode of adsorption on the solid surface, could represent another limiting factor (Figure 12).[146]

R = TBDPS
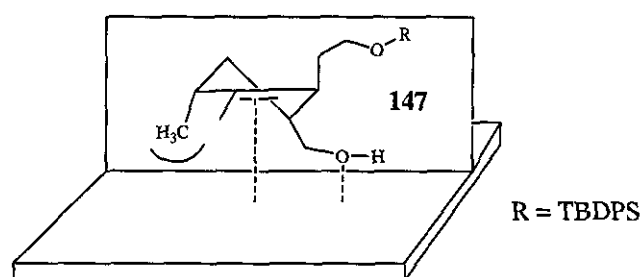
Figure 12

2.5.1.4.2. Oxidations using a catalytic amount of oxidant

The other methods tested followed catalytic procedures. Catalytic oxidations allow working with small amount of oxidizing agents, which may be expensive, toxic, and quite often both. Catalytic procedures require a co-oxidant.

2.5.1.4.2.1. Oxidation with TEMPO

The first catalytic system investigated involved the use of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) **177**. This oxidizing agent is often used for the mild conversion of primary alcohols to aldehydes.
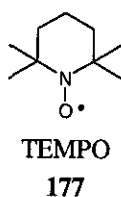
TEMPO
177

2.5.1.4.2.1.1. TEMPO/ bleach oxidation

In our case, TEMPO was used as a catalyst dissolved in dichloromethane, with aqueous sodium hypochlorite as co-oxidant and potassium bromide as co-catalyst in a two-phase system reaction.[148] This reaction requires an efficient cooling system (below 10-15 °C) to avoid the decomposition of the catalyst. The bleach was buffered at pH 8.5-9.5 by adding the appropriate amount of sodium bicarbonate (Scheme 147).

TEMPO cat., NaOCl $_{aq.}$ (1.25 equiv.)

DCM, NaHCO$_3$, KBr (0.1equiv.)

19%

147 → **112**
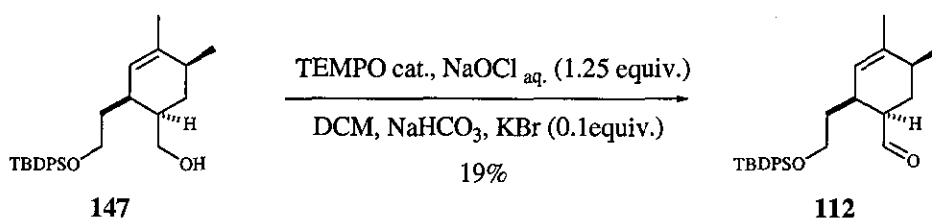
Scheme 147

At this pH, hypochlorous acid is the co-oxidant and is transformed into hypobromous acid, which is more efficient in the oxidation of nitroxide **177** to oxammonium bromide **178**. This salt is the active species in the oxidation process (Scheme 148).
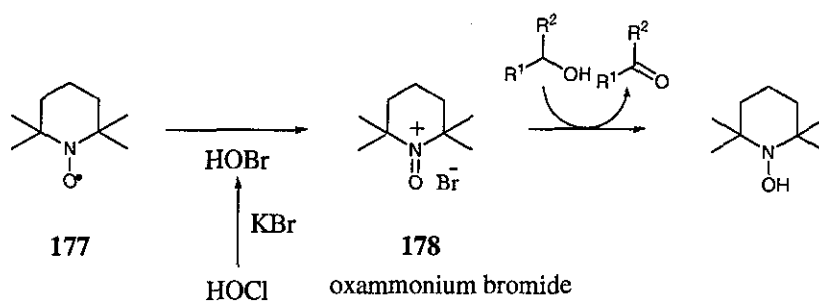
Scheme 148

The system operated rapidly. After only few minutes, the aldehyde appeared, but the reaction did not reach completion. The addition of more oxidant and catalyst did not improve the yield. The yield was only 19% even when the reaction was carried out under a strict control of the temperature at 0 °C.

2.5.1.4.2.1.2. TEMPO/ trichloroisocyanuric acid oxidation

In order to employ an easier procedure and to try to improve the yield, bleach was replaced by a molar equivalent of 1,3,5-trichloro-2,4,6-triazinetrione **179**, as co-oxidant.[149] This compound, also named trichloroisocyanuric acid, is a very cheap reagent. The procedure follows the mechanism shown in Scheme 149 and was reported to allow quantitative and rapid oxidation.[150]

Scheme 149

103

Unfortunately, after numerous attempts, no positive results were obtained (Scheme 150).

Scheme 150

We were concerned that the catalyst might be destroyed under the reaction conditions. To leave no stone unturned, we thereafter tested the reaction with a stoichiometric amount of TEMPO. This was not successful either.

2.5.1.4.2.2. Oxidation with TPAP/NMO

Oxidation using catalytic tetra-n-propylammonium perruthenate (TPAP) was developed by Ley and Griffiths.[79,151] It has a wide application due to its mildness and ease of execution. It involves a catalytic amount of the ruthenium complex. Ruthenium is famous for displaying the widest range of oxidation states of all the elements from Ru (VIII) to Ru (II). Tetra-n-propylammonium perruthenate (TPAP) **180** was chosen because of the large organic cation of the salt $(Pr_4N)^+$, which gave the best results. It is a readily soluble and air stable oxidant, with N-methylmorpholine N-oxide (NMO) **181** usually used as the co-oxidant (Figure 13).

Figure 13

The oxidation process involves ruthenium passing from oxidation degree 7 to 4. NMO is reduced to the amine, reoxidizing the ruthenium back to Ru (VI) (Figure 14).[79]

Ru (VII) + 2e⁻ $\longrightarrow$ Ru (V)

2 Ru (V) $\longrightarrow$ Ru (IV) + Ru (VI)

R_2CHOH + Ru (VI) $\longrightarrow$ R_2CHO + Ru (IV)

NMO + Ru (IV) $\longrightarrow$ N-methylmorpholine + Ru (VI)
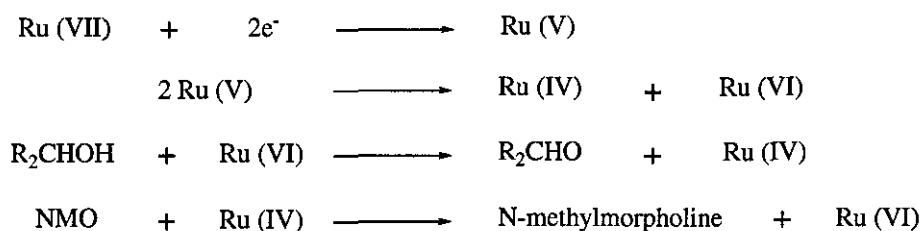
Figure 14

This method respects silyl ether integrity.[152] With our substrate, only the alcohol is oxidised and the double bond of the ring is not cleaved. The reaction was carried out at room temperature in presence of a slight excess of NMO. The reaction is autocatalytic. This is due to the formation of RuO_2, which coordinates with $[RuO_4]^-$. Water binds RuO_2 particles and reduces the number of sites available to $[RuO_4]^-$. This retards the autocatalysis and water must therefore be trapped. In this regard, activated powered molecular sieves were introduced to remove both the water formed during the oxidation, and the water of crystallisation of the NMO.[79] combination of dichloromethane-acetonitrile in a ratio 10:1 was employed as solvent (Scheme 151).

TPAP (5% mol.), NMO (1.5 equiv.)

DCM 10:1 ACN, r.t.

25 %

TBDPSO   OH

147

TBDPSO   O

112
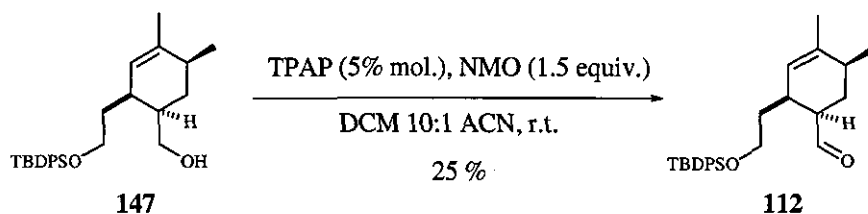
Scheme 151

On a small scale, we obtained about 25% oxidation. The oxidation did not reach completion, perhaps because the alkene interfered with the oxidation by binding to

the metal and inhibiting the catalytic process. Therefore, more catalyst was added but without success. The reagent is sterically demanding and the access to the hydroxyl could be difficult and explain the poor reactivity. On large scale, we moderated the reaction by cooling it and by adding TPAP and NMO slowly and in portions, dissolved in dichloromethane and predried with magnesium sulfate. Many by-products were formed. The reaction which was clean and efficient on a small scale became capricious on a large scale. This method was not deemed appropriate for further work.

Table 2 gives a summary of the oxidations attempted.

Method	Fetizon	DMP	TPAP/ NMO	TEMPO/ Bleach	IBX	Cr(VI)	Swern	TEMPO/ TCCA	Frémy's Salt
Scale (mmol of substrate)	11.80	161.0	2.10	0.90	0.64	1.04	0.76	0.47	0.47
Yield (%)	50	30	25	19	11	10	SM	SM	SM

Table 2: Summary of the oxidation attempts

The use of silver carbonate on Celite® as oxidizing reagent was the best of these tested, and allowed the passage to the next step. Overall, this route led to **112** in three steps from **4** in a 27% yield.

In the meantime, a second route leading to our first target was discovered.

2.5.2. Formation of 111 and 112 through route 2
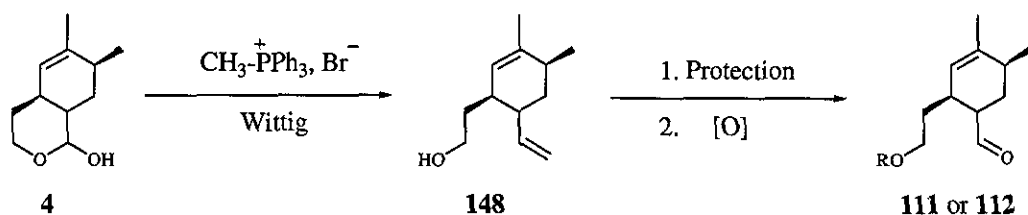
Scheme 152

2.5.2.1. Ring opening by Wittig reaction

Wittig reaction on the aldehyde of the open chain isomer of **4** was attempted in order to afford compound **148**.

Several methods found in the literature were investigated. The processes were quite similar and based on the use of methyl triphenylphosphonium bromide, with *n*-butyllithium or potassium *tert*-butoxide in tetrahydrofuran.

A typical example was reported by Pearson in his total synthesis of (-)-slaframine (Scheme 153).[119]

72%
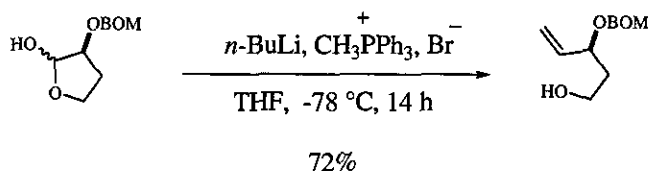
Scheme 153

Most of the time, a large excess of ylide, from 2.5 to 10 equivalents molar, was used to perform the reaction.

A minimal amount of two equivalents of *n*-BuLi had to be used because it initially deprotonates the alcohol.[153,154] The corresponding alkene was finally obtained by following the procedure utilised by Posner *et al.* (Scheme 154).[154]
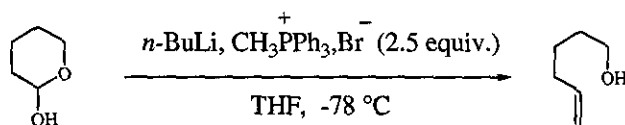
Scheme 154

The lactol **4** was treated with 2.5 equivalents of Wittig salt at -78 °C followed by warming to room temperature overnight (Scheme 155). The desired alkene **148** was isolated in 87% yield.
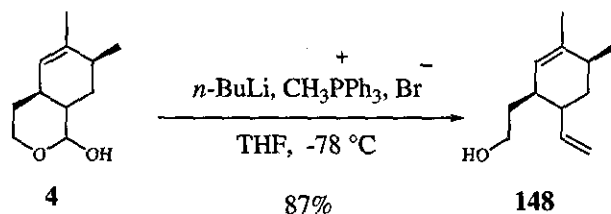
Scheme 155

2.5.2.2. Protection of compound 148

The next step was the protection of the hydroxyl group of **148**. Silyl groups were chosen to be the protecting groups. These groups are widely used and stable, except under hydrolysis or in presence of fluoride ions. The protected compound **149** was obtained in a 61% yield by using *tert*-butyl dimethylsilyl chloride, and **150** was formed in 58% yield with *tert*-butyldiphenylsilyl chloride (1.1 equiv.). In both cases, imidazole was used in a large excess (3 equiv.). Most of the rest of the material was unreacted starting material (Scheme 156).
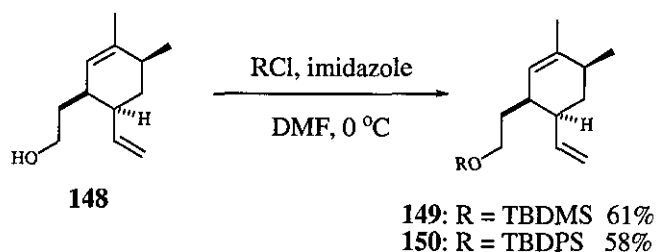
Scheme 156

2.5.2.3. Selective cleavage of the hindered double bond

2.5.2.3.1. Osmium tetroxide

Having generated the protected alcohol **149** and **150**, the next step in the synthesis was to form compound **111** and **112** (Scheme 152). Sodium periodate-osmium tetroxide is commonly used for the direct oxidative cleavage of alkene bonds to give carbonyl compounds. It complements the classical method of ozonolysis of double bonds followed by reductive cleavage, with the advantage that sodium periodate-osmium tetroxide can be employed for the selective cleavage of unhindered double bonds in presence of more hindered ones, as was achieved by Cantor *et al.*(Scheme 157).[155]
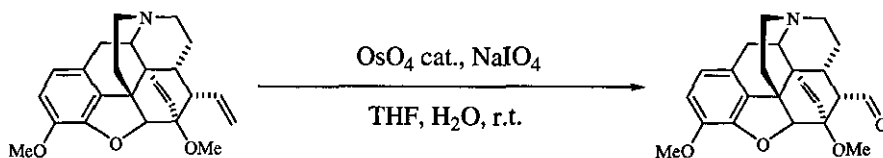
Scheme 157

This type of selective oxidation was applied to the compound **150**. Periodate serves to regenerate osmium tetroxide **182**, and allows the use of this expensive and toxic reagent in a minimal amount. The reaction has been proposed to proceed through a [3 + 2] or [2 + 2] pathway to give the intermediate osmium (VI)

monoglycolate ester **183**, which is then hydrolysed reductively to give the *cis*-1,2-diol **184** (Scheme 158).[156]
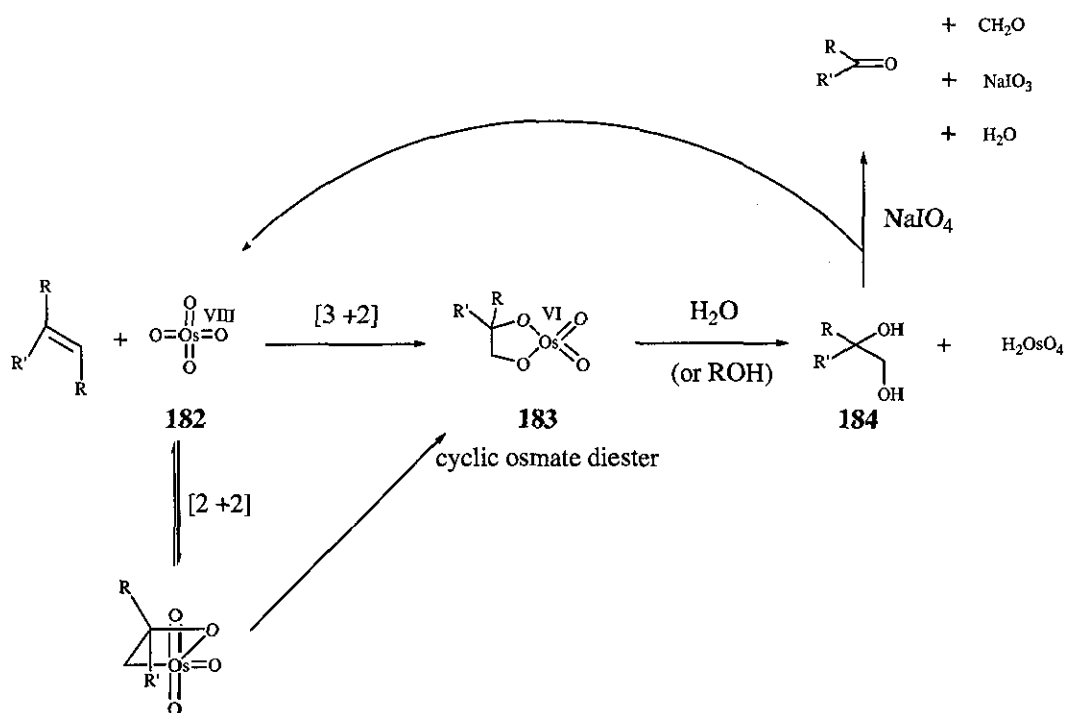
Scheme 158

During the work-up, excess of co-oxidant and osmium (VI) species **183** are reductively hydrolysed with sodium sulphite to form insoluble Os-sulphito species.

The reaction was carried out in mixed aqueous solvent systems such as aqueous *p*-dioxane[157] and aqueous tetrahydrofuran.[158] Indeed, water or an alcohol is required to hydrolyse the osmate intermediate. In both cases, the olefin **150** was dissolved in the corresponding solvent mixture and the osmium tetroxide (2.5 wt %) was added. After 30 minutes, the sodium periodate (2 equiv.) was added in portions to the reaction mixture. The reaction was subsequently allowed to stir for 1 to 5 hours before work-up. Despite the electrophilic nature of osmium tetroxide and its affinity for electron-rich double bonds, a complex mixture, probably due to the reaction of the other olefin was noted every time (Scheme 159).
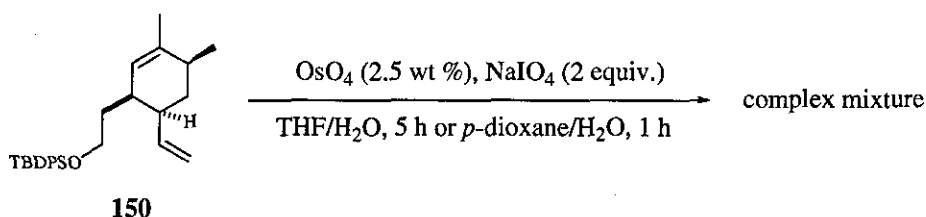
Scheme 159

2.5.2.3.2. Double bond cleavage by dioxygen

Transition metals such as vanadium or molybdenum form mononuclear peroxocomplexes with dioxygen. They are used as catalysts for the oxidation of organic substrates.

Vanadium species have shown a promising selectivity in oxidative cleavage, for example by cleavage of the exocyclic double bond of limonene **185** without touching the endocyclic olefin. The corresponding ketone **186** was obtained in 73% yield (Scheme 160).[159]
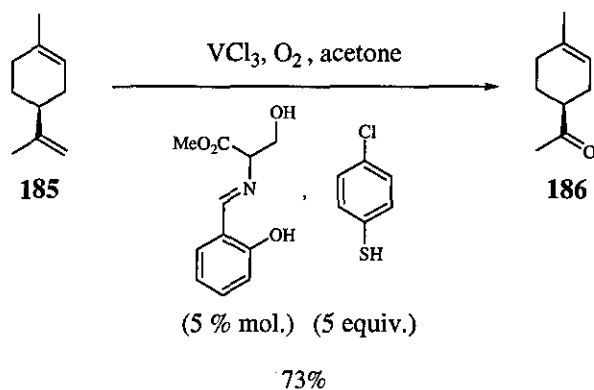
Scheme 160

This method proceeds under one atmosphere of oxygen, at room temperature, in the presence of a transition metal catalyst VCIL$_2$ **189** and an excess of 4-chlorothiophenol as the co-reagent. The preparation of the ligand L **188** was first

achieved from the reaction of **186** with **187**. This afforded **188** in 90% yield. The corresponding complex **189** was formed *in situ* prior to the reaction of the substrate **150** with molecular oxygen (Scheme 161).
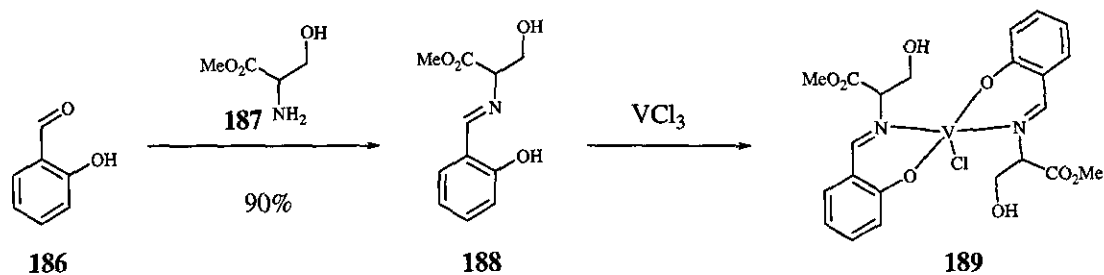
Scheme 161

The thiophenol **190** dimerises to give a disulfide **191**, used as a catalytic thiyl radical precursor. The C=C bond cleavage results from the vanadium-catalysed decomposition of a β-hydroperoxysulfide intermediate **193** formed *in situ* from the thiyl radical **192** addition to the olefin, followed by oxygen trapping (Scheme 162).
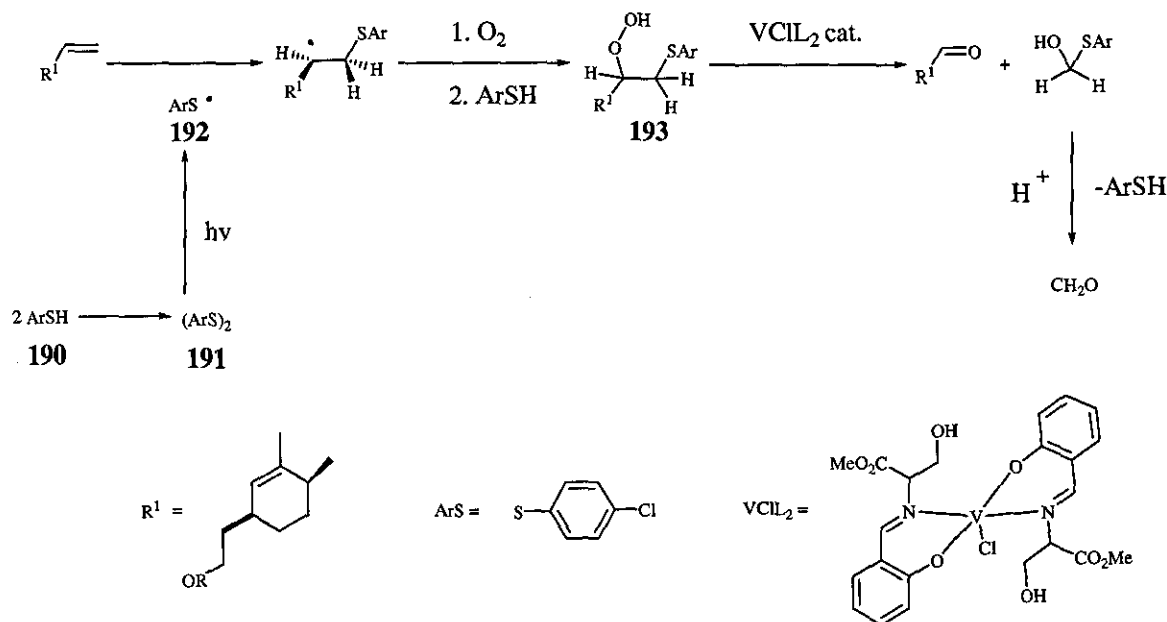
Scheme 162

112

The reaction was attempted using compound **149** as substrate. The olefin **149** was converted to the expected carbonyl **111** in 15% yield (Scheme 163).

15%
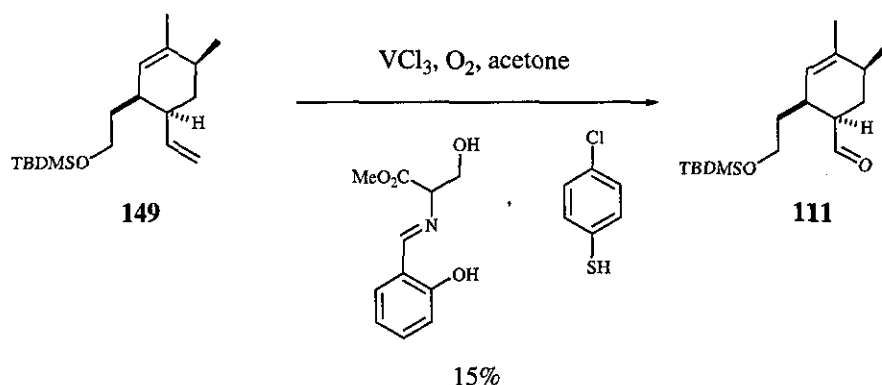
Scheme 163

The reaction was also achieved with UV irradiation using a medium pressure mercury lamp as described by Baucherel *et al.*[159] A similar result was obtained. Route 2 (Scheme 152) was thus achieved in three steps with a 6.6% overall yield, the oxidation step needing to be optimised. Therefore, route 1 (Scheme 116) was chosen to synthesise **112** because of the overall yield, which was 2.4 times better than by using route 2.

2.5.3. α-Hydroxylation

2.5.3.1. Direct α-hydroxylation

2.5.3.1.1. α-Oxygenation using dioxygen

Because a better accessibility to the upper face with the aldehyde **112** than with lactone **5** was possible, both molecular oxygen and MoOPD reactions, which afforded stereoselectively the less hindered α-hydroxy lactone **6** from **5**, were thought to be promising for this case (section 2.2.2.).

113

Nevertheless, during a meeting, Vedejs advised us not to use MoOPD because it would exclusively afford **194**.

Also, attempts using molecular oxygen gave a very messy and complex mixture, probably due to decomposition and over reactivity of oxygen radicals, and neither **194** nor **195** were obtained (Scheme 164).
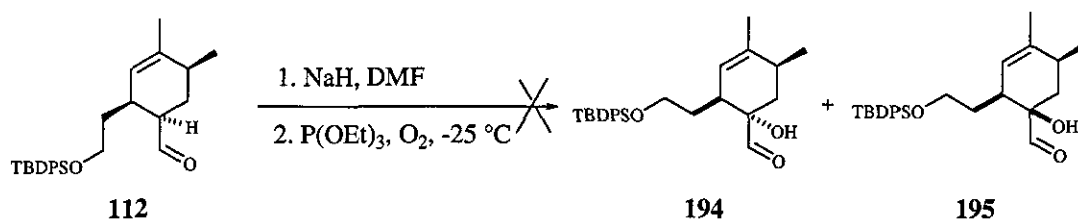
Scheme 164

2.5.3.1.2. Novel one pot method for α-oxygenation

A new mild method for the α-oxygenation of carbonyl compounds has been recently reported by Tomkinson (Scheme 165).[160]
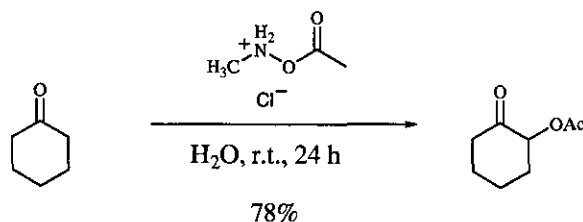
Scheme 165

This novel one pot method for the α-oxygenation is carried out in an aqueous environment in the presence of air which makes it easy to set up. The conversion is believed to proceed by condensation of the reagents to form the iminium salt **196**, isomerisation to the enamine **197**, rearrangement to give the α-acetoxyimine **198**,

followed by hydrolysis to regenerate the α-oxycarbonyl functionality **199** (Scheme 166).[161,162]
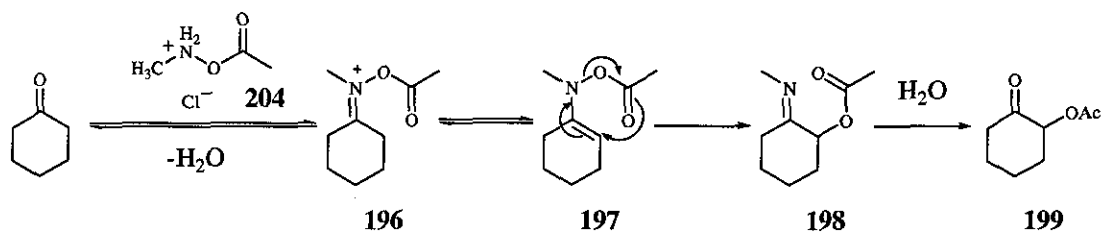
Scheme 166

This method was our last hope for direct α-oxygenation of the aldehyde **112**. First of all, the methylhydroxylamine hydrochloride salt **204** was synthesised following literature procedures (Scheme 167).[161,163,164]
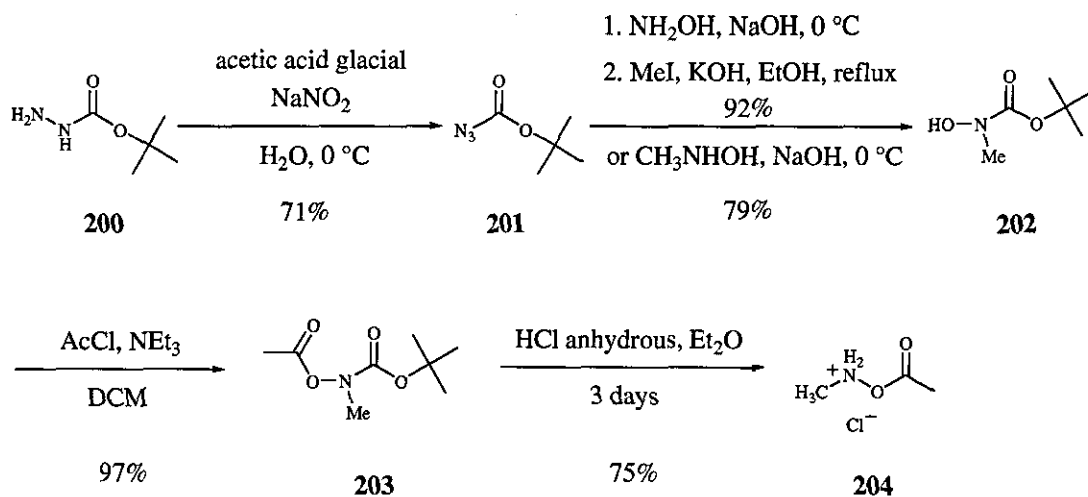
Scheme 167

tert-Butyl carbazate **200** reacted with sodium nitrite to generate the azidoformate **201**. Two pathways were next tried. The longer one gives the hydroxy(methyl)carbamate **202** in two steps *via* the formation of a hydroxycarbamate intermediate. The shorter one afforded the hydroxy(methyl)carbamate **202** in a convenient one step process, but with a loss of

yield. After acetylation to **203**, the salt **204** was obtained in a 47% overall yield by the longer route.

The α-oxidation reaction was attempted on aldehyde **112**. Aldehyde **112** was treated with one equivalent of *O*-acetoxy-*N*-methylhydroxylamine hydrochloride salt **204** in water (10 mL). The reaction was stirred at room temperature two days, but only starting material was recovered (Scheme 168).
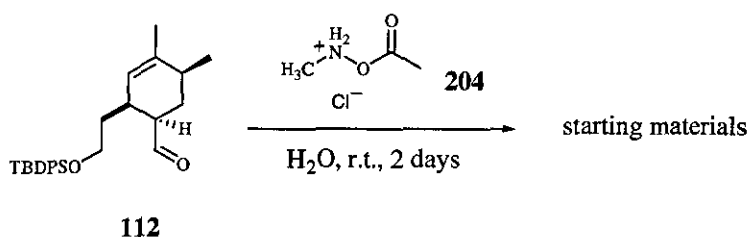
Scheme 168

The reaction was repeated in dichloromethane to provide greater solubility, but without more success.

2.5.3.2. Indirect α-hydroxylation

We decided next to try to convert the aldehyde **112** to the corresponding enol ether in order to synthesise the α-hydroxy aldehyde.
The enol acetates and methyl enol ethers were the first compounds that we attempted to synthesise.

2.5.3.3. Alternative based on the synthesis of the acetoxy ester 113

The following plan was developed. The first step is a simple transformation of the aldehyde **112** to the acetoxy ester **113**. Oxidation should occur from the less hindered face to give **114**. The Shi rearrangement would then afford the correct stereochemistry (Scheme 169).
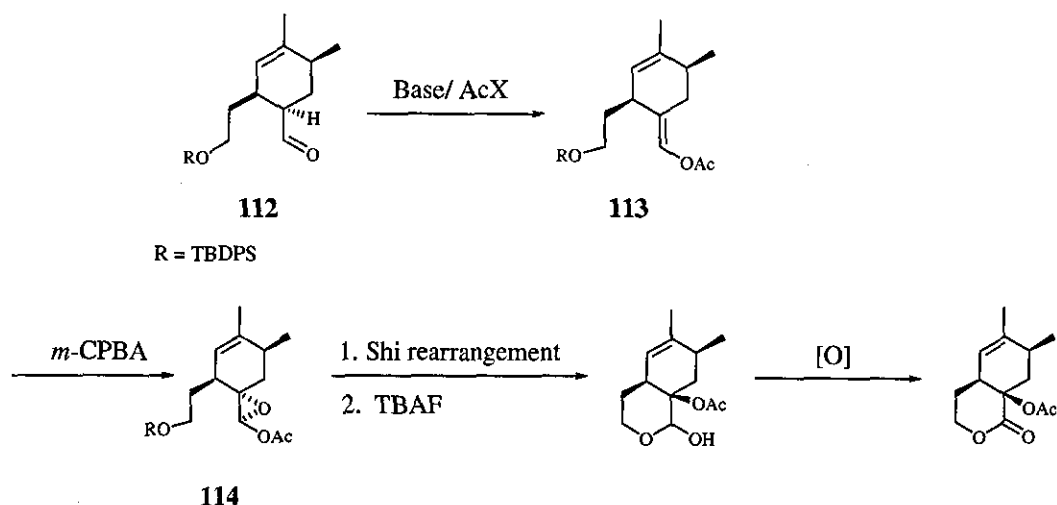
Scheme 169

During the Shi rearrangement, acetoxy epoxides deriving from enol acetates are rearranged by the action of heat or acid. The two conditions involve different mechanisms with opposite stereospecificity.

The acid catalysed reaction occurs through an intramolecular rearrangement with retention of configuration at the α-centre of the acetoxy epoxide **205** to give **206b** (Scheme 170).[165]
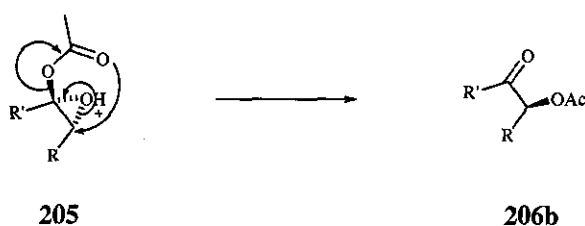
Scheme 170

In contrast, thermal (or weak acid catalysed) rearrangement leads to α-acetoxy ketone **206a** with clean inversion of configuration (Scheme 171).[165]
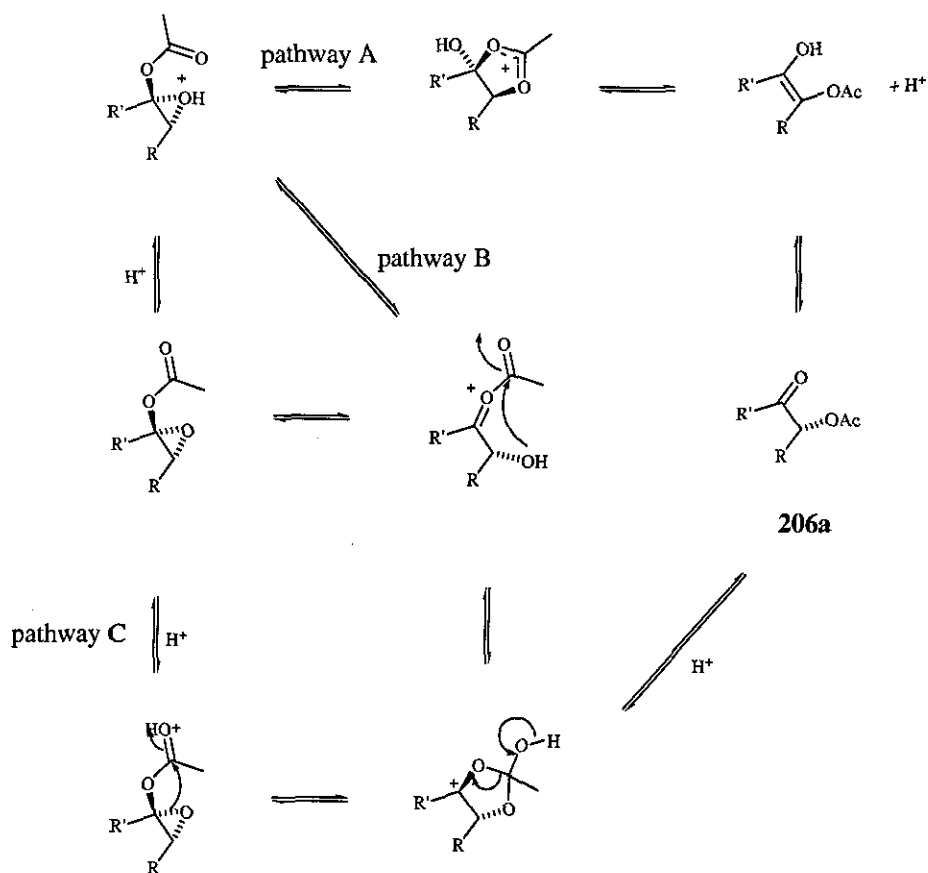
Scheme 171

Path A could be distinguished from paths B and C by ^{18}O labelling of the epoxide oxygen. If the reaction follows path A, the label would be incorporated in the final carbonyl in **206a**. If it follows path B or C, the label would reside in the acetate group of the product **206a**. To our knowledge such an experiment has not been carried out. The inversion of configuration would follow the second protocol.

The acylation reaction was expected to be really easy to achieve as it tends to occur at oxygen rather than at carbon. The tendency to attack through oxygen is the most marked with reactive acylating agents. The combination of a lithium enolate and an acid chloride usually gives an enol ester. Less reactive acylating reagents were also used to try to complete the first step of the strategy. These

attempts are recorded in Table 3. Unfortunately we could not achieve the transformation of **112** to **113**.
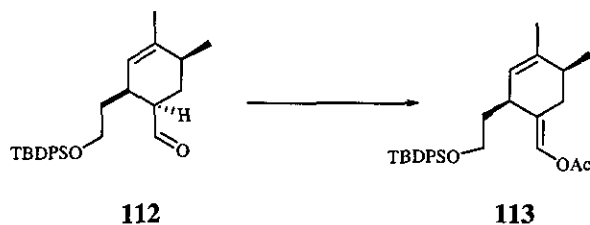
Conditions	Yield
Ac$_2$O, pyridine (10 equiv.), DMAP, reflux	Degradation
Ac$_2$O, K$_2$CO$_3$, MeCN, 60 °C	SM
AcCl, pyridine, DMAP, DCM, r.t.	SM
AcCl, LDA, THF, -78 °C to 0 °C	SM

Table 3: Acylation attempts

It is difficult to find an explanation for the lack of reactivity of **112** towards the acylation. Nevertheless, we had no other choice than to modify the route.

2.5.3.4. Alternative based on the synthesis of the methoxy ether 115

The strategy next proposed is illustrated in Scheme 172. The first target was the methoxy ether **115**. A chelated epoxidation using vanadyl bis(acetylacetonate)/ *t*-butyl hydroperoxide would potentially allow us to obtain the correct stereochemistry.
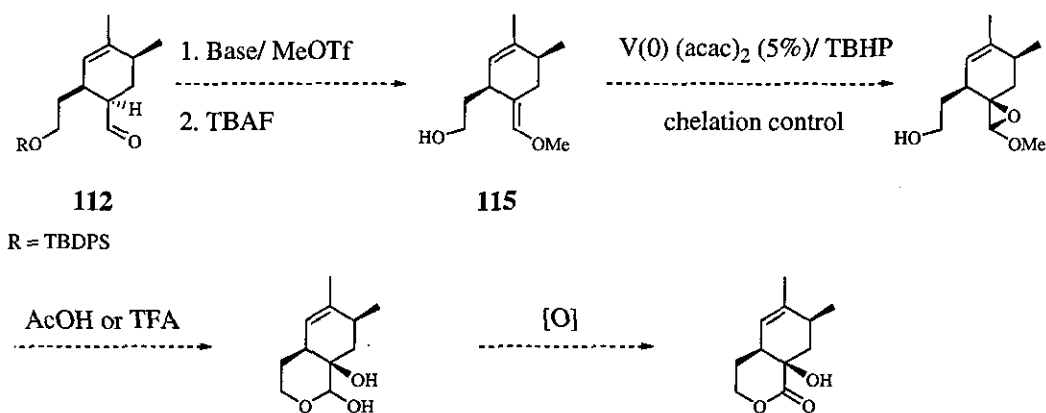
Scheme 172

Vanadyl bis(acetylacetonate) **207** is a catalyst used for the oxidation of several functional groups, usually using an alkyl hydroperoxide as the oxidant.

207
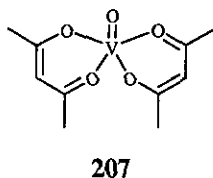
Hydroxyl-promoted epoxidation with high diastereofacial selection in homoallylic alcohols occurs more effectively by the use of vanadium (V) complexes than by the use of titanium (IV).[166-168] For example, **208** provides **209** as a single diastereoisomer (Scheme 173).[166]
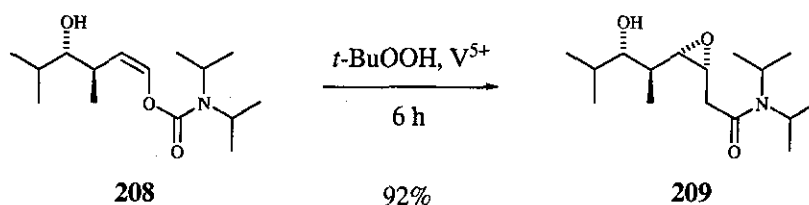
Scheme 173

Here, the idea is to direct the epoxidation with an alcohol separated from the double bond by four carbons. The spatial conformation of the molecule and the flexibility of the arm carrying the hydroxyl group is the key to the reaction's success. The objective was therefore to complete the synthesis of precursor **116** through the epoxidation of the enol ether **115** by forming a vanadium-peroxo complex as the key step (Scheme 174).
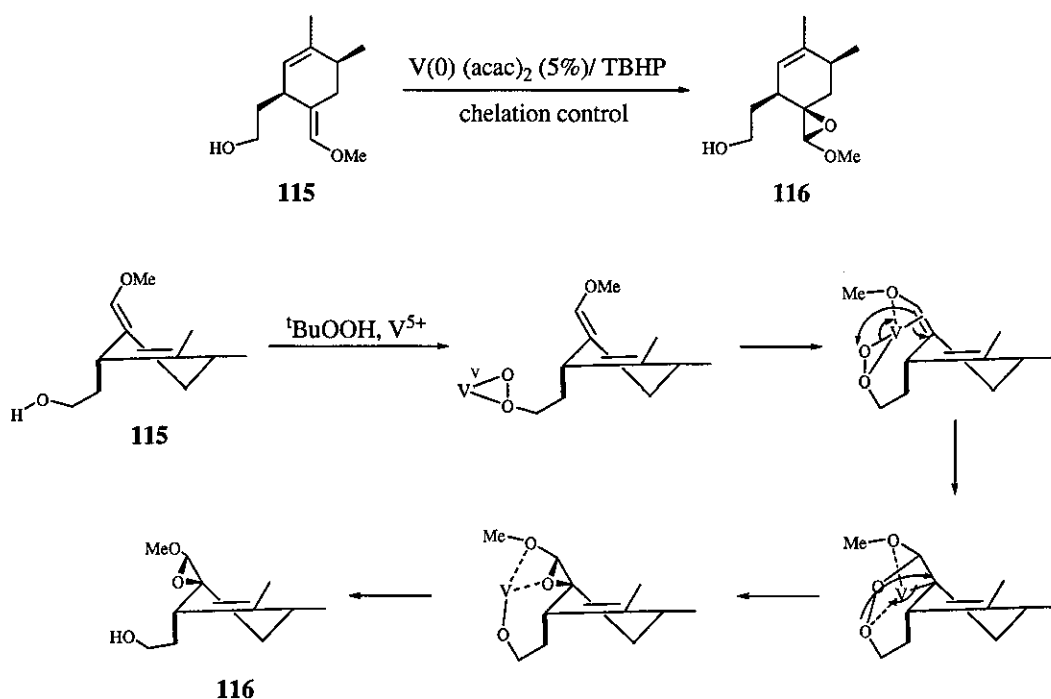
Scheme 174

Vanadyl bis(acetylacetonate) **207** is quickly raised from the (IV) to (V) oxidation state by *t*-butyl hydroperoxide. The resulting organic soluble vanadium (V) complexes are the reactive species in the reaction, which involves a π-σ rearrangement process.[169] The reactivity of alkenes increases with their nucleophilic character. Therefore, the reaction is highly regioselective in favour of vinyl ethers owing to the rigid metallacyclic intermediate.[170]

However, similar difficulties were encountered with the first step of this strategy to these experienced with the former route.

Aldehyde **112** was first used in reactions involving iodomethane or trimethyl orthoformate in attempts to prepare the enol ether. The lack of success of these attempts led us to test more powerful methylating agents such as methyl trifluoromethanesulfonate.

The use of the even more reactive Meerwein's trimethyloxonium salt, which is a hard electrophile with a highly polarized C-O bond and therefore reacts readily with hard oxygen atoms, was also investigated with no more success (Table 4).

| 112 | 210 |
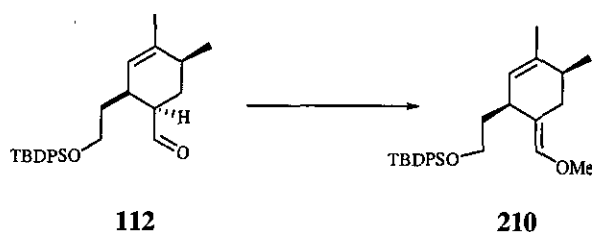
Conditions	Yield
Trimethyl orthoformate, PTSA, MeOH	SM
MeI, NaHMDS, THF, r.t.	SM
MeOTf, NEt$_3$ or Hunig's base, DCM or LDA in THF	SM
Meerwein's salt, Hunig's base, DCM, 0 °C to r.t.	SM

Table 4: Methylating attempts

The lack of success of these methods led us to consider that the problem may lie with the chemist rather than the chemistry. We therefore decided to repeat the exact procedure followed by Rozen *et al.* using the same substrate **211**. The product **212** was obtained as described in the literature (Scheme 175).[171]
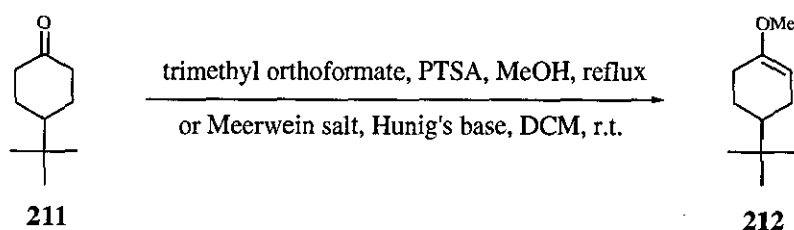
Scheme 175

Also, formation of **213a** and **213b**, in a 2:3 ratio, due to the polarity of tetrahydrofuran,[172] in a modified Julià reaction using the sulfone **107**, proved the reactivity of the aldehyde **112** (Scheme 176).
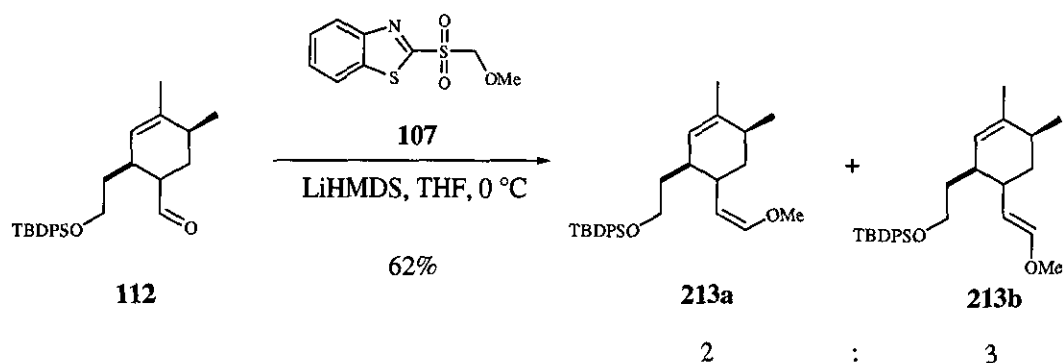
Scheme 176

The reaction follows the mechanism presented below, where addition of the lithiated sulfone **214** to the aldehyde **112** takes place faster than self-condensation (Scheme 177).[172]

123
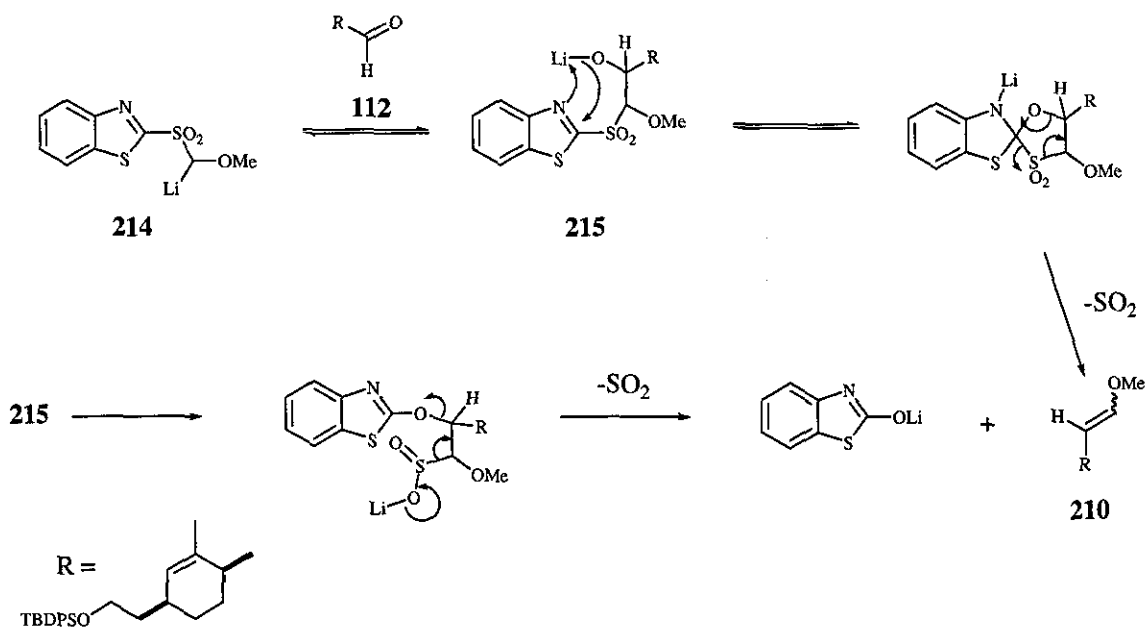
Scheme 177

Because of the two results described, we decided to continue working with the aldehyde **112**. The formation of a silyl ether was the next target, based upon the strong affinity of the silyl group for oxygen.

2.5.3.5. Alternative based on the synthesis of the silyl enol ether 418

After the failure of the direct α-hydroxylation methods and the failure of the two former indirect α-hydroxylation strategies, we decided to try perhaps the most convenient and reliable α-hydroxylation procedure, based on the treatment of the silyl enol ether **216** with a peracid. The initial epoxidation is followed by a silyl migration and the generation of the α-silyloxy carbonyl compound **219**. The silyl migration may occur through the formation of either **217** or **218** (Scheme 178).
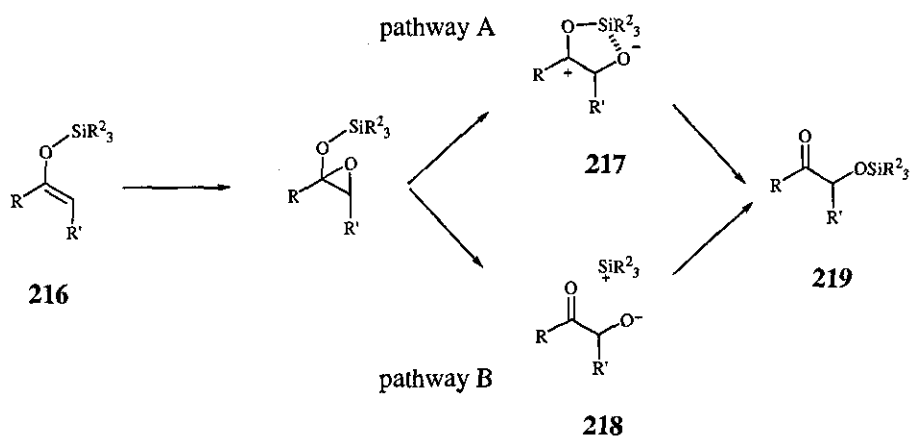
Scheme 178

Studies carried out during the total synthesis of sterpuric acid, by Paquette *et al.*,[173] allowed the first isolation of the trimethylsilyloxy epoxide **220** (Scheme 179).
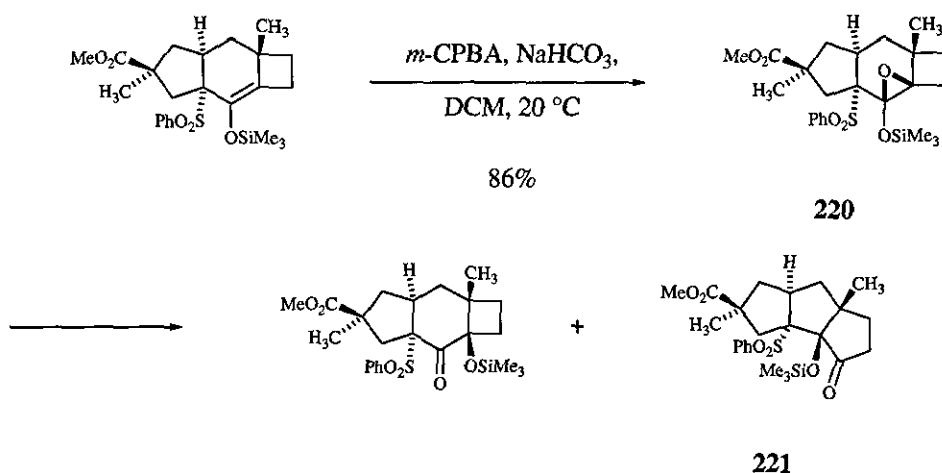
Scheme 179

Associated with the observation of the formation of the rearranged compound **221**, the mechanism shown in pathway A has been adopted, involving the formation of an oxocarbenium ion **217** in Scheme 178 (Scheme 180).
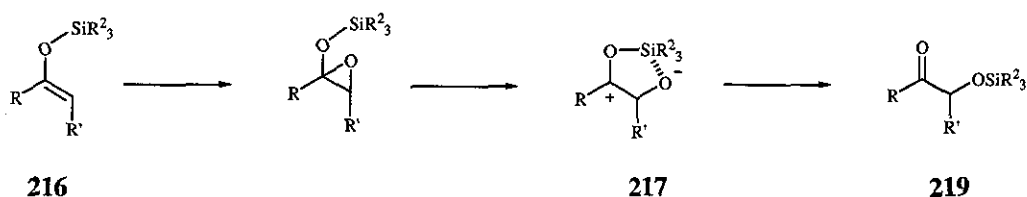
Scheme 180

α-Oxycarbonyl species **219** subsequently forms the hydroxy carbonyl species by rapid hydrolysis. The oxidation reactions are mostly performed using *m*-CPBA. In our case, the silyl enol ether **112** was treated with DMDO (section 2.5.4.2.2.). The α-silyloxy species was not isolated, and the reaction went straight to completion.

Both (E) **222E** and (Z)-isomers **222Z** of the silyl enol ether **222** were produced in a 3:2 ratio. One-isomer was isolated from the mixture (Scheme 181).
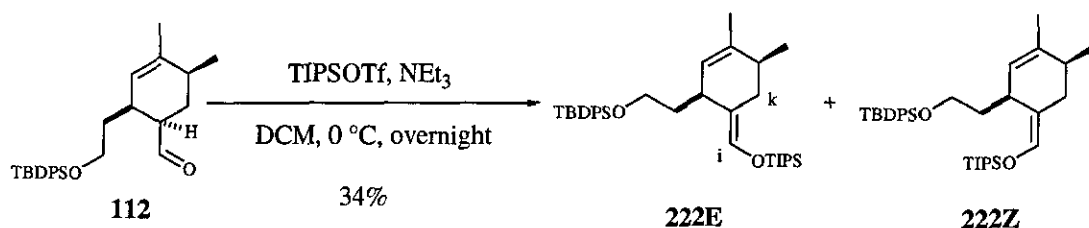
Scheme 181

The stereochemistry of **222** was not assigned by ^{1}H NMR nOe measurements. No presence of reciprocal nOe was observed between H_i and H_k or $H_{k'}$ of the isolated isomer. This could indicate that these two substituents are far from each other and that the isolated isomer is **222E**. But the absence of evidence did not allow us to give a firm conclusion.

2.5.4. Working with a free alcohol

First, the strategy proposed was a chelated epoxidation using vanadyl bis(acetylacetonate)/ *t*-butyl hydroperoxide, as described previously (Scheme 182).

126
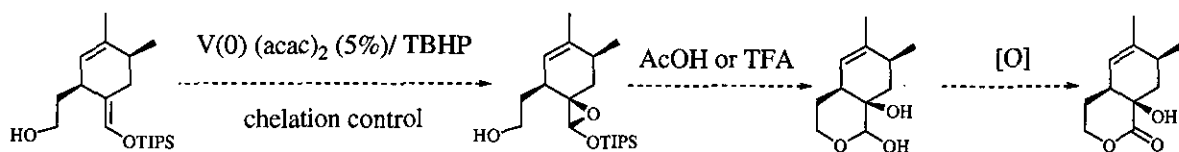
Scheme 182

Unfortunately, the silyl enol ether **222** could not be used in the directed epoxidation by vanadium, which requires the presence of a free alcohol. Monodeprotection of the alcohol without affecting the integrity of the enol ether was not possible due to the greater instability of the silyl enol ethers towards the conditions used to deprotect silyl ethers. Consequently, the VO(acac)$_2$ reaction with **222** was not attempted and new strategies allowing the presence of a free alcohol directing the α-oxygenation were investigated.

2.5.4.1.1. A sequence of protection and deprotection reactions

A sequence of protections-deprotections was proposed, but aborted after the first step due to the length of the strategy (Scheme 183).

Scheme 183

127
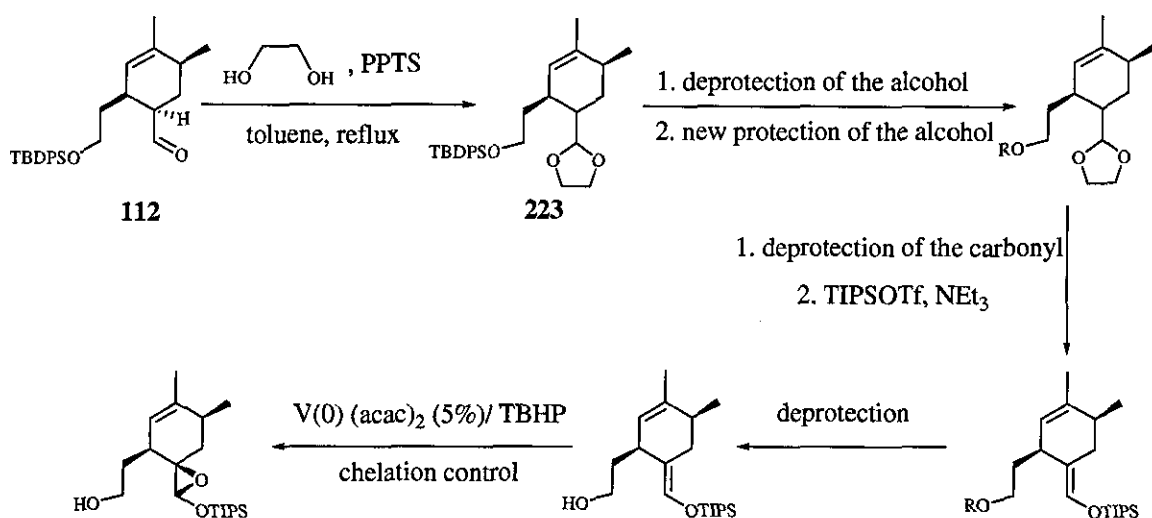
Nevertheless, it was interesting to see that the first step of the strategy, leading to the formation of **223**, was successful even though the yield was only 26%, although without optimisation of the reaction (Scheme 184).
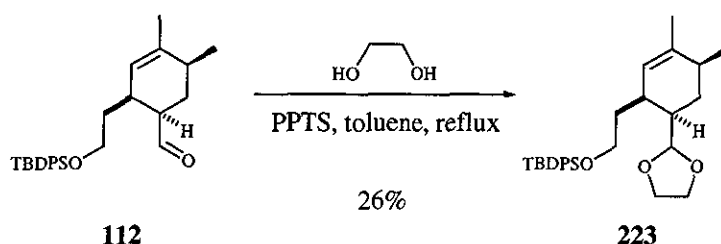
Scheme 184

2.5.4.1.2. Protection of primary alcohol using pivaloyl and trityl groups

We decided that the silyl protections should be replaced by a different protecting group. We needed a very selective protecting group, able to differentiate the two primary alcohols of the diol **145**, and which could also be removed under mild conditions, and respecting the integrity of the enol ether **222**. Due to their high steric demand, pivaloyl esters and trityl ethers are generally used to selectively protect primary alcohols in the presence of one or more secondary hydroxyl groups.[174] The removal of pivaloyl is carried out by transesterification with sodium methoxide in methanol, anhydrous hydroxide, or by enzyme catalysed hydrolysis.

The removal of trityl groups is accomplished with the aid of mineral or Lewis acids, or even with silica gel. Both can be deprotected in the presence of other alcohol protecting groups as in **146**.

Unfortunately, the usual protection procedures led to mixtures of different compounds, probably including the expected monoprotected alcohol **146** but also the other protected alcohols, in such a poor yield that they could not be isolated. Only the major diprotected compounds **224** and **225** and recovered diol **145** were isolated (Scheme 185).

145
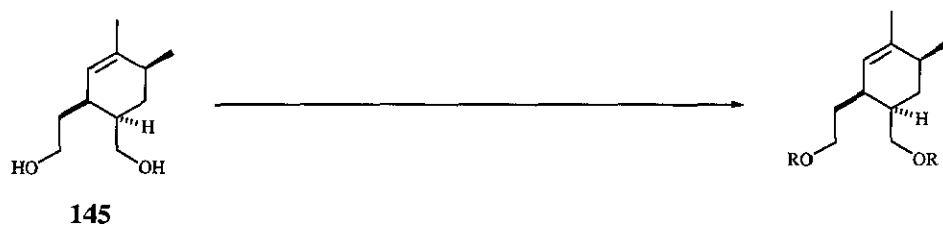
R = Piv   (CH₃)₃CCOCl, pyridine, DCM, r.t., overnight 42%   **224**

R = Tr   Ph₃CCl, DMAP, DMF, r.t., overnight   37%   **225**

Scheme 185

Changing the base or decreasing the rate of addition gave similar results. Decreasing the temperature afforded the recovery of the starting material.

2.5.4.1.3. Alternative protection in route 2

Route 2 (Scheme 152) could easily be modified to incorporate a protection other than silyl in its second step. The protection chosen could be methyl or benzyl aryl ethers which can be deprotected under basic conditions,[175] and which would allow the selective deprotection of the alcohol **222**. The free hydroxyl group in **226** has the potential to direct the epoxidation of the enol ether from the desired face. Similar directed epoxidations using vanadium have been described in the literature (Scheme 186).[170]

Scheme 186
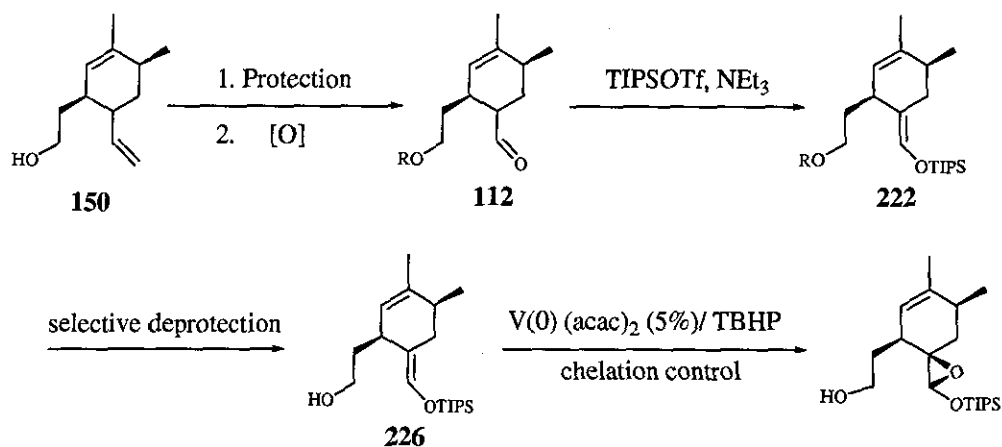
However, due to the lack of reliability and the poor yields obtained for the oxidation following the protection of **150**, we decided to work with **222**.

2.5.4.2. Working with the protected alcohol

2.5.4.2.1. Bromination

Silyl enol ethers are known to be oxidised to α-hydroxy ketones upon treatment with reagents such as *N*-bromosuccinimide. Silyl ether **222** was treated with one equivalent of NBS in aqueous dioxane. After a 30 minutes reaction, all **222** have been consumed (TLC), however after work-up, the crude reaction mixture was a complex mixture of unidentified products (Scheme 187).
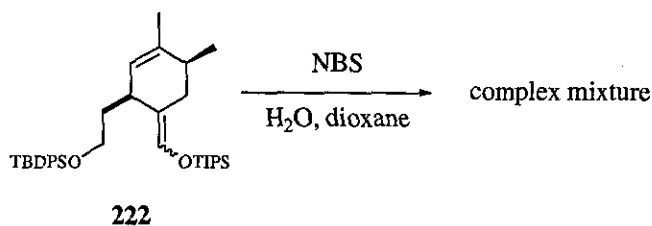
Scheme 187

2.5.4.2.2. Rubottom oxidation

The α-hydroxylation of the mixture of enol silanes **222** was to be the key step in establishing the desired stereochemistry. The Rubottom oxidation employs *m*-CPBA as the oxidant. In Scheme 188, a double Rubottom oxidation provides an example of the efficiency of the method.[176]
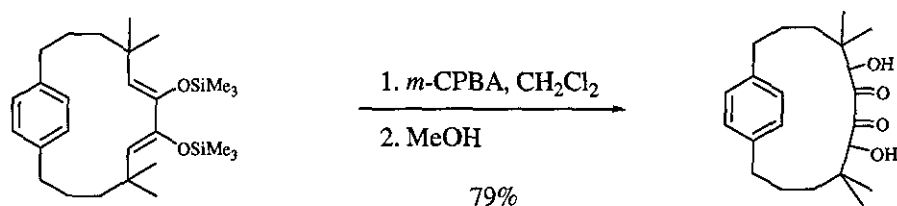
Scheme 188

It is generally assumed that the first step is the formation of the corresponding epoxide **227** followed by rearrangement and solvolysis to the hydroxy ketone **228** (Scheme 189).[177]

Scheme 189

131
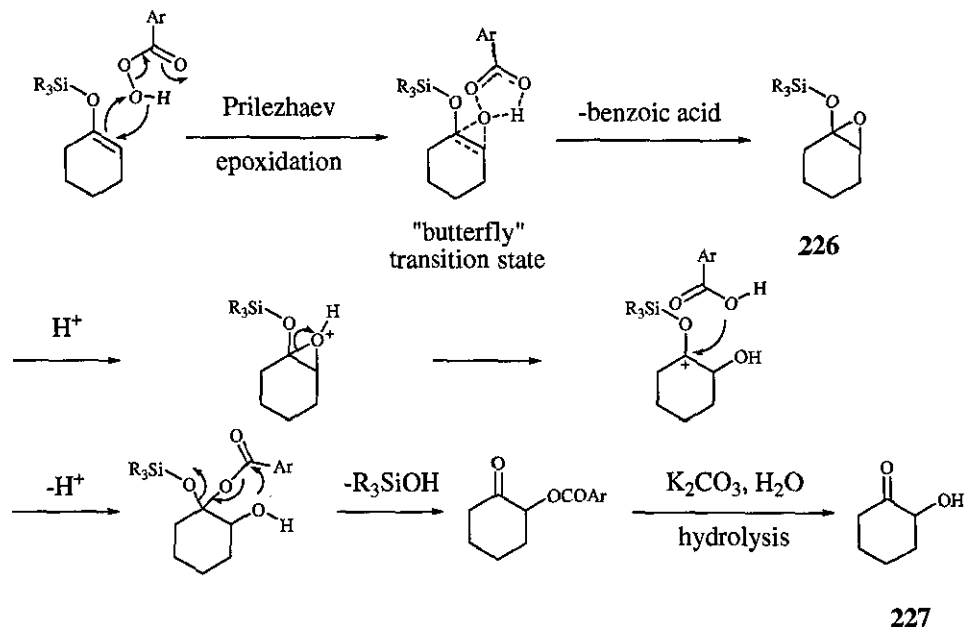
This method produces acidic by-products by loss of benzoic acid. Because our substrate was acid sensitive, this protocol was modified by using dimethyldioxirane (DMDO) **228** instead of *m*-CPBA as the oxidant. This reagent has been used extensively for the oxidation of silyl enol ethers.[176] The by-product of the DMDO oxidation is acetone, which of course is easily removed and prevents the formation of the acidic by-products obtained when using peroxy acids. As with *m*-CPBA, the epoxidation mechanism involves a concerted spiro "butterfly" type transition state **229** (Scheme 190).[178]

229

"butterfly"
transition state
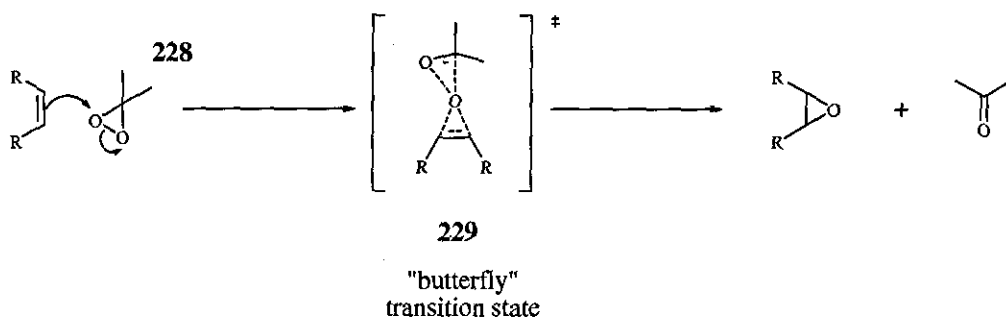
Scheme 190

DMDO **228** was used freshly prepared because of its instability. The DMDO was prepared by the Oxone® oxidation of aqueous acetone buffered with sodium hydrogen carbonate. It was co-distilled as an acetone solution and kept over molecular sieves (4 Å) in a freezer for few hours before use (Scheme 191).[179]
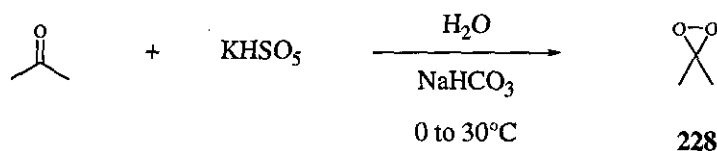
Scheme 191

The concentration of the DMDO solution (usually between 0.05-0.08 M) was determined by iodometric titration (Scheme 192).
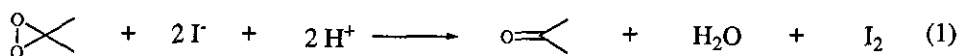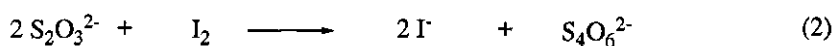
Scheme 192

Dimethyldioxirane **228** was first reacted with excess potassium iodide in an acidic medium to generate iodine. The redox process is described by equation (1). The amount of liberated iodine was then determined by titration with sodium thiosulfate solution according to equation (2). The end point was indicated by the total disappearence of the characteristic yellow colour of iodine.

The silyl ether **222** was dissolved in a solution of dimethyldioxirane in acetone at 0 °C. Only 1 equivalent of DMDO was added, as we did not want to oxidise the double bond in the ring even if tri-substituted double bonds are relatively unreactive, and even given that silyl enol ethers are electron rich and highly reactive. A mixture of two inseparable diastereoisomers **194** and **195** was obtained in a ratio 77:23 (Scheme 193).
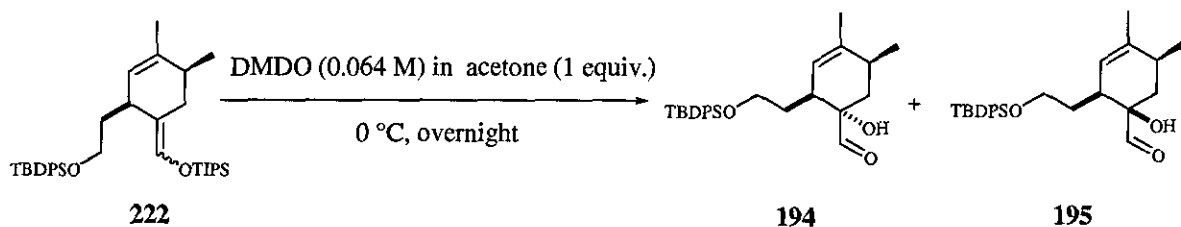
Scheme 193

Nothing allowed us to determine which of the two diastereoisomers was our target. Nevertheless, it seems reasonable to think that **195** is the minor product because the α-hydroxylation occurs, in this case, on the most hindered face. A challenge with this step is obviously the purification of **195**. However, as **194** and **195** co-

elute on silica gel it is possible that the mixture can be carried forward and separated at a later stage. The five steps described by Vahedi need to be repeated on this material, which contains the correct stereochemistry in order to complete the synthesis of target **11** (Scheme 195). Since my PhD was coming to its end, this work could not be done and will have to be carried on by the next researcher.

2.6. Conclusion

The challenge proposed for my PhD was to complete the synthesis of the diastereoisomer **11** of the oxaspirobyciclic unit already synthesised in our laboratories.

11
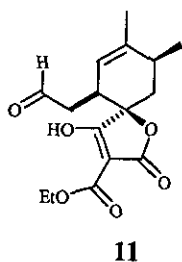
The desired stereochemistry was finally obtained by performing an epoxidation of a silyl enol ether **222** as the second stereochemical defining key step with the Diels-Alder reaction between diene **92** and acrolein. Finally, **222** was obtained in a 5.7% overall yield from **90** and the sequence of reactions was achieved in an eight step strategy and afforded the α-hydroxy lactone **195** as a diasteroisomeric mixture with **194** (Scheme 194).
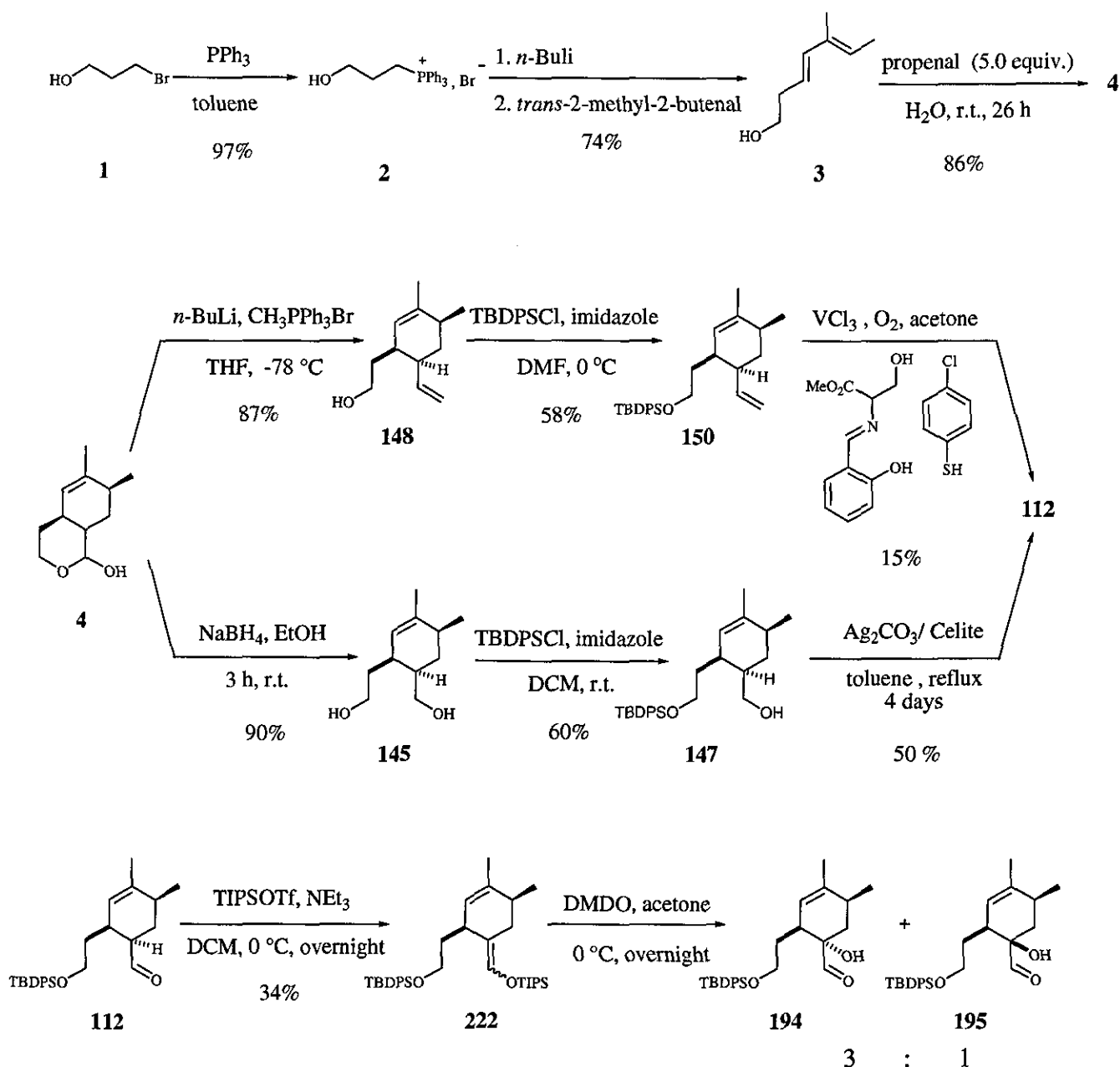
Scheme 194

After simple deprotection of **195**, the next researcher will only have to perform the oxidation to the α-hydroxy lactone **9** and repeat the work achieved by Vahedi on material which will now lead to spirocycle **11** with the same stereochemistry as that proposed for tetronothiodin (Scheme 195).
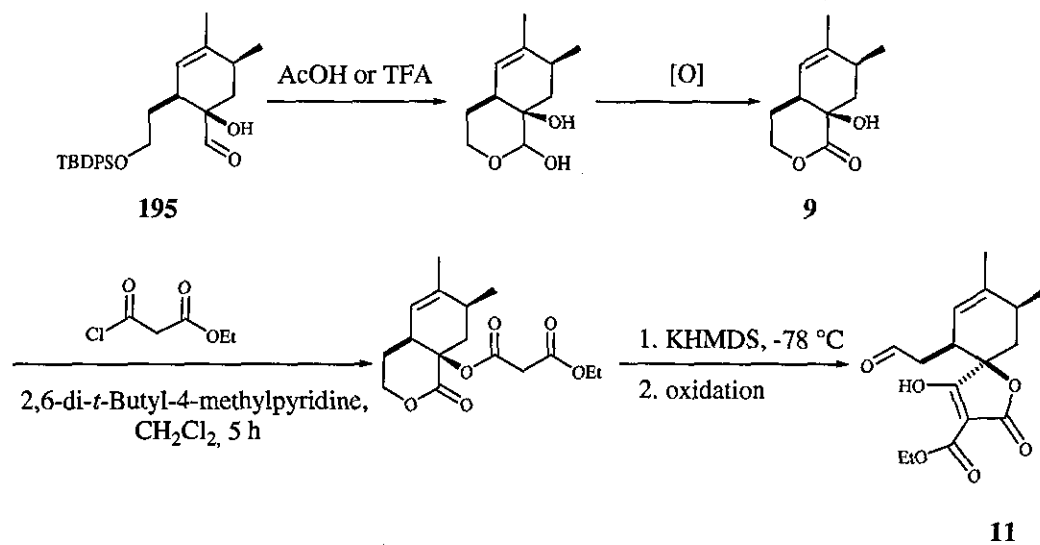
Scheme 195

2.7. References

(1)   Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44.

(2)   Streitwieser, J. A.; Rajca, A.; McDowell, R. S.; R., G. *J. Am. Chem. Soc.* **1987**, *109*, 4184.

(3)   Horner, L.; Hoffman, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61.

(4)   Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(5)   Dubert, O.; Gautier, A.; Condamine, E.; Piettre, S. R. *Org. Lett.* **2002**, *4*, 359.

(6)   Liu, Y. Y.; Thom, E.; Liebman, J. *Heterocycl. Chem.* **1979**, *16*, 799.

(7)   Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778.

(8)   Vedejs, E.; Meier, P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823.

(9)   Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, J. H. R.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664.

(10) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948.

(11) Vedejs, E.; Fleck, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 5861.

(12) Vedejs, E.; Marth, C. F. *Tetrahedron Lett.* **1987**, *28*, 3445.

(13) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821.

(14) Vedejs, E.; Fleck, T.; Hara, S. *J. Org. Chem.* **1982**, *52*, 4637.

(15) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1984**, *107*, 217.

(16) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

(17) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278.

(18) Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.

(19) Stephenson, L. M.; Smith, D. E.; Current, S. P. *J. Org. Chem.* **1982**, *47*, 4170.

(20) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Vol. 1; 3d ed.; Plenum Press: Bruxelles, 1990; Vol. 1.

(21) March, J. *Advanced Organic Chemistry; Reactions; Mechanisms and Structures*; Wiley-Interscience Publication: New York, 1992.

(22) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

(23) Gilchrist, T. L.; Storr, R. C. *Organic Reactions and Orbital Symmetry*; Second ed.; Cambridge University Press: London, 1979.

(24) Claiden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2001.

(25) Fleming, I. *Frontier Orbitals and Organic Chemical reactions*; Wiley: New York, 1976.

(26) Bulman Page, P. C.; Batchelor, K. J.; Hindley, S. J. *Abstr. Pap. Am. Chem. Soc.* **1999**, *218*, 548.

(27) Emmons, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 608.

(28) Horner, L.; Jurgens, E. *Chem. Ber.* **1957**, *90*, 2184.

(29) Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 4240.

(30) Davis, F. A.; Kumar, A.; Chen, B. C. *J. Org. Chem.* **1991**, *56*, 1143.

(31) Page, P. C. B.; Heer, J. P.; Bethell, D.; Lund, A.; Collington, E. W.; Andrews, D. M. *J. Org. Chem.* **1997**, *62*, 6093.

(32) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083.

(33) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

(34) Holmlund, C. E.; Andres, W. W.; Shay, A. J. *J. Am. Chem. Soc.* **1959**, *81*, 4748.

(35) Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1972**, 1.

(36) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825.

(37) Herold, P.; Mohr, P.; Tamm, C. *Helv. Chem. Acta* **1983**, *66*, 744.

(38) Boeckman, R. K.; Cheon, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 4112.

(39) Krohn, K.; Sarstedt, B. *Angew. Chem.* **1983**, *22*, 875.

(40) Hanessian, S.; Sahoo, S. P.; Murray, P. M. *Tetrahedron Lett.* **1985**, *26*, 5631.

(41) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944.

(42) Anderson, J. C.; Smith, S. C. *Synth. Lett.* **1990**, 107.

(43) Little, R. D.; Myong, S. O. *Tetrahedron* **1980**, *21*, 3339.

(44) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*.

(45) Vedejs, E.; Engler, D. A.; Telshow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(46) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578.

(47) Karasch, M. S.; Mosher, R. A.; Bengelsdorf, I. S. *J. Org. Chem.* **1960**, *25*, 1000.

(48) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, *21*, 1731.

(49) Doering, W. v. E.; Haines, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 482.

(50) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294.

(51) Sharp, B.; Patton, A.; Witcomb, G. P. *J. Am. Chem. Soc.* **1951**, *73*, 5600.

(52) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.

(53) Newman, M. S.; Zuech, E. A. *J. Org. Chem.* **1962**, *27*, 1436.

(54) Heiszwolf, G. J.; Kloosterziel, H. *Chem. Commun.* **1966**, 51.

(55) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *Org. Lett.* **2003**, *5*, 4037.

(56) Ladjama, D.; Riehl, J. *Chem. Commun.* **1979**, 504.

(57) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Baldwin, J. E. ed.; Pergamon Press: Oxford, 1986.

(58) Jones, D. N.; Mundy, N.; Whitehouse, R. D. *Chem. Commun.* **1970**, 86.

(59) Baker, R.; Carrick, C.; Leeson, P. D.; Lennon, I. C.; Liverton, N. J. *Chem. Commun.* **1991**, 298.

(60) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.

(61) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(62) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75.

(63) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(64) Reich, H. J. *J. Org. Chem.* **1974**, *39*, 428.

(65) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429.

(66) Arbelo, D. O.; Prieto, J. A. *Tetrahedron Lett.* **2002**, *43*, 4111.

(67) Kaneti, I. *Tetrahedron* **1986**, *42*, 4017.

(68) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280*, 263.

(69) Hawthorne, M. F. *J. Am. Chem. Soc.* **1957**, *79*, 2510.

(70) Hindley, S. J.; Loughborough University, 1998.

(71) Batchelor, K. J.; Loughborough University, 2001.

(72) Ceccherelli, P.; Curini, M.; Marcotulloi, M. C.; Epifano, F.; Rosati, O. *Synth. Commun.* **1998**, *28*, 3057.

(73) Galobardes, M. R.; Pinnick, H. W. *Tetrahedron Lett.* **1981**, *22*, 5235.

(74) Freeman, F.; Lin, D. K. *J. Org. Chem.* **1971**, *36*, 1335.

(75) Steliou, K.; Poupart, M. *J. Org. Chem.* **1985**, *50*, 4971.

(76) Palomo, C.; Aizpurua, J. M.; Oiarbide, M. *Tetrahedron Lett.* **1987**, *28*, 5361.

(77) Bartlett, P. A.; Green, F. R.; Webb, T. R. *Tetrahedron Lett.* **1977**, 331.

(78) Ley, S. V.; Griffith, W. P.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625.

(79) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(80) Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 207.

(81) Tokunaga, Y.; Yagihashi, M.; Ihara, M.; Fukumoto, K. *Chem. Commun.* **1995**, 955.

(82) Pinnick, H. W. *Org. React.* **1990**, *38*, 655.

(83) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.

(84) Kirchhoff, R. *Tetrahedron Lett.* **1976**, 2533.

(85) Urpi, F.; Viarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 7499.

(86) Culford Bell, R.; Briggs, L. H. *J. Chem. Soc.* **1942**, 1.

(87) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233.

(88) Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3861.

(89) Wilson, H.; Lewis, E. S. *J. Am. Chem. Soc.* **1972**, *94*, 2283.

(90) Boyle, P. H.; Convery, M. A.; Davis, A. P.; Hosken, G. D.; Murray, B. A. *Chem. Commun.* **1992**, 239.

(91) Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 5149.

(92) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.

(93) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(94) Surprenant, S.; Chan, W. Y.; Berthelette, C. *Org. Lett.* **2003**, *5*, 4851.

(95) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140.

(96) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19.

(97) Nicolaou, K. C.; Magolds, R. L. *J. Org. Chem.* **1981**, *46*, 1506.

(98) Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2717.

(99) Fetizon, M.; Jurion, M. *Chem. Commun.* **1972**, 382.

(100) Bulman-Page, P. C.; Roberts, R. A.; Paquette, L. A. *Tetrahedron. Lett.* **1983**, *24*, 3555.

(101) Roush, R.; D'Ambra, T. E. *J. Org. Chem.* **1980**, *45*, 3927.

(102) Bradley, D. C.; Hammersley, P. A. *J. Chem. Soc. Jap., Chem. Lett.* **1967**, 1894.

(103) Schmidt, R. R.; Abele, W. *Angew. Chem.* **1982**, *21*, 302.

(104) Caruso, A. J.; Polonsky, J.; Rodriguez, B. S. *Tetrahedron Lett.* **1982**, *23*, 2567.

(105) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051.

(106) Peng, S.-Q.; Winterfeldt, E. *Liebigs Ann. Chem.* **1989**, 1045.

(107) Paquette, L. A.; Bulman-Page, P. C.; Pansegrau, P. D.; Wiedeman, P. E. *J. Org. Chem.* **1988**, *53*, 1450.

(108) Corey, E. J.; Pan, B. C.; Hua, D. H.; Deardorff, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816.

(109) Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, *23*, 2619.

(110) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829.

(111) Mori, T.; Inokuchi, H. *J. Chem. Soc. Jap., Chem. lett.* **1992**, 1873.

(112) Dorsey, A. D.; Barbarow, J. E.; Trauner, D. *Org. Lett.* **2003**, *5*, 3237.

(113) Ermert, P.; Vasella, A. *Helv. Chem. Acta* **1991**, *74*, 2043.

(114) Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron* **1998**, *54*, 8123.

(115) Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron Asym.* **2001**, *12*, 2977.

(116) Johansson, T.; Kers, A.; Stawinski, J. *Tetrahedron Asym.* **2001**, *42*, 2217.

(117) Godin, G.; Compain, P.; Masson, G.; Martin, O. R. *J. Org. Chem.* **2002**, *67*, 6960.

(118) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791.

(119) Pearson, W. H.; Bergmeier, S.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977.

(120) Oestreich, M.; Frohlich, R.; Hoppe, D. *Tetrahedron Lett.* **1998**, *39*, 1745.

(121) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

(122) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214.

(123) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(124) Varkey, T. E.; Whitfield, G. F.; Swern, D. *J. Org. Chem.* **1974**, *39*, 3365.

(125) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

(126) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(127) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2741.

(128) Poos, G. I.; Arth, G. E.; Beyler, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 422.

(129) Andersson, F.; Samuelsson, B. *Cabohydr. Res.* **1984**, *129*, C1.

(130) Brown, H. C.; Rao, C. G.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2809.

(131) Herscovici, J.; Antonakis, K. *Chem. Commun.* **1980**, 561.

(132) Engler, T. A.; Sampath, U.; Naganathan, S.; Velde, D. V.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712.

(133) Sharma, P. K. *Synth. Commun.* **1993**, *23*, 389.

(134) Brown, P. E.; Lewis, R. A.; Waring, M. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2979.

(135) Zimmer, H.; Larkin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.

(136) Saa, J. M.; Llobera, A.; Garcia-Raso, A.; Costa, A.; Deya, P. M. *J. Org. Chem.* **1988**, *53*, 4263.

(137) Garcia-Raso, A.; Deya, P. M.; Saa, J. M. *J. Org. Chem.* **1986**, *51*, 4285.

(138) Palmisano, G.; Danieli, B.; Lesma, G.; Trupiano, F. *J. Org. Chem.* **1988**, *53*, 1056.

(139) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem.* **1979**, *18*, 917.

(140) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(141) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(142) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(143) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(144) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(145) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171.

(146) Kakis, F. J.; Fetizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P.; Prange, T. *J. Org. Chem.* **1974**, *39*, 523.

(147) Balogh, V.; Fetizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339.

(148) Anelli, P. L.; Biffi, C.; Montanari, F.; S., Q. *J. Org. Chem.* **1987**, *52*, 2559.

(149) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *19*, 3041.

(150) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999.

(151) Ley, S. V.; Griffith, W. P.; Withcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(152) Scheiss, P.; Dinkel, R. *Tetrahedron Lett.* **1975**, *29*, 2503.

(153) Krafft, M. E.; Cheung, Y. Y.; A., A. K. *J. Org. Chem.* **2001**, *66*, 7443.

(154) Posner, G. H.; Crouch, R. D.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, *56*, 6981.

(155) Cantor, S. E.; Tarbell, D. S. *J. Am. Chem. Soc.* **1964**, *86*, 2902.

(156) Haines, A. H. *Chem. Org. Soc.* **1991**, *7*, 437.

(157) Majetich, G.; Defauw, J.; Ringold, C.; Palmisano, G. *J. Org. Chem.* **1988**, *53*, 50.

(158)   Ireland, R. E.; Maienfisch, P. *J. Org. Chem.* **1988**, *53*, 640.

(159)   Baucherel, X.; Uziel, J.; Juge, S. *J. Org. Chem.* **2001**, *66*, 4504.

(160)   Beshara, C. S.; Hall, A.; Jenkins, R. L.; Teyron, C. J.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. *Chem. Commun.* **2005**, 1478.

(161)   House, H. O.; Richey, F. A. *J. Org. Chem.* **1969**, *34*, 1430.

(162)   Cummins, C. H.; Coates, R. M. *J. Org. Chem.* **1983**, *48*, 2070.

(163)   Carpino, L. A.; Giza, C. A.; Carpina, B. A. *J. Am. Chem. Soc.* **1959**, *81*, 955.

(164)   Boyland, E.; Nery, R. *J. Chem. Soc. (C)* **1966**, 346.

(165)   Williamson, K. L.; Coburn, J. I.; Herr, M. F. *J. Org. Chem.* **1967**, *32*, 3934.

(166)   Hoppe, D.; Lüßmann, J.; Jones, P. G.; Schmidt, D.; Sheldrick, G. M. *Tetrahedron Lett.* **1986**, *27*, 3591.

(167)   Hoppe, D.; Tarara, G.; Wilckens, M. *Synthesis* **1989**, 83.

(168)   Kramer, T.; Hoppe, D. *Tetrahedron Lett.* **1987**, *28*, 5149.

(169)   Mimoun, H. *Comprehensive Coordination Chemistry*; Wilkinson, G. ed.; Pergamon: Oxford, 1987; Vol. 6.

(170)   Caradonna, P. *Encyclopedia of Organic Chemistry*; Vol. 6.

(171)   Rozen, S.; Mishani, E.; M., K. *J. Am. Chem. Soc.* **1992**, *114*.

(172)   Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

(173)   Paquette, L. A.; Lin, H.-S.; Gallucci, J. C. *Tetrahedron Lett.* **1987**, *28*, 1363.

(174)   Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.

(175)   Hwu, J. R.; Wong, F. F.; Huang, J. J.; Tsay, S. C. *J. Organomet. Chem.* **1997**, *62*, 4097.

(176)   Gleiter, R.; Krämer, R.; Irngartinger, H.; Bissinger, C. *J. Org. Chem.* **1992**, *57*, 252.

(177)   Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

(178)   Angelis, Y.; Zhang, X.; Orfanopoulos, M. *Tetrahedron Lett.* **1996**, *37*, 5991.

(179)   Bovicelli, P.; Mincione, E.; Antonioletti, R.; Bernini, R.; Colombari, M. *Synth. Commun.* **2001**, *31*, 2955.

Chapter 3

Experimental detail

3. Experimental detail

3.1. General experimental procedures

3.1.1. Preparation of glassware

Reactions were carried out in round-bottomed flasks which had previously been dried in an oven at 150 °C for a minimum of three hours. The flasks were allowed to cool in a desiccator over P_2O_5, and were flushed with nitrogen before being covered with septum caps. Other equipment used, such as needles, syringes, distillation kits, magnetic stirrer bars and cannulas were dried and allowed to cool in a desiccator. All air-sensitive reactions were carried out under a nitrogen atmosphere; the solvents and reagents were introduced *via* syringe and cannula.

3.1.2. Solvents and reagents

Solvents, unless otherwise stated, were either obtained in an anhydrous form from commercially available sources. Dimethylformamide and dimethylsulfoxide which were bought in Sure Seal® bottles from Sigma Aldrich Chemical Co. Ltd., Lancaster Synthesis Ltd. and Strem Chemical Co. Ltd.

The other solvents were distilled and dried over the following reagents:

- Dichloromethane: distilled over phosphorus pentoxide or calcium hydride.
- Diethyl ether: distilled over sodium and benzophenone.
- Ethyl acetate: distilled over calcium chloride.
- Light petroleum ether: distilled over calcium chloride.
- Tetrahydrofuran: distilled over sodium and benzophenone.
- Toluene: distilled over calcium hydride.

Where applicable, deionised water was used in experiments.

3.1.3. Normal work-up procedure

Reactions were usually worked-up by the addition of saturated aqueous ammonium chloride solution. Extraction of the aqueous layer was achieved with dichloromethane, diethyl ether or ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate or sodium sulfate which was removed by filtration. Solvents were removed by evaporation under reduced pressure.

3.1.4. Purification methods

Compounds were purified using flash column chromatography, recrystallisation or vacuum distillation methods.

Flash silica gel column chromatography was carried out using Fluka Kiesel gel 60, 0.04-0.063 mm particle size. Hand bellows were used when required to apply pressure. Samples were applied as liquids, saturated aqueous solutions of the appropriate solvents system, or pre adsorbed onto Celite®.

Thin layer chromatography (TLC) was carried out using aluminium-backed plates coated with a 0.25 mm layer of silica gel 60 H containing fluorescer. The plates were visualised using ultra-violet light, and potassium permanganate on potassium molybdate dips.

Purification by vacuum distillation was achieved using a Buchi GKR-51 Kügelrohr as heat source for bulb-to-bulb distillations. Condensation of the liquid product was achieved by covering the bulb in acetone-soaked cotton wool.

3.1.5. Spectra and analyses

^{1}H NMR spectra were recorded on a Brüker DPX400 spectrometer. The internal standard used in the ^{1}H spectra was resonance of tetramethylsilane, assigned as 0

ppm. In the ^{13}C spectra the internal standard used was the central peak of the deuteriochloroform triplet, assigned as 77 ppm.

Chemical shifts (δ) are given in ppm downfield of tetramethyl silane (TMS). Coupling constants (J) are measured in Hertz. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), and combinations of these, for example, double doublet (dd), double triplet (dt), etc.

Infrared spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 Fourier transform spectrometer or a Pye-Unicam SP2000 spectrophotometer, in the range 4000-600 cm^{-1}. All samples were run on sodium chloride plates as thin films of pure liquid, deuteriochloroform solutions or Nujol® mulls.

Electron ionisation (EI), chemical ionisation (CI) and fast-atom bombardment (FAB) mass spectra were recorded on a Jeol-SX102.

Melting points were recorded on a Stuart Scientific (melting point apparatus SMP3), the melting points are uncorrected. Elemental analyses were performed on a Perkin Elmer 2400 CHN elemental Analyser.

3.2. Experimental procedures and analyses data

3-Hydroxypropyl triphenylphosphonium bromide 2
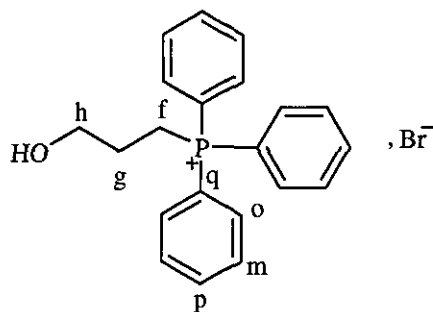
A mixture of 3-bromo-1-propanol **1** (25.0 g, 180.0 mmol) and triphenylphosphine (31.4 g, 120.0 mmol) in dry toluene (60 mL) was heated under reflux for 26 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature, filtered, washed with cold toluene, and dried *in vacuo* to yield **2** as a colourless solid (46.3 g, 97%); mp 232-233 °C (Found: M^+, 400.05836. $C_{21}H_{22}BrOP$ requires 400.05916); v_{max} (neat)/cm^{-1} 3444 (OH), 750 (ArCH); δ_H (400 MHz, CDCl$_3$) 1.7-1.8 (2H, m, 2H$_g$), 3.7-3.8 (4H, m, 2H$_f$, 2H$_h$), 4.8 (1H, br, OH), 7.5-7.8 (15H, m, 15 H arom); δ_C (400 MHz, CDCl$_3$) 21.3 (C$_g$), 26.3 (C$_f$), 60.2 (C$_h$), 120.5 (C$_q$), 128.2 (C$_m$), 128.8 (C$_p$), 135.1 (C$_o$).

(*E*,*E*)-5-Methyl-hepta-3,5-dien-1-ol 3
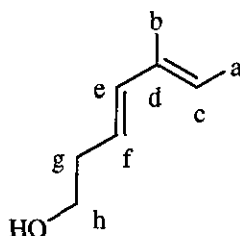
A solution of 3-Hydroxypropyl triphenylphosphonium bromide **2** (47.6 g, 118.4 mmol) in dry tetrahydrofuran (1 L) was allowed to cool to 0 °C under a nitrogen atmosphere. A solution of *n*-butyllithium (94.4 mL, 2.5 M solution in hexanes, 236.8 mmol) was added and the mixture was stirred for 15 minutes followed by addition of *trans*-2-methyl-butenal (9.9 g, 118.4 mmol). The reaction mixture was stirred at 0 °C for 22 hours. Brine (80 mL) was added, the organic layer was separated and aqueous layer washed with diethyl ether (5 × 50 mL). The combined organic layers were dried over magnesium sulfate, and concentrated *in vacuo*. The product was then poured into a solution of *tert*-butoxymethyl ether in which a majority of the triphenylphosphine formed a precipitate. Three precipitations allowed a better subsequent purification. Purification of the crude product by Kügelrohr distillation (75-90 °C under 0.1 mbar) afforded **3** as a colourless oil (5.4 g, 72%) (Found: M$^+$, 126.11001. $C_8H_{14}O$ requires 126.10447); v_{max} (DCM)/cm^{-1} 3348 (OH), 3030 (=CH), 1047 (C-O); δ_H (400 MHz, CDCl$_3$) 1.70 (3H, d, ^3J 8.4, 3H$_a$), 1.73 (3H, s, 3H$_b$), 2.2-2.4 (2H, q, ^3J 6.4, 2H$_g$), 3.6 (2H, t, ^3J 6.0, 2H$_h$), 5.4-5.6 (2H, m, H$_c$, H$_f$), 6.2 (1H, d, ^3J 15.6, H$_e$); δ_C (400 MHz, CDCl$_3$) 12.3 (C$_a$), 14.1 (C$_b$), 37.7 (C$_g$), 63.4 (C$_h$), 123.2 (C$_c$ or C$_f$), 126.0 (C$_c$ or C$_f$), 134.0 (C$_d$), 138.5 (C$_e$); *m/z* (EI) 126 (M$^+$, 30%), 108 (46), 95 (28), 77 (100), 67 (54), 55 (42), 41 (78).

6,7-Dimethyl-3,4,4a,7,8,8a-hexahydro-1H-isochromen-1-ol 4
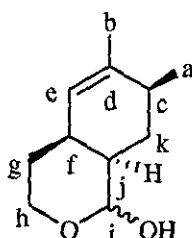
Distilled propenal was added by syringe pump to a solution of diene **3** (2.8 g, 22.0 mmol) in HPLC water (30 mL) in which hydroquinone (6.2 g, 5.0 equiv.) had been previously dissolved. The mixture was stirred for between 24 and 48 hours at room temperature under a nitrogen atmosphere. The mixture was dissolved by dichloromethane (40 mL) and the aqueous phase washed with dichloromethane (3 × 20 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was purified by Kügelrohr distillation (130-150 °C under 0.1 mbar) to give the lactol **4** as a yellow oil (3.4 g, 86%) (Found: M^+, 182.13068. $C_{11}H_{18}O_2$ requires 182.13068); v_{max} (DCM)/cm^{-1} 3399 (OH), 2936 (=CH), 2877 (O-C-O); δ_H (400 MHz, CDCl$_3$) 1.00 (3H, d, ^3J 7.2, 3H$_a$), 1.45-1.56 (3H, m, H$_g$, 2H$_k$), 1.57 (3H, s, 3H$_b$), 1.60-1.90 (2H, m, H$_j$, H$_{g'}$), 2.20 (1H, t, ^3J 4.0, H$_c$), 2.40 (1H, m, H$_f$), 3.09 (1H, br, OH), 3.40-3.50 (1H, dt, ^2J 11.2, ^3J 4.4, H$_h$), 3.50-3.60 (1H, ddd, ^2J 11.2, ^3J 4.4, ^3J 2.4, H$_h$), 3.90-3.97 (1H, ddd, ^2J 11.2, ^3J 4.4, ^3J 2.4, H$_{h'}$), 3.97-4.10 (1H, dt, ^2J 11.2, ^3J 4.4, H$_{h'}$), 4.80 (1H, d, ^3J 2.8, H$_i$), 5.00 (1H, s, H$_i$), 5.38 (1H, d, ^3J 4.6, H$_e$); δ_C (400 MHz, CDCl$_3$) 20.1 and 20.3 (C$_a$), 21.5 and 21.5 (C$_b$), 25.2 (C$_g$), 29.1 and 31.7 (C$_k$), 29.6 (C$_f$), 34.8 and 34.9 (C$_c$), 37.9 and 39.0 (C$_j$), 56.2 and 59.6 (C$_h$), 96.8 and 97.9 (C$_i$), 125.9 and 126.5 (C$_e$), 138.4 and 139.2 (C$_d$); *m/z* (EI) 182 (M^+, 40%), 164 (11), 149 (10), 136 (14), 121 (30), 107 (51), 93 (100), 91 (41), 77 (28), 67 (17), 55 (14), 41 (20).

The following isomer was isolated from the mixture:
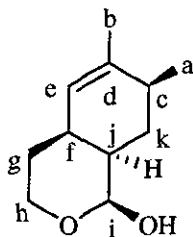
δ_H (400 MHz, CDCl$_3$) 1.00 (3H, d, ^3J 6.8, 3H$_a$), 1.43-1.67 (4H, m, 2H$_g$, 2H$_k$), 1.61 (3H, s, 3H$_b$), 1.79 (1H, dt, ^3J 13.2, ^3J 4.0, H$_j$), 2.16-2.19 (1H, m, H$_c$), 2.40 (1H, dt, ^3J 5.2, ^3J 4.4 H$_f$), 3.53 (1H, ddd, ^2J 11.0, ^3J 4.6, ^3J 2.8, H$_h$), 3.79 (1H, dt, ^2J 11.0, ^3J 2.8, H$_{h'}$) 4.88 (1H, s, H$_i$), 5.37 (1H, br d, ^3J 4.4, H$_e$); δ_C (400 MHz, CDCl$_3$) 20.1 (C$_a$), 21.4 (C$_b$), 29.3 (C$_g$), 30.0 (C$_f$), 31.8 (C$_k$), 35.02 (C$_c$), 37.9 (C$_j$), 59.8 (C$_h$), 96.8 (C$_i$), 126.5 (C$_e$), 138.4 (C$_d$).

6,7-Dimethyl-3,4,4a,7,8,8a-hexahydro-isochromen-1-one 5
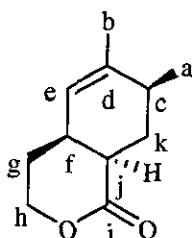
The mixture of the lactol **4** (2.4 g, 13.2 mmol) and pyridinium dichromate (14.9 g, 3.0 equiv.) in dry *N,N*-dimethylformamide (30 mL) under a nitrogen atmosphere was stirred first at 0 °C for 1 hour, then at room temperature for 5 hours. The solvent was removed *in vacuo*. The residue was dissolved in ethanol (20 mL) and allowed to stir for 10 minutes. The solution was poured into ethyl acetate (50 mL). A mix of silica gel-Celite® (1:1) was added and the mixture stirred for 10 minutes. The product was collected by filtration, the waste chromium residues trapped in silica gel-Celite® were easily removed. The solvent was removed *in vacuo*. Flash column chromatography using dichloromethane/ethyl acetate (5:1) afforded the product **5** as a colourless oil (1.6 g, 67%) (Found: M^+, 180.11490. $C_{11}H_{16}O_2$ requires 180.11503); v_{max} (DCM)/cm^{-1} 2962 (=CH), 1729 (O=C-O-C), 1066 (2 bands, O=C-O-C)); δ_H (400 MHz, CDCl$_3$) 1.00 (3H, d, ^3J 7.1, 3H$_a$), 1.75 (3H, s, 3H$_b$), 1.60-1.80 (2H, m, H$_g$, H$_k$), 1.80-1.95 (1H, ddd, ^2J 12.7, ^3J 3.6, ^3J 0.8, H$_{g'}$), 2.00-2.10 (1H, ddd, ^2J 13.1, ^3J 4.6, ^3J 1.3, H$_{k'}$), 2.10-2.30 (1H, br q, ^3J 10.3, H$_c$), 2.40-2.60 (1H, m, H$_f$), 2.70-2.90 (1H, m, H$_j$), 4.10-4.30 (1H, td, ^2J 12.6, ^3J 3.2, H$_h$), 4.30-4.50 (1H, ddd, ^2J 12.2, ^3J 4.0, ^3J 1.6, H$_h$), 5.29 (1H, s, H$_e$); δ_C (400 MHz, CDCl$_3$) 19.6 (C$_a$), 20.1 (C$_b$), 22.2 (C$_g$), 33.3 (C$_k$), 33.4 (C$_f$), 33.9 (C$_c$), 40.1 (C$_j$), 69.2 (C$_h$), 123.0 (C$_e$), 140.7 (C$_d$), 174.7 (C$_i$); *m/z* (EI) 180 (M^+, 64%), 165 (20), 152 (29), 121 (34), 107 (100), 93 (93), 77 (49), 67 (21), 53 (20), 43 (62).

8a-Hydroxy-6,7-dimethyl-3,4,4a,7,8,8a-hexahydro-isochromen-1-one 6

α-Hydroxylation using camphorsulphonyl oxaziridine 29

In a dry flask was placed dry tetrahydrofuran (10 mL) at -78 °C, followed by sodium bis(trimethylsilyl)amide (3.3 mL, 1.0 M solution in tetrahydrofuran, 3 equiv.). The lactone **5** (0.2 g, 1.1 mmol) in tetrahydrofuran (3 mL), was added dropwise to the reaction mixture, and stirred for 1 hour, followed by addition of (1S)-(+)-(10-camphorsulphonyl)oxaziridine **29** (0.8 g, 3.0 equiv.) in tetrahydrofuran (4 mL). The mixture was stirred for 1.5 hours at -78 °C, and 1 hour at -5 °C and quenched by adding brine (30 mL). The solution was acidified by hydrochloric acid to pH 1, and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate and the solvent removed *in vacuo*. Purification of the crude product by flash column chromatography using dichloromethane / ethyl acetate (7:1) afforded the hydroxylactone **6** as a colourless oil (0.1 g, 57%);

α-Hydroxylation using MoOPD[1]

A solution of dry diisopropylamine (1.6 mL, 1 equiv.) in dry tetrahydrofuran (10 mL) was allowed to stir at -78 °C for 30 minutes. A solution of *n*-butyllithium (2.5 M in hexanes, 5.5 mL, 1.2 equiv.) was added, and the reaction mixture warmed to 0 °C then stirred for 30 minutes. The solution was allowed to cool to -78 °C. A solution of lactone **5** (0.2 g, 1.1 mmol) in tetrahydrofuran (5 mL), was added

dropwise to the reaction mixture, and stirred for 30 minutes in a nitrogen atmosphere. MoOPD **38** (0.5 g, 1.3 equiv.) was added to the formed enolate and an orange colour developed as **38** slowly dissolved. After 1 hour at -70 °C, the cooling bath was removed resulting in a gradual colour change to blue.

After the reaction mixture reached 0 °C, water was added and the product was extracted with diethyl ether (4 × 30 mL). The combined organic phases were washed with a solution of carbonate (5%) and hydrochloric acid (2%) to remove molybdenum salts and pyridine, dried over magnesium sulfate and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography using dichloromethane / ethyl acetate (7:1) afforded the hydroxylactone **6** as a colourless oil (0.03 g, 14%);

α-Hydroxylation using O_2/P(OEt)$_3$

Triethyl phosphate (0.5 mL) was added to a solution of sodium hydride (10 mL) in *t*-butyl alcohol (2mL) and *N,N*-dimethylformamide (20 mL). The mixture was allowed to cool to -25 °C under an oxygen atmosphere. A solution of lactone **5** in tetrahydrofuran (8 mL) was added. The atmosphere of oxygen was continued for 22 hours. A solution of sodium hydroxide (0.5 g) in methanol-water (2:1, 15 mL) was added; the mixture was stirred for 1 hour at room temperature. After acidification with acetic acid, the product was precipitated by addition of water, isolated by filtration, and dried over sodium sulfate. Purification of the crude product by flash column chromatography using dichloromethane / ethyl acetate (7:1) afforded the hydroxylactone **6** as a colourless oil (0.1 g, 47%); (Found: M$^+$, 196.10995. $C_{11}H_{16}O_3$ requires 196.10995); υ_{max} (DCM)/cm^{-1} 3431 (OH), 2964 (=CH), 1722 (O-C=O), 1035 (2 bands O=C-O)); δ_H (400 MHz, CDCl$_3$) 1.06 (3H, d, ^3J 7.1, 3H$_a$), 1.60-1.67 (1H, dd, ^2J 13.7, ^3J 10.5, H$_k$), 1.73 (3H, s, 3H$_b$), 1.73-1.83 (1H, ddd, ^2J 14.7, ^3J 6.1, ^3J 4.5, H$_g$), 1.85-2.03 (1H, ddd, ^2J 13.7, ^3J 5.6, ^3J 1.4, H$_{k'}$), 2.04-2.09 (1H, dddd, ^2J 14.7, ^3J 4.6, ^3J 4.0, ^3J 3.3, H$_{g'}$), 2.45-2.50 (1H, m, H$_c$), 2.50-2.60 (1H, m, H$_f$), 3.09 (1H, s, OH), 4.28-4.35 (1H, ddd, ^2J 11.2, ^3J 10.7, ^3J

3.3, H_h), 4.37-4.44 (1H, ddd, ^2J 12.0, ^3J 4.4, ^3J 4.1, $H_{h'}$), 5.30 (1H, s, H_e); δ_C (400 MHz, CDCl$_3$) 18.6 (C_a), 21.0 (C_b), 29.9 (C_c), 30.1 (C_g), 39.3 (C_f), 39.9 (C_k), 68.9 (C_h), 72.3 (C_j), 121.2 (C_e), 138.8 (C_d), 177.3 (C_i); m/z (EI) 196 (M$^+$, 22%), 178 (30), 163 (19), 150 (44), 135 (31), 124 (33), 109 (100), 93 (44), 77 (27), 67 (28), 55 (20), 41 (35).

(+)-[(3,3-Dimethoxycamphoryl) sulfonyl]oxaziridine 29[2]
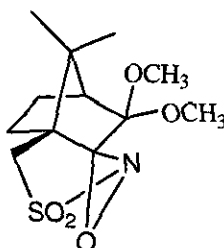
The oxaziridine was prepared as reported by Bulman Page and Bethell.[2] Potassium carbonate (2.0 g, 14.5 mmol) was stirred in methanol (20 mL) at room temperature, and hydrogen peroxide (3.3 mL, 4.0 equiv.) was added, followed by (+)-[(3,3-dimethylcamphoryl) sulfonyl]imine 28 (2.0 g, 1.0 equiv.). The mixture was stirred overnight.

The organic layer was separated and the aqueous phase washed with dichloromethane (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium sulfite (10 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo*, in a water bath with the temperature not exceeding 40 °C, yielded 29 as a colourless solid (1.4 g, 92%), mp 188-190 °C (from EtOH); $[\alpha]^{20}_D$ +91.3 (c 3.39 in CHCl$_3$); υ_{max} (CHCl$_3$)/cm^{-1} 1355, 1164; (Found: C, 49.92; H, 6.68; N, 4.71. C$_{12}$H$_{19}$NO$_5$S requires C, 49.81; H, 6.62; N, 4.84%); δ_H (300 MHz, CDCl$_3$) 1.06 (3H, s, CCH_3), 1.32 (3H, s, CCH_3), 1.76-1.98 (5H, m, 2CH_2, CH), 3.20 (2H, q, ^4J 14, SCH_2), 3.28 (3H, s, OCH_3), 3.34 (3H, s, OCH_3); δ_C (300 MHz, CDCl$_3$) 11.9 (*C*H$_2$), 20.5 (C*C*H$_3$), 21.7 (*C*H$_2$), 28.2 (C*C*H$_3$), 47.5 (S*C*H$_3$), 50.5 (O*C*H$_3$), 50.8 (O*C*H$_3$), 53.0 (C$_4$*C*), 54.6 (C$_3$*C*), 102.9 (N-*C*-O), 121.3 (O-*C*-O).

Oxodiperoxymolybdenum(water)-1,3-dimethyl-3,4,5,6-terahydro-2(1H)-pyrimidinone 37[3]

L = DMPU
L' = H_2O
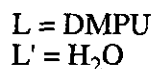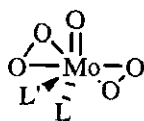
A solution of Hydrogen peroxide (30%) (30 mL) was added to MoO_3 **36** (5.0 g, 35.0 mmol). The mixture was stirred vigorously and the temperature maintained between 30 and 40 °C for 3.5 hours. The reaction mixture was allowed to cool to room temperature and filtered to remove solids. The yellow solution was cooled to 10 °C. DMPU (4.2 mL, 1 equiv.) was added to the solution under stirring and the crystalline precipitate was collected and recrystalised from hot methanol (40 °C) to give $MoO_5.H_2O.DMPU$ **37** as a yellow crystalline solid (10.3 g, 96%); mp 76 °C (lit.,[3] 76 °C) (Found: C 22.49, H 4.14, N 8.71%. $C_6H_{13}MoN_2O_4$ requires C 22.37, H 4.38, N 8.70%); ν_{max} (KBr disc))/ cm^{-1} 1615 (=CO), 973 (Mo=O), 856 (O-O).

Oxodiperoxymolybdenum(pyridine)-1,3-dimethyl-3,4,5,6-terahydro-2(1*H*)-pyrimidinone 38[3]
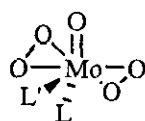
L = DMPU
L′ = Pyridine

$MoO_5.H_2O.DMPU$ **37** was dried in a vacuum desiccator for 24 hours over P_2O_5 to give $MoO_5.DMPU$. A solution of $MoO_5.DMPU$ (5.2 g, 17.0 mmol) in dry tetrahydrofuran (30 mL) was allowed to cool to room temperature while pyridine (1.4 mL, 1 equiv.) was added dropwise. The yellow crystalline precipitate was collected, washed with dry tetrahydrofuran (5 mL), dry diethyl ether (5 mL) and dried *in vacuo* to give $MoO_5.Py.DMPU$ **38** as a yellow solid (3.0 g, 28%); mp 91-92 °C (lit.,[3] 94 °C); (Found: C 34.40, H 4.48, N 11.04%. $C_{11}H_{18}MoN_3O_6$ requires C 34.48, H 4.47, N 10.97%); v_{max} (KBr disc))/ cm^{-1} 2946 (=CH), 1631 (C=O), 951 (Mo=O), 849 (O-O).

6,7-Dimethyl-4,4a,7,8-tetrahedroydro-3H-isochromene 64
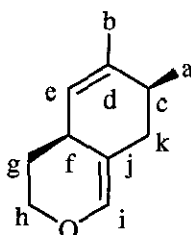
To a solution of lactol **4** (3.1 g, 17.0 mmol) in dry dichloromethane (40 mL), mesyl chloride was added (2.9 g, 1.5 equiv.) followed by addition of triethylamine (4.0 g, 2.3 equiv.) at 0 °C, under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight at room temperature. A saturated aqueous solution of ammonium chloride was added, and the aqueous phase was washed with diethyl ether (2 × 40 mL). The combined organic layers were finally dried over magnesium sulfate and concentrated *in vacuo*. Purification of the crude product by distillation (80-120 °C under 0.1 mbar) afforded **64** as a colourless oil (1.7 g, 63%); v_{max} (neat)/cm^{-1} 2944 (=CH), 1260 (C-O); δ_H (400 MHz, CDCl$_3$) 0.93 (3H, dd, ^3J 7.0, ^4J 0.4, 3H$_a$), 1.43-1.48 (1H, m, H$_g$), 1.66 (3H, dd, ^3J 2.0, ^4J 0.3, 3H$_b$), 1.75 (1H, dd, ^2J 13.0, ^3J 1.4, H$_k$), 1.78-1.90 (1H, dddd, ^2J 13.3, ^3J 5.9, ^3J 2.4, ^3J 2.1, H$_{g'}$), 2.08-2.10 (1H, m, H$_c$), 2.31 (1H, ddt, ^2J 13.4, ^3J 5.5, ^4J 1.8, H$_{k'}$), 2.77-2.79 (1H, m, H$_f$), 3.87 (1H, dt, ^2J 10.7, ^3J 1.9, H$_h$), 4.12-4.17 (1H, ddd, ^2J 10.7, ^3J 3.7, ^3J 2.5, H$_{h'}$) 5.22 (1H, d, ^3J 4.8, H$_e$), 6.17 (1H, br t, ^4J 1.9, H$_i$); δ_C (400 MHz, CDCl$_3$) 19.9 (C$_a$), 22.7 (C$_b$), 30.7 (C$_g$), 33.0 (C$_f$), 33.9 (C$_c$), 34.9 (C$_k$), 66.0 (C$_h$), 110.1 (C$_j$), 123.2 (C$_e$), 138.1 (C$_d$), 139.3 (C$_i$); compound too unstable to obtain the mass data.

2-(Ethyloxy)oxirane 87
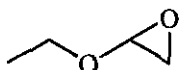
A solution of butyl vinyl ether (0.3 g, 4.2 mmol) was added to saturated sodium carbonate (1.8 g, 4.0 equiv.) in dichloromethane (12 mL). The mixture was allowed to stir 20 minutes under a nitrogen atmosphere at 0 °C. *meta*-Chloroperbenzoic acid (70%) (1 g, 4 equiv.) was added in portions every 5 minutes. The reaction was stirred for 2 hours. The solution was washed successively with saturated aqueous sodium sulphite (2 × 20 mL), sodium hydrogen carbonate (4 × 20 mL), and brine (20 mL). The organic layer was dried over sodium sulfate and the solvent removed *in vacuo*. The epoxide **87** was afforded as a colourless crude oil.

This reaction was only a test, IR and ^{1}H NMR are the only data, which have been taken; ν_{max} (neat)/cm^{-1} 2780 (epoxide), 1252 (epoxide); δ_H (400 MHz, CDCl$_3$) 1.26 (3H, d, *J* 7.0, C*H*$_3$), 3.70-3.92 (4H, m, 2 C*H*$_2$O), 6.13 (1H, t, *J* 4.85, O-C*H*-O).

Nitroethylene 88
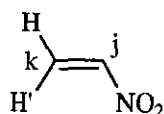
2-Nitroethanol (5.0 g, 54.9 mmol) and phtalic anhydride (12.9 g, 1.5 equiv.) were mixed in a distillation unit fitted with an ice-cooled receiver. The mixture was heated until it became homogeneous (bath temperature at 140-150 °C) and then the temperature was increased to 175-180 °C until the distillation had completed. This afforded **88** nitroethylene as a green oil (0.45 g, 11%) (Found: M$^+$, 73.01638. $C_2H_3NO_2$ requires 73.15108); v_{max} (DCM)/ cm^{-1} 1534 and 1368 (C-NO$_2$); δ_H (400 MHz, CDCl$_3$) 5.22 (1H, dd, ^3J 7.3, ^2J 2.3, H$_k$), 5.93 (1H, dd, ^3J 14.8, ^2J 2.3, H$_{k'}$), 6.65 (1H, dd, ^3J 14.8, ^3J 7.3, H$_j$); δ_C (400 MHz, CDCl$_3$) 120.4 (C$_k$), 139.8 (C$_j$).

1,6-Dimethyl-3-(2-hydroxyethyl)-4-nitrocyclohex-1-ene 89
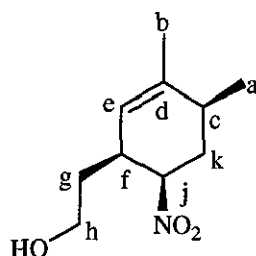
Diene **3** (0.4 g, 3.6 mmol) was added to a solution of nitroethylene **88** (0.39 g, 1.5 equiv.) in dry toluene (2 mL) at room temperature. The reaction mixture was allowed to stir for 36 hours under a nitrogen atmosphere. The mixture was then removed *in vacuo*. Purification of the crude product by flash column chromatography using light petroleum / ethyl acetate (4:1) afforded compound **89** as a green oil (0.14 g, 20%) (Found: M$^+$, 198.88391. $C_{10}H_{16}NO_2$ requires 199.12084); v_{max} (DCM)/ cm^{-1} 3404 (OH), 2925 (CH), 1545 and 1376 (C-NO$_2$); δ_H (400 MHz, CDCl$_3$) 1.11 (3H, d, ^3J 6.6, 3H$_a$), 1.48-1.54 (2H, m, 2H$_g$), 1.68 (3H, s, 3H$_b$), 1.84 (1H, dd, ^3J 14.9, ^2J 2.0, H$_k$), 2.24-2.27 (2H, m, H$_c$ and H$_{k'}$), 2.99-3.01 (1H, m, H$_f$), 3.70 (2H, t, ^3J 6.4, 2H$_h$), 4.67 (1H, m, H$_j$), 5.50 (1H, d, ^3J 5.4, H$_e$); δ_C (400 MHz, CDCl$_3$) 20.0 (C$_a$), 22.2 (C$_b$), 31.3 (C$_g$), 31.9 (C$_k$), 32.7 (C$_c$), 33.7 (C$_f$), 59.4 (C$_h$), 86.3 (C$_j$), 125.1 (C$_e$), 136.4 (C$_d$).

1,3-Benzothiazol-2-ylsulfanyl)methyl methyl ether 106
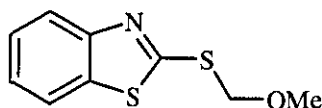
A solution of 2-mercaptobenzothiazole **104** (1.0 g, 6.0 mmol) in *N,N*-dimethylformamide (15mL) was added dropwise over 5 minutes at 0 °C to a solution of sodium hydride (0.3 g, 1.3 equiv.) in dry *N,N*-dimethylformamide (15 mL). When the addition was completed and gas evolution stopped, chloro(methoxy)methane (0.5 mL, 1.1 equiv.) was added dropwise over 5 minutes. The reaction was stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride at 0 °C, dissolved with ethyl acetate and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), saturated aqueous sodium chloride (50 mL), and dried over magnesium sulfate then concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using light petroleum/ ethyl acetate (95:5) as eluent to give the desired thioether **106** as a yellow oil (1.2 g, 86%) (Found: M$^+$, 211.01244. $C_9H_9NOS_2$ requires 211.01256); v_{max} (DCM)/cm^{-1} 1587 (acetate $S_2C=N$), 2821 (OCH$_3$); δ_H (400 MHz, CDCl$_3$) 3.50 (3H, s, OC*H*$_3$), 5.43 (2H, s, SC*H*$_2$O), 7.33 (1H, ddd, ^3J 8.3, ^3J 4.6, ^4J 0.7 , H arom), 7.44 (1H, ddd, ^3J 8.2, ^3J 4.6, ^4J 0.3, H arom), 7.77 (1H, dd, ^3J 8.3, ^4J 0.7, H arom), 7.93 (1H, dd, ^3J 8.2, ^4J 0.3, H arom); δ_C (400 MHz, CDCl$_3$) 57.1 (OCH$_3$), 76.5 (SCH$_2$O), 121.0 (CH arom), 122.0 (CH arom), 124.6 (CH arom), 126.2 (CH arom), 135.6 (S-C arom), 153.0 (N-C arom), 165.2 (N=CS$_2$); *m/z* (EI) 211 (M$^+$, 100%), 196 (78), 181 (55), 168 (87), 108 (50), 69 (33), 45 (100).

1,3-Benzothiazol-2-yl methoxymethyl sulfone 107
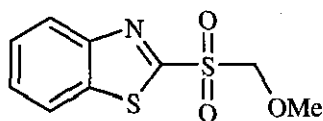
To a solution of (1,3-benzothiazol-2-ylsulfanyl)methyl methyl ether **106** (1.0 g, 4.7 mmol) in methanol (85 mL) at 0 °C, sodium tungstate dihydrate (0.8 g, 0.5 equiv.) was added, followed 5 minutes later by addition of hydrogen peroxide (35%) (1.6 mL, 4 equiv.). The reaction was stirred overnight at room temperature. The reaction mixture was quenched with sodium *meta*-bisulfite (2.7 g) in water (30 mL) at 0 °C, dissolved with dichloromethane (160 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with 30 mL of brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using light petroleum/ ethyl acetate (3:1) as eluent to give the desired product **107** as a colourless oil (0.85 g, 61%) (Found: MH$^+$, 244.01065. C$_9$H$_9$NO$_3$S$_2$ requires 244.01022) (Found: C, 45.24; H, 8.37; N, 10.47. requires C, 45.13; H, 8.33; N, 10.53%); v_{max} (DCM)/cm^{-1} 1507 (acetate S$_2$C=N), 2838 (OCH$_3$), 1320 (SO$_2$); δ_H (400 MHz, CDCl$_3$) 3.74 (3H, s, OC*H*$_3$), 4.98 (2H, s, SC*H*$_2$O), 7.67 (2H, m, 2H arom), 8.05 (1H, dd, ^3J 7.4, ^4J 1.4, H arom), 8.27 (1H, dd, ^3J 7.3, ^4J 1.5, H arom); δ_C (400 MHz, CDCl$_3$) 61.5 (OC*H*$_3$), 87.1 (SC*H*$_2$O), 122.3 (*C*H arom), 125.7 (*C*H arom), 127.7 (*C*H arom), 128.2 (*C*H arom), 132.6 (S-*C* arom), 152.9 (N-*C* arom), 157.0 (N=*C*SO$_2$); *m/z* (EI) 244 (M$^+$, 27%), 219 (46), 176 (90), 154 (100), 138 (100), 107 (97), 77 (95), 55 (66), 41 (54).

2-(2-{[1-(1,1-Dimethylethyl)-1,1-dimethylsilyl]oxy}ethyl)-4,5-dimethylcyclohex-3-ene-1-carbaldehyde 111
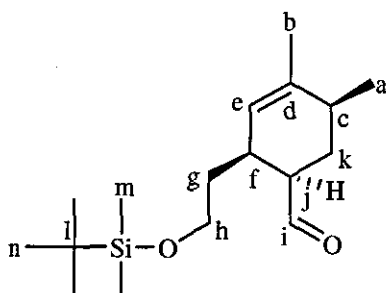
Oxidation with vanadium complex/ dioxygen

Molecular oxygen was allowed to bubble in a solution of vanadium (III) chloride (25.0 mg, 0.05 equiv.) and ligand **188** (71.0 mg, 0.1 equiv.) in acetone (15 mL). The mixture was allowed to stir for 30 minutes at room temperature. A solution of olefin **149** (880.0 mg, 2.4 mmol) and 4-chlorothiophenol (2.2 g, 5.0 equiv.) in acetone (15 mL) was added and the mixture was allowed to stir for 15 hours at room temperature. After removal of the solvent *in vacuo*, the residue was purified by Kügelrohr distillation (bp=140-150 °C; 1mmHg), to give the crude aldehyde **111** purified by chromatography on silica gel using light petroleum/ diethyl ether (98:2) as eluent. **111** was obtained as a colourless oil (30 mg, 15%);

The reaction was also achieved in an annular Pyrex reactor, equipped with a diving mercury medium-pressure lamp 250W, in ethyl acetate. The solution was irradiated under oxygen bubbling.

Oxidation with DMP

Dess-Martin Periodinane **169** (0.4 g, 1.5 equiv.) was added to a solution of **146** (0.3 g, 0.9 mmol) in dry dichloromethane (10 mL) and the solution was allowed to stir overnight at room temperature. The solution was washed with saturated

sodium carbonate (2 × 10 mL). The aqueous phase was washed with diethyl ether (2 × 20 mL). The combined organic layers were finally dried over magnesium sulfate. The solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography using petroleum ether / ethyl acetate (100:1) afforded **111** as a colourless oil (71.0 mg, 26%) (Found: M^+, 295.20913. $C_{17}H_{32}O_2Si$ requires 296.21716); ν_{max} (DCM)/cm^{-1} 2931 (CHO), 1723 (CHO), 836 (C=CH); δ_H (400 MHz, CDCl$_3$) 0.01 (6H, s, 6H$_m$), 0.86 (9H, s, 9H$_n$), 0.99 (3H, d, ^3J 6.8, 3H$_a$), 1.24-1.31 (1H, m, H$_k$), 1.31-1.40 (1H, m, H$_g$), 1.40-1.58 (1H, m, H$_{g'}$), 1.62 (3H, s, 3H$_b$), 1.94-1.98 (1H, dd, ^3J 7.1, ^3J 2.6, H$_{k'}$), 1.98-2.02 (1H, dd, ^2J 19.5, ^3J 2.6, H$_{k'}$), 2.02-2.10 (1H, m, H$_c$), 2.52-2.56 (1H, dd, ^3J 17.3, ^3J 2.8, H$_j$), 2.56-2.60 (1H, dd, ^3J 7.1, ^3J 2.8, H$_j$), 2.70-2.80 (1H, br q, ^3J 4.3, H$_f$), 3.59-3.67 (2H, m, 2H$_h$), 5.48 (1H, dt, ^3J 5.3, ^3J 1.6, H$_e$), 5.50 (1H, dt, ^3J 5.5, ^3J 1.6, H$_e$), 9.72 (1H, s, H$_i$); δ_C (400 MHz, CDCl$_3$) -5.30 (C$_m$), 18.3 (C$_l$), 19.8 (C$_a$), 21.4 (C$_b$), 25.9 (C$_n$), 27.5 (C$_k$), 31.3 (C$_f$), 33.9 (C$_c$), 35.5 (C$_g$), 50.9 (C$_j$), 61.2 (C$_h$), 124.3 (C$_e$), 138.7 (C$_d$), 205.1 (C$_i$); *m/z* (EI) 296 (M$^+$, 5%), 271 (6), 255 (12), 183 (11), 133 (40), 121 (35), 107 (34), 93 (24), 75 (100), 59 (17), 41 (17).

2-(2-{[1-(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy}ethyl)-4,5-dimethylcyclohex-3-ene-1-carbaldehyde 112
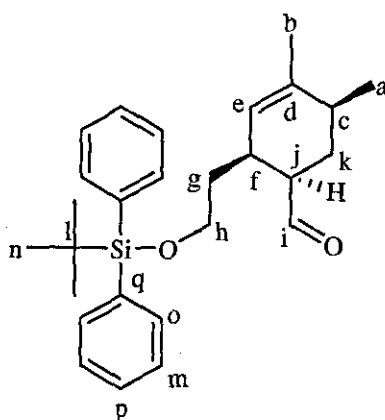
Oxidation with silver carbonate/Celite®

In a 1L flask equipped with a Dean-Stark head, Fetizon's salt **173** (20.0 g) was heated under reflux for 1h and dried out. A solution of alcohol **147** (5.0 g, 11.8 mmol) in dried toluene (20 mL) was added to the reaction mixture which was allowed to stir for a period of 4 days. The mixture was allowed to cool and the salt residue was filtered off on Celite®. The solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography using petroleum ether / diethyl ether (50:1) afforded aldehyde **112** as a yellow oil (2.1 g, 42%).

Oxidation with DMP

Dess Martin Periodinane **169** (13.7 g, 2.0 equiv.) was added to a solution of **147** (6.8 g, 161.0 mmol) in dry dichloromethane (135 mL) and the reaction mixture was allowed to stir overnight at room temperature. The solution was washed with saturated sodium carbonate (2 × 50 mL). The aqueous phase was washed with diethyl ether (4 x 50 mL). The combined organic layers were finally dried over magnesium sulfate. The solvent was removed *in vacuo*. Purification of the crude

product by flash column chromatography using petroleum ether / ethyl acetate (100:1) afforded **112** as a colourless oil (20.5 g, 30.2%).

Oxidation with TPAP/NMO

To a solution of **147** (0.9 g, 2.1 mmol) and 4-methylmorpholine *N*-oxide (0.4 g, 2.0 equiv.) in a mixture of dichloromethane-acetonitrile 9:1 (18 mL), molecular sieves (4 Å, 0.10 g) and tetrapropylammonium perruthenate (37.0 mg, 0.05 equiv.) was added. The mixture was allowed to stir for 6 hours at room temperature under a nitrogen atmosphere. The reaction mixture was filtered through a short pad of silica gel using dichloromethane or ethyl acetate as eluent. The resulted filtrate was removed *in vacuo*. Purification of the crude product by flash column chromatography using light petroleum / diethyl ether (25:1) afforded **258** as a colourless oil (0.22 g, 25%).

Oxidation with TEMPO/Bleach

To a mixture of **147** (0.4 g, 0.9 mmol), 2,2,6,6-tetramethylpiperidin-1-oxyl (1.4 mg, 0.01 equiv.) and potassium bromide (0.1 g, 0.1 equiv.) in dichloromethane (10 mL) at 0 °C, was added an appropriate amount of a 1M aqueous solution of sodium hypochlorite buffered with sodium bicarbonate (0.07 mL, 1.25 equiv.) until the mixture had a of pH 8-9. The solution was stirred for 1 hour at 0 °C. The organic phase was separated and washed with 10 mL of 10% hydrochloric acid containing 125 mg (0.75 mmol) of KI, 10 mL of 10% aqueous sodium thiosulfate and 10 mL of water. The crude was dried over magnesium sulfate and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography using petroleum ether / ethyl acetate (50:1) afforded **112** as a colourless oil (70 mg, 18.5%).

Oxidation with IBX

IBX **168** (0.2 g, 1.1 equiv.) was added to a solution of **147** (0.27 g, 0.64 mmol) in dimethyl sulfoxide (10 mL) and the reaction mixture was allowed to stir overnight at room temperature. Water (20 mL) was added to the mixture. The crude was filtrated and extracted with diethyl ether (3 × 50 mL), and the organic layers were dried over sodium sulfate. The solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography using petroleum ether / ethyl acetate (50:1) afforded **112** as a colourless oil (30.0 mg, 11.2%).

Oxidation with PDC

A suspension of pyridinium dichromate(1.2 g, 3.0 equiv.) was added to the alcohol **147** (0.44 g, 1.04 mmol) in a mixture of dichloromethane (20 mL)-acetic anhydride (1.3 mL, 12.8 equiv.). The reaction mixture was allowed to stir for 1 hour at 0 °C, and for 5 hours at room temperature under a nitrogen atmosphere. The solvent was removed *in vacuo*. The residue was dissolved in ethanol (20 mL) and allowed to stir for 10 minutes. The solution was poured into ethyl acetate (50 mL). A mix of silica gel-Celite® 1:1 was added and the mixture was allowed to stir for an additional 10 minutes. The product was collected by filtration and the waste chromium trapped in silica gel-Celite® was easily removed. The solvent was removed *in vacuo*. Flash column chromatography using light petroleum / ethyl acetate (50:1) afforded the product **112** as a colourless oil (44 mg, 10%).

Oxidation with PCC

A mixture of alcohol **147** (0.44 g, 1.04 mmol), pyridinium chlorochromate (0.7 g, 3.0 equiv.) and molecular sieves (4Å, 0.5 g) in *N,N*-dimethylformamide (10 mL) was buffered at pH 7 with addition of sodium acetate. The mixture was stirred for 1 hour at 0 °C, then overnight at room temperature under a nitrogen atmosphere.

The solvent was removed *in vacuo*. The residue was dissolved in ethanol (20 mL) and allowed to stir for 10 minutes. The solution was poured into ethyl acetate (50 mL). A mix of silica gel-Celite® 1:1 was added and the mixture was stirred for an additional 10 minutes. The product was collected by filtration and the waste chromium trapped in silica gel-Celite® was easily removed. The solvent was removed *in vacuo*. Flash column chromatography using light petroleum / ethyl acetate (50:1) afforded the product **112** as a colourless oil (35 mg, 8%); (Found: M^+, 420.24612. $C_{27}H_{36}O_2Si$ requires 420.24846); v_{max} (neat)/cm^{-1} 2952 (CHO), 1737 (CHO), 760 (ArCH); δ_H (400 MHz, CDCl$_3$) 1.03 (3H, d, ^3J 7.0, 3H$_a$), 1.05 (9H, s, 9H$_n$), 1.50-1.53 (1H, m, H$_k$), 1.53-1.61 (1H, m, H$_g$), 1.61 (3H, s, 3H$_b$), 1.61-1.70 (1H, m, H$_{g'}$), 1.79-1.88 (1H, ddd, ^2J 13.1, ^3J 9.6, ^3J 5.7, H$_k$), 2.05-2.11 (1H, m, H$_c$), 2.27-2.31 (1H, m, H$_j$), 2.63-2.66 (1H, m, H$_f$), 3.67-3.75 (2H, m, 2H$_h$), 5.25 (1H, m, H$_e$), 7.37-7.41 (6H, m, 4H$_m$, 2H$_p$), 7.64-7.68 (4H, m, 4H$_o$), 9.62 (1H, d, ^3J 2.1, H$_i$); δ_C (400 MHz, CDCl$_3$) 19.2 (C$_l$), 19.6 (C$_a$), 21.3 (C$_b$), 26.9 (C$_n$), 27.5 (C$_k$), 31.2 (C$_f$), 33.9 (C$_c$), 35.3 (C$_g$), 50.9 (C$_j$), 61.7 (C$_h$), 124.3 (C$_e$), 127.7 (C$_m$), 129.8 (C$_p$), 134.3 (C$_q$), 135.6 (C$_o$), 138.7 (C$_d$), 205.0 (C$_i$); *m/z* (EI) 420 (M^+, 47%), 392 (13), 261 (80), 224 (77), 199 (52), 165 (25), 135 (78), 121 (61), 107 (95), 91 (77), 77 (91), 57 (100), 41 (88).

(1,1-Dimethyl)(dimethyl){[(3E,5E)-5-methylhepta-3,5-dienyl]oxy}-silane 117
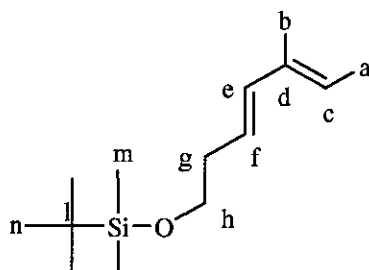
tert-Butyldimethylsilyl chloride (2.6 g, 1.1 equiv.) and imidazole (3.2 g, 3.0 equiv.) in dry N,N-dimethylformamide (20 mL) were added successively to a solution of diene **3** (2 g, 15.9 mmol), in dry N,N-dimethylformamide (15 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred overnight at room temperature. The solution was concentrated *in vacuo* in order to evaporate N,N-dimethylformamide, which is partly soluble in water. The product was dissolved by dichloromethane (30 mL) and washed with a solution of hydrochloric acid (0.2 M) until the aqueous layer became acidic. The aqueous layer was washed with diethyl ether (2 × 30 mL). The combined organic layers were finally washed with brine (40 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give the protected alcohol **117** as a yellow oil (2.5 g, 65%) (Found: M^+, 210.31065. $C_{12}H_{22}OSi$ requires 240.19094); ν_{max} (DCM)/cm^{-1} 3031 (=CH), 964 (HC=CH); δ_H (400 MHz, CDCl$_3$) 0.00 (6H, s, 6H$_m$), 0.84 (9H, s, 9H$_n$), 1.65 (3H, d, ^3J 8.0, H$_a$), 1.66 (3H, s, 3H$_b$), 2.26 (2H, q, ^3J 6.4, 2H$_g$), 3.60 (2H, t, ^3J 6.2, 2H$_h$), 5.40-5.60 (2H, m, H$_c$, H$_f$), 6.20 (1H, d, ^3J 15.6, H$_e$); δ_C (400 MHz, CDCl$_3$) -5.3 (C$_m$), 12.0 (C$_a$), 14.1 (C$_b$), 26.2 (C$_l$), 26.7 (C$_n$), 37.7 (C$_g$), 64.2 (C$_h$), 123.4 (C$_c$ or C$_f$), 125.2 (C$_c$ or C$_f$), 133.1 (C$_d$), 137.0 (C$_e$); *m/z* (EI) 239 (M$^+$, 52%), 213 (40), 199 (44), 115 (15), 95 (26), 89 (42), 75 (100), 57 (43).

{[6,7-Dimethyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-yl]oxy}(*tert*-butyl)dimethylsilane 124 [4]
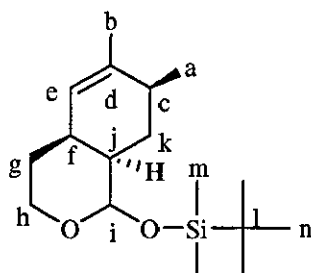
To a solution of lactol **4** (52.0 mg, 0.3 mmol) in dry *N,N*-dimethylformamide (10 mL) stirred at 25 °C under a nitrogen atmosphere, were added successively *tert*-butyldimethylsilyl chloride (65.0 mg, 1.5 equiv.) in dry *N,N*-dimethylformamide (10 mL) and imidazole (29.0 mg, 1.5 equiv.) dissolved in dry *N,N*-dimethylformamide (10 mL). The mixture was stirred overnight at room temperature. The solution was concentrated *in vacuo* in order to evaporate *N,N*-dimethylformamide, which is partly soluble in water. The product was dissolved by dichloromethane (20 mL) and washed with a solution of brine (10 mL). The aqueous layer was washed with diethyl ether (2 × 10 mL). The combined organic layers were finally dried over magnesium sulfate. The solvent was removed in vacuo to give the protected alcohol as a colorless oil of **124** (75.0 mg, 85%) (Found: M$^+$, 297.01436. C$_{17}$H$_{32}$O$_2$Si requires 296.21716); ν_{max} (DCM)/cm^{-1} 2766 (O-C-O), 962 (C=CH); δ_H (400 MHz, CDCl$_3$) 0.12 (6H, s, 6H$_m$), 0.89 (9H, s, 9H$_n$), 1.00 (3H, d, ^3J 7.0, 3H$_a$), 1.42-1.53 (1H, m, H$_k$), 1.53-1.69 (3H, m, 2H$_g$, H$_k$), 1.60 (3H, s, 3H$_b$), 1.72-1.78 (1H, m, H$_j$), 1.82-1.90 (1H, m, H$_g$·), 2.12 (1H, t, ^3J 4.4, H$_c$), 2.36-2.40 (1H, m, H$_f$), 3.26-4.04 (2H, m, 2H$_h$), 4.98 (1H, s, H$_i$); 5.11 (1H, 2s, H$_i$); 5.36 (1H, d, ^3J 5.2, H$_e$); δ_C (400 MHz, CDCl$_3$) -5.0 (C$_n$), 19.7 (C$_l$), 20.1 and 20.3 (C$_a$), 21.3 and 21.4 (C$_b$), 26.3 (C$_m$), 28.8 and 31.4 (C$_k$), 29.1 (C$_f$), 35.0 and 35.2 (C$_c$), 39.1 and 40.0 (C$_j$), 56.2 and 57.9 (C$_h$), 92.8 and 94.0 (C$_i$), 124.7 and 126.1 (C$_e$), 138.3 and 138.9 (C$_d$); *m/z* (EI) 297 (M$^+$, 32%), 181 (31), 164 (45), 135 (24), 121 (52), 107 (100), 93 (72), 77 (49), 67 (27), 57 (89), 41 (31).

2-{[6,7-Dimethyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-yl]sulfanyl}
ethanethiol 135
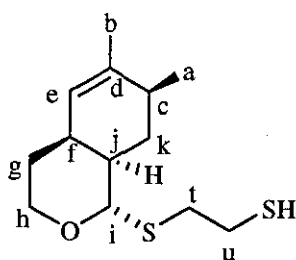
To a solution of lactol **4** (0.7 g, 4.0 mmol) in dry dichloromethane (2 mL), ethanedithiol was added (1.1 g, 3.0 equiv.) and a catalytic amount of either titanium tetrachloride or 6*N* hydrochloric acid solution. The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The solution was neutralised by a saturated aqueous solution of sodium carbonate (30 mL). The aqueous layer was washed with dichloromethane (2 × 20 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was filtrated on silica gel using a solution of petroleum ether/ ethyl acetate (9:1) to give **135** as a colourless oil (0.47 g, 46%) (Found: M$^+$, 258.11151. $C_{13}H_{22}OS_2$ requires 258.11121); v_{max} (DCM)/cm^{-1} 2920 (=CH), 2548 (SH); δ_H (400 MHz, CDCl$_3$) 1.05 (3H, d, ^3J 7.0, 3H$_a$), 1.51-1.58 (2H, m, 2H$_g$), 1.58-1.63 (1H, m, H$_k$), 1.63 (3H, s, 3H$_b$), 1.67 (1H, m, SH), 1.69-1.77 (1H, m, H$_{k'}$), 1.85 (1H, m, H$_j$), 2.10-2.20 (1H, m, H$_c$), 2.35-2.50 (1H, m, H$_f$), 2.75 (2H, dd, ^2J 6.6, ^3J 1.2, 2H$_t$), 2.80-3.00 (2H, m, 2H$_u$), 3.55 (1H, ddd, ^2J 11.3, ^3J 3.9, ^3J 2.7, H$_h$), 4.12 (1H, ddd, ^2J 11.3, ^3J 4.0, ^3J 3.7, H$_h$), 5.12 (1H, s, H$_i$), 5.33 (1H, d, ^3J 5.6, H$_e$); δ_C (400 MHz, CDCl$_3$) 20.0 (C$_a$), 22.4 (C$_b$), 25.6 (C$_g$), 29.6 (C$_k$), 30.9 (C$_f$), 33.7 (C$_u$), 35.0 (C$_c$), 35.1 (C$_t$), 39.2 (C$_j$), 59.8 (C$_h$), 86.8 (C$_i$), 126.1 (C$_e$), 138.4 (C$_d$); *m/z* (EI) 257 (M$^+$, 6%), 209 (5), 165 (100), 149 (35), 135 (17), 107 (47), 93 (45), 83 (38), 79 (28), 55 (22), 43 (54).

2-[6-(Hydroxymethyl)-3,4-dimethylcyclohex-2-enyl]ethan-1-ol 145
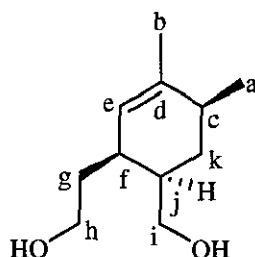
To a solution of lactone **5** (12.0 g, 65.8 mmol) in ethanol (120 mL) cooled 0 °C, sodium borohydride (5.2 g, 2.2 equiv.) was added in portions every 30 minutes. After the addition was complete, the reaction mixture was stirred at room temperature for 3 hours. The reaction was quenched by cooling the mixture back down to 0 °C and adding concentrated hydrochloric acid (11 mL), followed by water (100 mL). The ethanol was removed under reduced pressure and the remaining aqueous solution extracted with ethyl acetate (5 × 50 mL). The combined organic layers were finally dried over magnesium sulfate and solvents removed *in vacuo*. Purification of the crude product was filtered on silica gel using a solution of petroleum ether / ethyl acetate (3:2) and afforded a colourless oil of the diol **145** (10.9g, 90%) (Found: M$^+$, 184.14022. C$_{11}$H$_{20}$O$_2$ requires 184.14633); v_{max} (DCM)/cm^{-1} 3340 (OH), 2929 (=CH); δ_H (400 MHz, CDCl$_3$) 0.93-1.02 (1H, m, H$_k$), 0.98 (3H, d, ^3J 7.0, 3H$_a$), 1.28-1.31 (1H, ddd, ^2J 15.3, ^3J 9.9, ^3J 5.2, H$_g$), 1.48-1.52 (1H, ddd, ^2J 11.8, ^3J 6.1, ^3J 1.3, H$_{k'}$), 1.64 (3H, s, 3H$_b$), 1.64-1.71 (1H, m, H$_{g'}$), 1.88-2.00 (1H, m, H$_j$), 2.06-2.20 (1H, m, H$_c$), 2.32-2.40 (1H, m, H$_f$), 3.48-3.55 (1H, d, ^3J 2.1, H$_i$), 3.55-3.63 (1H, d, ^3J 5.0, H$_{i'}$), 3.58-3.67 (1H, ddd, ^2J 10.4, ^3J 9.1, ^3J 5.4, H$_h$), 3.68-3.77 (1H, ddd, ^2J 10.4, ^3J 6.5, ^3J 4.3, H$_{h'}$), 3.92 (2H, s, 2×OH), 5.53 (1H, br d, ^3J 5.6, H$_e$); δ_C (400 MHz, CDCl$_3$) 20.0 (C$_a$), 21.8 (C$_b$), 31.7 (C$_k$), 32.2 (C$_f$), 33.7 (C$_g$), 35.1 (C$_c$), 40.2 (C$_j$), 61.2 (C$_h$), 65.9 (C$_i$), 124.8 (C$_e$), 138.4 (C$_d$); *m/z* (EI) 184 (M$^+$, 26%), 166 (39), 135 (84), 121 (84), 107 (95), 93 (100), 79 (53), 67 (47), 55 (46), 41 (55).

[2-(2-{[1-(1,1-Dimethylethyl)-1,1-dimethylsilyl]oxy}ethyl)-4,5-dimethylcyclohex-3-enyl]methanol 146
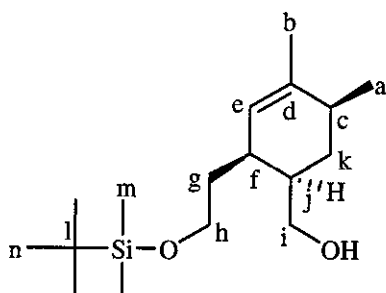
A mixture of diol **145** (0.8 g, 4.2 mmol), triethylamine (0.6 mL, 1.0 equiv.), *tert*-butyldimethylsilyl chloride (0.8 g, 1.2 equiv.) and dimethylamino pyridine (0.3 g, 0.5 equiv.) in dry dichloromethane (10 mL) was heated under reflux for 2 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temperature. The solution was washed with brine (10 mL), the organic layer was dried over magnesium sulphate and the solvent removed *in vacuo*. Purification of the crude product by flash column chromatography using petroleum ether / ethyl acetate (50:1) afforded the monoprotected compound **146** as a colourless oil (0.50g, 40%) (Found: M$^+$, 298.22971. C$_{17}$H$_{34}$O$_2$Si requires 298.23281); v$_{max}$ (DCM)/cm^{-1} 3363 (OH), 2356 (=CH); δ$_H$ (400 MHz, CDCl$_3$) 0.00 (6H, s, 6H$_m$), 0.82 (9H, s, 9H$_n$), 0.91 (3H, d, ^3J 6.8, 3H$_a$), 0.92-0.96 (1H, m, H$_k$), 1.14-1.26 (1H, tdd, ^2J 10.1, ^3J 4.5, ^3J 1.2, H$_g$), 1.46-1.52 (1H, br dd, ^2J 8.6, ^3J 2.0, H$_{k'}$), 1.58 (3H, br q, ^4J 1.2, 3H$_b$), 1.58-1.64 (1H, m, H$_{g'}$), 1.76-1.86 (1H, m, H$_j$), 1.90-2.07 (1H, m, H$_c$), 2.15-2.25 (1H, m, H$_f$), 3.40-3.51 (2H, m, 2H$_i$), 3.51-3.55 (1H, ddd, ^2J 9.9, ^3J 6.7, ^3J 4.5, H$_h$), 3.55-3.60 (1H, ddd, ^2J 9.9, ^3J 8.7, ^3J 5.7, H$_{h'}$), 3.60-3.68 (1H, m, H$_{h'}$), 5.42 (1H, d, ^3J 5.6, H$_e$); δ$_C$ (400 MHz, CDCl$_3$) -4.93 (C$_n$), 19.8 (C$_l$), 20.3 (C$_a$), 21.7 (C$_b$), 26.3 (C$_m$), 31.4 (C$_k$), 32.4 (C$_f$), 33.5 (C$_g$), 35.1 (C$_c$), 40.4 (C$_j$), 62.2 (C$_h$), 65.3 (C$_i$), 126.3 (C$_e$), 138.2 (C$_d$); *m/z* (EI) 298 (M$^+$, 62%), 280 (43), 270 (12), 166 (35), 156 (40), 121 (64), 115 (11), 107 (92), 93 (100), 77 (46), 67 (42), 55 (37), 41 (67).

**[2-(2-{[1-(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy}ethyl)-4,5-dimethylcyclohex-3-enyl]methanol 147**
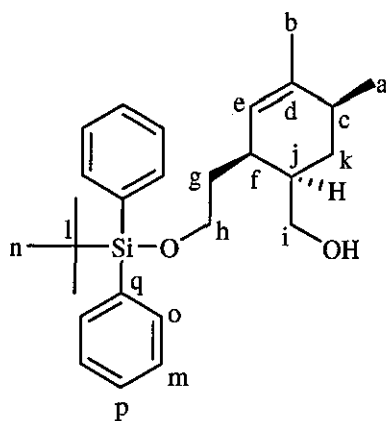
tert-Butyldiphenylsilyl chloride (14.7 mL, 1.1 equiv.) was added dropwise with a syringe pump to a mixture of diol **145** (9.6 g, 52.1 mmol) and imidazole (5.3 g, 1.5 equiv.) in dry dichloromethane (120 mL) at 0 °C. The solution was then allowed to stir overnight at room temperature. The solution was washed with sodium bicarbonate (50 mL), the organic layer was dried over magnesium sulfate and the solvent removed *in vacuo*. Purification of the crude product by flash column chromatography using petroleum ether / ethyl acetate (50:1) afforded the monoprotected compound **147** as a colourless oil (13.2 g, 60%) (Found: M^+, 422.44377. $C_{27}H_{38}O_2Si$ requires 422.26411); ν_{max} (DCM)/cm^{-1} 3341 (OH), 708 (ArCH); δ_H (400 MHz, CDCl$_3$) 0.98 (3H, d, ^3J 6.8, 3H$_a$), 1.04 (9H, d, 9H$_n$), 1.10-1.30 (1H, m, H$_g$), 1.56-1.60 (1H, m, H$_k$), 1.60 (3H, s, 3H$_b$), 1.60-1.68 (2H, m, H$_{k'}$, H$_{g'}$), 1.85-1.95 (1H, m, H$_j$), 2.05-2.10 (1H, m, H$_c$), 2.33-2.45 (1H, m, H$_f$), 3.45-3.51 (1H, dd, ^2J 10.7, ^3J 8.1, H$_i$), 3.51-3.57 (1H, dd, ^2J 10.7, ^3J 7.1, H$_{i'}$), 3.68-3.73 (1H, ddd, ^2J 10.2, ^3J 8.4, ^3J 6.0, H$_h$), 3.73-3.78 (1H, ddd, ^2J 10.2, ^3J 7.0, ^3J 4.6, H$_{h'}$), 5.39 (1H, br d, ^3J 5.6, H$_e$), 7.24-7.41 (6H, m, 4H$_m$, 2H$_p$), 7.65-7.70 (4H, m, 4H$_o$); δ_C (400 MHz, CDCl$_3$) 19.6 (C$_l$), 20.2 (C$_a$), 21.8 (C$_b$), 27.3 (C$_n$), 31.5 (C$_k$), 32.4 (C$_f$), 33.5 (C$_g$), 35.1 (C$_c$), 40.4 (C$_j$), 62.9 (C$_h$), 65.6 (C$_i$), 125.9 (C$_e$), 128.0 (C$_m$), 130.0 (C$_p$), 134.3 (C$_q$), 136.0 (C$_o$), 138.3 (C$_d$); *m/z* (EI) 423 (M^+, 4%), 405 (6), 395 (12), 331 (11), 269 (11), 239 (23), 199 (100), 181 (59), 165 (46), 135 (100), 121 (52), 107 (100), 91 (94), 77 (57), 55 (57), 43 (87).

2-[6-Eth-1-enyl-3,4-dimethylcyclohex-2-enyl]ethan-1-ol 148
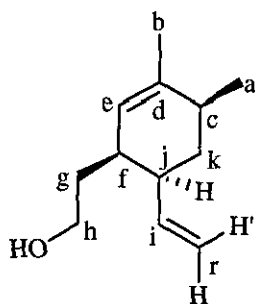
A solution of *n*-butyllithium (28 mL, 2.5 M solution in hexanes, 2.5 equiv.) was added to a solution of methyl triphenylphosphonium bromide (5.1 g, 28 mmol) in dry tetrahydrofuran (150 mL) at -78 °C under a nitrogen atmosphere. The mixture was allowed to stir for 15 minutes before addition of the lactol 4 (25.0 g, 2.5 equiv.). The reaction mixture was stirred overnight at room temperature. Brine (40 mL) was added, the organic layer was separated and aqueous layer washed with diethyl ether (5 × 30 mL). The combined organic layers were dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by Kügelrohr distillation (110-130 °C under 0.1 mbar) to give the olefin **148** as a yellow oil (4.4 g, 87%); ν_{max} (DCM)/cm^{-1} 3333 (OH), 3076 (CH$_2$=C), 1639 (C=C); δ_H (400 MHz, CDCl$_3$) 1.02 (3H, d, ^3J 7.0, 3H$_a$), 1.25-1.28 (1H, m, H$_k$), 1.28-1.41 (1H, m, H$_g$), 1.66 (3H, s, 3H$_b$), 1.66-1.75 (1H, m, H$_{g'}$, H$_{k'}$), 2.02-2.13 (1H, m, H$_j$), 2.13-2.20 (1H, m, H$_c$), 2.40-2.45 (1H, m, H$_f$), 3.63-3.70 (1H, ddd, ^2J 24.9, ^3J 10.4, ^3J 7.3, H$_h$), 3.70-3.76 (1H, ddd, ^2J 10.4, ^3J 7.8, ^3J 5.4, H$_{h'}$), 4.98-5.00 (1H, ddd, ^2J 1.2, ^3J 1.3, ^3J 4.8, H$_{r'}$), 5.01-5.04 (1H, ddd, ^2J 1.2, ^3J 1.3, ^3J 1.9, H$_r$), 5.48 (1H, dd, ^3J 6.2, ^3J 1.6, H$_e$), 5.50 (1H, dd, ^3J 3.7, ^3J 1.7, H$_e$), 5.81-5.90 (1H, ddd, ^3J 17.9, ^3J 9.9, ^3J 6.7, H$_i$); δ_C (400 MHz, CDCl$_3$) 19.9 (C$_a$), 21.4 (C$_b$), 32.6 (C$_k$), 32.4 (C$_j$), 32.5 (C$_g$), 35.7 (C$_c$), 41.2 (C$_f$), 61.7 (C$_h$), 113.6 (C$_r$), 125.5 (C$_e$), 138.3 (C$_d$), 141.9 (C$_i$); *m/z* (EI) 180 (M$^+$, 35%), 162 (4), 147 (17), 133 (22), 126 (100), 119 (23), 107 (31), 95 (89), 79 (29), 67 (21), 55 (21), 41 (25).

(1,1-Dimethylethyl)({2-[6-eth-1-enyl-3,4-dimethulcyclohex-2-enyl]ethyl}oxy) dimethylsilane 149
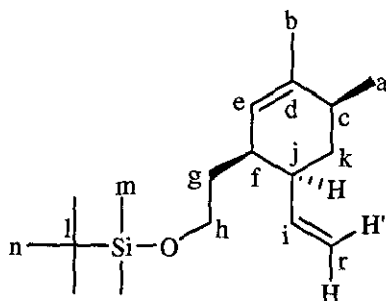
tert-Butyldimethylsilyl chloride (1.8 g, 1.1 equiv.) and imidazole (3.8 g, 5.0 equiv.) dissolved in dry N,N-dimethylformamide (10 mL) were added successively to a solution of olefin **148** (2.0 g, 11.1 mmol) in dry N,N-dimethylformamide (15 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred overnight at room temperature. The solution was concentrated *in vacuo* in order to evaporate N,N-dimethylformamide, which is partly soluble in water. The product was dissolved in dichloromethane (30 mL) and washed with a solution of hydrochloric acid (0.2M) until the aqueous layer became acidic. The aqueous layer was washed with diethyl ether (2 × 30 mL). The combined organic layers were finally washed with brine (40 mL) then dried over magnesium sulfate. The solvent was removed *in vacuo* to give the protected alcohol **149** as a yellow oil (2.0 g, 61%) (Found: M^+, 294.25001. $C_{18}H_{34}OSi$ requires 294.23789); v_{max} (DCM)/cm^{-1} 3077 ($CH_2=C$), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 0.00 (6H, s, $6H_m$), 0.84 (9H, t, ^3J 3.0, $9H_n$), 0.96 (3H, d, ^3J 7.1 Hz, $3H_a$), 1.19-1.25 (2H, m, H_g, H_k), 1.60-1.67 (1H, m, $H_{g'}$), 1.67-1.70 (1H, ddd, ^2J 6.1, ^3J 2.8, ^3J 1.1, $H_{k'}$), 1.60 (3H, s, $3H_b$), 2.02-2.11 (1H, m, H_j), 2.11-2.16 (1H, br q, ^3J 5.0, H_c), 2.30-2.37 (1H, m, H_f), 3.54-3.60 (1H, dd, ^2J 10.0, ^3J 7.4, H_h), 3.60-3.65 (1H, dd, ^2J 10.0, ^3J 8.8, $H_{h'}$), 3.51-3.60 (1H, m, H_h), 4.92-4.94 (1H, m, $H_{r'}$), 4.96-4.97 (1H, m, H_r), 5.42 (1H, d, ^3J 5.6, H_e), 5.76-5.85 (1H, m, H_i); δ_C (400 MHz, $CDCl_3$) -4.9 (C_m), 18.7 (C_l), 20.3 (C_a), 21.8 (C_b), 26.3 (C_n), 31.5 (C_k), 34.8 (C_j), 34.9 (C_g), 35.9 (C_c), 41.7 (C_f), 62.2 (C_h), 113.7 (C_r),

126.4 (C$_e$), 137.9 (C$_d$), 142.5 (C$_i$); *m/z* (EI) 325 (M$^+$, 3%), 221 (14), 177 (48), 133 (75), 119 (60), 105 (54), 89 (100), 75 (100), 69 (36), 50 (55), 43 (77).

(1,1-Dimethylethyl)({2-[6-eth-1-enyl-3,4-dimethulcyclohex-2-enyl]ethyl}oxy) diphenylsilane 150
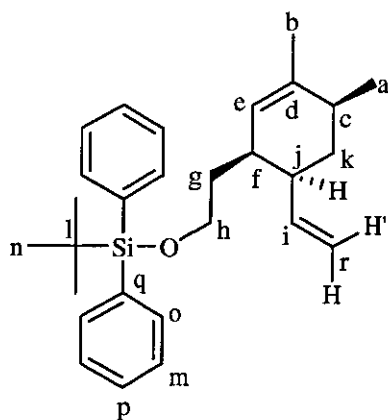
To a solution of olefin **148** (2.0 g, 11.1 mmol) in dry *N,N*-dimethylformamide (15 mL), were added successively *tert*-butyldiphenylsilyl chloride (3.1 mL, 1.1 equiv.) and imidazole (3.8 g, 5 equiv.) dissolved in dry *N,N*-dimethylformamide (20 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred overnight at room temperature. The solution was concentrated *in vacuo* in order to evaporate *N,N*-dimethylformamide, which is partly soluble in water. The product was dissolved in dichloromethane (30 mL) and washed with a solution of hydrochloric acid (0.2M) until the aqueous layer became acidic. The aqueous layer was washed with diethyl ether (2 × 30 mL). The combined organic layers were finally washed with brine (40 mL) then dried over magnesium sulfate. The solvent was removed *in vacuo* to give the protected alcohol **150** as a yellow oil (2.7 g, 58%); (Found: M$^+$, 418.18566. C$_{28}$H$_{38}$OSi requires 418.26919) ; ν_{max} (DCM)/cm^{-1} 3069 (CH$_2$=C), 1638 (C=C); δ_H (400 MHz, CDCl$_3$) 1.00 (3H, d, ^3J 6.8, 3H$_a$), 1.04 (9H, s, 9H$_n$), 1.10-1.38 (2H, m, H$_g$, H$_k$), 1.73 (3H, br q, ^3J 1.3, 3H$_b$), 1.62-1.79 (1H, m, H$_{g'}$, H$_{k'}$), 2.03-2.17 (1H, m, H$_j$), 2.21-2.30 (1H, m, H$_c$), 2.30-2.47 (1H, m, H$_f$), 3.67-3.73 (2H, m, 2H$_h$), 4.94-4.96 (1H, m, H$_{r'}$), 4.96-4.98 (1H, br d, ^3J 1.3, H$_r$), 5.40 (1H, td,

35

^3J 5.2, ^3J 1.6, H_e), 5.77-5.90 (1H, m, H_i), 7.36-7.40 (6H, m, $4H_m$, $2H_p$), 7.65-7.69 (4H, m, $4H_o$); δ_C (400 MHz, CDCl$_3$) 19.2 (C_l), 19.9 (C_a), 21.4 (C_b), 26.9 (C_n), 33.1 (C_k), 34.2 (C_j), 34.4 (C_g), 35.5 (C_c), 42.0 (C_f), 62.5 (C_h), 113.3 (C_r), 124.3 (C_e), 126.0 (C_m), 127.6 (C_p), 134.0 (C_q), 134.1 (C_o) 142.1 (C_d), 143.3 (C_i); m/z (EI) 418 (M$^+$, 7%), 361 (35), 283 (23), 255 (38), 239 (15), 225 (81), 199 (100), 183 (57), 161 (16), 135 (26), 105 (25), 91 (19), 77 (18), 43 (14).

tert-Butyl{2-[6-({[tert-butyl(dimethyl)silyl]oxy}methyl)-3,4-dimethyl-2-cyclohexen-1-yl]ethoxy}dimethylsilane 155
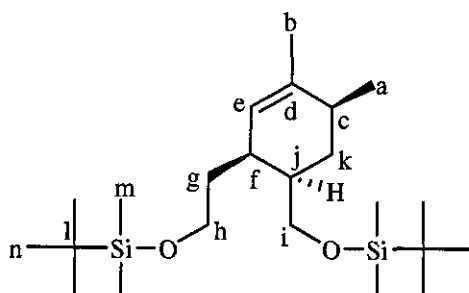
The diprotected compound **155** was formed during the synthesis of **146**:

(Found: M⁺, 412.48547. $C_{23}H_{48}O_2Si_2$ requires 412.31928); ν_{max} (DCM)/cm⁻¹ 1666 (C=CH), 843 (C=CH); δ_H (400 MHz, CDCl₃) 0.01 (12H, 2 s, 12H$_m$), 0.86 (18H, s, 18H$_n$), 0.94 (3H, d, ^3J 6.8, 3H$_a$), 1.21-1.26 (1H, tdd, ^3J 10.6, ^3J 7.8, ^2J 4.9, H$_g$), 1.55-1.62 (3H, m, H$_g$, 2H$_k$), 1.60 (3H, br d, ^3J 1.2, 3H$_b$), 1.75-1.90 (1H, m, H$_j$), 1.95-2.05 (1H, m, H$_c$), 2.10-2.30 (1H, br q, ^3J 5.0, H$_f$), 3.39-3.45 (1H, dd, ^2J 10.0, ^3J 8.0, H$_i$), 3.45-3.50 (1H, dd, ^2J 10.0, ^3J 7.1, H$_{i'}$), 3.57-3.68 (2H, m, H$_h$), 5.43 (1H, dt, ^3J 5.52, ^3J 1.58, H$_e$); δ_C (400 MHz, CDCl₃) -4.9 (C$_m$), 18.7 (C$_l$), 20.0 (C$_a$), 21.8 (C$_b$), 26.3 (C$_n$), 31.5 (C$_k$), 32.7 (C$_f$), 33.9(C$_g$), 35.1 (C$_c$), 40.4 (C$_j$), 62.3 (C$_h$), 65.7 (C$_i$), 125.1 (C$_e$), 138.3 (C$_d$).
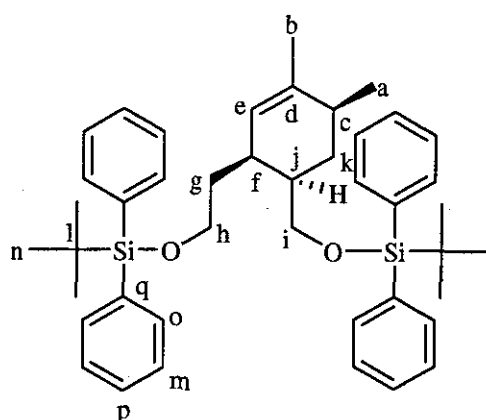
tert-Butyl{2-[6-({[tert-butyl(diphenyl)silyl]oxy}methyl)-3,4-dimethyl-2-cyclohexen-1-yl]ethoxy}diphenylsilane 156

The diprotected compound **156** was isolated during the synthesis of **147**:

(Found: M^+, 660.65417. $C_{43}H_{56}O_2Si_2$ requires 660.38188); ν_{max} (DCM)/cm^{-1} 2917 (=CH), 726 (ArCH); δ_H (400 MHz, CDCl$_3$) 0.98 (3H, d, ^3J 7.0, 3H$_a$), 1.04 (18H, s, 18H$_n$), 1.04-1.56 (1H, m, H$_g$), 1.56-1.70 (3H, m, 2 H$_k$, H$_{g'}$), 1.59 (3H, s, 3H$_b$), 1.81-1.88 (1H, m, H$_j$), 2.05-2.10 (1H, m, H$_c$), 2.30-2.45 (1H, m, H$_f$), 3.49-3.56 (2H, m, 2H$_i$), 3.69-3.75 (2H, m, 2H$_h$), 5.39 (1H, m, H$_e$), 7.35-7.38 (12H, m, 8H$_m$, 4H$_p$), 7.63-7.66 (8H, m, 8H$_o$); δ_C (400 MHz, CDCl$_3$) 19.2 (C$_l$), 19.9 (C$_a$), 21.0 (C$_b$), 26.7 (C$_n$), 31.0 (C$_k$), 31.8 (C$_f$), 32.6 (C$_g$), 33.2 (C$_c$), 36.5 (C$_j$), 62.0 (C$_h$), 66.0 (C$_i$), 126.1 (C$_e$), 127.6 (C$_m$), 129.5 (C$_p$), 134.1 (C$_q$), 135.6 (C$_o$), 137.9 (C$_d$).

1-Hydroxy-1,2-benziodoxol-3(1H)-one (IBX) 168[5]
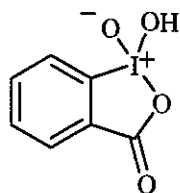
In a 1L, three necked, round-bottomed flask fitted with a mechanical stirrer, condenser and a thermometer in immersion, potassium bromate (40.0 g, 1.5 equiv) was vigorously stirred in 2M sulphuric acid (375 mL) at 60 °C. 2-iodobenzoic acid (40.0 g, 0.2 mol) was added in portions to the mixture over 40 minutes. The mixture was stirred for 2.5 hours at 65 °C and subsequently allowed to cool to 0°C. Filtration and washing of the solid with 250 mL of cold distilled water and ethanol (2 × 40 mL) followed by a second washing with 250 mL of cold distilled water gave **168** as a colourless solid (73.5 g, 95%); mp 232-233 °C (lit.,[5] mp 233)

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (DMP) 169[6]

AcO OAc
I—OAc
O
O
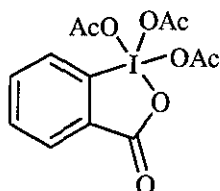
IBX **168** (20.1 g, 62.4 mmol) was added to a 250 mL round-bottomed flask containing acetic anhydride, *para*-toluenesulphonic acid monohydrate (0.1 g, 9.3 mmol), and a magnetic stirring bar. The flask was equipped with a drying tube and was immersed in an oil bath at 80 °C. The mixture was stirred for 2 hours and then allowed to cool in an ice-water bath. The cold mixture was filtered through a fritted glass funnel and washed with anhydrous ether (5 × 50 mL) under a nitrogen atmosphere. The resulting white solid **169** (20.0 g, 75.5%) was quickly transferred to a nitrogen flushed glass pot and stored in a freezer: mp 135 °C (lit.,[5] 133-134 °C); v_{max} (neat)/cm^{-1} 1732.4 (acetate C=O), 1721.5 (endocyclic C=O); δ_H (400 MHz, CDCl$_3$) 1.99 (6H, s, COCH_3), 2.29 (3H, s, COCH_3), 7.86 (1H, t, *J* 7.2, H arom), 8.04 (1H, t, *J* 8.5, H arom), 8.27 (1H, d, *J* 8.5, H arom), 8.29 (1H, d, *J* 7.2, H arom); δ_C (400 MHz, CDCl$_3$) 20.2 (2 COCH_3), 20.3 (COCH_3), 126.8 (*C* arom), 127.2 (*C*H arom), 131.6 (*C*H arom), 133.6 (*C* arom), 135.7 (*C*H arom), 141.9 (*C*H arom), 168.1 (endocyclic C=O), 172.5 (acetate C=O), 175.5 (2 acetate C=O).

Sodium carbonate/Celite® 173[7]

$$Ag_2CO_3 / Celite$$

The preparation of the reagent was reported by Fetizon *et al.*[7]

The Celite® support (35.0 g) was washed with methanol (500 mL) containing 10% concentrated hydrochloric acid followed with distilled water until neutral (about 500 mL).The purified Celite® was dried at 120 °C overnight in an oven.

The dried purified Celite® (31.2 g) was added to a mechanically stirred solution of silver nitrate (35.4 g, 209.0 mmol) in distilled water (215 mL). Saturated sodium carbonate (11.3 g, 107.0 mmol) in distilled water (355 mL) was then added slowly to the resulting homogenous suspension. When the addition was completed, stirring was continued for a further 10 minutes. The yellow-green precipitate formed was filtered off and dried *in vacuo* overnight. The silver carbonate/Celite® reagent contains about 1mmol of silver carbonate, 0.6 g.[7]

Methyl 3-hydroxy-2-{[(*E*)-(2-hydroxyphenyl)methylidene]amino}propanoate 188
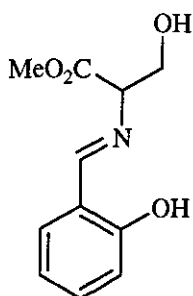
To a solution of methyl D,L-serinate hydrochloride **186** (1.1 g, 7.0 mmol) in ethanol (35 mL) were added successively, at room temperature, triethylamine (1.1 mL, 7.9 mmol) and salicylaldehyde (0.8 mL, 1.0 equiv.). The mixture was allowed to stir for 5 hours. After removal of the solvent *in vacuo*, the residue was purified by chromatography on silica gel using acetonitrile as eluent. The ligand **188** was obtained as a yellow oil (1.4 g, 90%) (Found: M$^+$, 223.08446. C$_{11}$H$_{13}$NO$_4$ requires 223.08446); v$_{max}$ (neat)/cm^{-1} 3444, 1740, 1632, 1279; δ$_H$ (400 MHz, CDCl$_3$) 3.77 (3H, s, C*H*$_3$), 3.95 (1H, m, C*H*), 4.13 (2H, m, C*H*$_2$), 6.90-6.98 (2H, m, *H* arom), 7.22-7.40 (2H, m, *H* arom), 8.42 (1H, s, C*H*-Ar), 12.85 (1H, s, OH); δ$_C$ (400 MHz, CDCl$_3$) 52.6 (*C*H$_3$), 63.7 (*C*H$_2$O), 72.6 (*C*H), 117.2 (*C*H arom), 118.6 (*C* arom), 119.0 (*C*H arom), 132.0 (*C*H arom), 133.2 (*C*H arom), 160.9 (*C* arom), 168.6 (*C*HPh), 170.5 (*C*O$_2$Me); *m/z* (EI) 223 (M$^+$, 62%), 192 (28), 164 (38), 132 (100), 107 (62), 77 (33).

2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-1-hydroxy-4,5-dimethyl-3-cyclohexene-1-carbaldehyde 194 and 195
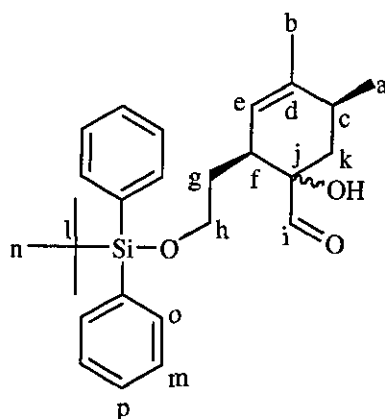
The silyl ether **228** (0.5 g, 0.8 mmol) was added to a solution of dimethyldioxirane in acetone (0.064 M, 12.2 mL, 1 equiv.) at 0 °C. The solution was allowed to reach room temperature and stirred overnight.

The reaction mixture was washed with 10 mL of brine and extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The reaction afforded **194** and **195** as a yellow oil. The mixture was inseparable but characterised.

The LC/MS (ACN 100%) 476.67 ($C_{27}H_{36}O_3Si$ + ACN); v_{max} (neat)/cm^{-1} 3429 (OH), 2933 (CHO), 1716 (CHO); δ_H (400 MHz, CDCl$_3$) 0.96 (3H, m, 3H$_a$), 1.12 (9H, s, 9H$_n$), 1.20-2.00 (5H, m, 2H$_k$, 2H$_g$, H$_c$), 1.68 (3H, s, 3H$_b$), 2.40-2.50 (1H, m, H$_f$), 3.65-3.85 (2H, m, 2H$_h$), 5.35 (1H, m, H$_e$), 7.30-7.40 (6H, m, 4H$_m$, 2H$_p$), 7.50-7.62 (4H, m, 4H$_o$), 9.60 (0.3H, m, 0.3H$_i$), 9.69 (0.7H, m, 0.7H$_i$); δ_C (400 MHz, CDCl$_3$) 17.7 (C$_l$), 19.0 (C$_a$), 19.2 (C$_b$), 25.6 (C$_n$), 31.7 (C$_c$ or C$_f$), 34.5 (C$_k$ or C$_g$), 37.7 (C$_k$ or C$_g$), 41.4 (C$_c$ or C$_f$), 61.7 (C$_h$), 64.5 (C$_j$), 121.5 (C$_e$), 127.7 (C$_m$), 129.6 (C$_p$), 134.8 (C$_o$), 135.2 (C$_q$), 135.6 (C$_d$), 204.7 (C$_i$).

tert-Butyl azidoformate 201[8]
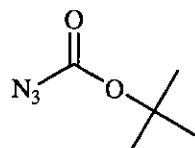
A solution of *tert*-butyl carbazate **200** (100.0 g, 0.8 mmol) in glacial acetic acid (82 mL) and water (125 mL) was allowed to cool in an ice-bath. A solution of sodium nitrite (57.4 g, 1.0 equiv.) in water (80 mL) was added to the mixture over a period of 1 hour under vigorous stirring, keeping the temperature at about 10 °C. The mixture was allowed to stir in the ice-bath for 30 minutes and water (125 mL) was added. The yellow azide layer was separated and the aqueous layer extracted with diethyl ether (4 × 40 mL). The combined organic layers were washed subsequently with water (3 × 50 mL) and 1M sodium bicarbonate solution (3× 40 mL). The light yellow solution was dried over magnesium sulfate and the solvent removed *in vacuo*. The compound **201** was obtained by Kügelrohr distillation as a light yellow oil (76.8 g, 71%); bp 74 °C (70mmHg); v_{max} (DCM)/cm^{-1} 2180 (N$_3$), 1732 (O-C=O), 1396 (-C(CH$_3$)); δ_H (400 MHz, CDCl$_3$) 1.51 (9H, s, 3 CH$_3$); δ_C (400 MHz, CDCl$_3$) 28.2 (CH$_3$), 85.3 (C), 156.3 (CO); too volatile to get mass data.

tert-Butyl *N*-hydroxycarbamate 201a[8]
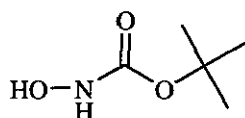
To a cold (0 °C) and vigorously stirred solution of *tert*-butyl azidoformate **201** (13.0 g, 0.1 mol) and hydroxylamine hydrochloride (13.0 g, 1.3 equiv.) in water (500 mL), a cold solution of sodium hydroxide (22.4 g, 4.0 equiv.) in water (80 mL) was added dropwise over 1 hour. The reaction was allowed to stir for 1 hour at 0 °C. The solid precipitate formed was then dissolved with water (100 mL).The solution was extracted with diethyl ether (2 × 50 mL) and the extracts discarded. The aqueous solution was allowed to cool in an ice bath and acidified to pH 5 with about 75 mL of 6M hydrochloric acid. The resulting mixture was extracted with diethyl ether (5 × 50 mL). The combined organic layers were dried and concentrated *in vacuo.* The thick oil was drained to leave a solid giving **201'** as a white powder (18.5 g, quantitative) (Found: M$^+$, 133.08200. $C_5H_{11}NO_3$ requires 133.07389) (Found: C, 45.24; H, 8.37; N, 10.47. requires C, 45.13; H, 8.33; N, 10.53%); mp 57 °C (lit.,[8] 58-59 °C); ν_{max} (DCM)/cm^{-1} 3300 (OH) and 1715 (carbamate C=O); δ_H (400 MHz, CDCl$_3$) 1.48 (9H, s, C(CH_3)$_3$), 7.05 (1H, br, OH); δ_C (400 MHz, CDCl$_3$) 28.2 (*C*H$_3$), 82.1 (O*C*Me$_3$), 156.7 (*C*O); *m/z* (EI) 134 (M$^+$, 12%), 115 (77), 77 (33), 57 (100), 43 (34).

### *tert*-Butyl hydroxy(methyl)carbamate 202[9,10]
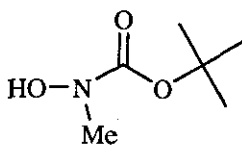
202 was prepared as it was reported by House and Richey.[9]

To a cold (0 °C) stirred mixture of *tert*-butoxycarbonyl azide **201** (15.6 g, 0.1 mol) and *N*-methylhydroxyl amine hydrochloride (10.0 g, 2.0 equiv.), a solution of sodium hydroxide (16.4 g, 4.0 equiv.) in water (145 mL) was added, dropwise over 1 hour. The cooling bath was removed and the reaction was let to stir for 3 hours and partitioned between ethyl ether (100 mL) and water. The aqueous phase was acidified to pH 5 with 6*N* hydrochloric acid and extracted with diethyl ether (5 × 50 mL). The combined organic layers were dried and concentrated *in vacuo*. Distillation of the residual liquid gave the *N*-hydroxycarbamate **202** as a colourless liquid (12.8 g, 79%).

202 was also prepared by following this procedure:[10]

A solution mixture of *tert*-butyl hydroxycarbamate **201a** (12.0 g, 91.0 mmol), potassium hydroxyde (6.1 g, 1.2 equiv.) and methyl iodide (8.5 mL, 1.5 equiv.) in ethanol (750 mL) was heated under reflux for 5 hours. The resulting mixture was allowed to cool to 0 °C and filtered. After evaporation of the solvent, the residue was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with water (3 × 20 mL) and dried with sodium sulfate. The solvent was removed. Distillation of the residual liquid gave the *N*-hydroxycarbamate **202** as a colourless liquid (12.3 g, 92%) (Found: M$^+$, 147.48831. $C_6H_{13}NO_3$ requires 147.08954); v_{max} (DCM)/cm^{-1} 3176 (OH) and 1720 (carbamate C=O); δ_H (400 MHz, CDCl$_3$) 1.47 (9H, s, C(CH_3)$_3$), 3.11 (3H, m, NCH_3), 7.34 (1H, br, OH); δ_C (400 MHz, CDCl$_3$) 28.2 (CH_3), 38.1 (NCH_3), 82.4 (OCMe$_3$), 157.9 (CO); m/z (EI) 147 (M$^+$, 21%), 133 (42), 129 (52), 91 (64), 57 (100), 43 (53).

tert-Butyl acetyloxy(methyl)carbamate 203[9]
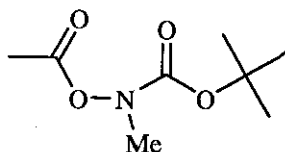
To a cold (0 °C) solution of carbamate **202** (12.8 g, 87.0 mmol) and anhydrous triethylamine (14.5 mL, 1.2 equiv.) in dichloromethane (420 mL) acetyl chloride (8.0 mL, 1.3 equiv.) was added dropwise. The resulting mixture was stirred for 1 hour at room temperature and then partitioned between a saturated aqueous solution of bicarbonate (50 mL) and dichloromethane. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Distillation of the residual liquid gave the *N*-acetoxycarbamate **203** as a colourless liquid (16.0 g, 97%) (Found: M$^+$, 189.6773. $C_8H_{15}NO_4$ requires 189.10011); v_{max} (neat)/cm^{-1} 1791 (acetate C=O), 1717 (carbamate C=O); δ_H (400 MHz, CDCl$_3$) 1.47 (9H, s, C(CH_3)$_3$), 2.14 (3H, m, CH_3CO), 3.22 (3H, br, CH_3N); δ_C (400 MHz, CDCl$_3$) 18.5 (*C*H$_3$CO), 27.9 (*C*H$_3$), 37.8 (N*C*H$_3$), 82.3 (O*C*Me$_3$), 157.9 (N*C*=O), 155.1 (CH$_3$*C*O); *m/z* (EI) 189 (M$^+$, 42%), 133 (46), 115 (100), 99 (45), 89 (100), 74 (21), 57 (100), 43 (100).

N-(Acetyloxy)methanaminium chloride 204[9]
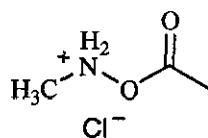
A solution of N-acetoxy carbamate **203** (1.6 g, 6.4 mmol) in anhydrous diethyl ether (10 mL) was treated with anhydrous hydrochloric acid (0.2 M) in diethyl ether (50 mL, 100 mmol). The reaction mixture was allowed to stir for 3 days at room temperature under a nitrogen atmosphere. The white precipitate formed was filtered and washed with anhydrous diethyl ether, and dried *in vacuo*. N-acetoxyamine hydrochloride **204** was obtained as a white powder (0.8 g, 75%) (Found: M^+, 89.047765. $C_3H_8ClNO_2$ requires 90.055504) (Found: C, 29.14; H, 6.15; N, 11.18. requires C, 28.82; H, 6.45; N, 11.20%); mp 115 °C (0.70 mm) (lit.,[9] 109-111 °C (0.70 mm)); ν_{max} (DCM)/cm^{-1} 1797 (acetate C=O); δ_H (400 MHz, CDCl₃) 2.28 (3H, m, CH_3CO), 3.10 (3H, t, J 11, CH_3N); δ_C (400 MHz, CDCl₃) 18.4 (CH₃CO), 35.8 (NCH₃), 154.1 (CO); m/z (EI) 89 (M^+, 40%), 77 (62), 46 (24), 43 (100).

tert-Butyl(2-{6-[(2-methoxyethenyl]-3,4-dimethyl-2-cyclohexen-1-yl}ethoxy)diphenylsilane 213
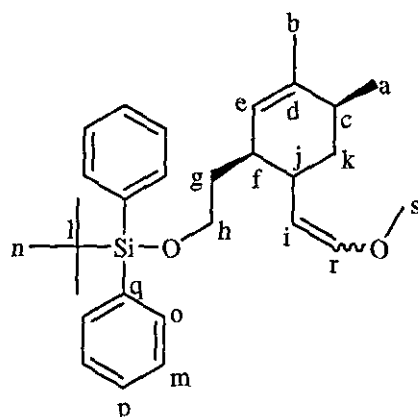
To a solution of aldehyde **112** (0.2 g, 0.5 mmol) and sulfone **107** (0.1 g, 1.2 equiv.) in tetrahydrofuran (6 mL) at 0 °C, lithium hexamethyldisilylazide 1M (0.2 g, 2.4 equiv.) was added dropwise. The reaction was stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 50 mL of brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using light petroleum/ ethyl acetate (9:1) as eluent to give the desired product **213** as a colourless oil (0.14 g, 62%) (Found: M$^+$, 448.27200. $C_{29}H_{40}O_2Si$ requires 448.27976); v_{max} (DCM)/cm^{-1} 2855 (CH$_3$O), 1650 (enol ether), 744 (ArCH); δ_H (400 MHz, CDCl$_3$) 0.88 (3H, s, 3H$_a$), 0.95 (9H, s, 9H$_n$), 1.01-1.30 (1H, m, H$_g$), 1.30-1.61 (1H, m, H$_k$), 1.51 (3H, m, 3H$_b$), 1.69-1.78 (1H, m, H$_{g'}$), 2.04-2.07 (1H, m, H$_c$), 2.07-2.10 (0.4H, m, H$_{j\,cis}$), 2.10-2.19 (1H, m, H$_{k'}$), 2.19-2.25 (0.6H, m, H$_{j\,trans}$), 2.71-2.78 (1H, m, H$_f$), 3.41 and 3.45 (3H, 2 s, 3H$_s$), 3.60-3.68 (2H, m, 2H$_h$), 4.26 (0.4H, ddd, ^3J 12.7, ^3J 9.3, ^3J 6.4, H$_{r\,cis}$), 4.70 (0.6H, ddd, ^3J 15.6, ^3J 12.7, ^3J 7.2, H$_{r\,trans}$), 5.82 (0.4H, dd, ^3J 6.3, ^3J 1.2, H$_{i\,cis}$), 6.27 (0.6H, dd, ^3J 12.7, ^3J 0.7, H$_{i\,trans}$), 5.25-5.30 (1H, m, H$_e$), 7.26-7.33 (6H, m, 4H$_m$, 2H$_p$), 7.57-7.61 (4H, m, 4H$_o$); δ_C (400 MHz, CDCl$_3$) 19.3 (C$_l$), 19.9 (C$_a$),

21.4 and 21.5 (C_b), 26.9 and 26.9 (C_n), 32.9 (C_f), 34.1 and 34.5 (C_g), 34.6 and 35.1 (C_c), 34.9 and 35.0 (C_k), 36.7 (C_j), 55.9 and 59.5 (C_s), 62.6 and 62.8 (C_h), 106.4 and 109.8 (C_r), 126.2 and 126.3 (C_e), 127.6 and 127.6 (C_m), 129.5 and 129.5 (C_p), 134.18 and 134.26 (C_q), 135.63 (C_o), 137.2 and 137.4 (C_d), 145.3 and 146.4 (C_i); m/z (EI) 448 (M^+, 24%), 417 (20), 390 (33), 224 (38), 239 (11), 209 (100), 193 (52), 161 (24), 135 (32), 105 (19), 77 (34), 43 (52).

({[2-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-4,5-dimethyl-3-cyclohexen-1-ylidene]methyl}oxy)(triisopropyl)silane 222
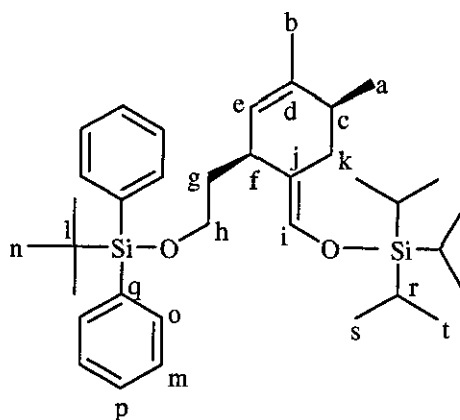
To a solution of aldehyde **112** (0.9 g, 2.2 mmol) in dry dichloromethane (20 mL) at 0 °C successively triisopropyl silyl triflate (0.7 mL, 1.2 equiv.) and triethylamine (0.5 mL, 2.6 equiv.) was added. The solution was allowed to reach room temperature and was stirred overnight. The crude reaction mixture was washed with a saturated aqueous solution of copper sulfate (3 × 30 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using light petroleum/ diethyl ether (100:1) as eluent to give the desired product **222** as a colourless oil (0.97 g, 34%); one isomer has been isolated: (Found: M$^+$, 576.38267. C$_{36}$H$_{56}$O$_2$Si$_2$ requires 576.38189); ν_{max} (neat)/cm^{-1} 3069 (=CH), 1673 (enol ether), 738 (=CH aromatic); δ_H (400 MHz, CDCl$_3$) 0.00 (3H, s, 3H$_r$), 0.95 (18H, s, 9H$_s$, 9H$_t$), 0.98 (3H, d, *J* 6.8, 3H$_a$), 1.07 (9H, s, 9H$_n$), 1.60 (3H, s, 3H$_b$), 1.60-1.80 (3H, m, 2H$_g$, H$_k$), 1.85-1.95 (1H, s, H$_{k'}$), 1.95-2.05 (1H, m, H$_c$), 3.10-3.20 (1H, m, H$_f$), 3.65-3.72 (2H, m, 2H$_h$), 5.30 (1H, m, H$_e$), 6.07 (1H, m, H$_i$), 7.33-7.40 (6H, m, 4H$_m$, 2H$_p$), 7.64-7.68 (4H, m, 4H$_o$); δ_C (400 MHz, CDCl$_3$) 0.0 (C$_r$), 11.9 (C$_s$ or C$_t$), 17.8 (C$_s$ or C$_t$), 19.2 (C$_l$), 19.4 (C$_a$), 21.1 (C$_b$), 26.9 (C$_n$), 31.7 (C$_f$), 33.8 (C$_k$), 36.2 (C$_c$), 38.5 (C$_g$), 63.1 (C$_h$), 119.4 (C$_j$), 125.5 (C$_e$), 127.7 (C$_m$), 129.4 (C$_p$), 132.1 (C$_i$), 134.3 (C$_q$), 135.6 (C$_o$), 137.3 (C$_d$); *m/z* (EI) 576 (M$^+$, 1%), 535

(7), 361 (6), 287 (36), 199 (100), 181 (35), 131 (79), 103 (69), 75 (100), 61 (54), 45 (60).

tert-Butyl{2-[6-(1,3-dioxolan-2-yl)-3,4-dimethyl-2-cyclohexen-1-yl]ethoxy}diphenylsilane 223
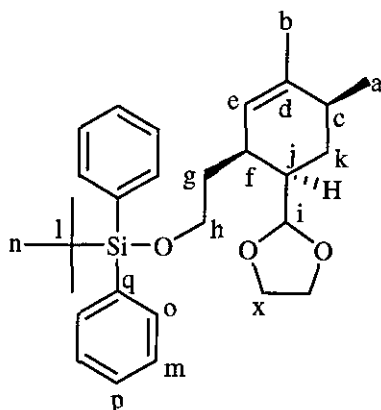
A mixture of lactone **112** (0.3 g, 0.7 mmol), ethylene glycol (0.4 g, 10.0 equiv.) and PPTS (10% mol.) in toluene (10 mL) was heated under reflux with azeotropique removal of the water using a Dean-Stark apparatus and was allowed to stir for 5 hours. The mixture was cooled down and poured into saturated aqueous sodium bicarbonate (50 mL). The organic phase was washed with saturated sodium chloride (50 mL), dried over sodium sulfate and concentrated _in vacuo_. The crude product was purified by column chromatography using petroleum ether / ethyl acetate (49:1) and afforded the acetal **223** as a colourless oil (85.7 mg, 26%) (Found: M$^+$, 465.17583. C$_{29}$H$_{40}$O$_3$Si requires 464.27467); ν_{max} (neat)/cm^{-1} 2932 (=CH), 2781 (O-CH-O); δ_H (400 MHz, CDCl$_3$) 1.02 (3H, d, ^3J 7.0, 3H$_a$), 1.04 (9H, d, 9H$_n$), 1.30-1.64 (2H, m, H$_g$, H$_k$), 1.62 (3H, s, 3H$_b$), 1.63-1.69 (2H, m, H$_{g'}$, H$_{k'}$), 1.90-2.10 (1H, m, H$_c$), 2.27-2.35 (1H, m, H$_f$), 2.44-2.56 (1H, m, H$_j$), 3.64-3.69 (1H, m, H$_h$), 3.70-3.79 (1H, m, H$_{h'}$), 3.84 (2H, m, 2H$_x$), 3.91 (2H, m, 2H$_x$), 4.74 (1H, m, H$_i$), 5.53 (1H, d, ^3J 5.2, H$_e$) 7.26-7.43 (6H, m, 4H$_m$, 2H$_p$), 7.66-7.70 (4H, m, 4H$_o$); δ_C (400 MHz, CDCl$_3$) 19.8 (C$_l$), 20.0 (C$_a$), 21.5 (C$_b$), 27.4 (C$_n$), 31.7 (C$_k$), 32.4 (C$_f$), 35.0 (C$_g$), 35.4 (C$_c$), 41.0 (C$_j$), 61.9 (C$_h$), 66.7 (C$_x$), 106.7 (C$_i$), 126.8 (C$_e$), 127.4 (C$_m$), 129.9 (C$_p$), 134.3 (C$_q$), 136.1 (C$_o$),

137.9 (C$_d$); m/z (EI) 464 (M$^+$, 12%), 337 (15), 239 (14), 225 (56), 165 (25), 127 (74), 107 (35), 99 (24), 77 (88), 73 (54), 57 (63), 41 (57).

(2-{2-[(2,2-Dimethylpropanoyl)oxy]ethyl}-4,5-dimethyl-3-cyclohexen-1-yl)methyl pivalate 224
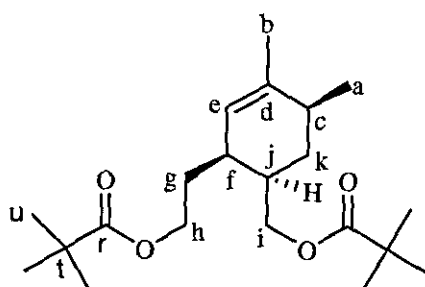
To a solution of diol **145** (0.5 g, 2.7 mmol) in dichloromethane (10 mL) pyridine (0.3 mL, 1.2 equiv.) and pivaloyl chloride (0.32 g, 1 equiv) was added at 0 °C. The reaction mixture was allowed to stir for 5 hours at room temperature. The reaction was quenched by addition of saturated ammonium chloride (11 mL). The aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were finally dried over magnesium sulfate and solvent removed *in vacuo*. Purification of the crude product was done by column chromatography on silica gel using a solution of petroleum ether / ethyl acetate (9:1) and afforded the diprotected alcohol **224** as a yellow oil (0.95 g, 42%) (Found: M$^+$, 352.63675. C$_{21}$H$_{36}$O$_4$ requires 352.26136); v_{max} (neat)/cm^{-1} 1725 (O-C=O); δ_H (400 MHz, CDCl$_3$) 0.90-1.30 (3H, m, 2H$_g$, H$_k$), 0.99 (3H, d, ^3J 6.8, 3H$_a$), 1.32 (18H, s, 18H$_u$), 1.42-1.47 (1H, m, H$_{k'}$), 1.58 (3H, s, 3H$_b$), 1.90-2.00 (1H, m, H$_c$), 2.39-2.45(1H, m, H$_j$), 2.48-2.55 (1H, m, H$_f$), 3.92 and 4.27 (2H, 2 m, 2 H$_i$), 4.13-4.22 (1H, m, H$_h$), 4.23-4.32 (1H, m, H$_{h'}$), 5.37 (1H, d, ^3J 5.2, H$_e$); δ_C (400 MHz, CDCl$_3$) 20.0 (C$_a$), 21.6 (C$_b$), 25.3 (C$_u$), 31.9 (C$_k$), 30.1 (C$_g$), 32.7(C$_f$), 34.8 (C$_c$), 36.6 (C$_j$), 38.6 (C$_t$), 63.7 (C$_h$), 68.7 (C$_i$), 124.6 (C$_e$), 137.8 (C$_d$), 175.0 (C$_r$).

[(2-{3,4-Dimethyl-6-[(trityloxy)methyl]-2-cyclohexen-1-yl}ethoxy)(diphenyl)methyl] benzene 225
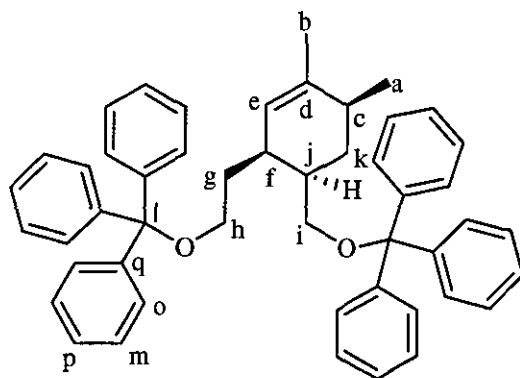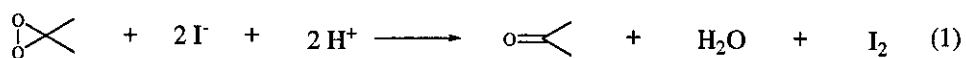

To a solution of diol **145** (0.5 g, 2.7 mmol) in *N,N*-dimethylformamide (10 mL) a catalytic amount of DMAP (10% mol.) and trityl chloride (75.2 mg, 1 equiv.) was added at 0 °C. The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (20 mL) and washed with saturated aqueous ammonium chloride (10 mL). The two phases were separated and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic layers were finally dried over magnesium sulfate and solvents removed *in vacuo*. Purification of the crude product was done by column chromatography on silica gel using a solution of petroleum ether / ethyl acetate (4:1) and afforded the diprotected alcohol **225** as a yellow oil (0.67 g, 37%) (Found: M^+, 669.254537. $C_{49}H_{48}O_2$ requires 668.36543); v_{max} (neat)/cm^{-1} 720 (CH arom), 698 (CH arom); δ_H (400 MHz, CDCl$_3$) 0.94-1.00 (1H, m, H_k),1.00 (3H, d, ^3J 6.8, 3H$_a$), 1.26-1.30 (1H, m, H_g), 1.40-1.45 (1H, m, $H_{k'}$), 1.62-1.70 (1H, m, $H_{g'}$), 1.62 (3H, s, 3H$_b$), 1.90-2.00 (1H, m, H_c), 2.12-2.24 (1H, m, H_j), 2.41-2.51 (1H, m, H_f), 3.46 and 3.56 (2H, 2 m, 2H$_i$), 3.42-3.51 (1H, m, H_h), 3.52-3.61 (1H, m, $H_{h'}$), 5.29-5.35 (1H, m, H_e), 7.15-7.26 (30H, m, 12H$_m$, 6H$_p$, 12H$_o$); δ_C (400 MHz, CDCl$_3$) 20.0 (C_a), 21.5 (C_b), 32.0 (C_k), 31.2 (C_g), 32.6(C_f), 35.1 (C_c), 38.6 (C_j), 64.6 (C_h), 70.6 (C_i), 86.0 and 86.4(C_l), 123.8 (C_m), 125.6 (C_e), 126.9 (C_p), 129.8 (C_o), 136.6 (C_d), 143.9 (C_q).

54

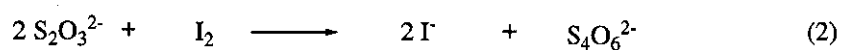## Solution of dimethyldioxirane in acetone 228 [11]

A 2 L flask was filled with water (127 mL) and acetone (96 mL). Sodium hydrogenocarbonate (29.0 g) was added through a solid addition funnel. The resulting white suspension was stirred mechanically and vigorously, and the reaction was allowed to cool to 0 °C in an ice bath. Oxone (60.0 g) was added to the reaction mixture under vigorous stirring. The solid addition funnel was then removed and replaced with a thermometer adapter fitted with the thermometer in order to keep the temperature of the exothermic reaction mixture between 0 and 5 °C. After 15 minutes, a cone/flexible tubing adapter was connected to a pump and a moderate vacuum (100 mmHg) was applied. The reaction mixture was allowed to rise 30 °C by means of a warm water bath. The pale yellow effluent of dimethyldioxirane-acetone solution was collected in the previously cooled receiving flask at -78 °C over 4 hours. When the distillation was over, the pump was disconnected and a nitrogen flux was connected to the cone/flexible tubing adapter. The dimethyldioxirane solution obtained was kept on molecular sieves (4 Å) in a freezer. Iodometric titration allowed us to determine the concentration of dimethyldioxirane in the solution (75 mL, 0.05-0.08 M, 5% yield); v_{max} (neat)/cm^{-1} 2980 (O-C-O), 1210 (C-O); δ_H (400 MHz, CDCl$_3$) 1.65 (6H, s, 6CH_3); δ_C (400 MHz, CDCl$_3$) 22.1 (CH_3), 214.0 (C(CH$_3$)$_2$).

Iodometric titration of dimethyldioxirane solution in acetone

$$\underset{\textbf{228}}{\overset{O}{\underset{O}{\rlap{\,}}}}\!\!\!\bowtie \quad + \quad 2\,I^- \quad + \quad 2\,H^+ \quad \longrightarrow \quad O=\!\!\!< \quad + \quad H_2O \quad + \quad I_2 \qquad (1)$$

$$2\,S_2O_3^{2-} \quad + \quad I_2 \quad \longrightarrow \quad 2\,I^- \quad + \quad S_4O_6^{2-} \qquad (2)$$

Dimethyldioxirane **228** was first reacted with potassium iodide in an acidic medium. The oxidation-reduction reaction involved corresponds to the equation (1).

The amount of iodine thereby liberated was subsequently titrated by an aqueous sodium thiosulfate solution according to the equation (2).

The end point is, therefore, indicated by the total disappearence of the characteristic yellow colour of iodine.

3.3. References

(1)   Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944.
(2)   Page, P. C. B.; Heer, J. P.; Bethell, D.; Lund, A.; Collington, E. W.; Andrews, D. M. *J. Org. Chem.* **1997**, *62*, 6093.
(3)   Little, R. D.; Myong, S. O. *Tetrahedron* **1980**, *21*, 3339.
(4)   Nicolaou, K. C.; Magolds, R. L. *J. Org. Chem.* **1981**, *46*, 1506.
(5)   Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(6)   Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(7)   Balogh, V.; Fetizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339.
(8)   Carpino, L. A.; Giza, C. A.; Carpina, B. A. *J. Am. Chem. Soc.* **1959**, *81*, 955.
(9)   House, H. O.; Richey, F. A. *J. Org. Chem.* **1969**, *34*, 1430.
(10)   Boyland, E.; Nery, R. *J. Chem. Soc. (C)* **1966**, 346.
(11)   Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.