UNIVERSITY OF SOUTHAMPTON

STUDIES TOWARDS THE TOTAL SYNTHESIS OF MANOALIDE

by

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A Thesis submitted for the Degree of Doctor of Philosophy

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MASTER COPY

To my Mother, brothers and sisters, with love.

Preface

The research described in this Thesis was carried out under the supervision of Professor P. J. Kocienski at the University of Southampton between October 1988 and October 1991. No part of this Thesis has been previously submitted for a degree at this or any other University, except where specific acknowledgement has been made.

Some of the work detailed in this Thesis has been the subject of the following publication: Barber, C.; Bury, P.; Kocienski, P.; O'Shea, M. *J. Chem. Soc. Chem. Commun.*, **1991**, 1595.

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ABSTRACT

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Two different synthetic approaches to the terpenoid natural product Manoalide are described.

The first of these approaches was based upon a novel copper (I)-catalysed coupling reaction between Grignard reagents and α-metallated cyclic enol-ethers. 4-Methyl-3-pentenyl magnesium bromide and 5-lithio-2,3-dihydrofuran were coupled in the presence of copper (I) cyanide to produce a vinylmetallic intermediate. The intermediate was reacted with a number of electrophiles to form trans-geometry homoallylic alkenol products with a very high degree of stereocontrol. Attempts to further elaborate the products of the coupling reaction to bring about the synthesis of Manoalide were unsuccessful.

The second approach to Manoalide was based upon the use of a carbo-magnesiation reaction between 4-di-butylamino-2-butyn-1-ol and a homoallylic Grignard reagent. In this fashion the trisubstituted C6-C7 double bond of the Manoalide skeleton was constructed with a very high degree of stereocontrol. The product of the carbomagnesiation reaction was then further manipulated to prepare 2-trimethylsilyl-4-[(3'E,7'E)-10'-(2",6",6"-trimethyl-1"-cyclohexen-1"-yl)-8'-methyl-4'-formyl-1'-hydroxy-3',7'-decadien-1'-yl]-furan. Since Garst and co-workers have reported the conversion of this compound to Manoalide in two steps, its preparation constitutes a formal synthesis of the natural product.

ABBREVIATIONS

Ac	acetyl
B:	Base
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bu, ^{s}Bu, ^{t}Bu	*n*-butyl, *sec*-butyl, *tert*-butyl
Bz	Benzoyl
cat.	catalytic
CI	Chemical ionisation
Cp	η^5-Cyclopentadienyl
DCM	dichloromethane
de	diasteroisomeric excess
DIBAL-H	Diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethylsulphoxide
DMS	dimethyl sulphide
EI	Electron impact
ee	enantiomeric excess
Et	ethyl
EtOAc	Ethyl acetate
h	hour(s)
HMPA	Hexamethylphosphoramide
HRMS	high resolution mass spectrum
IR	infra red
LDA	lithium diisopropylamine
LRMS	low resolution mass spectrum
M	molar or metal
Me	methyl
MEM	Methoxy-ethoxy-methyl
min	minutes
ml	millilitre
mmol	millimole
MOM	Methoxymethyl
Ms	methanesulphonyl (mesyl)

Nu	nucleophile
NMR	nuclear magnetic resonance
OCb	N,N-diisopropylcarbamate
OTf	trifluoromethane sulphonate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	phenyl
PMB	*para*-methoxybenzyl
^{i}Pr	*iso*-Propyl
R, R', R"	alkyl
r. t.	room temperature
SEM	2-trimethylsilylethoxymethyl
TBS	t-butyldimethylsilyl
TFA	Trifluoroacetyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylene-diamine
TMS	trimethylsilyl
TPAP	*tetra-n*-propylammonium perruthenate
Ts	*para*-toluenesulphonyl (tosyl)
UV	Ultra Violet.

Chapter 1

The structure and biological activity of The Marine Natural Product Manoalide.

1.1. The Isolation And Structure Determination Of The Manoalide Series Of Terpenoids.

Over the past two decades the study of natural products derived from marine sources has become of increasing importance. The range and variety of organic compounds possessing interesting biological activity has been impressive,[1-5] and marine sponges, which are the most primitive of all of the multicellular invertebrates, have been among the most prolific sources of these natural products and have been the focus of a great deal of study.[2-5] One such natural product, the sesterterpenoid **Manoalide** (**1**, *cf.* Fig. 1.1) was first reported by de Silva and Scheuer in 1980 as an extract of the marine sponge *Luffariella variabilis*.[6] The compound has since been the focus of a considerable amount of attention due to the fact that it possesses an interesting profile of biological activities. These will be discussed in greater detail later in this chapter.

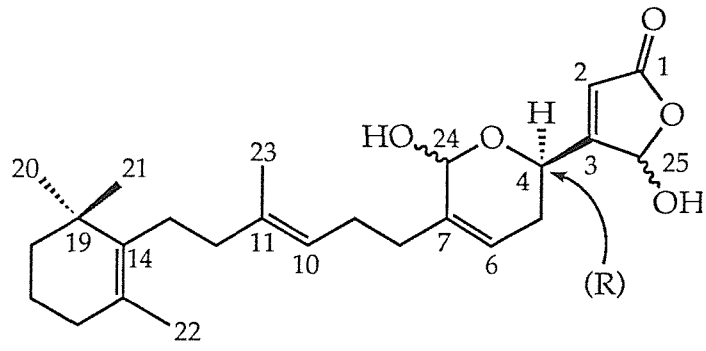
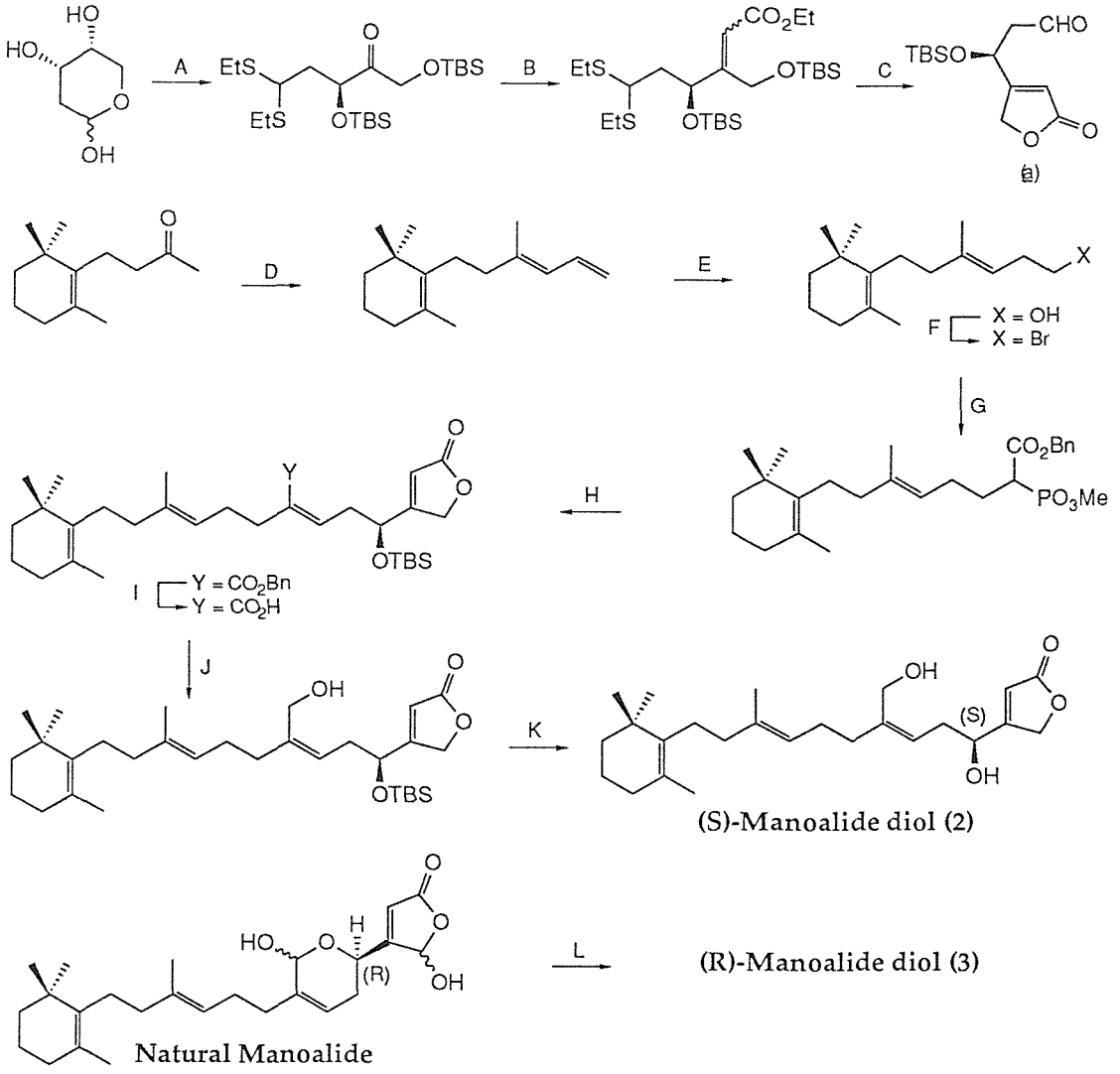


Figure 1.1: The structure of Manoalide (**1**).

The initial determination of the chemical structure of (**1**) was achieved by means of high field NMR and mass spectroscopy studies.[6] Figure 1.1 clearly shows the three stereogenic centres which are present in the compound at carbons C4, C24 and C25. The two hemiacetal centres, C24 and C25, are not stereochemically fixed, due to racemisation *via* an equilibrium between acyclic and cyclised forms. The only stereochemically rigid centre is C4. The use of X-ray analysis to show the absolute configuration of (**1**) is not possible as the compound is non-crystalline and as a result the spacial arrangement about C4 was not determined until 1988.[7] Amoo and co-workers synthesised the S-geometry homochiral diol (**2**) from dihydro-β-ionone and 2-deoxy-D-ribose[7] (*cf.* Scheme 1.1). A similar diol (**3**, *cf.* Scheme 1.1) had previously been derived by the sodium borohydride reduction of Manoalide.[8]The use of circular dichroism studies showed that the totally synthetic diol (**2**), was the enantiomer of (**3**) and so the stereochemistry of (**1**) was assigned to the R geometry as shown in Fig. 1.1.



REAGENTS AND YIELDS

A	92%	(i) EtSH, $ZnCl_2$ catalyst, rt;
	70%	(ii) 2.2 TBS-Cl, pyridine / DCM, rt, 8d, mixture;
	45%	(iii) DMSO, TFA-anhydride / DCM, -65°C to rt; (iv) separate;
B	86%	Triethylphosphonoacetate sodium salt / DME, -20°C, 60h;
C	72%	(i) 80% aqueous AcOH, 5h, 50°C;
	96%	(ii) $HgCl_2$, HgO / 80% aqueous CH_3CN, 30 min, rt;
D	-	$PhPCH_2CH{=}CH_2$, n-BuLi / THF, HMPA, 15 min, rt;
E	19%	(i) 9-BBN / THF, 2h, rt; (ii) 30% H_2O_2, 0°C;
F	77%	CBr_4, Ph_3P / CH_3CN, 12h, rt;
G	69%	69% benzyldimethylphosphonoacetate Lithium salt / DMF, 15h, rt;
H	59%	(i) LDA / THF, -78°C; (ii) (a); (iii) separate;
I	76%	HCO_2NH_4 / MeOH, 10% Pd / C, 8h, rt;
J	68%	(i) $EtOCOCl$, Et_3N / THF, 1h, -10°C; (ii) $NaBH_4$ / DME, 4h, rt;
K	82%	aqueous HF in CH_3CN, 15h, rt;
L	-	$NaBH_4$

NOTES

1. Step A. The reaction gave a mixture of two inseperable diprotected triols which were oxidised and then separated.
2. Step B. A 3: 2, E : Z ratio of isomers was obtained.
3. Step H. Some 15.4% of the E isomer was also obtained.

Scheme 1.1: The Amoo synthesis of (S)-manoalide diol and the proof of the absolute stereochemistry of manoalide.[7]

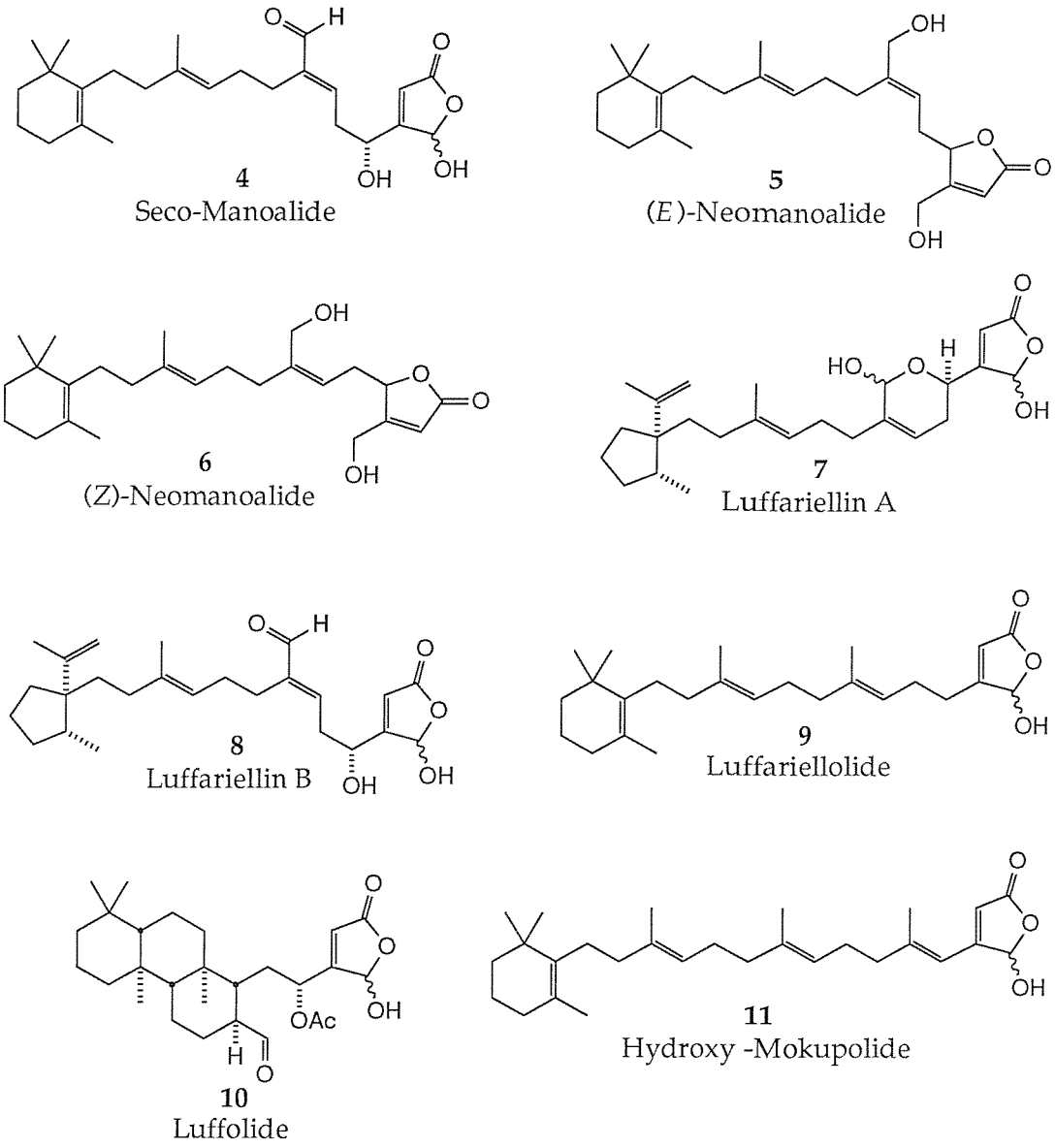


Figure 1.2: The Manoalide series of terpenoid natural products.

The *Luffariella variabilis* species of marine sponge has proven to be a rich source of a number of terpenoids which are structurally related to manoalide. In 1981 de Silva and Scheuer reported the isolation of **Seco-Manoalide** (4, *cf.* Fig 1.2), a sesterterpenoid which is a very closely related structural isomer of (**1**), differing only in the geometry about the C6-C7 double bond. In manoalide this bond has the *Z* geometry which allows the formation of a hemiacetal between the C4 alcohol and the C24 aldehyde centres, to give an α-hydroxydihydropyranyl ring. In the case of (4) the *E* double bond geometry prevents the formation of the hemiacetal ring.

De Silva and Scheuer also reported the isolation of the **E-** and **Z- neomanoalides** (**5** and **6** respectively, *cf.* Fig. 1. 2).[9] These two compounds are again

structural isomers of (**1**), in which the γ-hyroxybutenolide moiety is replaced by a hydroxymethyl-substituted dihydrofuranone ring. The E- and Z- neomanoalides are differentiated by their geometries about the C6-C7 double bond. Two other members of the manoalide group of terpenoids which have been isolated from *Luffariella sp.*are the compounds **Luffariellin A** (**7**) and **Luffariellin B** (**8**).[10] These are analogues of (**1**) and (**4**) respectively in which the trimethylcyclohexene ring has been replaced by a substituted cyclopentene moiety (*cf.* Fig. 1.2). The two luffariellins are otherwise identical to manoalide and secomanoalide and display similar biological activity.[10] Two other secondary metabolites which may be classed as members of the manoalide series of compounds have also been isolated from specimens of *Luffariella sp.*. **Luffariellolide** (**9**, *cf.* Fig. 1.2) was extracted as the major metabolite from sponges collected near the island of Palaou.[11] This sesterterpenoid has some of the same structural features displayed by Manoalide, however it contains neither the C4 hydroxyl functionality, nor the C24 aldehyde. The same animals also contained, as a minor metabolite, the crystalline tetracyclic compound **luffolide** (**10**, *cf.* Fig. 1.2), the structure of which was established by *X*-ray analysis.[12]
Finally, one more natural compound which may be loosely described as a member of the manoalide series, is the triterpenoid **Hydroxy-mokupolide** (**11** *cf.* Fig. 1.2).[13] This compound, which may be best considered as an analogue of luffariellolide (**9**), was isolated from specimens of an unidentified pacific marine sponge.

1.2 The Arachidonic Acid Cascade

The terpenoids of the Manoalide series display an interesting range of biological activities resulting from an ability to interact with one of the body's major metabolic pathways, the arachidonic acid cascade. In order to properly discuss the implications of this interaction, a brief review of the cascade is presented below. A more detailed study is beyond the scope of this thesis; however, an excellent review has recently been published.[15]
The arachidonic acid cascade is the metabolic system responsible for the production of the eicosanoid natural products. The eicosanoids, so named because they all share a basic twenty carbon skeleton, are responsible for the regulation of a large number of physiological processes and are believed, in particular, to be among the principal mediators of the body's inflammatory response mechanism.
The starting point in the cascade concerns the release of the polyunsaturated essential fatty acid, **Arachidonic acid** (**AA**, **12**, *cf.* Scheme 1.2), or (5Z, 8Z, 11Z,

14Z)-eicosa-5, 8, 11, 14-tetraenoic acid. In the body this is predominantly stored as a constituent of cell membrane phospholipids; in particular in the *sn*-2 position of phosphocholines.[15] The release of the side chain groups bound up in such cell- membrane phospholipids is mediated by the phospholipases, a group of ubiquitous hydrolytic enzymes which are found in cells throughout the body. The enzymes **Phospholipase C** (PLC) and **Phospholipase D** (PLD) are responsible for the cleavage of the internal and external glycerophosphate bonds (*cf.* Fig. 1.3) respectively. The cleavage of the internal alkyl-ester, or acyl-ester *sn*-1 bond is carried out by a **Phospholipase A_1** species. The key enzyme with regards to the AA cascade and eicosanoid biosynthesis, is **Phospholipase A_2** (PLA_2). It is this enzyme which is responsible for the cleavage of substituents bound to the *sn*-2 position of phospholipids, and hence is the primary agent for the release of AA into the cell (*cf.* Fig. 1.3 and Scheme 1.2). The action of PLA_2 has been the subject of a recent review.[16]

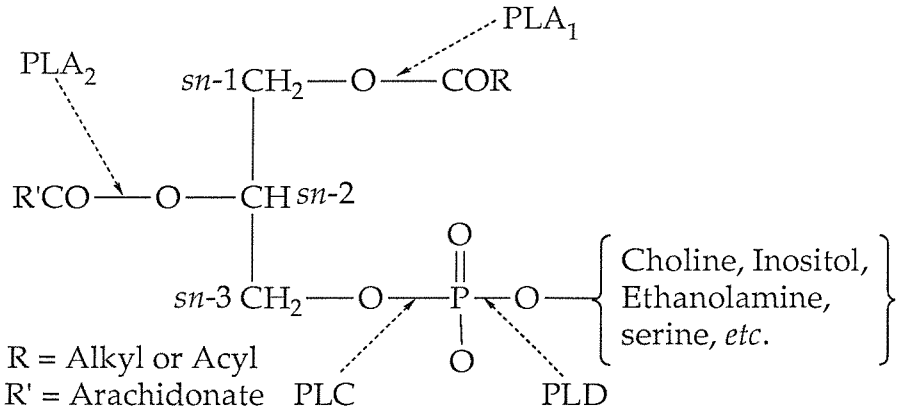


Figure 1.3: The hydrolysis of phospholipids by phospholipase enzymes.

When PLA_2 acts on phosphocholine phospholipids containing arachidonate in the *sn*-2 position and an alkyl chain in the *sn*-1 position, (*i.e.* a 1-*O*-alkyl-2-acyl-*sn*-glycero-3-phosphocholine) the hydrolysis of the *sn*-2 arachidonate bond produces two compounds; *i.e.* free AA and a 1-*O*-alkyl-2-lyso-*sn*-glycero-3-phophocholine species. Each of these possess biological activity, with the latter compound being the immediate precursor of the **Platelet Aggregating Factor** (PAF), which is formed by acetylation at the free sn-2 position. PAF is believed to play an intermediary role in a number of different diseases.[16]

1.2.1. The Prostaglandins, Thromboxanes and Prostacyclin.

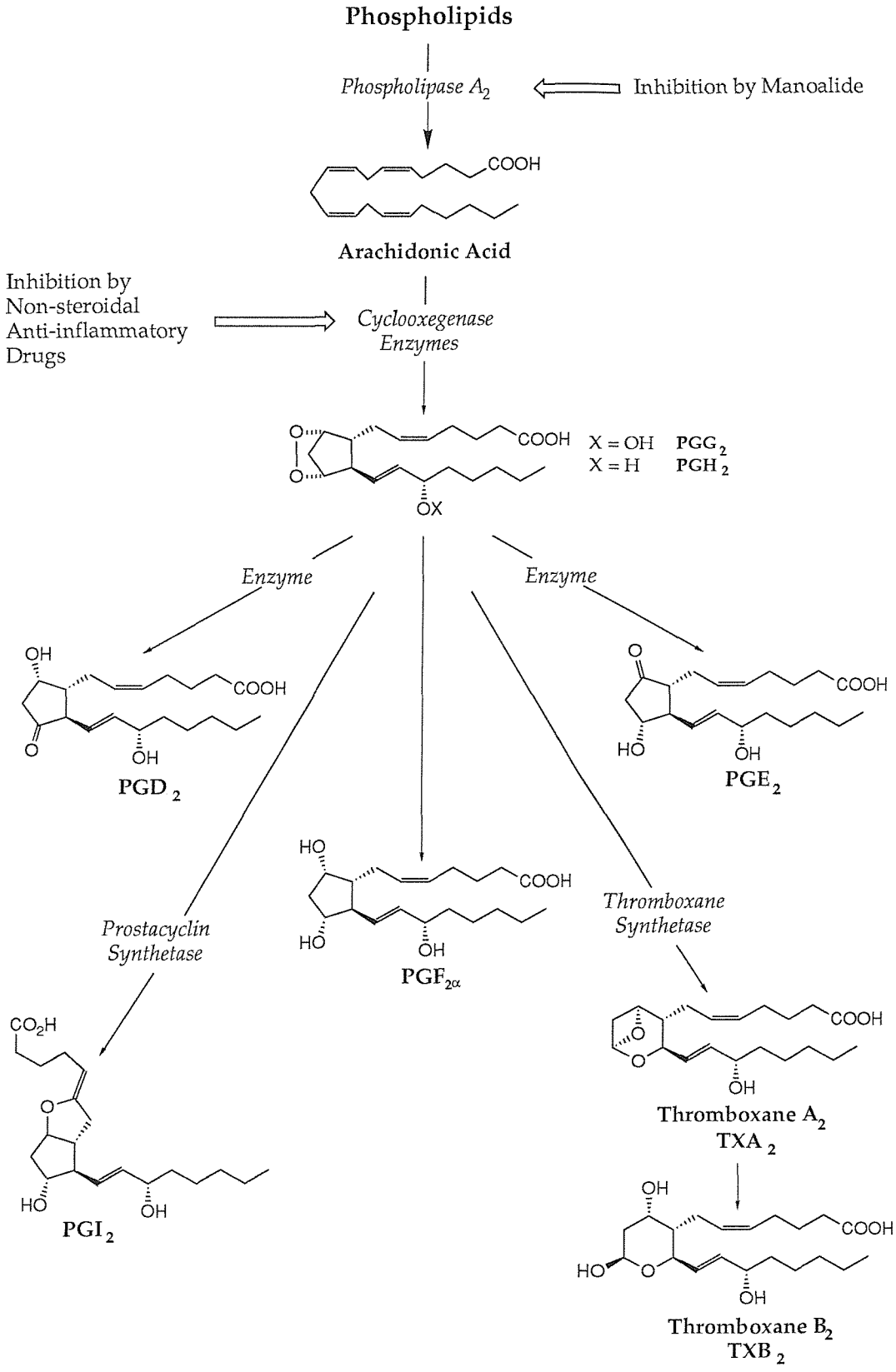
The release of AA from phospholipids heralds the beginning of a number of different metabolic processes. The AA may undergo one of two major enzyme-

catalysed sequences. The first of these involves the **Cyclooxygenase** enzymes, which incorporate molecular oxygen into the C11 and C15 positions of AA to produce a diperoxide species, which undergoes a ring closure reaction to give the two unstable endo-peroxide natural products, Prostaglandin G_2 (PGG_2) and PGH_2. These are the first of the prostaglandin series of eicosanoid natural products (*cf.* Scheme 1.2). The unstable PGH_2 is converted into the more stable products PGD_2, PGE_2, and $PGF_{2\alpha}$, either by nonenzymic degradation, or *via* the activity of isomerases.[17] These stable prostaglandins were first isolated from semen by Von Euler[18] and their name stems from the original belief that they were produced by the prostate gland. They have potent vasodilatory properties and are believed to be involved in the pathogenesis of hypertensive diseases. An even more significant form of biological activity however, is displayed by PGE_2. This prostaglandin has been implicated as a key mediator of a number of human inflammatory diseases ranging from sunburn to chronic arthritis. It is believed to cause the vasodilation and redness which is seen in acute inflammation, and is probably also involved in the development of inflammatory pain.[15]
One of the alternatives to the isomerase route for the bio-conversion of PGH_2, involves the enzyme prostacyclin synthetase. This enzyme catalyses a ring closure reaction to bring about the formation of the bicyclic compound, Prostacyclin (PGI_2, *cf.* Scheme 1.2). PGI_2 is produced by the endothelial cells of vascular tissues and is the most potent endogenous inhibitor of blood platelet aggregation so far discovered. PGI_2 therefore prevents the spontaneous formation of platelet aggregates which would lead to the formation of thrombi.
The last of the major routes for PGH_2 metabolism is the reaction catalysed by thromboxane synthetase. This enzyme is found principally within blood platelets and it catalyses the formation of the highly unstable compound, Thromboxane A_2 (TXA_2, *cf.* Scheme 1.2). TXA_2 degrades very rapidly to the somewhat less reactive TXB_2. Thromboxane A_2 is an extremely potent promoter of blood platelet aggregation[19] and is also a powerful vasoconstrictor. The thromboxanes can be considered as having biological properties opposite to those of PGI_2 and the two compounds are in metabolic balance.
As a result of the powerful biological activities displayed by the prostaglandins, thromboxanes and prostacyclin, any agent which inhibits their production clearly has potential medical applications. A number of well known drugs which owe their activities to the inhibition of the above sections of the AA cascade are the non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen, paracetamol, and indomethacin. These compounds inhibit the reactivity of the cyclooxygenase enzymes which produce PGH_2, and so reduce the amounts of the other eicosanoids derived by the routes described above. As a consequence

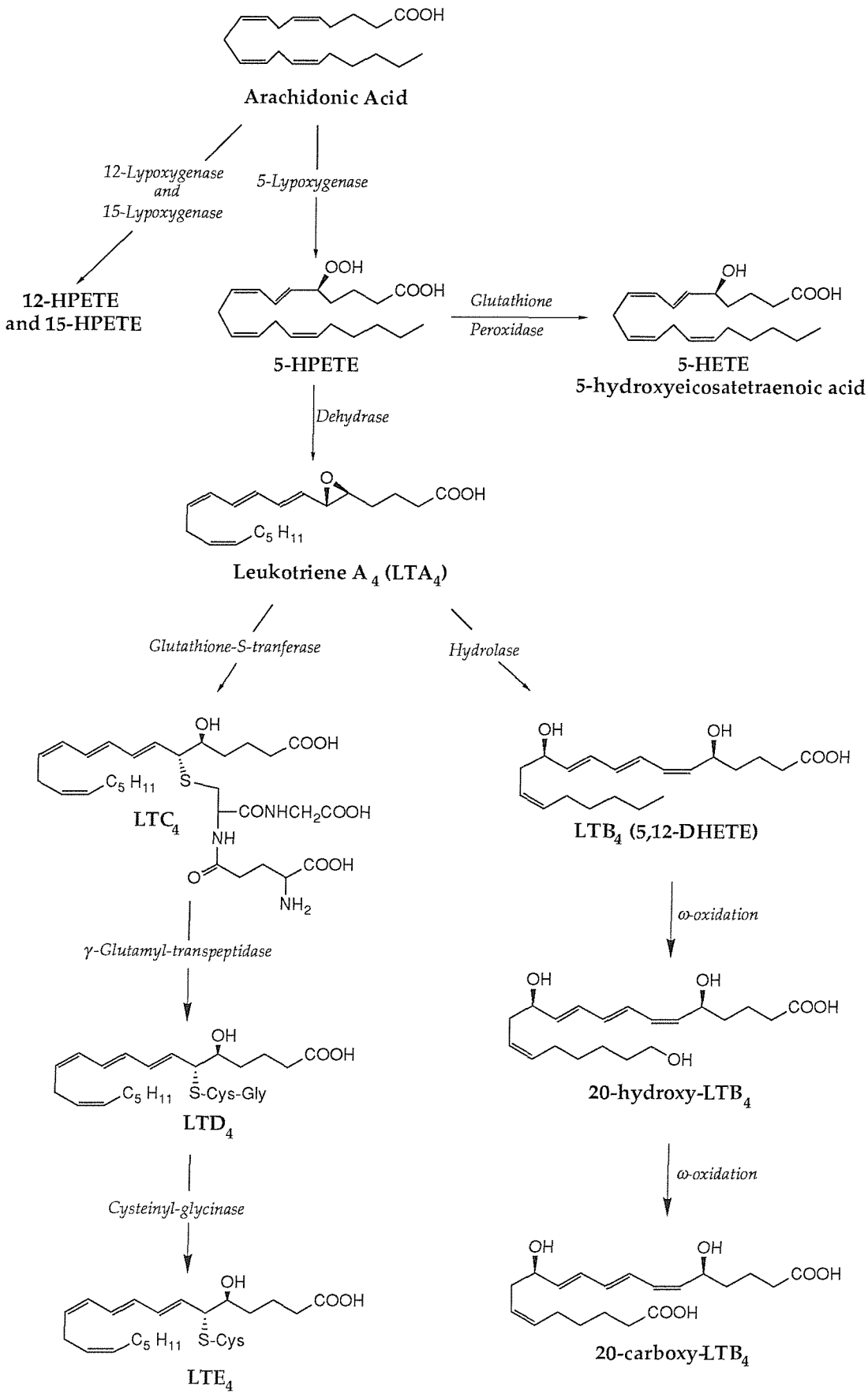
of this action they display anti-inflammatory, anti-pyritic and analgesic properties.

1.2.2. The Leukotrienes.

In addition to the cyclooxygenase pathway described above, the AA liberated from cell-membrane phospholipids may also be metabolised *via*a second set of enzymes which are found principally within leukocytes, (cells which form part of the body's immune response mechanism) and blood platelets. These are **Lipoxygenase** enzymes; with blood platelets typically containing 12-lipoxygenases,[20] and polymorphonuclear leukocytes such as neutrophils, phagocytes and eosinophils, containing 5-lipoxygenases.[21] The latter proteins catalyse the peroxidation of AA to form the acyclic species, 5-HPETE (5-Hydro-Peroxy-Eicosa-Tetraenoic Acid, *cf.* Scheme 1.3). This straight-chain peroxide can either be degraded to the hydroxy compound 5-HETE, or it can undergo an enzyme catalysed reaction to give the first of the Leukotriene class of eicosanoids; namely the epoxide, Leukotriene A_4 (LTA_4 *cf.* Scheme 1.3). Further enzymic modification may produce the dihydroxy species Leukotriene B_4 (LTB_4), or alternatively a glutathione moiety may be introduced by the enzyme glutathione-S-transferase, to give the first of the peptido-leukotrienes, Leukotriene C_4 (LTC_4, *cf.*Scheme 1.3). The other peptido-leukotrienes are then produced by enzymic activity on the peptide side chains (*cf.* Scheme 1.3).
In common with all of the eicosanoid natural products so far described, the leukotrienes display a range of potent biological activities. The substance SRS-A (Slow Reacting Substance of Anaphylaxis) is produced in response to a number of stimuli and causes the contraction of smooth musculature seen in the respiratory and kidney failure of anaphylactic and septic shock. SRS-A has been identified as consisting of a mixture of LTC_4, LTD_4 and LTE_4.[15] The leukotrienes show very potent activity as bronchoconstrictors and the peptido-leukotrienes have been found in the sputem of asthmatics.[22] Leukotrienes are also key mediators of the inflammatory response and have been isolated from the synovial fluid of arthritic patients.[23] Of particular importance is the fact that LTB_4, 5-HETE and its isomer 12-HETE (formed by the action of 12-lipoxygenase on AA, *cf.* Scheme 1.3) all show chemotactic properties towards polymorphonuclear leukocytes. It is possible that these compounds are involved in stimulating and amplifying the number of inflammatory leukocyte cells such as neutrophils found in the vicinity of damaged tissues. Leukocytes produce and release a number of the proteinase enzymes which may be the cause of the joint damage seen in cases of chronic arthritis.



Scheme 1.2: The biosynthesis of the Prostaglandins, Thromboxanes and Prostacyclin from Phospholipid-bound Arachidonic Acid.



Scheme 1.3: The Biosynthesis of the Leukotrienes from Arachidonic Acid.

1.3. The Biological Activity of Manoalide.

The major driving force for the study of Manoalide and its analogues has been derived from their very interesting pharmacological properties. These stem largely from an ability to interrupt the functions of the arachidonic acid cascade at various stages.

1.3.1. The Inhibition of the Arachidonic Acid Cascade by Manoalide.

For each of the pro-inflammatory eicosanoids discussed above the key starting material was the free endogenous AA, which was made available by the actions of a PLA_2 enzyme. A compound possessing PLA_2-blocking activity reduces the amount of free AA available to the cell and hence reduces the quantities of eicosanoids which the cell produces. In this fashion a PLA_2-blocker compound has the potential to act as an anti-inflammatory drug by directly preventing the production of some of the biochemical agents which mediate the body's inflammatory response. An example of compounds exhibiting just such a therapeutic effect are the glucocorticoids. These stimulate the production of the protein lipocortin, which is known to be an inhibitor of PLA_2.[24-26] The potential use of PLA_2-inhibitor compounds as drugs has generated intense interest in any compound displaying this form of biological activity.

The investigation of the biological activities of manoalide was first stimulated by the discovery by Jacobs and co-workers that (**1**) possesses analgesic properties and is able to alleviate the murine ear inflammation induced by the application of phorbol esters but not that brought about by the application of arachidonic acid.[14, 27, 28] The implication drawn from these observations was that manoalide owed its activity to an ability to interrupt the AA cascade at a stage prior to the cyclooxygenases, *i.e.* by preventing the release of AA by acting as a PLA_2 inhibitor.[14] Supportive evidence for this hypothesis was obtained by showing that manoalide is a powerful blocker of the neurotoxic effects of β-bungarotoxin on isolated muscle tissues.[29] This toxin owes its activity, in part, to the presence of a PLA_2 sub-unit within its structure.[30] Further studies have since confirmed that manoalide is a potent inhibitor of a variety of PLA_2 enzymes. These include the enzymes derived from *Apis mellifera* bee stings,[31] the *Naja naja* cobra venom,[32, 33] and the venom of the *Crotalus durissus* rattlesnake.[34] The terpenoid has also been shown to be an inhibitor of purified mammalian PLA_2 enzymes derived from rabbit polymorphonuclear leukocytes,[35] porcine pancreas,[34] and guinea pig lung and uterus,[34] along with the non-purified intracellular PLA_2's found in cytosolic fractions of rat leukemia cells and the

BC_3H_1 strain of smooth muscle-like cells.[34] In addition, the purified PLA_2 extracted from human synovial fluid has also been shown to be susceptible to manoalide inhibition.[36] Interestingly, the activity of synovial PLA_2's isolated from the inflamed joints of rheumatoid arthritis sufferers has been shown to correlate directly with the extent of progression of the disease.[37]

The studies discussed above have highlighted a number of key features about the PLA_2-blocking activities of manoalide:

i) the inhibition is pH dependent[31, 33] with the terpenoid's maximum activity typically being observed at between pH 7 and 8;[33, 38, 39]

ii) although the presence of calcium ions is required for the enzyme's hydrolytic activity[40] the inhibitory effect of manoalide is not itself calcium dependent;[33]

iii) the kinetics of the inhibition are non-linear[33] implying a complex mechanism for the interaction between the enzyme and the terpenoid;

iv)the inhibition is concentration dependent[14, 33, 34], with the IC_{50} values displayed by the PLA_2 enzymes varying considerably with the source of the enzyme under study;

v) the inhibition of the PLA_2 enzymes is essentially irreversible;[31, 33] and

vi)the hydrolytic activity of the enzymes is not totally destroyed by manoalide, as the terpenoid-treated enzymes are still capable of reacting with phosphatidyl ethanolamine phospholipids.[33]

The development of an understanding of the interactions between an inhibitor compound and an enzyme allows, in theory, the rational design of analogues with improved pharmacological properties, such as greater selectivity or greater potency. A review has been published[41] summarising the findings of a number of structure activity relationship (SAR) studies carried out in order to investigate the mechanism by which PLA_2 enzymes are inactivated by (**1**). The key structural features required for the inhibitory activity displayed by manoalide and its analogues, are the γ-hydroxybutenolide (5-hydroxy-2(5H)-furanone) moiety and the C24 α,β-unsaturated aldehyde group. The presence of the γ-hydroxybutenolide is a crucial requirement for potent PLA_2 inhibitory activity. Garst and co-workers have prepared a number of compounds[42, 43] containing this heterocycle, with a variety of different alkyl substituents. Many of these synthetic species display significant biological activity, an example of particular interest being the Allergan compound, **AGN-190383** (**13**, *cf.* Fig. 1.4) which is a topical anti-inflammatory agent.[43] Another interesting synthetic compound of this type is the potent, partially reversible PLA_2 inhibitor, **Manoalogue** (**14**, *cf.* Fig. 1.4).[44]

The C24 aldehyde group is the structural feature which dictates the irreversibil-

ity of the interaction of compounds with PLA_2. The two manoalide analogues **HDHB (15**, *cf.* Fig. 1.4)[45] and Luffariellolide (**9**, *cf.* Fig. 1.2),[11] are both potent inhibitors of PLA_2. Unlike (**1**) however, neither (**15**), nor (**9**) contain the C24 aldehyde grouping and as such they are both reversible rather than irreversible inhibitors of the enzyme.

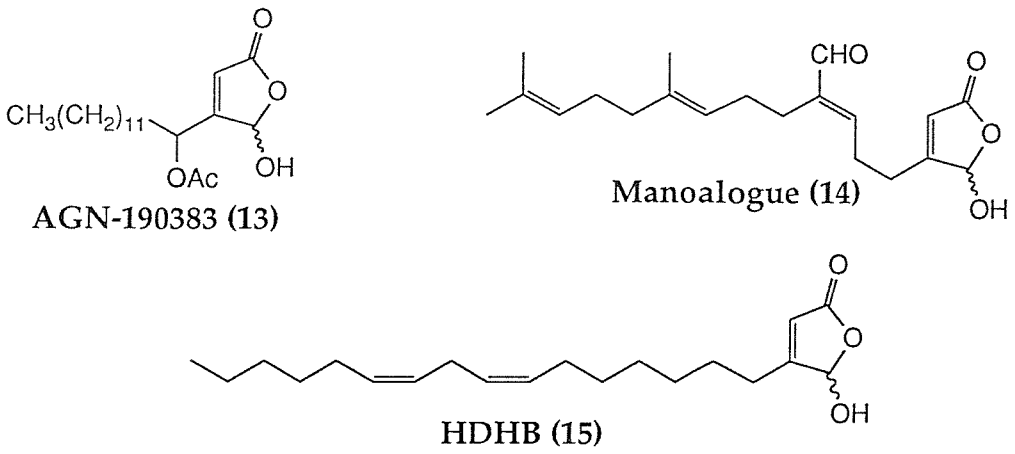


Figure 1.4: Synthetic analogues of Manoalide.

Whilst SAR studies have given some insight into the nature of the interaction between manoalide and PLA_2, the actual mechanism of the inhibition is still not fully understood. The key interaction probably takes place between (**1**) and the side chain ε-amino groups of lysine residues found near the active site of the enzyme. Lombardo and Dennis observed a strong interaction with the lysine residues found in the cobra venom enzyme[33] and studies by Jacobs and co-workers showed similar results for the bee sting protein.[39] Manoalide forms compounds with lysine-containing peptides; in particular with tetrapeptides containing a 1,4 arrangement of lysines.[39] The amino acid sequence of the bee sting protein contains just such a 1,4-pattern of lysine residues[46] in close proximity to the core of the proposed active site of the enzyme.[47] Thus the inhibition of PLA_2 by manoalide probably involves a specific interaction with lysine residues and the different sensitivities of the various PLA_2's studied can be explained by the slight variations in the sequences of the proteins; varying numbers and positions of lysine residues being available for reaction. The enzymes are inactivated by the blocking of the arachidonate-containing phosphocholine lipid's approach to the active site, thereby preventing hydrolysis. The fact that the active site itself does not directly participate in the manoalide interaction is shown by the fact that manoalide-inactivated cobra venom enzyme is still capable of hydrolysing phosphatidylethanolamine lipids.[33] The exact nature of the interaction between the lysine residues and (**1**) again is not fully understood.

Manoalide contains two masked α,β-unsaturated aldehyde functionalities, in

the form of α-hydroxydihydropyran and γ-hydroxybutenolide rings (*cf.* Fig. 1.1). Both rings exist in pH dependent equilibria with their acyclic forms (*cf.* Fig. 1.5), in which the aldehydes are free to undergo chemical reactions.[33]

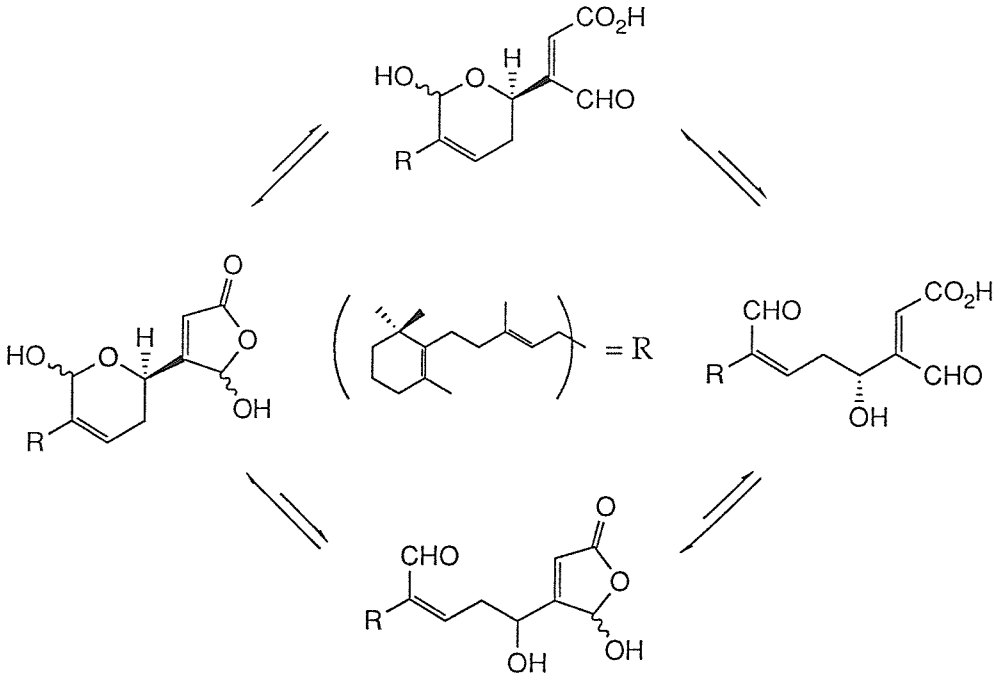


Figure 1.5: The ring-opening/cyclisation equilibria of the manoalide structure.

The initiating step of the PLA_2 inhibition probably involves an interaction between the closed-ring form of manoalide and a specific binding site on the enzyme,[41] inducing the ring-opening of the γ-hydroxybutenolide species and liberating the C25 aldehyde. This is then believed to form a Schiff base with a lysine residue.[41] The irreversible inactivation of the enzyme is then achieved by the formation of a second Schiff base between another enzymic lysine residue and the free C24 aldehyde formed by the ring-opening of the α-hydroxydihydropyran (*cf.* Fig. 1.6). An alternative mechanism may be possible in which the lysine residues undergo Michael reactions with the α,β-unsaturated aldehydes, rather than Schiff base formation.[33] It must be stressed once more that the exact nature of the reaction has not yet been established.

In addition to the systemic effect on the AA cascade brought about by inhibiting PLA_2 enzymes, manoalide has also been shown to specifically inhibit the production of the leukotrienes. Manoalide and its analogues reduce the formation of the leukotrienes LTB_4, LTC_4 and LTD_4 by acting as potent inhibitors of the 5-lipoxygenase enzymes involved in their biosynthesis.[48-50] The inhibitory effect of (**1**) and its analogues has been demonstrated in particular for the 5-lipoxygenase enzymes present in rat basophilic leukemia cells and human polymorphonuclear leukocytes.[49]

The net result of of the activities displayed by (**1**) which have been discussed above is an overall reduction of the amounts of the eicosanoids produced by cells.

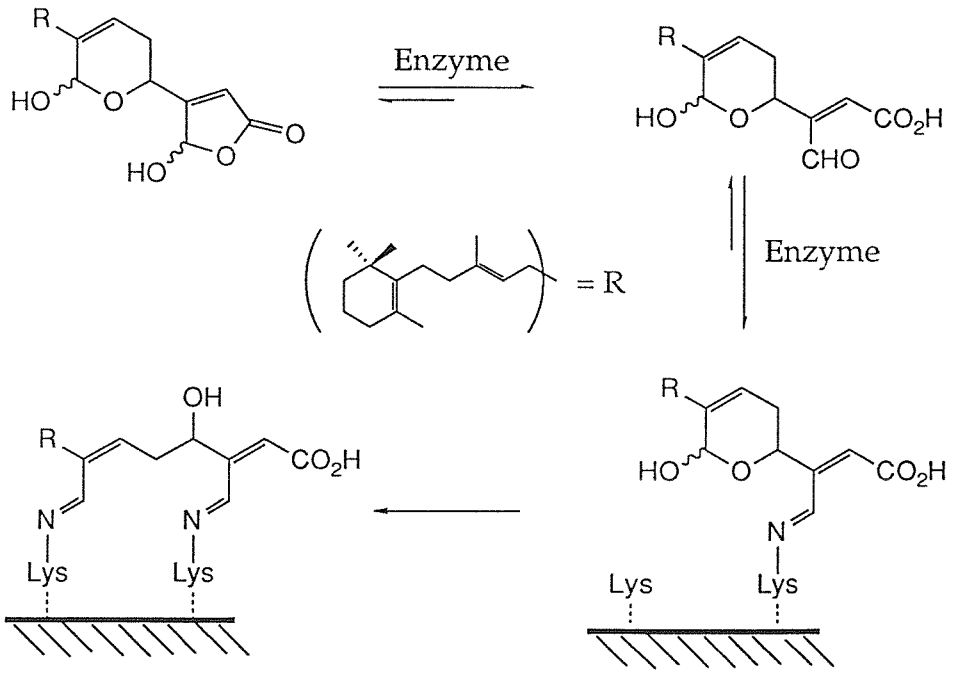


Figure 1.6: Proposed mechanism of interaction between manoalide and PLA_2

1.3.2. The Clinical Application Of Manoalide As An Anti Inflammatory Drug.

In addition to bringing about the reduction in the formation of the pro-inflammatory eicosanoids discussed above, manoalide has also be shown to effect other metabolic processes which have been implicated in the body's inflammatory response. A number of hormones, neurotransmitters, growth factors and pro-inflammatory stimuli are known to cause a rapid turnover of phosphoinositides *via* the activation of phosphoinositide-specific phospholipase C (PI-PLC) enzymes.[51] The phosphoinositides are believed to participate in the release of calcium ions from intracellular storage sites. Calcium ions are important mediators in the processes leading to the development of inflammation[51]. Manoalide affects the release of intracellular calcium stores by acting as a powerful inhibitor of the PI-PLC enzymes.[51] In addition, (**1**) was also able to interfere with calcium mobilisation by inhibiting the cell mebrane hormone- and voltage-stimulated calcium channels found in a number of different cell types.[52] Finally, manoalide inhibits both the infiltration of inflamed tissues by human neutrophil cells[53] and the subsequent release of the elastase enzymes produced by these cells.[54] These elastases are thought to play an important role in the development of the joint damage seen in chronic arthritis.

An overall consideration of the pharmacological activities of manoalide discussed above provides a rationalisation for the anti-inflammatory properties first described by Jacobs.[14] The pharmacological studies have not, however, been of purely academic interest, as the development of (**1**) and its analogues for use as ethical pharmaceuticals holds a great deal of potential for the future. For example, manoalide is presently undergoing phase II clinical trials for the treatment of psoriasis.[55]

The manoalide series of natural products and its analogues may well prove to be the source of novel clinical agents for a whole range of unpleasant and debilitating inflammatory diseases which have, on the whole, been poorly treated to date.

Chapter 2

The Literature Syntheses of Manoalide.

2.1. General Requirements For The Total Synthesis Of Manoalide.

With the advent of the use of manoalide in clinical trials and its development as a therapeutic agent, a need arose for substantially greater quantities of the terpenoid than could be feasibly obtained by extraction from the very limited natural sources. As a consequence, the development of totally synthetic routes became essential.

Any synthetic route designed for the preparation of manoalide must address the construction of the four key structural features of the compound:

i) the terminal 2,2,6-trimethyl-1-cyclohexen-1-yl group;
ii) the C10-C11 *E*-geometry trisubstituted double bond;
iii) the 5-hydroxy-2(5H)-furanone, or γ-hydroxybutenolide moiety; and
iv) the C6-C7 aldehyde functionalised trisubstituted double bond.

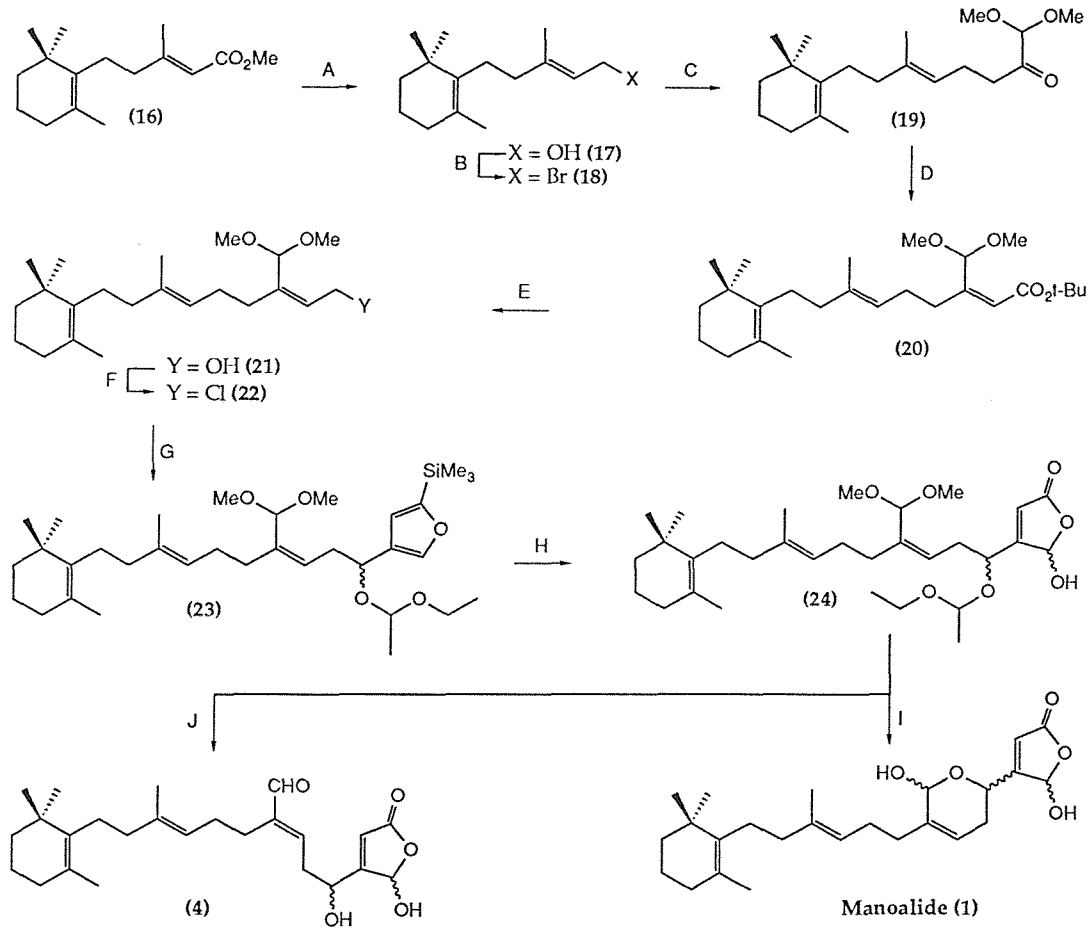
In addition, an ideal route should be short, stereoselective and cheap.

To date, three total syntheses of (**1**) have been reported.[56-58] These three routes are summarised below in Schemes 2.1, 2.2 and 2.3, and a brief study highlights their key differences and similarities. The methods used for the construction of the different structural features are discussed in turn below.

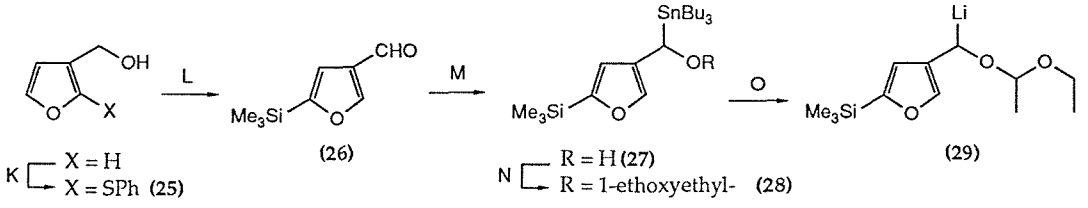
2.2. The Introduction Of The Trimethylcyclohexenyl Ring And The C10-C11 Double Bond.

The method employed for the construction of these two structural features was identical in both of the syntheses published by Katsumura and co-workers[56, 57] (*cf.* Schemes 2.1 and 2.2). The starting material employed was methyl (2Z)-3-methyl-5-(2',2',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentenoate (**16**, *cf.* Scheme 2.1), which contained both of the required structural features intact. However, this starting material is not commercially available and therefore had to be synthesised. Katsumura prepared (**16**) by the method of Schmidt *et al.*,[59] from the very expensive precursor 2,2,6-trimethylcyclohexanone. The high cost of the initial starting material, along with the length of the sequence used to produce (**16**), must be considered as weak points in the Katsumura routes in terms of the development of a general, economical synthesis of (**1**).

The third total synthesis of manoalide, which was reported by Garst and co-workers, is shown in Scheme 2.3.[58] Garst employed the readily available, inexpensive starting material, β-ionone (**37**) as the source of the trimethylcyclohexene ring present in the manoalide structure. The C10-C11 double bond was introduced in two steps *via* a regiospecific 1,4-reduction of (**37**) to the dihydro-β-ionone species (**38**), followed by a Wittig reaction to give the alcohol (**39**).

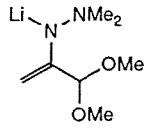


Synthesis of furan fragment (29)



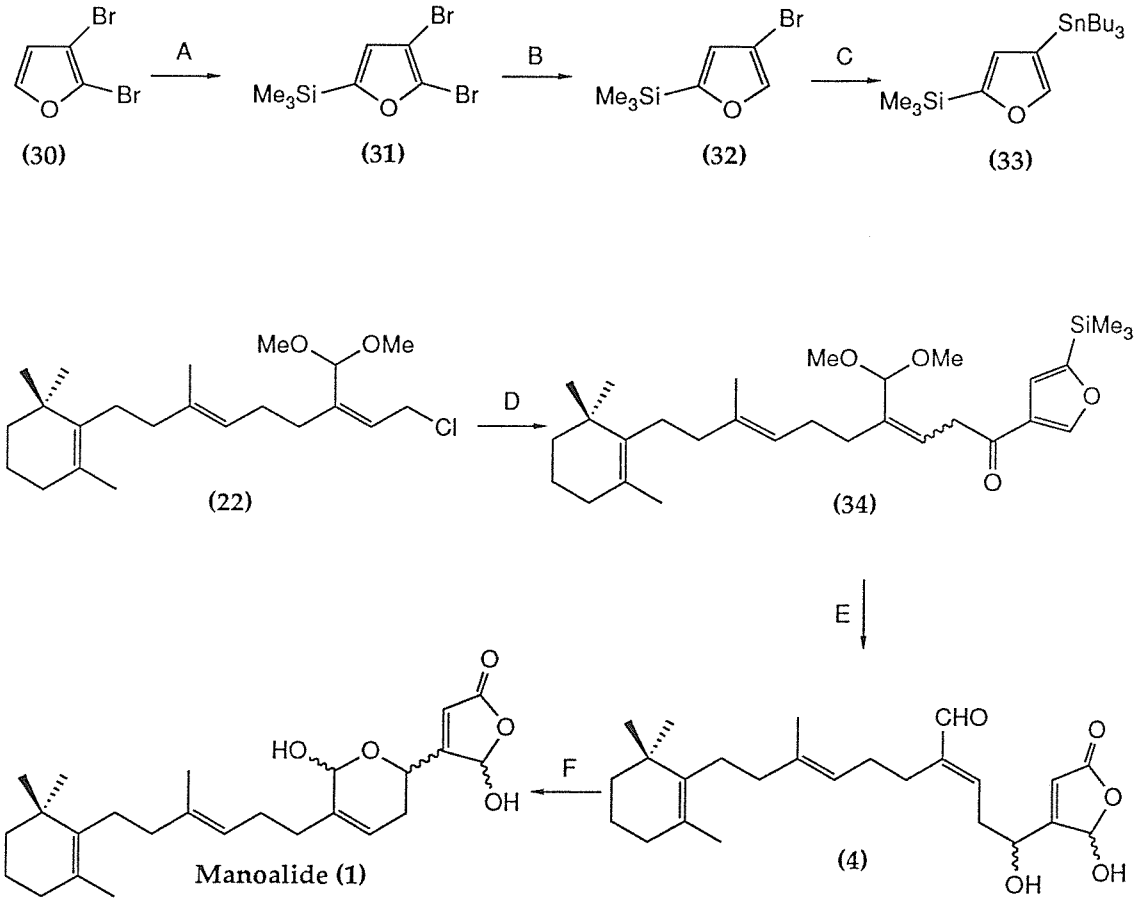
REAGENTS AND YIELDS

A	-	$LiAlH_4$;
B	86%	PBr_3 / Pyridine;
C	72%	(i) (a); (ii) 2N HCl, 0°C, 3 min;
D	95%	t-Butyl-2-trimethylsilyl-acetate anion;
E	95%	DIBAL-H / DCM;
F	90%	(i) MsCl, Et_3N, DMAP/ DCM, 0°C, 30 min; LiCl / DMF, 0°C, 3h;
G	89%	(29) / THF, -78°C, 1h;
H	-	O_2, UV, rose Bengal / DCM, MeOH, 78°C;
I	55%	70% aqueous AcOH / THF, rt, 7h;
J	100%	2N HCl / THF, rt, 2h
K	91%	(i) dilithiation, sulphenylation;
L	41%	(i) 2 n-BuLi / THF, -78°C, 1h; (ii) Me_3SiCl / THF, 0°C, 1h; (iii) 1% HCl / THF, 0°C, 5min; (iv) Raney-Ni / EtOH, 16h; (v) $Ba(MnO_4)_2$ / DCM, 16h;
M	-	n-Bu_3SnLi / THF, -78°C, 1h;
N	95%	1-chloroethyl-ethyl ether, i-Pr_2NEt / DCM, 0°C, 1h;
O	-	n-BuLi / THF, -78°C, 15 min.



(a)

Scheme 2.1: The first Katsumura synthesis of Manoalide.[56]



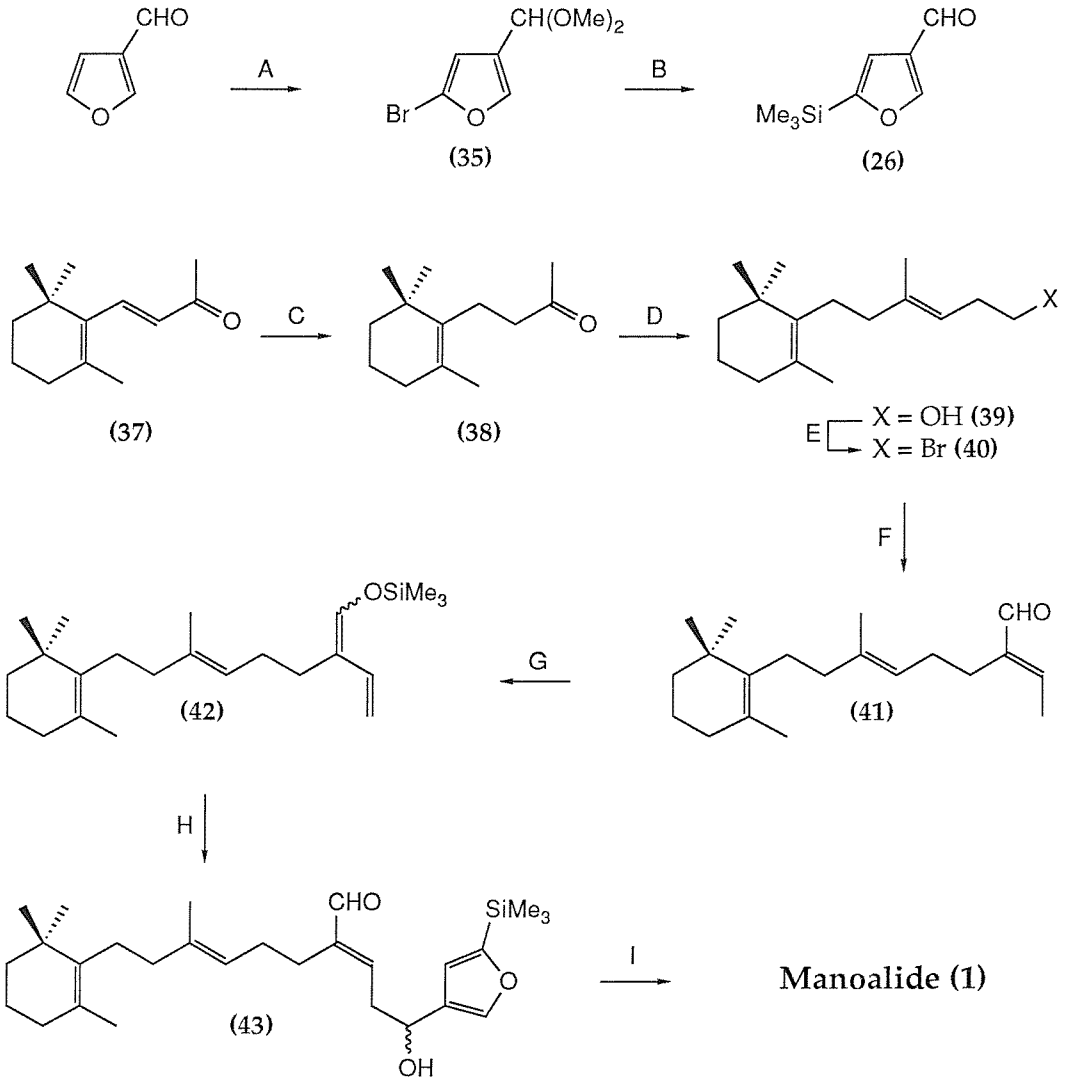
Reagents

A	86%	LDA, TMS-chloride / THF;
B	84%	(i) n-BuLi / Et_2O, -78°C, 3 min; (ii)H_2O;
C	80%	(i) s-BuLi / Et_2O, -78°C, 30 min; (i)Bu_3SnCl, rt, 1h;
D	94%	**(33)** , CO (3 atm), Pallidium dibenzylideneacetone (10 M %), PPh_3 (20 M %), 50°C, 36h;
E	60%	(i) $LiAlH_4$; (ii) 1-chloroethyl ethyl ether, i-Pr_2NEt, Et_3N / DCM, (iii) O_2, UV, rose Bengal; (iv) 2N HCl / THF-H_2O;
F	100%	UV irradiation / PhH, 0°C.

Scheme 2.2: The second Katsumura synthesis of Manoalide.[57]

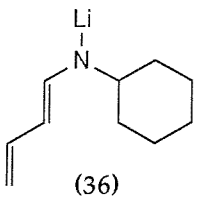
The Wittig step was probably the weakest point in the Garst synthesis, as it generated a 1:1 mixture of the *E* and *Z* double bond isomers, which then had to be separated. In this way the *E* form of **(39)** was produced in a poor overall yield of only 29%.

In summary therefore, all of the procedures published to date for the preparation of **(1)** contain weak steps in their initial stages, which should be improved upon in the design of a new synthetic route.



Reagents

A	85%	(i) Br_2, $AlBr_3$, / $CHCl_3$; (ii) $CeCl_3.7H_2O$, $CH(OMe)_3$ / MeOH;
B	44%	(i) t-BuLi / THF; (ii) TMS-Cl.
C	-	Ph_3SnH;
D	29%	$[Ph_3P(CH_2)OH]Br$, n-BuLi / THF, separate;
E	74%	(i) p-TsCl / pyridine; (ii) LiBr / acetone, Δ;
F	-	**(36)**, DMPU / THF, -78°C;
G	-	TMS-Cl, Et_3N / PhH;
H	52%	**(26)**, $BF_3.OEt_2$ / DCM, -55°C;
I	-	(i) 300nm UV irradiation / PhH; (ii) O_2 (singlet), rose Bengal / MeOH;



(36)

Scheme 2.3: The Garst total synthesis of Manoalide.[58]

2.3. The Preparation of the 5-hydroxy-2(5H)-furanone Ring Moiety.

The method of introduction of the 5-hydroxy-2(5H)-furanone group was the one feature common to all three published syntheses of (**1**).[56-58] The heterocycle has been found as a sub-unit in a number of different natural products of marine origin, including cacospongionolide,[60] strigol,[61] palauolide[62] (*cf.* Fig. 2.1) and of course the manoalide series of terpenoids. The interest in the synthesis of these natural products has resulted in the development of different procedures for the construction of the heterocycle.

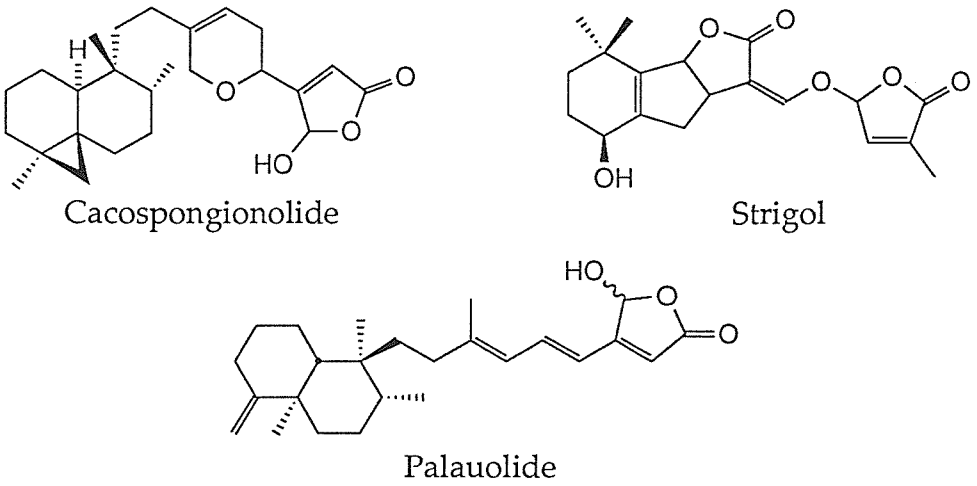


Figure 2.1: Marine natural products containing γ-hydroxybutenolides.

A 5-hydroxy-2(5H)-furanone ring, or γ-hydroxybutenolide, is essentially the cyclic hemiacetal formed by the intramolecular cyclisation of *cis*-4-oxo-2-butenoic acid derivatives (*cf.* Fig. 2.2). Many of the early literature routes to the heterocycle therefore concentrated on the preparation of these acyclic α,β-unsaturated acid-aldehyde (or ketone) precursors.[44, 63-70] Most approaches involved aldol reactions between aldehydes or ketones and esters of glyoxylic acid[64-67] which gave β-hydroxy-ester products. These then eliminated water to produce unsaturated intermediates, which were then saponified and cyclised to the desired butenolide structures (*cf.* Fig. 2.2). Variations on this theme, using enamines instead of aldehydes, or morpholine derivatives of glyoxylic acid instead of esters, were developed by Laugrand,[68] and Bourguignon[69] respectively. The cyclisation of open-chain acid-aldehydes to form 5-hydroxy-2(5H)-furanone rings has been given genuine synthetic application in the Cooper synthesis of strigol[70] and the Dennis synthesis of manoalogue (**14**).[44]

The formation of the heterocycle by the hydrolysis of 5-bromo-2(5H)-furanones, (five-membered-ring lactones), has also been reported[71, 72].

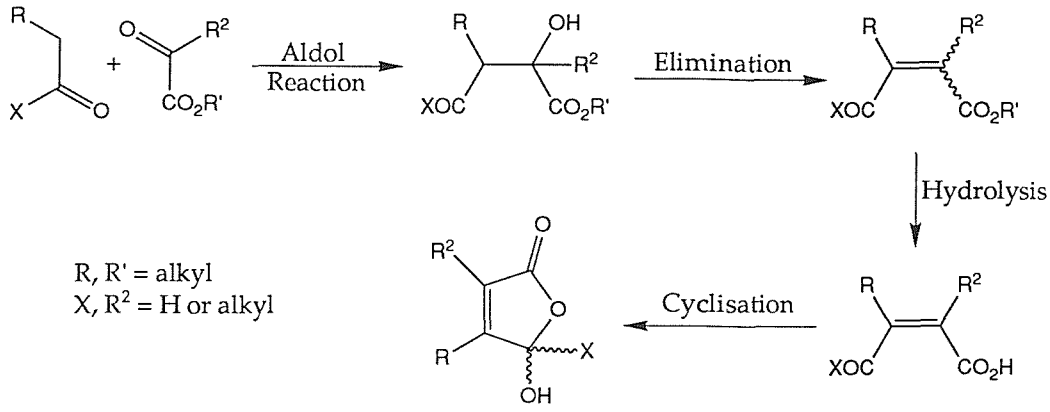


Figure 2.2: The formation of 5-hydroxy-2(5H)-furanones from hydroxy-aldehydes.

The methods discussed above have now been largely replaced by a superior procedure based on the singlet-oxygen oxidation of substituted furans. The oxidation of furans with singlet-oxygen has been of considerable interest in recent years, as it has allowed the facile generation of a number of different structures under mild reaction conditions.[73] Treatment of a simple alkyl-substituted furan with singlet-oxygen, which is readily generated by irradiating molecular oxygen with visible light in the presence of a photosensitising dye, gives an endoperoxide species (44), *via* a [4+2] cyclisation reaction (*cf.* Fig. 2.3).

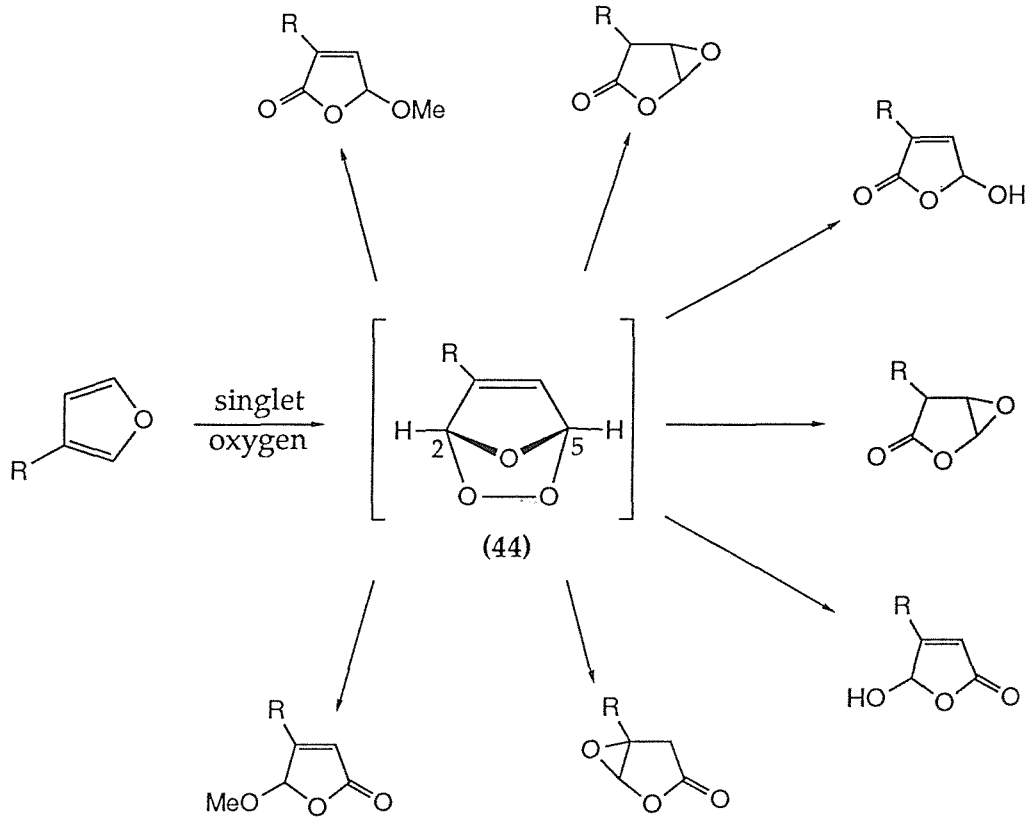


Figure 2.3: The singlet oxygen-oxidation of furans.

The endoperoxide (44), may rearrange in a variety of ways to give a number of different products, such as butenolides, epoxides *etc.*, depending on the reaction conditions employed (*cf.* Fig. 2.3). The loss of a proton from C2 or C5 in (44), and the subsequent collapse of the endoperoxide, results in the formation of the carbonyl and hydroxyl functionalities of the desired 5-hydroxy-2(5H)-furanone structure. The major problem with the reaction in this simple case however, is that the loss of the proton is equally likely from either C2 or C5 and so a mixture of products is obtained. The addition of a hindered base such as diisopropylethylamine or 2,2,6,6-tetramethylpiperidine to the reaction mixture allows the regioselective synthesis of 5-hydroxy-4-alkyl-2(5H)-furanones from 4-alkyl furans.[74] The selectivity is achieved because the steric interactions between the bulky base and the alkyl group on the endoperoxide intermediate prevent the deprotonation from taking place at the C5 position. The interactions direct the deprotonation towards the C2 position, and the subsequent collapse of the endoperoxide generates the desired product (*cf.* Fig. 2.4). The use of the hindered base procedure, however, is ineffective for large scale preparations.[42]

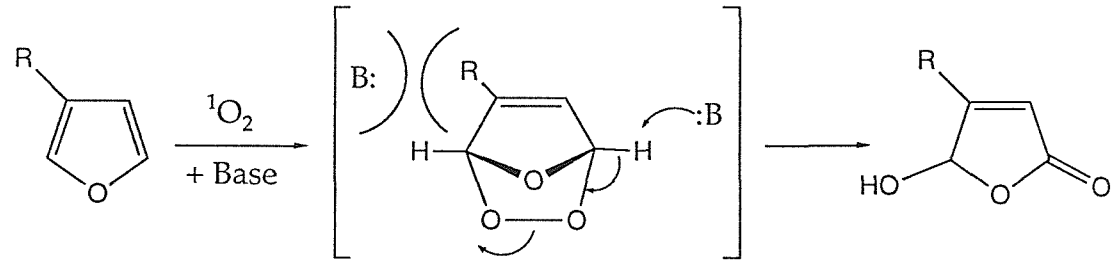


Figure 2.4: The Faulkner synthesis of 5-hydroxy-2(5H)-furanones.[74]

Much more effective methods for achieving the regio-controlled singlet-oxygen oxidation of furans have been developed. These have been based upon the principle of introducing 'directing functionalities' onto the furan ring, which control the rearrangement of the endoperoxide intermediates. The first example of such a method was developed by Schenk and co-workers, who showed that the introduction of a carboxylic acid group onto the C2 position of a furan, followed by treatment with singlet-oxygen, resulted in the **regiospecific** generation of 5-hydroxy-2(5H)-furanones; with the acid functionalised carbon centre of the furan eventually becoming the carbonyl-carbon in the product[75] (*cf.* Fig. 2.5). The same general principle was used by Katsumura and co-workers in their development of the use of the trimethylsilyl group as the directing functionality.[76] The singlet-oxygen oxidation of 2-TMS-substituted furans results in the formation of a TMS-substituted endoperoxide, which rearranges in a regiospecific manner to give a 5-hydroxy-2(5H)-furanone (*cf.* Fig. 2.5). The TMS-substituted

C2 carbon becomes the carbonyl-carbon of the product. A detailed study of this reaction, including the use of trialkylsilyl groups other than TMS, has been recently reported.[42] The reactions are extremely simple to perform; they are carried out under essentially neutral conditions and are tolerant of a wide range of functionalities, including esters, alcohols, ethers and even tri-and tetra-substituted double bonds. They also have the advantage of being cheap; the principal reagent oxygen, is inexpensive, and the dye-sensitisers such as rose Bengal or tetraphenylporphyrin are used in only catalytic quantities. The technique of using a 2-trimethylsilylfuran as the precursors to the desired 5-hydroxy-2(5H)-furanone was used in all three of the published manoalide syntheses,[56-58] and the same method has since been used in the synthesis of the simple analogues of manoalide such as AGN-190383 (**13**), discussed previously.[42, 43]

In summary; the preparation of the 5-hydroxy-2(5H)-furanone ring in manoalide has been readily achieved by means of the regiospecific singlet-oxygen oxidation of a 2-trimethylsilyl-substituted furan. The reaction in question has given fair yields of the desired product, typically 55-60%, and has been carried out without the formation of isolable byproducts. The reaction may therefore be considered as being the method of choice for the introduction of the 5-hydroxy-(2(5H)-furanone ring moiety.

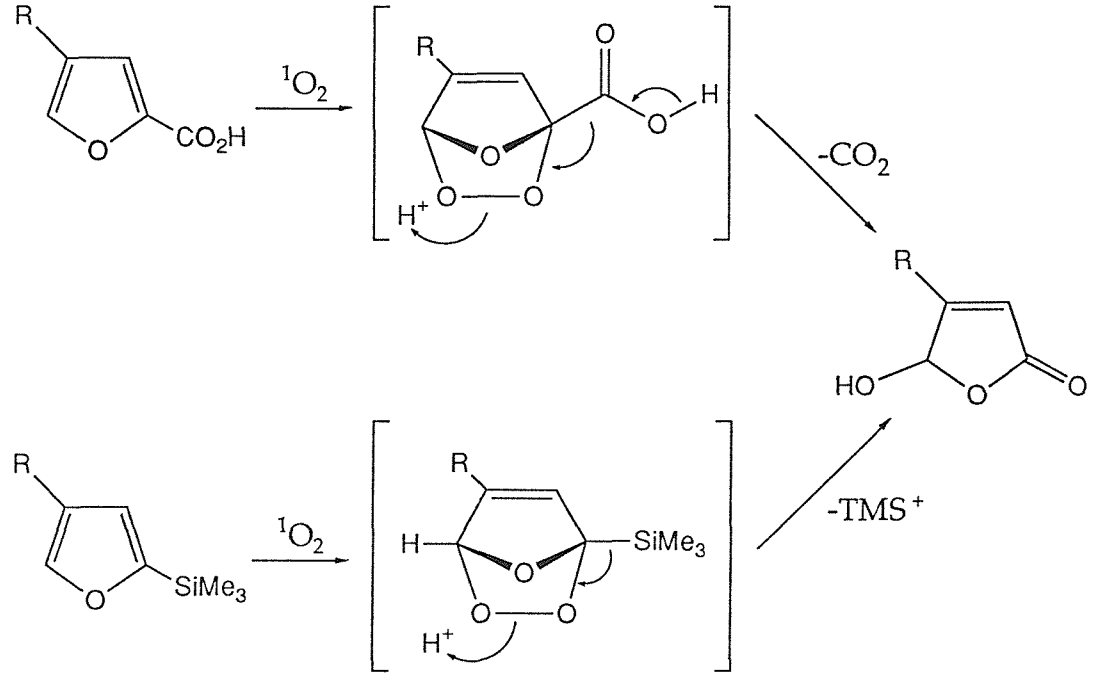


Figure 2.5: The directed singlet oxygen-oxidation of substituted furans.

2.4. The Construction Of The C6-C7 Aldehyde-Substituted Double Bond.

The generation of the C6-C7 double bond of manoalide may be rightly considered as being the key point in a total synthesis of (**1**), as it is the geometry of this bond which determines whether the final product of the route is manoalide or seco-manoalide. In contrast with the formation of the γ-hydroxybutenolide group, the construction of the C6-C7 double bond and the coupling of the furan moiety required for the introduction of the butenolide, constitutes the point where the most significant divergence occurs between the published manaolide syntheses.

In the first of the Katsumura syntheses,[56] (*cf.* Scheme 2.1) the introduction of the key double bond was achieved by means of the Peterson olefination sequence described by Larcheveque *et al.*[63] Treatment of the α-keto-acetal (**19**) with the anion of *t*-butyl trimethylsilylacetate, produced the α,β-unsaturated ester (**20**) in a very good chemical yield (95%), of which approximately 95% was the required *Z*-geometry double bond isomer. The butenolide moiety was then introduced by alkylation of the allylic chloride intermediate (**22**) with the anionic TMS-furan derivative (**29**). The resulting furan (**23**), was then oxidised to the furanone (**24**), which contained the whole of the basic molecular framework of manoalide. The synthesis was completed by acidic deprotection of the C4 alcohol and C24 aldehyde groups; the choice of conditions allowing the selective preparation of either manoalide (**1**), or seco-manoalide (**4**).

The second of the two Katsumura syntheses (*cf.* Scheme 2.2),[57] contained a number of elements which were common to the route discussed above; the allylic chloride (**22**) once again being a key intermediate in the synthesis. In the second route, however, the alkylation reaction was replaced by a palladium (0) catalysed Stille[77] coupling, between carbon monoxide, (**22**) and the stannylated-furan species (**33**). The resulting unstable ketone (**34**), isolated as a mixture of both the *E* and *Z* double bond isomers, was immediately reduced in order to avoid the rearrangement of the β,γ-unsaturation, and the resulting alcohols were protected as their ethoxyethyl ethers. The furan was then oxidised to the butenolide, giving a mixture of *E*- and *Z*-(**24**). Deprotection of the alcohol and aldehyde functionalities under strongly acidic, aqueous conditions resulted in the exclusive formation of seco-manoalide (**4**); *i.e.* the mixture of the *E* and *Z* protected hydroxy-aldehydes was converted into the exclusively *E*-geometry product. By judicious use of reaction conditions therefore, Katsumura cleverly brought about the stereoselective formation of a pure natural product from a mixture of starting materials.

The rearrangement of the *Z* form of (**24**) into (**4**) was not surprising, since it par-

alleled the deprotection step described in the first Katsumura route. Finally, manoalide was prepared by the photolytic isomerisation of (4) as described by Scheuer and de Silva.[9]

The Garst synthesis of manoalide (*cf.* Scheme 2.3),[58] used an entirely different approach for the introduction of the C6-C7 double bond from those employed by Katsumura. The bond in question was initially introduced *via* the alkylation of the primary bromide (40) with the cyclohexylimine anion, (a) (*cf.* Scheme 2.3). The bond was then destroyed by converting the intermediate (41), into the α,β,γ,δ-unsaturated silyl-enol ether (42). The TMS-substituted furan group, required for later elaboration into the butenolide moiety, was then introduced into the molecule *via* a γ-alkylation reaction. Treatment of (42) with boron trifluoride etherate and 2-trimethylsilyl-4-furancarboxaldehyde (26) regenerated the required C6-C7 double bond and resulted in the formation of the intermediate (43), which was converted into seco-manoalide *via* the singlet-oxygen oxidation reaction discussed previously. The synthesis was then completed by photolytic isomerisation of (4).

In summary, the final construction of the C6-C7 double bond in all three published routes was strongly influenced by the method used for the introduction of the TMS-furan group required for elaboration into the butenolide present in the final product. The formation of only one geometrical isomer about the C6-C7 bond was not essential, as the careful use of reaction conditions allowed the rearrangement of one or other of the isomers, and allowed the eventual formation of a stereochemically pure product.

2.5. The Design Of New Synthetic Routes To Manoalide.

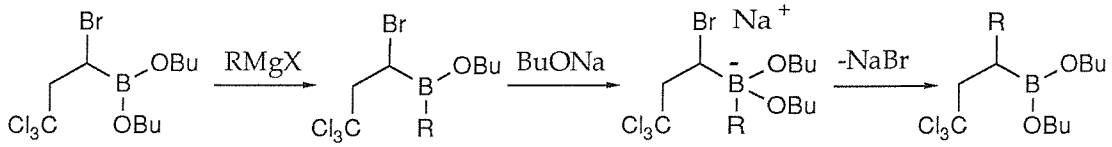
A key point to note for all three of the syntheses of manoalide published to date, is the fact that none of the routes have addressed the problem of the asymmetric synthesis of the terpenoid. The one stereochemically fixed carbon centre in the compound, that at C4, was produced in all three cases, as a racemic mixture. The design of a synthetic route capable of producing homochiral manoalide would, potentially, be of considerable value, as it is possible that the use of manoalide as a racemic mixture may well have significance in the clinical properties of the compound. The availability of C4-epi-manoalide, along with natural manoalide may well prove to be of pharmacological importance. To the best of our knowledge, no study of the pharmacological properties of racemic manoalide relative to the natural compound have been published.
Taking into consideration all of the above points a new synthetic route to (**1**) should, ideally, be sufficiently flexible to allow the synthesis of analogues of the natural product, whilst also allowing the eventual synthesis of homochiral compounds. Our efforts to design such synthetic routes are detailed in the remainder of this thesis.

Chapter 3

Organic Reactions Involving 1,2-Metallate Rearrangements : The Application Of A Novel Copper-Mediated Reaction To The Design Of A New Synthetic Route To Manoalide.

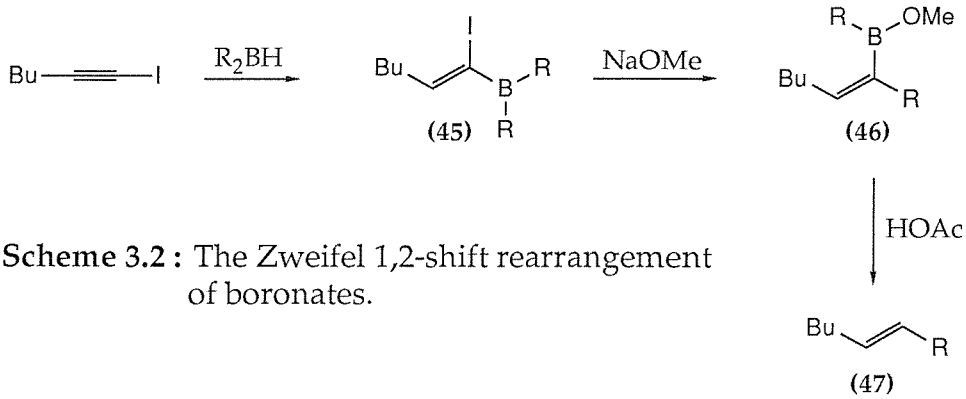
3.1. 1,2-Metallate Rearrangements Of 1-Alkenyl-1-Hetero Metallate Complexes.

In recent years a number of reaction processes have been reported which are believed to take place *via* a 1,2-shift within 1-hetero-1-alkenylmetallate intermediates. These reactions, which have been the subject of a recent review[78], have great potential for use in organic synthesis, and have been observed for a wide range of metals, including main group and transition series elements.



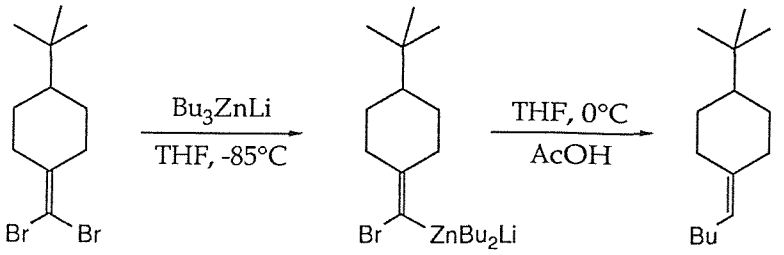
Scheme 3.1

One of the earliest examples of a reaction believed to take place *via* a 1,2-metallate shift was the rearrangement of 1-bromoalkenylborates (*cf.* Scheme 3.1) developed by Matteson and co-workers.[79] Matteson has since applied the procedure to a number of asymmetric syntheses,[80] and analogous reactions have been demonstrated by Negishi's group for the 1-chloroalkyl complexes of a very wide range of metals, including Al, Cd, Co, Cr, Fe, Hf, Mg, Ni, Zn and Zr.[81]



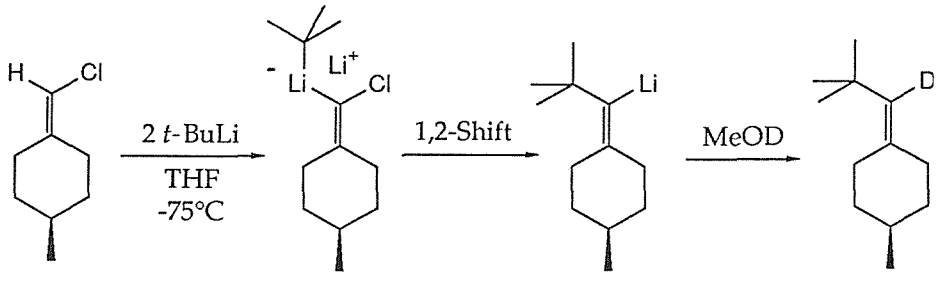
Scheme 3.2 : The Zweifel 1,2-shift rearrangement of boronates.

A similar procedure was reported by Zweifel,[82] in which the complex derived by treating the 1-iodo-1-alkenylborane (**45**) with sodium methoxide underwent a 1,2-shift, with inversion of configuration, to form the alkenylborane (**46**). Protonolysis then resulted in the formation of the *E*-geometry 1,2-disubstituted alkene (**47**) (*cf.* Scheme 3.2).



Scheme 3.3

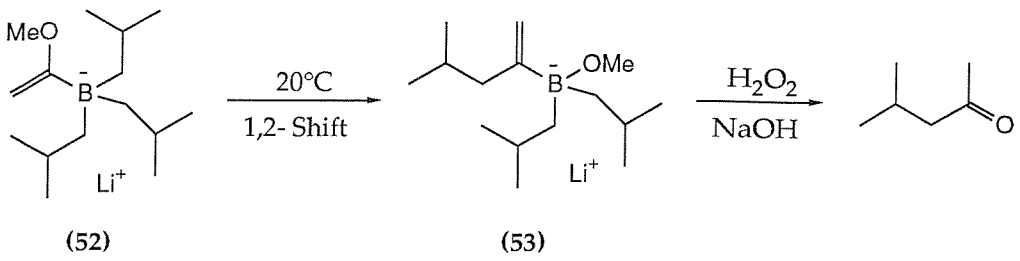
Complexes derived from divalent metals such as zinc are also believed to undergo 1,2-shifts[83] (*cf.* Scheme 3.3 above), as are complexes of monovalent metals. For example, the intermediacy of a 1,2-metallate rearrangement may be invoked to explain the reaction of the chloroalkene (48) observed by Duraisamy and Walborsky.[84] The reaction of (48) with two equivalents of ^{t}BuLi resulted, on quenching with MeOD, in the formation of the deuterated alkene (**51**). It is possible that a 'lithium-ate' species such as (**49**), formed by metallation and further reaction with ^{t}BuLi, may rearrange with displacement of chloride to give the intermediate (**50**), and hence the alkene product (**51**) (*cf.* Scheme 3.4).



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

Scheme 3.4

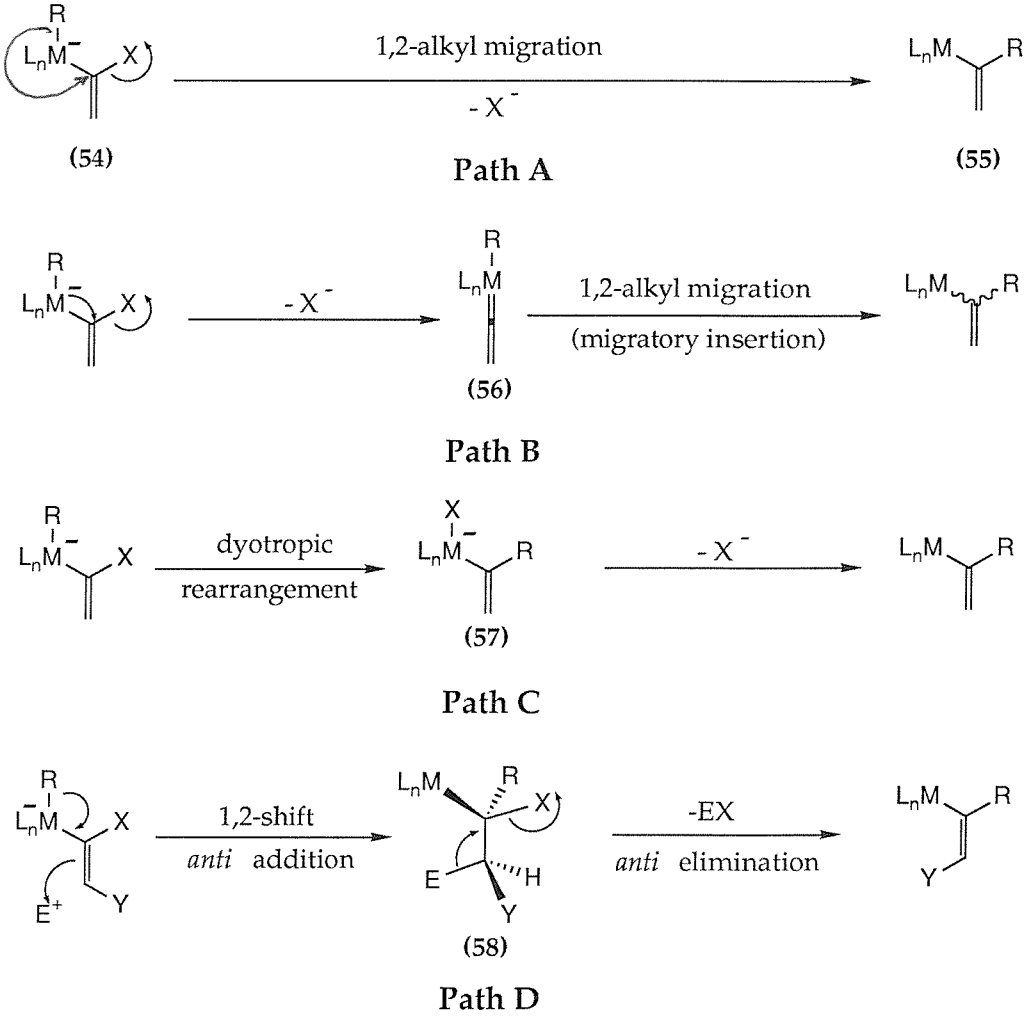
The reactions considered above all involved the use of halides as the leaving groups rather than alkoxides, which are normally considered as being poor nucleofuges. Levy and co-workers, however, reported that the reaction of $(^{i}Bu)_3B$ with α-methoxy-vinyllithium produced the borate complex (**52**), which on warming to room temperature underwent a 1,2-shift, with methoxide as the nucleofuge, to give the intermediate (**53**) (*cf.* Scheme 3.5). Subsequent oxidation of (**53**) produced 4-methyl-2-pentanone.[85] Interestingly, further investigations carried out by both Soderquist and co-workers[86] and Birkinshaw[87] have shown that 'boron-ate' complexes such as (**52**) are remarkably stable, surviving for days at room temperature; and that the rearrangement processes take place only on addition of TMS-chloride, demonstrating the poor nucleofugacity of alkoxides.



(52) (53)

Scheme 3.5

It is possible to envisage four major mechanistic pathways by which a 1-hetero-1-alkenyl-metallate complex such as (54) may undergo a 1,2-shift to produce a vinylmetallic product (55). The rearrangement in question essentially involves a carbon ligand, R (which is bonded directly to the metal centre M), undergoing a 1,2-shift onto the electrophilic α-carbon of an alkene moiety which is also bonded to M; the shift of R resulting in the elimination of a nucleofuge, X^-. The different mechanisms for the process are detailed in in Scheme 3.6 below.



Scheme 3.6: 1,2-metallate rearrangement mechanisms.

The first of the mechanisms, and conceptually the most simple, involves an S_N2-like attack of R on the sp^2 hybridised α-carbon of the alkene, with a concerted expulsion of the nucleofuge X^- (*cf.* Scheme 3.6, Path A). This process results in the inversion of the geometry of the double bond.

The second possibility, (*cf.* Scheme 3.6, Path B) involves the donation of a pair of electrons from the metal centre into the α-carbon of the alkene, resulting in the loss of X^- and the formation of an alkylidene-carbene intermediate (**56**). The migratory insertion of R into the carbene then generates the product (**55**). The shift of R would be expected to take place from either face of the carbene, and therefore leads to the scrambling of the geometry of the double bond.

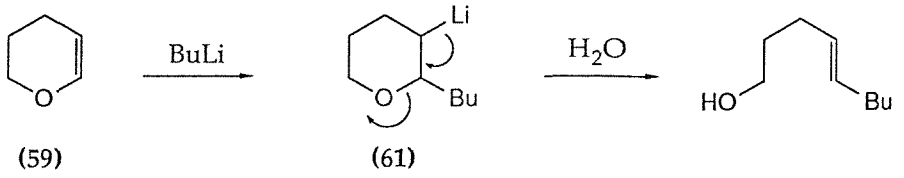
The third mechanism (*cf.* Path C, Scheme 3.6) involves the direct interchange of the R and X groups, (if this is concerted it is called a dyotropic shift; *i.e.* an uncatalysed process in which two σ-bonds simultaneously migrate in an intramolecular fashion[88]) to produce the intermediate (**57**). The loss of X^- from the metal would then generate (**55**). The R and X groups would have to migrate across opposite faces of the metal complex, so again an inversion of the double bond geometry would result.

The final reaction pathway (*cf.* Path D, Scheme 3.6) requires the addition of an electrophile, E^+, to the reaction system. A 1,2-shift of R onto the α-carbon of the double bond takes place, with concomitant *anti* addition of E^+ to the β-carbon, to produce the intermediate (**58**). The shift of R could be induced, or potentiated, by the pre-coordination of E^+ to the double bond. The subsequent *anti*-elimination of EX again generates (**55**), once more with net inversion of the double bond geometry.

3.2. The Discovery And Development Of A Novel Copper-Mediated Reaction Of Cyclic Enol-Ethers.

In 1963 Pattison and Dear reported the preparation of (4*E*)-4-nonen-1-ol *via* the treatment of 3,4-dihydro-2*H*-pyran (**59**) with butyllithium.[89] An analogous reaction was later reported between (**59**) and ^{t}BuLi, resulting in the formation of (4*E*)-2,2-dimethyl-4-hepten-1-ol.[90] Fujisawa *et al.* have since reported a modification of the Pattison procedure, which allows the stereospecific synthesis of (3*E*)-3-alken-1-ols through the reaction of organolithium reagents with 2,3-dihydrofuran (**60**).[91] Fujisawa noted that carrying out the reactions in the presence of stoichiometric quantities of copper (I) iodide resulted in significantly improved rates and yields. The reaction, however, requires the use of five equivalents of the organolithium reagent; making the reaction extremely inefficient for those cases where the organometallic is difficult to prepare. Pattison

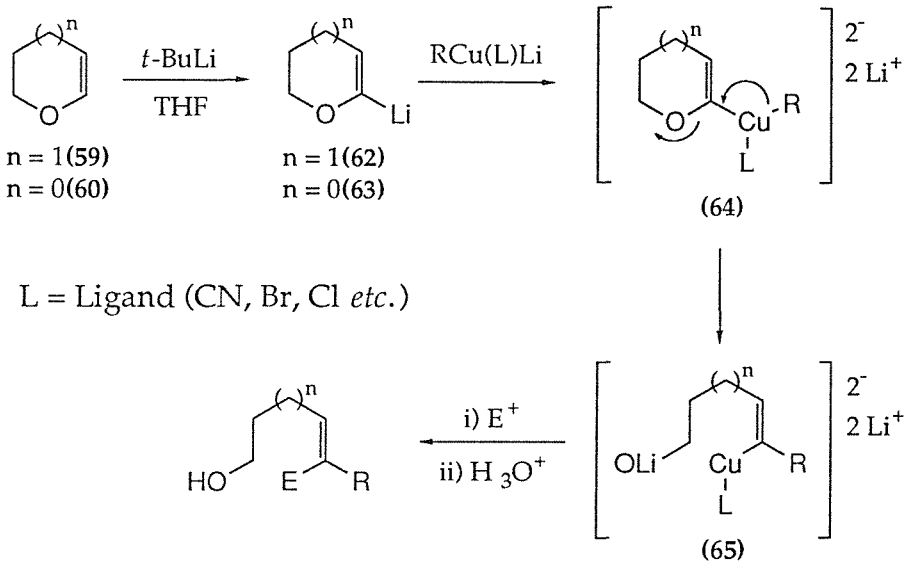
and Dear proposed that the reaction proceeds by the mechanism shown in Scheme 3.7; *i.e. via* the addition of the butyllithium across the double bond of (**59**), followed by a subsequent elimination of the β-lithiated-alkoxide intermediate (**61**), regenerating the double bond with an inversion of geometry.



(59) (61)

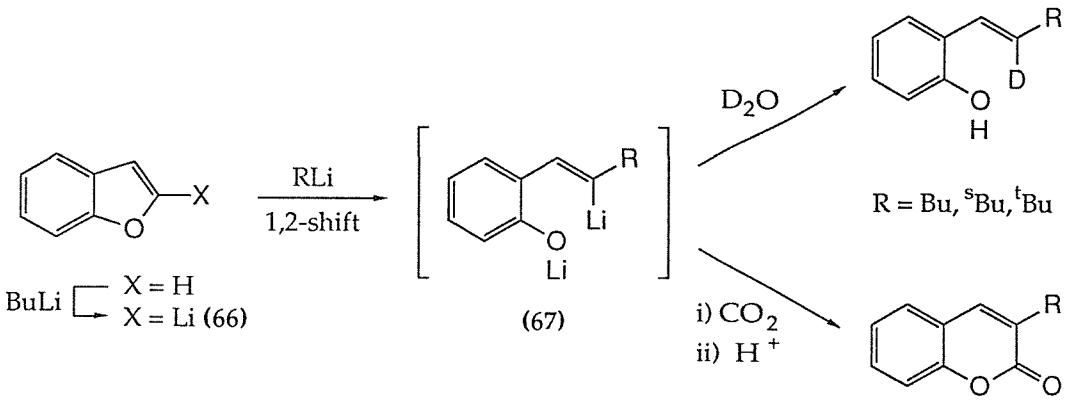
Scheme 3.7: Pattison and Dear's proposed mechanism for the reaction between (**59**) and BuLi.

Our interest in the above processes, and in the metallate rearrangements discussed earlier, arose from the discovery within our group, by Kocienski and Wadman, of a novel copper-mediated reaction for the stereospecific preparation of alkenols.[92, 93] The reaction involves the treatment of α-metallated cyclic enol-ethers (for example 6-lithio-3,4-dihydro-2*H*-pyran (**62**)[94], or 5-lithio-2,3-dihydrofuran (**63**), *cf.* Scheme 3.8), with organolithium reagents, in the presence of a copper (I) catalyst, and results in the stereospecific synthesis of *trans*-alkenols as shown in Scheme 3.8. The exact mechanism of the reaction has not yet been conclusively established; however, we believe that it proceeds *via* a higher order cuprate (**64**), which subsequently undergoes a 1,2-shift to produce a vinylmetallic intermediate (**65**) (*cf.* Scheme 3.8); the rearrangement resulting in the inversion of the geometry of the double bond relative to that of the enol-ether starting material. Protonolysis of (**65**) therefore results in the formation of alkenol products containing *trans*-disubstituted double bonds. The intermediacy of the vinylmetallic species (**65**) was the crucial discovery made by Wadman.[93] The introduction of additional functionality, by means of the use of electrophilic quenches other than simple protonolysis, has allowed the extension of the reaction to the stereospecific synthesis of alkenols containing trisubstituted double bonds. For example, Wadman demonstrated that the use of electrophiles such as deuterium oxide, methyl iodide, ethyl iodide or allyl bromide allowed the deuteration or alkylation of (**65**).[93] The development of the cuprate reaction into an efficient and connective methodology for use in organic synthesis has since been a goal within our group, and the reaction has been the subject of a considerable amount of research. Barber, in particular has studied the reaction in detail, investigating the relative importance of such parameters as reaction temperature, copper (I) source, solvent *etc.*[95]



Scheme 3.8: The copper (I) catalysed reaction of organolithia with α-metallated cyclic enol-ethers.[92]

As an interesting addendum to the above discussions regarding the mechanism of the cuprate rearrangements, a recent report has been published by Negishi and co-workers describing an analogous reaction displayed by benzofuran.[96] Treatment of benzofuran with butyllithium resulted in the formation of 2-lithiobenzofuran (**66**), which on addition of a further equivalent of an organolithium (BuLi, *s*-BuLi or *t*-BuLi) underwent a 1,2-metallate rearrangement such as those discussed above, to form a vinyllithium species (**67**). The intermediacy of this species was proven by means of deuterium oxide and carbon-dioxide quenching experiments (*cf.* Scheme 3.9). The crucial feature of Negishi's experiments was that they were run in the absence of any copper catalysts. It is possible, therefore, that the reaction based on benzofuran may take place *via* a 'lithium-ate' of the sort previously proposed for the Duraisamy and Walborsky reaction (*cf.* Scheme 3.4). Negishi also reported that an investigation of the Pattison and Dear reaction between butyllithium and (**59**) had revealed that no vinyllithium intermediate was formed during the course of the reaction. When, however, the pre-metallated species, 6-lithio-3,4-dihydro-2*H*-pyran (**62**) was treated with butyllithium, then a vinylmetallic intermediate was identified. It is clear therefore that two different mechanisms operate for the reactions between organolithium reagents and either cyclic enol-ethers or their metallated analogues. For the metallated species 1,2-metallate rearrangements probably take place, whereas for the neutral enol-ethers the addition-elimination sequence proposed by Pattison and Dear (*cf.* Scheme 3.7) may operate.



Scheme 3.9: The reaction between organolithia and benzofuran.[96]

3.2.1. The Influence Of Copper Source And Reaction Temperature On The Reaction Yields.

Barber has shown that several different sources of copper (I) may be used to catalyse the rearrangement reaction; including CuCN, CuI, CuBr and the CuBr•Me_2S complex.[95] The source of the catalyst has implications for the mechanism of the reaction, as there is some controversy as to whether higher order cuprates such as (64) can be formed from copper halides. In copper cyanide the CN ligand is essentially non-transferable[97] and so the formation of a higher order cyanocuprate (*cf.* Scheme 3.8 where L is CN), is relatively facile. The halide ions in CuBr and CuI are less tightly bound to the metal centre and therefore usually migrate on introduction of a carbon ligand; *i.e.* on formation of an organocopper reagent or a cuprate. Recent *X*-ray studies have, however, shown that higher order cuprates can be derived from copper (I) halides[98] so the mechanism proposed in Scheme 3.8 is still valid.

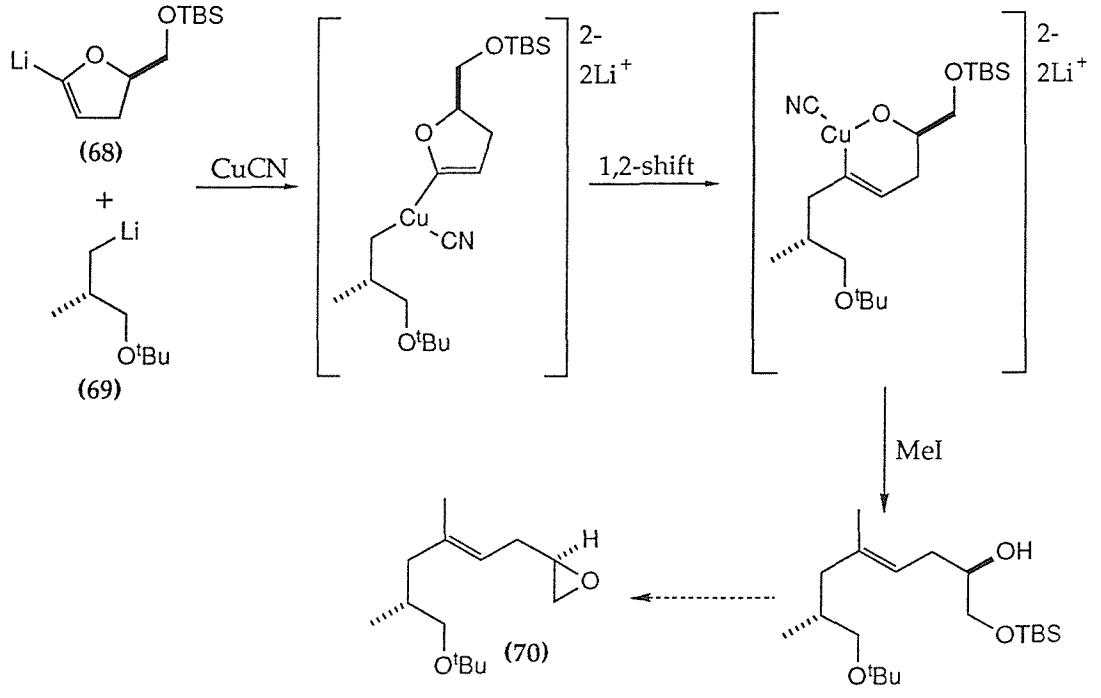
The best overall yields of the alkenol products were obtained when CuI or CuCN were used as catalysts. The CuBr•Me_2S complex, which is readily prepared and purified,[99] was almost as effective, however, and offered the advantage of producing soluble cuprate solutions when methyl sulfide was added to the reaction solvent. The use of the soluble cyanide species, CuCN•2LiCl[100] resulted in dramatically lower yields.[95] In all cases the copper salts were typically added to the reaction in half-stoichiometric quantities (*i.e.* 50 mol%).[95]

Whilst the copper (I) source employed in the reaction is important, the key factor affecting the yields of the alkenols derived from the cuprate rearrangements is the reaction temperature. Preliminary studies carried out by Wadman suggested that low reaction temperatures of the order of -78°C were required.[93] However, the work carried out by Barber has since shown that this is incorrect and that the rearrangement process only takes place at temperatures greater

than -30°C. Furthermore, Barber showed that the optimum yields are achieved at between 0° and +35°C.[95]

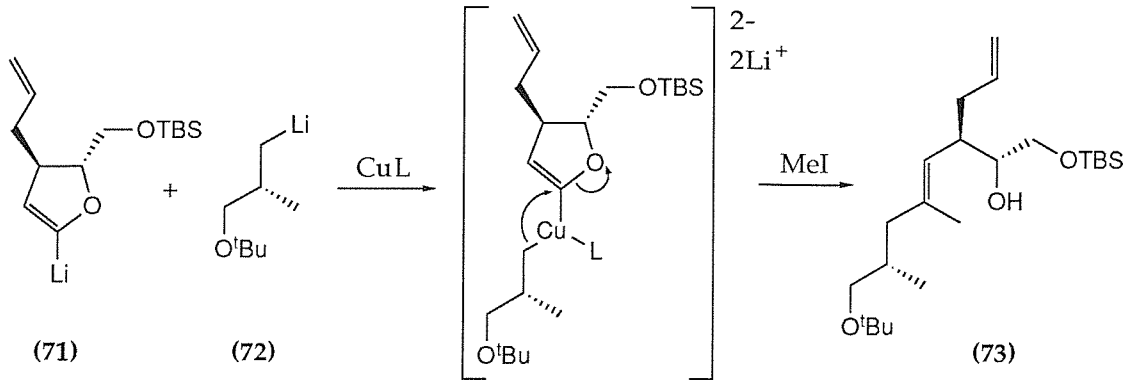
3.3. Application Of The Copper-Mediated 1,2-Metallate Rearrangement Reaction To The Total Synthesis Of Natural Products.

The development of new methodologies for use in organic chemistry is rightly regarded as being an important academic goal in itself. The value of any new synthetic technique however, can only be adequately judged following its application to the synthesis of target molecules. With this principle in mind, the discovery of the novel cuprate reaction discussed above led to the design of a number of synthetic strategies within our group at Southampton, which involved the reaction as a key step. The first of these applications was seen in the total synthesis of the antihypotensive agent, Lacrimin A.[101, 102] Takle prepared the key oxirane fragment (70) in an overall yield of 29% *via* the reaction of the substituted α-metallated dihydrofuran (68) with the organolithium reagent (69), as indicated in Scheme 3.10. The organocuprate rearrangement in this case was highly successful, despite the relatively modest yield, as it allowed the stereospecific generation of the required trisubstituted double bond by means of a methyl iodide alkylation step, whilst at the same time introducing an hydroxyl functionality as a handle for further elaboration to the desired oxirane (70).



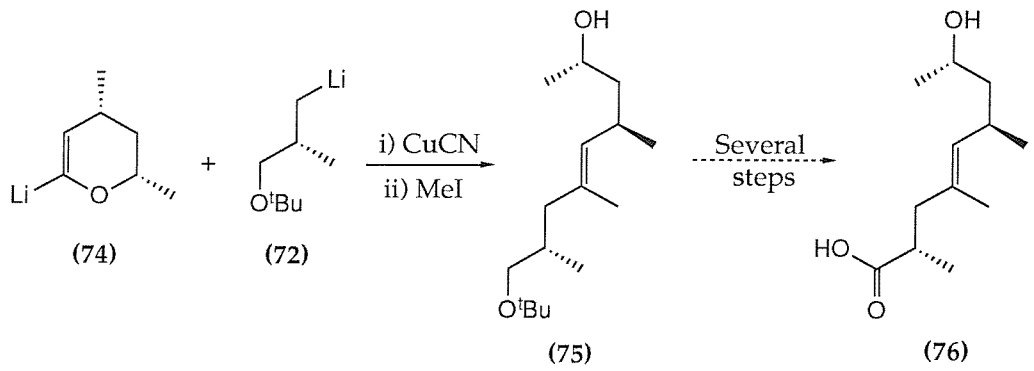
Scheme 3.10: The application of the copper-catalysed reaction to the synthesis of Lacrimin A.[102]

A further example of the reaction's potential was displayed in the synthesis of the C16-C23 fragment (**73**) of the potent immunosuppresant FK-506. The efficient and highly stereoselective synthesis of (**73**), which is summarised in Scheme 3.11,[103] was achieved *via* the reaction of the substituted 2,3-dihydrofuran (**71**) with the organolithium species (**72**). A methyl iodide quench was again employed, generating the desired *E*-geometry trisubstituted double bond.



Scheme 3.11: The synthesis of a key fragment of FK-506.[103]

Investigations into the use of the cuprate reaction based on metallated dihydropyrans have also been carried out. A key example has been seen in the synthesis of the polyketide (**76**),[104] which is found as a structural sub-unit of the cyclodepsipeptide Jaspamide (jasplakinolide),[104] and the structurally related geodiamolides.[105] The synthesis of (**76**), which is summarised in Scheme 3.12, involved the reaction of the metallated dihydropyran (**74**) with (**72**) in the presence of cuprous cyanide, followed by a methyl iodide quench; resulting in the formation of the alkenol (**75**), which was further elaborated to produce the desired carboxylic acid (**76**).[106]



Scheme 3.12: The synthesis of the polyketide fragment of Jaspamide.

3.3.1. The Design Of A Novel Route To Manoalide.

As a result of our desire to further extend the applicability of the copper-mediated reaction to the synthesis of natural products, we set out to attempt the total synthesis of Manoalide (**1**); the aim being to employ the copper based reaction to construct the key C6-C7 double bond. Our retrosynthetic analysis, which is summarised in Figure 3.1, began with what can essentially be considered as a functional group interconversion (FGI), with the 5-hydroxy-2(5H)-furanone moiety being replaced by a TMS-substituted furan. We hoped to eventually effect the 'forward' reaction by means of the singlet-oxygen oxidation process discussed in chapter 2. Disconnection of the resulting species, as shown in Figure 3.1, revealed the two synthetic intermediates (A) and (B). We envisaged the lithiated furan (A) as being derived *via* a metal-halogen exchange from the corresponding 2-trimethylsilyl-4-bromofuran (**32**), the preparation of which has been briefly described by Katsumura *et al.*[57] We did not identify the exact nature of the group 'X' in the intermediate (B); we intended X to be some functionality which we could readily elaborate to introduce the aldehyde group required in the final compound. A FGI on the aldehyde of (B) produced the key intermediate alkenol species (C), which we hoped to synthesize using the copper-mediated metallate rearrangement. The relevant disconnection (as shown in Fig. 3.1), revealed that the two precursors required for the reaction were the homoallylic organolithium species (D), and 5-lithio-2,3-dihydrofuran (**63**). Analysis of (D) showed that two further FGI's took us back, *via* a halogenated compound such as the bromide (**40**), to the homoallylic alcohol (**39**). Both the bromide (**40**) and the alcohol (**39**) were employed in the Garst synthesis of (**1**).[58] We hoped to improve on the results obtained by Garst and co-workers for the preparation of (**39**), by replacing their weak Wittig reaction step for the introduction of the *E*-geometry C10-C11 double bond, with an adaptation of Negishi's published syntheses of homoallylic alcohols and monocyclofarnesol.[107-109] The Negishi procedure required the terminal acetylene (**77**) as its immediate precursor, which was in turn derived from the dihydro-β-ionone species (**38**). We envisaged the preparation of (**38**) as being achieved *via* a conjugate reduction of β-ionone (**37**) itself, completing the retrosynthetic analysis.

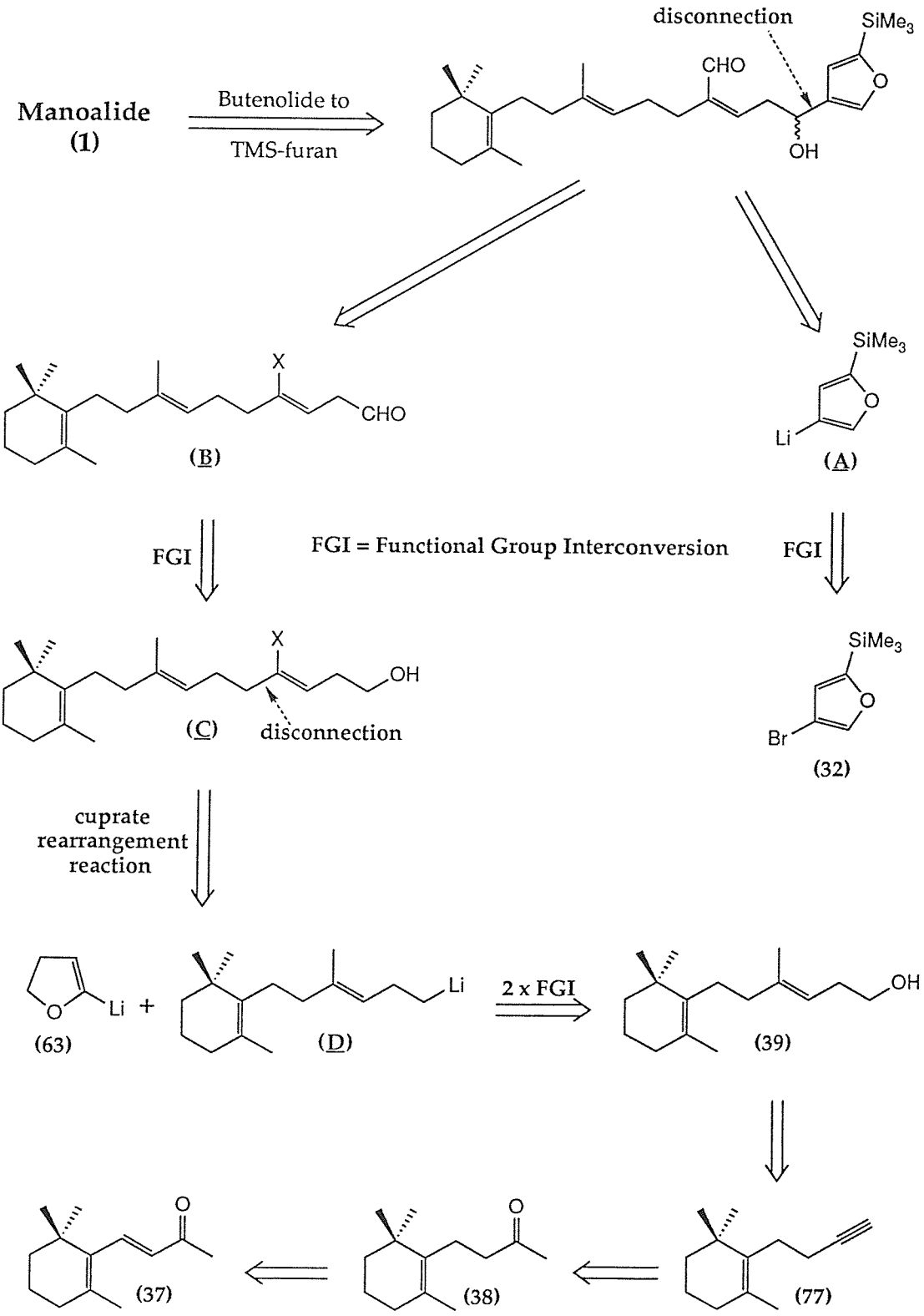


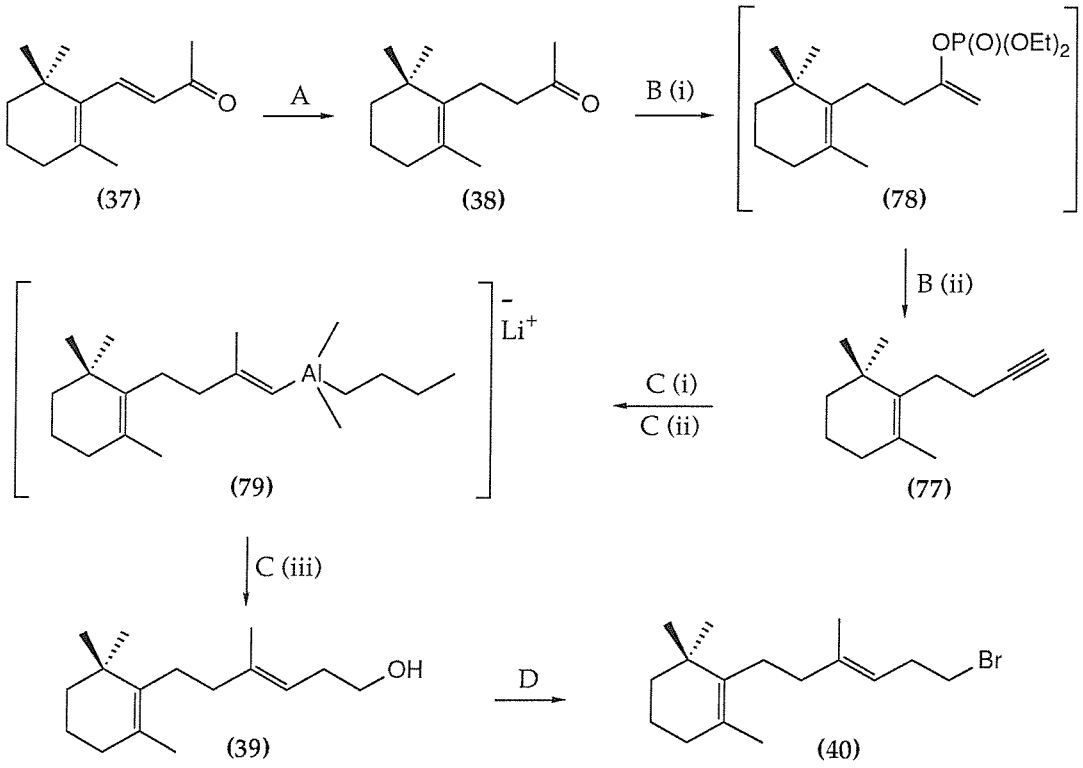
Figure 3.1: A retrosynthetic analysis of manoalide based on the use of the cuprate rearangement reaction to construct the key C6-C7 double bond.

3.3.2. The Preparation Of The Key Homoallylic Bromide Intermediate (40).

The route employed for the preparation of the homoallylic bromide (40) is summarised in Scheme 3.13. The starting point in our synthetic sequence was the preparation of the dihydro-β-ionone species (38), derived from readily available, inexpensive, β-ionone (37). To affect this conversion we needed to carry out a regiospecific conjugate reduction of the α,β,γ,δ-unsaturated enone system present in (37). A plethora of reagents and experimental procedures are available for the conjugate (Michael) reduction of enones to ketones,[110] a number of which are based on the use of copper species as the reducing agents. Typically, copper hydride complexes are employed, which are formed *in situ* by the reaction of cuprous halide salts with strong hydride sources such as $LiAlH_4$,[111] Red-Al®,[112] or Bu_3SnH.[113] The preparation of monocyclofarnesol reported by Negishi *et al.* achieved the desired reduction of (37) to (38) by using a copper hydride complex derived from CuI and $LiAlH_4$[107]

One of the major problems encountered with many of the conjugate reduction procedures described in the literature, however, is that they require the use of reagents which are either expensive, difficult to handle, or highly toxic. As the reduction of (37) to (38) was the first step in our synthesis, we required a method that could be used on quite a large scale; hence we needed a procedure which used relatively non-toxic and inexpensive reagents. With these factors in mind, we decided to use the method developed by Camps, Coll and Guitart, which employs sodium dithionite as the reducing agent.[114] Sodium dithionite, $Na_2S_2O_4$, is a powerful, inexpensive reducing agent used on a large scale as a bleach by the textile industry. It has, however, very poor solubility in organic solvents. The Camps method circumvents this solubility problem by using a two-phase benzene/water solvent system in the presence of the tertiary ammonium salt Adogen®464, which acts as a phase transfer catalyst and allows an interaction of the substrate with the reductant. In their initial report on the method, Camps and his co-workers quoted a 65% yield for the reduction of (37) to (38).[114] However, when we attempted this same reaction, using identical conditions to those reported, we were never able to isolate (38) in a yield higher than 40%, and invariably found that substantial quantities of (37) were recovered unreacted. As a result of these disappointing yields, we investigated the course of the reaction when carried out in a toluene/water solvent system. By this variation we hoped not only to avoid the use of carcinogenic benzene, but also we hypothesized that the higher reaction temperatures obtained using refluxing toluene/water solvents rather than benzene/water mixtures, would drive the reaction further over to completion. Gratifyingly, we found that our ideas bore

fruit. Carrying out the reaction in a vigorously stirred, refluxing 2:1 water/ toluene solvent system, with the reagents (37): $NaHCO_3$: $Na_2S_2O_4$: Adogen®464 in a ratio of 1: 5: 2.2: 0.3, resulted in the production of the desired dihydro-β-ionone (38) in an improved 60% yield. Traces of unreacted starting material were present in the compound; these, however, could be readily removed by flash column chromatography.



Reagents

A	60%	$Na_2S_2O_4$, $NaHCO_3$, Adogen 464 / PhMe-H_2O (1:2), Δ, 3 h.
B	70%	(i) LDA / THF, -80°C, 1 h; (ii) $ClP(O)(OEt)_2$, -80°C to r. t. (iii) 2 LDA / THF, -80°C to r. t.
C	64%	(i) Cp_2ZrCl_2, $AlMe_3$ / $ClCH_2CH_2Cl$, r. t., 3 h; (ii) n-BuLi / THF-pentane, -80°C, 30 min; (iii) oxirane / Et_2O -80°C to r.t., 18 h.
D	90%	(i) MsCl, NEt_3 / DCM, -10°C, 10 min; (ii) LiBr / acetone, Δ, 2 h.

Scheme 3.13: The synthesis of the homoallylic bromide (40).

With the ketone (38) in hand, we then proceeded to prepare the vinyl aluminate species (79) *via* the method detailed by Negishi and co-workers.[107] Conversion of the methyl ketone (38) into the terminal acetylene (77) was achieved by means of a one-pot reaction, which involved treating (38) with LDA, followed by diethylchlorophosphate, to form an enol-phosphate intermediate (78). Treatment of (78) with a futher two equivalents of LDA gave the acetylene (77) in a

70% yield. The acetylene functionality of (77) was then reacted with the complex derived from mixing zirconocene dichloride with trimethylaluminium, resulting in a *syn*-specific methyl-alumination reaction, to give a vinyl-alane intermediate, which was treated with butyllithium to produce the desired aluminate complex (79). The aluminate species was then treated with oxirane to produce, on protonolysis, the homoallylic alcohol (39).
The alcohol (39) was then converted into the corresponding homoallylic bromide (40), by means of the mesylation/halogenation sequence indicated in Scheme 3.13. The bromide (40) was therefore prepared from β-ionone (37) in an overall yield of 21%. Several attempts to prepare the analogous homoallylic iodo compound were, unfortunately, completely unsuccessful, due to the compound's thermal instability. The iodide invariably turned dark brown and polymerized (thickened to a gel) even when stored over copper gauze at -20°C.

3.3.3. Initial Investigations Into The Construction Of The C6-C7 Double Bond Of Manoalide.

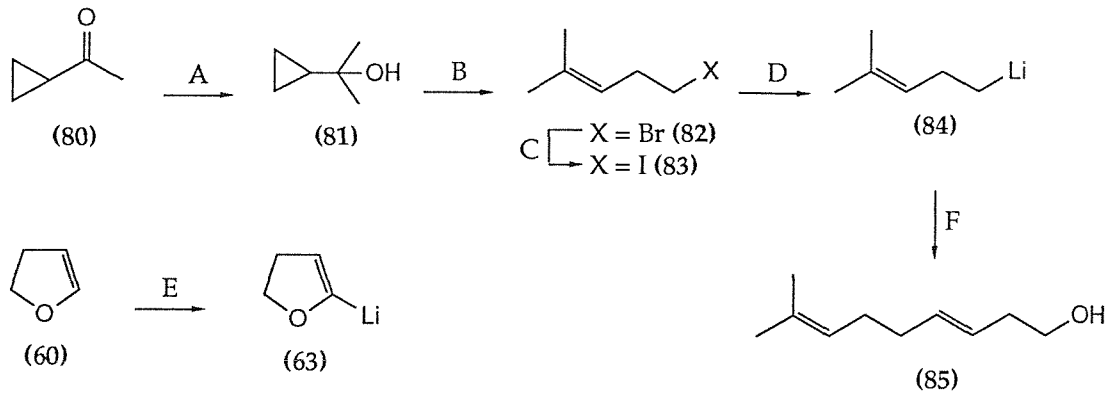
Following the successful preparation of the bromide (40), the next step in our proposed synthetic sequence was the construction of the crucial C6-C7 trisubstituted double bond *via* the cuprate reaction discussed above. In order to conserve our stocks of the precious 'real system' bromide (40), we decided to carry out model studies into the cuprate reaction, based on the analogous homoallylic system found in 1-bromo-4-methyl-3-pentene (82). This model bromide was readily prepared on a large scale from cyclopropyl methyl ketone (80), *via* 2-cyclopropyl-2-propanol (81), using the synthetic route developed by Julia *et al.*, as summarised in Scheme 3.14.[115] In order to carry out the cuprate reaction we required the organometallic reagent 4-methyl-3-pentenyllithium (84) as a starting material. However, the preparation of (84) from the bromide (82) proved to be extremely troublesome. Direct lithium-halogen exchange between (82) and 'high sodium' lithium metal (improved yields of organolithia are normally obtained when the metallation is carried out using Li doped with 0.5 to 1 mol% Na[116]) gave very poor yields of (84); typically of the order of 20%. The reaction was attempted using several different physical forms of the metal, including 1 mm diameter wire and a finely divided lithium dispersion. A number of different techniques for the activation of the metal were also tested, including irradiation with ultrasound and entrainment with 1,2-dibromoethane. In all cases the yields of (84) were extremely poor. We believe that the inefficiency of the metallation may be chiefly attributed to side reactions of the type seen in the Wurtz-Fittig process;[117] which in the case of simple alkyl halides normally results in

the symmetrical coupling of two molecules of the halide. In the case of our own preparation of (84) we believe that substantial quantities of the bromide (82) were consumed in this fashion.

As a consequence of the disappointing yields of (84) obtained by the reaction of (82) with lithium metal, we decided to produce (84) *via* a lithium-halogen exchange between the homoallylic halide and ^{t}BuLi.[118] By this method the desired reagent (84) was prepared from (82) in a modest 60% yield. The ^{t}BuLi-halogen exchange process is much more efficient when alkyl iodides are used in the place of bromides.[119] This is principally due to the consumption of starting materials in the bromide case, which takes place *via* competing radical processes. The homoallylic iodide, 1-iodo-4-methyl-2-pentene (83) was therefore prepared in a 62% yield from (82) (by means of a Finkelstein reaction) and the metal halogen exchange was carried out; leading to the production of the desired organolithium reagent (84) in an excellent 95% yield. In all of the above cases the titres of the organolithium products were ascertained by means of the titration technique developed by Shapiro *et al.*, which involves the use of 1,3-diphenylacetone-*p*-toluenesulphonyl hydrazone as an indicator.[120]

With the difficulties encountered in the preparation of the organolithium reagent (84) having been solved, we set about investigating the key cuprate reaction itself. As we discussed earlier, much of the detailed study of the rearrangement process was carried out by Barber,[95] who found that the best yields of the alkenol products are obtained by carrying out the reactions between 0°C and +35°C. However, the application of Barber's conditions to the copper-mediated reaction between (84) and 5-lithio-2,3-dihydrofuran (63) gave a very disappointing 32% yield of the desired simple protonolysis product (85) (*cf.* Scheme 3.14). The key observation which we made during the course of this reaction involved the state of the cuprate derived from (84). The addition of (84) to a suspension of $CuBr \bullet SMe_2$ in ether at -80°C, resulted in the formation a clear, orange coloured cuprate solution. As the solution was allowed to warm slowly to 0°C, prior to the addition of (63), the appearance of the cuprate mixture steadily deteriorated, the colour changing from orange to brown, with the formation of a dark brown solid. The very poor yields for the copper mediated reaction between (84) and (63) were, therefore, almost certainly due to the decomposition of the cuprate at a stage prior to the desired rearrangement process. On repetition, the obvious decomposition of the cuprate mixture was found to take place at temperatures above -25°C; *i.e.* on the borderline of the -30°C temperature limit observed by Barber for the onset of the cuprate rearrangement.[95] In an attempt to improve the yields of (85) we repeated the reaction a number of times, varying the reaction conditions. One repetition involved the addition of the solution of (63) to

the cuprate at -80°C, followed by gradually warming the mixture to room temperature. We hoped that the cuprate rearrangement would take place faster than the decomposition process, however, the revised procedure did not lead to any improvement in the yield, and TLC tests showed that the quantities of by-products increased substantially.



Reagents		
A	65%	MeMgBr / Et_2O, Δ, 1 h;
B	95%	c. HBr (aq), 0°C;
C	62%	NaI / acetone, Δ, 2 h;
D	95%	i) *t*-BuLi / Et_2O-pentane (2:3), -80°C, 5 min; ii) THF, -80°C to 0°C, 2 h;
E	100%	*t*-BuLi / THF, -80°C to 0°C, 0.5 h;
F	32%	i) 0.5 CuBr•SMe_2 / THF, -80°C to 0°C; ii) (63) / THF, 0°C to r. t., 2h;

Scheme 3.14: The rearrangement of the cuprate derived from the homoallylic lithium reagent (84).

As a consequence of these somewhat disheartening results, we decided to abandon the use of the rearrangement reaction based on the organolithium species (84). Instead we concentrated our efforts on developing a variant of the copper-catalysed rearrangement reaction, which employed a different organometallic species to act as the reaction partner to the lithiated dihydrofuran (63); namely a Grignard reagent. The results of our efforts are detailed in the next chapter.

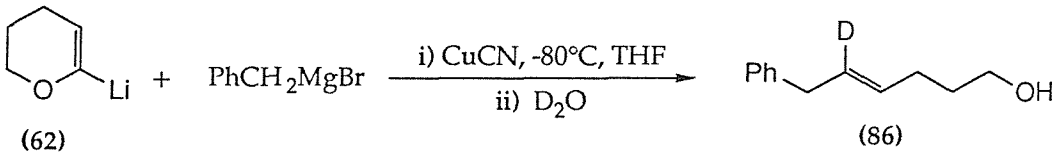
Chapter 4

The Development Of A Copper-Mediated Reaction Between Grignard Reagents And α-Lithiated Cyclic Enol-Ethers.

4.1. The Application Of Grignard Reagents To The Copper (I)-Catalysed Reaction Of α-Lithiated Cyclic Enol-Ethers.

The early work carried out by Wadman on the copper (I)-catalysed reaction between organolithia and α-lithiated cyclic enol-ethers, was inspired in part, by the report published by Pattison and Dear detailing the reaction between 3,4-dihydro-2*H*-pyran (**59**) and butyllithium.[89] A similar report by Hill *et al.*, revealed that an analogous reaction occurs between (**59**) and Grignard reagents.[121] This inspired us to reinvestigate the copper-catalysed reaction using Grignard reagents in the place of the organolithium species. The preparation of Grignard reagents is very commonplace in organic chemistry, whereas the preparation of alkyllithium reagents is often approached with a degree of trepidation. We believed that broadening the scope of the copper-catalysed reaction by developing a methodology based on the application of Grignard reagents would increase the utility of the process.

The first example of the desired rearrangement was examined by Takle as part of his work on the synthesis of Lacrimin A.[102c] He attempted to carry out the Grignard reagent equivalent of the reaction detailed in Scheme 3.10 between the lithiated dihydrofuran (**68**) and the magnesium analogue of the organolithium species (**69**). Whilst the desired reaction did occur, the yields were very low and so the process was not investigated further. Takle's work was subsequently followed-up by Wadman,[93] who studied the reaction between 6-lithio-3,4-dihydro-2*H*-pyran (**62**) and benzyl magnesium bromide (*cf.* Scheme 4.1) in the presence of 1 equivalent of CuCN. Following a D_2O quench, Wadman found that the reaction gave a 60% yield of the deuterated alkenol (**86**).[92, 93] Other than these two brief examples, however, the use of Grignard reagents as the organometallic partners to the lithiated enol-ethers had been ignored.



(62) (86)

Scheme 4.1: Wadman's Investigation into the application of Grignard reagents to the copper-catalysed coupling reaction.

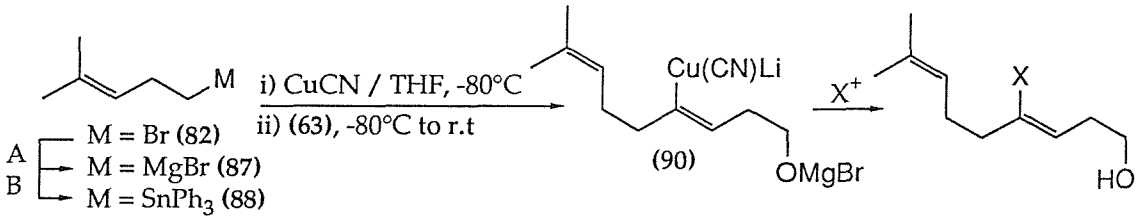
4.1.1. Investigations Into The Reaction Of 5-Lithio-2,3-dihydrofuran (63) With A Grignard Reagent.

We based our investigations on the copper-catalysed reaction between (63) and 4-methyl-3-pentenylmagnesium bromide (87); *i.e.* we studied a reaction which was exactly analogous to the organolithium case discussed above. Unfortunately, the preparation of the required organometallic intermediate once again proved to be extremely problematical. The standard technique for the formation of Grignard reagents involves the addition of an alkyl halide to a gently refluxing mixture of magnesium turnings in ether.[122] When we applied these conditions to the formation of (87) however, very poor yields of the Grignard reagent were obtained. A variety of different experimental procedures for the preparation of (87) were subsequently studied, which included the use of different sources of the metal, *e.g.* high purity magnesium chunks and finely divided magnesium powder. Experiments were also run using several methods for the activation of the surface of the metal, including entrainment with 1,2-dibromoethane, ultrasonic irradiation and stirring for long periods of time under a nitrogen atmosphere.[123] As a result of these studies we finally established a reliable method for the efficient preparation of (87) from the bromide (82). Magnesium turnings activated by the addition of a small crystal of I_2 were used as the metal source, with THF being employed as the solvent, which allowed the use of a relatively high reaction temperature, *i.e.* 50 to 55°C. The crucial factor for the success of the procedure however, was the rate of addition of the halide to the magnesium mixture, which had to be maintained at a very slow, dropwise rate, or else the yield of the Grignard reagent was seriously reduced. The reason for this is not entirely clear; however, one possible explanation is that radical species formed on the surface of the metal during the course of the formation of the Grignard reagent undergo destructive side-reactions to give Wurtz coupling by-products.[124] By maintaining a very low concentration of unreacted (82), the concentration of these radicals remains sufficiently low such that Grignard reagent formation is favoured over the competing processes.
The problems which we encountered in the preparation of (87) were exacerbated by difficulties involving the reliable estimation of the titres of the Grignard reagent products. A common technique used for the estimation of Grignard reagent-strength is the 'total base' method, in which an aliquot of the organometallic is added to standardised HCl and the excess HCl is then back-titrated against NaOH with phenolphthalein as the indicator. This method proved unreliable in our case, as it could not identify whether the Grignard reagent had decomposed slightly through contamination with water, since the products of

the hydrolysis themselves are alkaline. A second general technique involves the addition of a portion of a Grignard reagent to a known amount of iodine, (to form the alkyl iodide, plus the iodide anion) followed by titration of the excess iodine against sodium thiosulphate. In our case this reaction proved unreliable because (87) reacted almost as rapidly with the homoallylic iodide by-product (83), as it did with molecular I_2; as a consequence the Grignard reagent titre was severely underestimated. We finally developed an extremely reliable gravimetric analysis technique, which involved the preparation and isolation of the triphenyltin derivative of (87). Thus, a measured aliquot of (87) was treated with Ph_3SnCl, to produce 1-triphenylstannyl-4-methyl-3-pentene (88), which was isolated and purified by flash column chromatography (*cf.*Scheme 4.2). Measurement of the isolated mass of (88) allowed the calculation of the titre of (87).

With the difficulties involved in the formation of (87) having been solved, the actual cuprate reaction itself was addressed. Our initial studies used essentially the same conditions as those employed for the reaction based on (84); however, a stoichiometric quantity of CuCN was employed as the copper (I) source, in place of the $CuBr \bullet SMe_2$. This replacement was made as a result of Wadman's observations regarding the reaction of (62) with $PhCH_2MgBr$.[93] The addition of (87) to a suspension of CuCN in THF at -80°C formed a cyanocuprate suspension, which was treated with a solution of 5-lithio-2,3-dihydrofuran (63). The resulting mixture was allowed to warm very slowly to room temperature, then deuterium oxide was added, resulting in the formation of the deuterated homoallylic alcohol product (89) in an excellent 75% yield (*cf.* Scheme 4.2). This contrasted markedly with the 32% yield previously achieved by the reaction of (84). We proposed that the improved yield was due to an increase in the rate of the rearrangement reaction at lower temperatures, which had allowed the rearrangement process to take place before the thermal decomposition of the cuprate. The fact that the cuprate was still thermally labile was confirmed by allowing another sample of the cyanocuprate mixture to warm slowly to room temperature from -80°C. In this test the cuprate clearly decomposed at approximately -25°C, as shown by an extreme darkening of the mixture's colour above this temperature. Further studies have since been carried out by Barber and O'Shea, which have confirmed that the cuprate reactions based on the use of Grignard reagents do indeed take place at -80°C, allowing the rearrangement to occur in cases where the lithiocuprates are thermally sensitive.[95, 125] In general, however, where the cuprates are not thermally sensitive the yields are slightly lower for the Grignard reagent reactions than for the corresponding lithium processes.[95] Our results, along with those obtained by Barber and O'Shea, have been the subject of a recent communication.[126]

We next set out to apply the rearrangement process to our proposed synthesis of Manoalide. In order to prepare synthetically useful quantities of the desired alkenol products, we were required to increase the scale of the reactions from *ca.* 2 mmol up to *ca.* 50 mmol. When we studied the scaled-up reactions, however, we were surprised to find that, although essentially identical conditions were employed, the yields became subject to an unpredictable variation, giving between 30 and 70% of the desired alkenol products. We believe that the most probable cause of this variation was inefficiency of stirring within the reaction mixture, caused by solubility problems encountered with the use of the insoluble CuCN as the catalyst. On an increased scale it is possible that inefficient stirring may lead to the formation of aggregates; within which side-reactions or decomposition of the cuprates may take place. We found that these problems could be avoided by using CuBr•SMe_2 as the reaction catalyst. The cuprates derived from the latter copper source are readily solubilised by adding methyl sulphide to the reaction mixture; in this way the stirring difficulties were largely circumvented. The yields of the CuBr•SMe_2 catalysed reactions were very reliable, although they were always lower than the best yields achieved in the CuCN catalysed processes (*cf.* entries b and i in Scheme 4.2).



A 90% Mg turnings / THF, 50-55°C;
B 100% Ph_3SnCl / THF, -50°C.

Entry	Electrophile	X	Product	Yield (%)
a	D_2O	-D	(89)	75
b	D_2O	-D	(89)	58*
c	EtOCOCl	-COOEt	-	0
d	EtCOCN	-COOEt	-	0
e	HCON(Me)Ph	-CHO	-	0
f	$HCONMe_2$	-CHO	-	0
g	H_2CO	$-CH_2OH$	(91)	79
h	Me_3SnCl	$-SnMe_3$	(92)	73
i	Me_3SnCl	$-SnMe_3$	(92)	30*

*Entries b and i were performed using CuBr•SMe_2 as catalyst
All compounds were fully characterised.

Scheme 4.2

4.1.2. Investigations Into The Fuctionalisation Of The Vinylmetallic Intermediate Of The Copper (I)-Catalysed Reaction.

As we discussed above, the discovery of the novel copper (I)-catalysed reaction led to a number of different synthetic applications, aimed at the production of key fragments of natural products. One common denominator of these synthetic studies was the fact that the vinylmetallic intermediates derived from the copper (I)-catalysed reactions were only ever quenched with simple electrophiles such as H_2O, D_2O, allyl iodide, or methyl iodide.[93, 95, 102, 103, 106] On no occasion was any attempt made to extend the scope of the quenching reaction to allow the introduction of oxygen containing functionalities. Our proposed synthetic route to manoalide required the introduction of a substituent onto the 'C7' vinylic carbon, which could be readily elaborated to the aldehyde present in the final structure (*cf.* Fig. 3.1). In response to this requirement we set about studying the applicability of some alternative electrophilic quenches with the aim of introducing a suitable group, 'X', as demanded by our retrosynthetic analysis (*cf.* Fig. 3.1). We once again used the model reaction between (87) and (63) as the basis for our studies (*cf.* Scheme 4.2 above)

Our first studies attempted to use ethyl chloroformate as the quenching reagent; the aim being to introduce an ester group onto the vinylic centre of the intermediate (90, *cf.* Scheme 4.2) in a manner similar to that seen in Zweifel's α,β-unsaturated ester synthesis.[127] We hoped that the ester could be reduced to the required aldehyde group at a later stage. The cuprate reaction was therefore carried out as described above for the preparation of (89), with ethyl chloroformate being added in the place of the deuterium oxide. Unfortunately, the reaction proved to be extraordinarily messy. A TLC test of the cuprate mixture, run immediately prior to the addition of the chloroformate, showed one major product, which was co-polar with (89), formed by the simple protonolysis of (90). After the addition of the chloroformate, however, an inseparable mixture was formed, with the TLC showing at least 30 different products with a wide range of polarities. Clearly therefore, the chloroformate was an unsuitable quenching reagent for our use. A similar result was also obtained when the reaction was repeated using ethyl cyanoformate as the electrophile.

We next attempted to react (90) with trimethylorthoformate, in the hope of directly introducing a dimethylacetal moiety, *i.e.* a protected aldehyde onto the double bond.[128] These attempts also proved to be totally unsuccessful; formation of (85) by simple protonolysis was the sole quenching reaction observed. A similarly disappointing result was also obtained when (90) was treated with either N-methyl-formanilide or DMF. We hoped that (90) would react with the

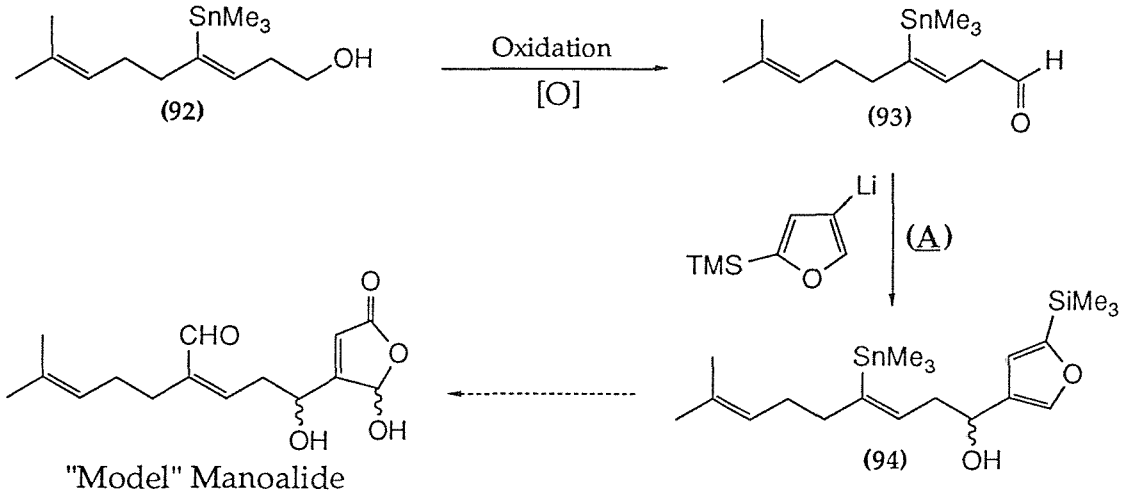
formamides to introduce an aldehyde group onto the vinylic carbon.[129] Again, the only isolable product was the protonated species (**85**).

We next addressed the preparation of the diol (**91**), by introducing a hydroxymethyl group into (**90**) by means of a formaldehyde quench (*cf.* Scheme 4.2 entry g). Gaseous formaldehyde (formed by the pyrolysis of solid paraformaldehyde) was bubbled through the solution of (**90**), resulting in the formation of the desired diol (**91**) in a 79% yield; *i.e.* the formaldehyde quench was as efficient as the simple 'protonolysis' with D_2O. We hoped that we would be able to selectively elaborate the allylic alcohol of (**91**) without affecting the homoallylic hydroxyl group. All of our attempts in this vein, however, were totally unsuccessful.

The final quench which we investigated involved the addition of trimethyltin chloride to the intermediate (**90**). This resulted in the preparation of the vinyltrimethyltin species (**92**) in an excellent 73% yield; *i.e.* once again the quench was almost as efficient as the simple protonolysis reaction. The alcohol (**92**) became a key intermediate in our model studies aimed towards the synthesis of manoalide.

4.2. The Elaboration Of The Vinylstannane (92).

Vinyl trialkylstannanes such as the homoallylic alcohol (**92**), have an enormous potential for use in organic synthesis. They may be employed as key starting materials for the introduction of a whole host of different functionalities onto double bonds. In particular, the palladium (0)-catalysed reaction developed by Stille has been used to couple vinylstannanes with a wide variety of different electrophilic reagents.[77]



Scheme 4.3: The first proposed elaboration of stannane (**92**)

The trimethyltin group present in (**92**) may be thought of as a masked, air-stable, form of the vinylmetallic intermediate (**90**). Trialkylstannanes may be readily transmetallated to form alkyllithium reagents, by simply treating the stannane with a solution of butyllithium. A similar transmetallation process also takes place when stannanes are treated with dialkyl-lithiocyanocuprates such as $Me_2Cu(CN)Li_2$.[130]

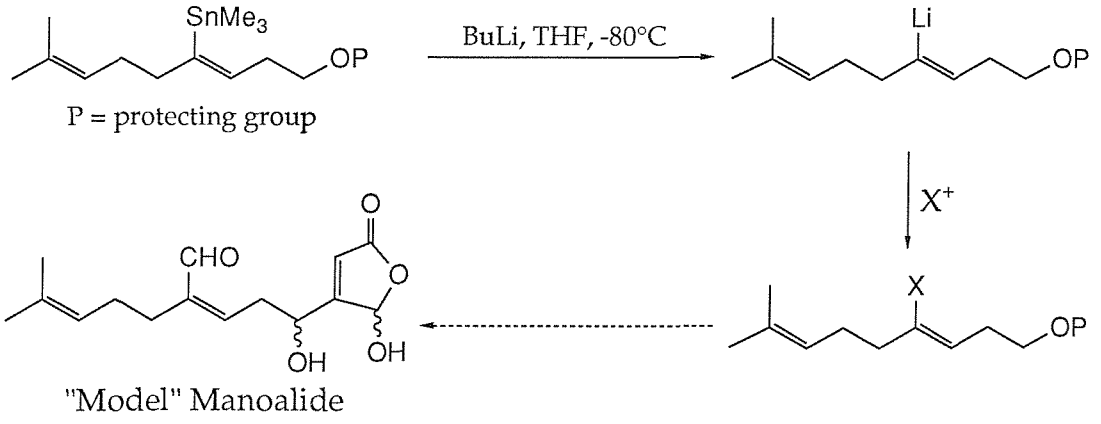
Bearing this potential in mind, we hoped that we would be able to use the stannane (**92**) as a key intermediate in our synthesis of manoalide.

Our first proposal for the elaboration of (**92**), which is summarised above in Scheme 4.3, involved the simple oxidation of the hydroxyl group to generate the aldehyde functionality of the desired intermediate (**93**), which we then aimed to react with the lithiated furan (**A**) to construct the stannane (**94**). We hoped then to utilise the vinylstannane for the introduction of the aldehyde group required in (**1**). To this end we studied a number of oxidation reactions with the express aim of producing the aldehyde (**93**) from (**92**). The first method which we attempted was a Swern oxidation.[131] This procedure is one of the most widely employed techniques for the selective preparation of aldehydes from alcohols, and is generally very reliable. Unfortunately, in our case, the only product which we were able to isolate from the reaction mixture was the α,β-unsaturated aldehyde (2*E*)-8-methyl-2,7-nonadienal (**95**); *i.e.* the trimethyltin moiety had been lost and the double bond had moved into conjugation with the aldehyde. The same aldehyde product (**95**) was also obtained when the oxidation was attempted *via* the mild Swern variant developed within our group, which employs N-methylmorpholine as the reaction base rather than Et_3N.[132]

We next attempted to carry out the oxidation of (**92**) using both the pyridinium chlorochromate,[133, 134] and the pyridinium dichromate[135] oxidation methods. In neither case was there any evidence of the formation of the desired aldehyde product, and both methods caused the complete decomposition of the stannane starting material. A similar lack of success was also observed when we attempted to carry out the oxidation using the Dess-Martin periodinane reagent.[136] The last of the methods which we tried involved the use of the TPAP reagent developed by Ley and Griffith.[137] Three distinct sets of reaction conditions have been reported for the use of this reagent, however none were successful when applied to the oxidation of (**92**). Once again the vinylstannane suffered total decomposition.

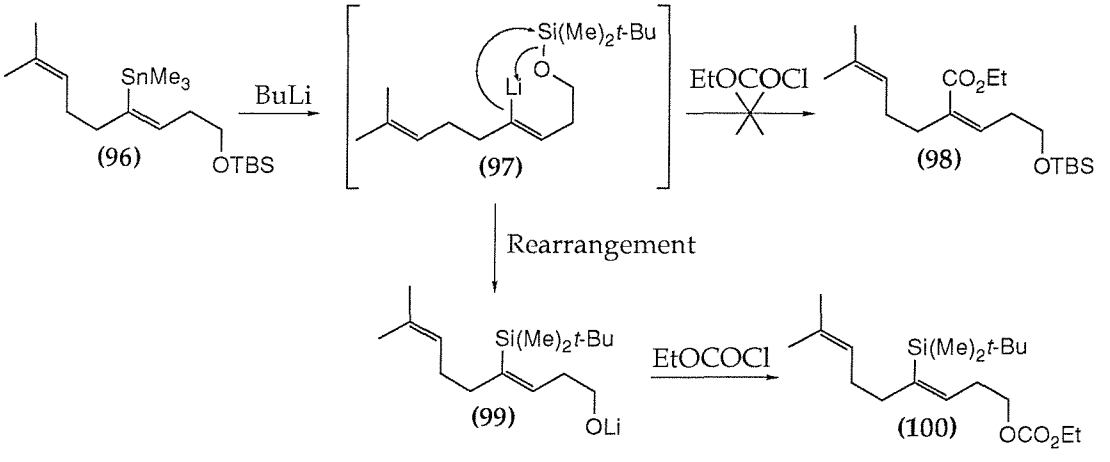
Following our failure to oxidise the alcohol group of (**92**), a modified strategy for the elaboration of the vinylstannane was formulated (*cf.* Scheme 4.4) which involved the protection of the alcohol group, followed by the transmetallation of the trimethylstannane to form a vinyllithium species. We then hoped to in-

troduce a suitable group 'X' which could be subsequently used for the introduction of the desired aldehyde.



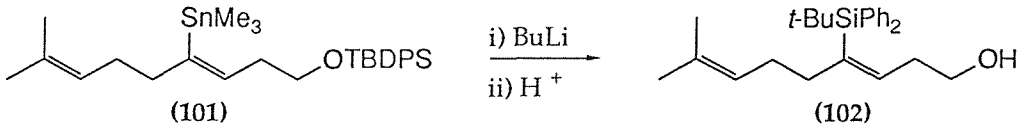
Scheme 4.4: The second proposed route for the elaboration of the stannane (**92**)

We first investigated the applicability of silyl ether protecting groups to our revised strategy (*cf.* Scheme 4.5).[138] The alcohol functionality of (**92**) was protected as the TBS ether and the resulting stannane (**96**) was then treated with butyllithium in order to effect the transmetallation. We attempted to quench what we believed was the resulting vinyllithium species (**97**) with ethylchloroformate; with the intention of forming the α,β-unsaturated ester compound (**98**). The product of the chloroformate quench, however, was not the desired ester species; instead the carbonate compound (**100**) was isolated as the sole product of the reaction, in a 78% yield. The carbonate compound was formed as the result of a rearrangement of (**97**), which involved the migration of the TBS group from the oxygen to the anionic double bond, resulting in the formation of the alkoxide (**99**). Subsequent reaction of (**99**) with ethyl chloroformate produced (**100**).



Scheme 4.5: The rearrangement of transmetallated (**96**)

In an attempt to prevent the migration of the silicon group, the whole transmetallation procedure was repeated using the TBDPS protected alcohol (**101**). We hoped that the increased steric bulk of the silicon group's substituents would prevent the migration reaction from taking place. Unfortunately, the only product isolated upon aqueous quenching of the transmetallation mixture was the rearranged vinylsilane product (**102**), which was isolated in a 66% yield (*cf.* Scheme 4.6).



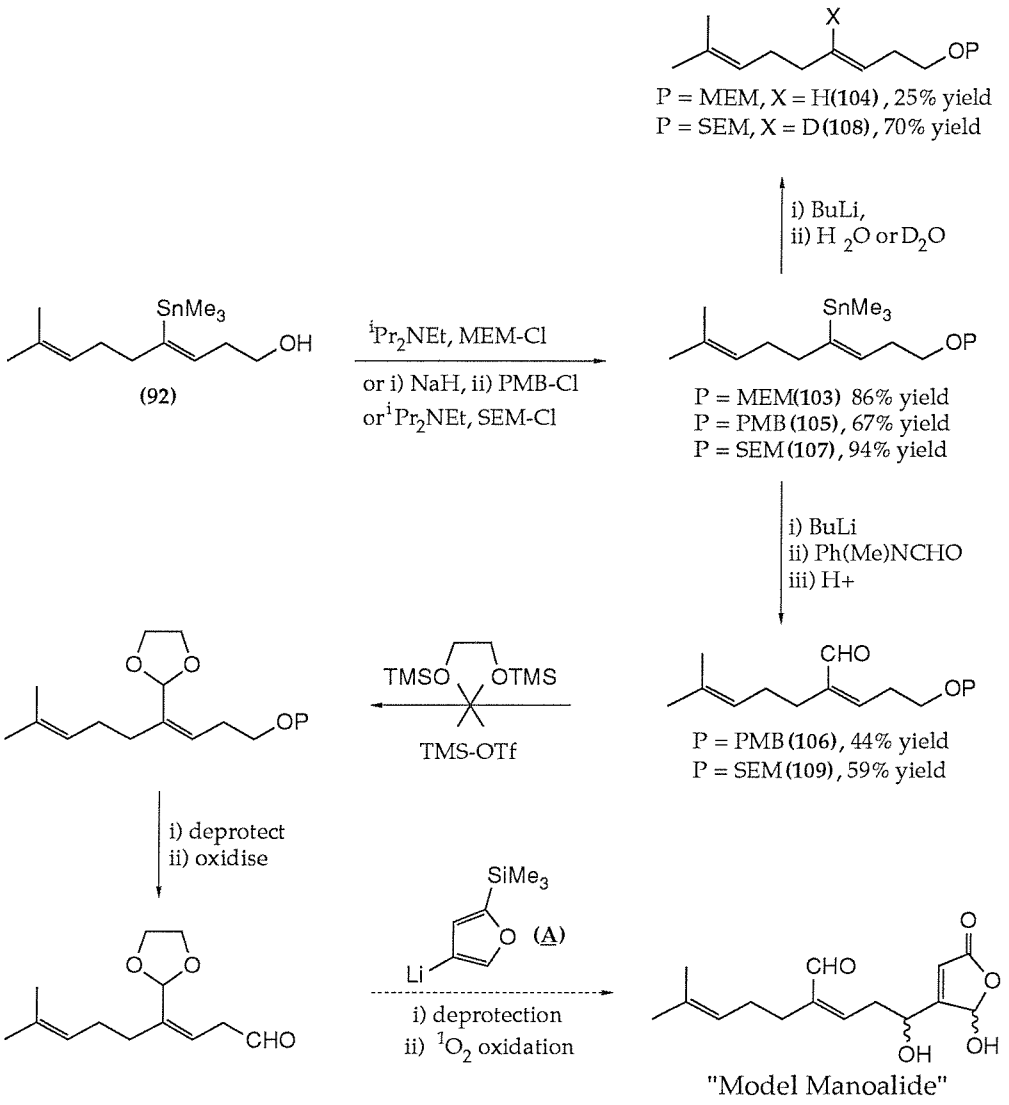
(101) (102)

Scheme 4.6

We next examined the applicability of various substituted methyl-ether protecting groups to our revised strategy.[139] We first studied the use of the methoxy-ethoxy-methyl (MEM) protecting group[140] (*cf.* Scheme 4.7) which unfortunately proved to be unsuitable for our purposes. The transmetallation of the stannylated MEM-ether (**103**), achieved by treatment with BuLi, resulted in a considerable amount of decomposition; protonolysis of the reaction mixture giving only a very poor 25% yield of the diene compound (**104**).

The application of two alternative protecting groups, the *p*-methoxybenzyl (PMB)[141] and 2-trimethylsilylethoxymethyl (SEM)[142] groups (*cf.* Scheme 4.7), was then investigated. In each case the transmetallation reactions proceeded quite smoothly; for example quenching the anion derived from the SEM-protected stannane (**107**) with D_2O, gave a 70% yield of the corresponding deuterated compound (**108**). Aldehyde functionalities were therefore introduced onto the double bonds of both of the transmetallated stannanes by reacting the vinyl-anions with N-methyl formanilide,[129] giving the α,β-unsaturated aldehydes (**106**) and (**109**) for the PMB and SEM series respectively. Our aim was to protect the aldehydes as acetals, then deprotect and oxidise the alcohols, and finally introduce the furan anion, (A) as shown in Scheme 4.7. The protection of α,β-unsaturated aldehydes as acetals poses a difficulty which is not normally encountered with acetalisation reactions. Use of standard methods, which involve reacting aldehydes with alcohols in the presence of acids, causes a rearrangement of the double bond such that the product acetal is β,γ-unsaturated; *i.e.* the double bond moves out of conjugation with the aldehyde. This would clearly be disastrous for our synthesis, as such a rearrangement would destroy the very double bond which we had expended so much effort in constructing. The rearrangement can usually be avoided, however, by using a method devel-

oped by Noyori, which reacts aldehydes with bis-trimethylsilyl ethers of diols in the presence of TMS-triflate.[143] All of our attempts to bring about the required acetalisation reaction, however, proved ineffective, with aldehydes (**106**) and (**109**) being unreactive under the conditions described by Noyori.

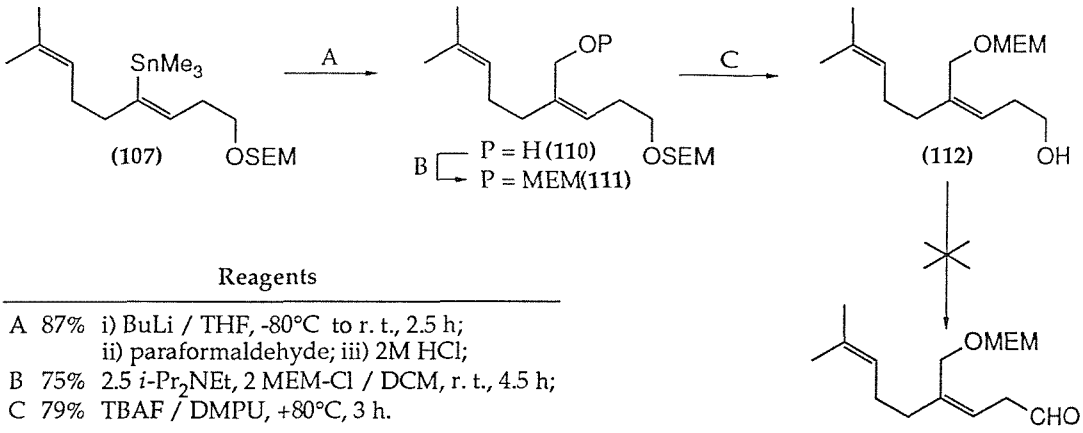


Scheme 4.7

With the acetal route having failed, another modification to our proposed synthesis was devised (*cf.* Scheme 4.8). The SEM-protected stannane (**107**) was transmetallated with BuLi and the resulting vinyllithium reacted with paraformaldehyde to produce the allylic alcohol (**110**), which was then protected as its MEM ether to give the fully protected diol (**111**). The SEM group was then removed *via* the method reported by Lipshutz and Miller,[144] to reveal the homoallylic alcohol functionality of (**112**). We aimed to then oxidise (**112**) to introduce an aldehyde functionality which could then be attacked by the familiar furan

anion (A) seen in Fig. 3.1. Once again the oxidation step proved to be our undoing; with all of our attempts (which included the TPAP, Dess-Martin, Swern and PCC methods) proving to be totally unsuccessful.

With our inability to elaborate the products of the copper (I)-catalysed reaction between (**63**) and Grignard reagent (**87**), we decided to abandon the simple copper-catalysed routes and try a more convergent approach to manoalide instead.



Reagents

A 87% i) BuLi / THF, -80°C to r. t., 2.5 h; ii) paraformaldehyde; iii) 2M HCl;
B 75% 2.5 *i*-Pr_2NEt, 2 MEM-Cl / DCM, r. t., 4.5 h;
C 79% TBAF / DMPU, +80°C, 3 h.

Scheme 4.8

4.3. The Furanyl-2,3-Dihydrofuran Approach To Manoalide.

The methods which we have described so far for the application of the copper (I)-catalysed rearrangement reaction to the synthesis of manoalide, have all involved the same basic principle of introducing the TMS-furan moiety after the construction of the key trisubstituted double bond. Following our failure to elaborate the stannane (**92**), we decided to attempt a much more convergent approach to (**1**) which involved applying the cuprate reaction to a dihydrofuran species which already contained the desired TMS-furan. This principle is highlighted by the retrosynthetic analysis shown below in Fig. 4.1.

To this end we set about the preparation of the requisite 5-(2'-TMS-4'-furanyl)-2,3-dihydrofuran (**115**) by the route indicated in Scheme 4.9. The iodofuran derivative (**113**), which was readily prepared from 2-TMS-4-bromofuran (**32**) *via* a metal-halogen exchange followed by treatment with iodine, was coupled to 2,3-dihydrofuran (**60**), using the palladium-catalysed coupling reaction developed by Larock.[145] In the Larock process, aromatic systems (typically benzene aromatics) bearing iodo substituents are coupled to 2,3-dihydrofurans, to form 2,3-dihydrofuran products in which the unsaturation is shifted to what were the original 4,5-positions of the starting material. The Larock report states that the

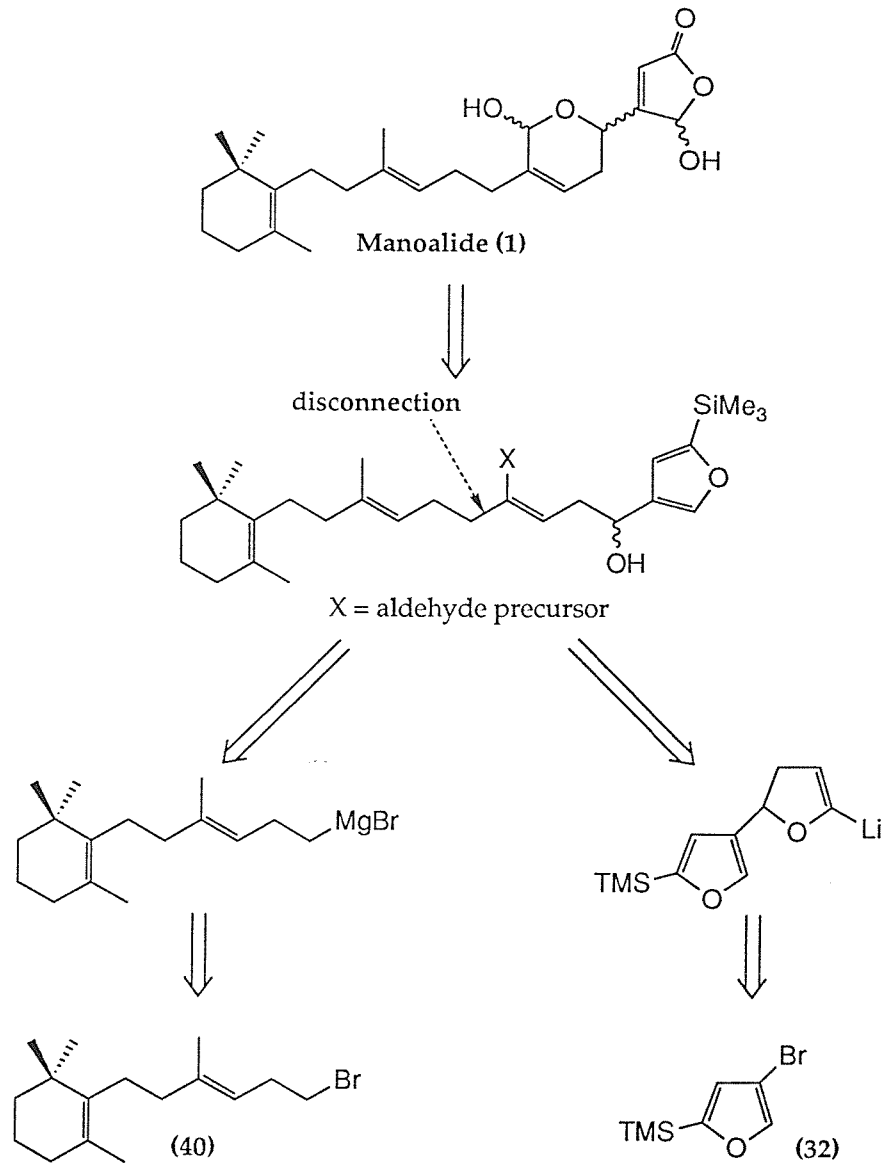
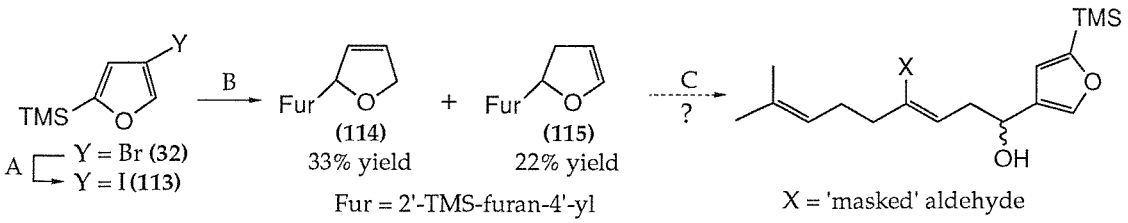


Figure 4.1: A retrosynthetic analysis of Manoalide based on the use of a furanyl-dihydrofuran

products of the reactions are exclusively 2,3-dihydrofurans.[145] In our hands, however, the coupling of (**113**) with (**60**) always resulted in the production of both the 2,5- and the 2,3-dihydrofuran isomers (**114**) and (**115**) in respective yields of 33 and 22% (*cf.* Scheme 4.9). The two compounds were, however, easily separated by column chromatography. We envisaged a synthetic route in which the treatment of (**115**) with ^{t}BuLi would result in the deprotonation of the 2-position of the dihydrofuran moiety. We hoped that the lithiated furanyl-dihydrofuran would undergo the copper-catalysed reaction with Grignard reagents such as (**87**), as discussed above. Suitable quenching of such a coupling reaction would give rise to products containing both the desired trisubstituted double bond and the TMS-furan group as shown in Scheme 4.9.

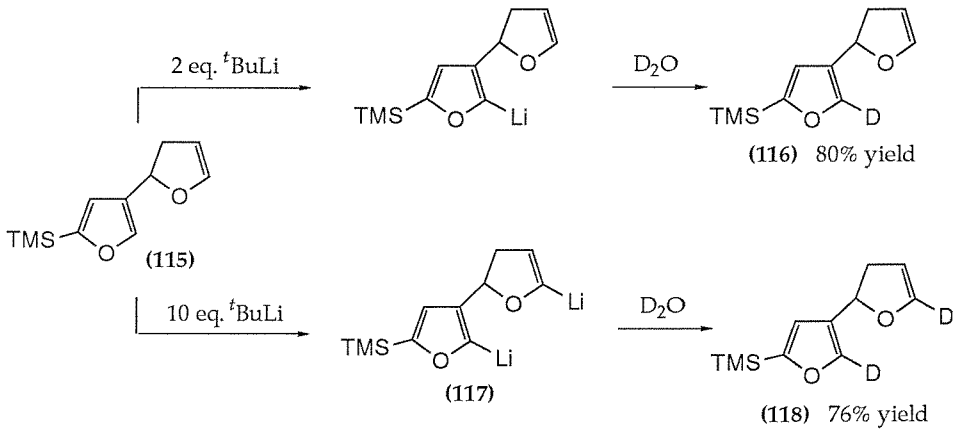


Reagents

A	78%	i) *s*-BuLi / Et_2O, -80°C, 0.5 h; ii) I_2, -80° to -50°C, 1 h;
B	33 and 22	$Pd(OAc)_2$, KOAc, PPh_3, Bu_4NCl, (60), DMF, 80°C, 24 h
C	?	Copper catalysed coupling with (87)

Scheme 4.9

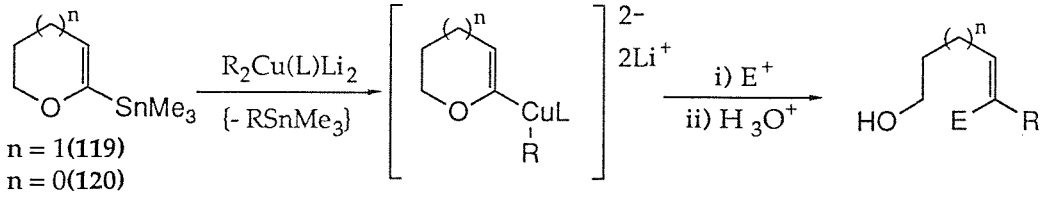
We anticipated that the most acidic position of (**115**) would be the 5'-position of the furan ring and this was confirmed by means of a deprotonation/D_2O-quench experiment, which resulted in the exclusive preparation of the mono-deuterated species (**116**) (*cf.* Scheme 4.10). We hoped that the treatment of (**115**) with an excess of ^{t}BuLi would allow the preparation of the dianion (**117**), which might then participate in the cuprate rearrangement. Test experiments showed that the Cu(I)-catalysed reaction did not take place between (**87**) and 2-lithiofuran and so we were confident that the anionic furan centre in the putative intermediate species (**117**) would not interfere with the Cu(I)-catalysed reaction of the dihydrofuran moiety. Unfortunately, our attempts to form (**117**) were largely unsuccessful. A number of reactions were carried out between (**115**) and up to ten equivalents of ^{t}BuLi, however on only one occasion were we able to isolate the di-deuterated compound (**118**), formed by D_2O quench of (**117**), and we were unable to successfully repeat this reaction.



Scheme 4.10

4.3.1. The Attempted Application Of Stannylated Dihydrofurans To The Synthesis Of Manoalide.

As part of his studies into the Cu(I)-catalysed reaction, Barber found that α-lithiated cyclic enol-ethers such as (62) and (63) could be replaced by their stannylated analogues (119) and (120) respectively (*cf.* Scheme 4.11). In common with all vinylstannanes, the stannylated enol-ethers underwent transmetallation reactions when treated with higher order cuprates, to form tetra-alkylstannanes and the α-metallated cyclic enol-ethers. Thus by treating (119) or (120) with a solution of an alkyllithium in the presence of $CuBr \bullet SMe_2$ the cuprate rearrangement took place to give the normal alkenol products (*cf.* Scheme 4.11).[95]



Scheme 4.11

As no actual deprotonation step is required when stannylated dihydrofurans are employed in the cuprate reaction, we hoped to avoid our difficulties with the deprotonation of (115), by carrying out the copper-catalysed coupling with the analogous stannylated compound (121). The key step of our revised synthetic proposal is shown in Fig. 4.2.

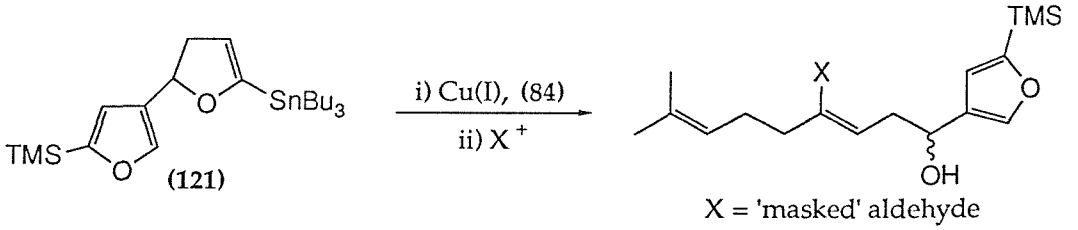
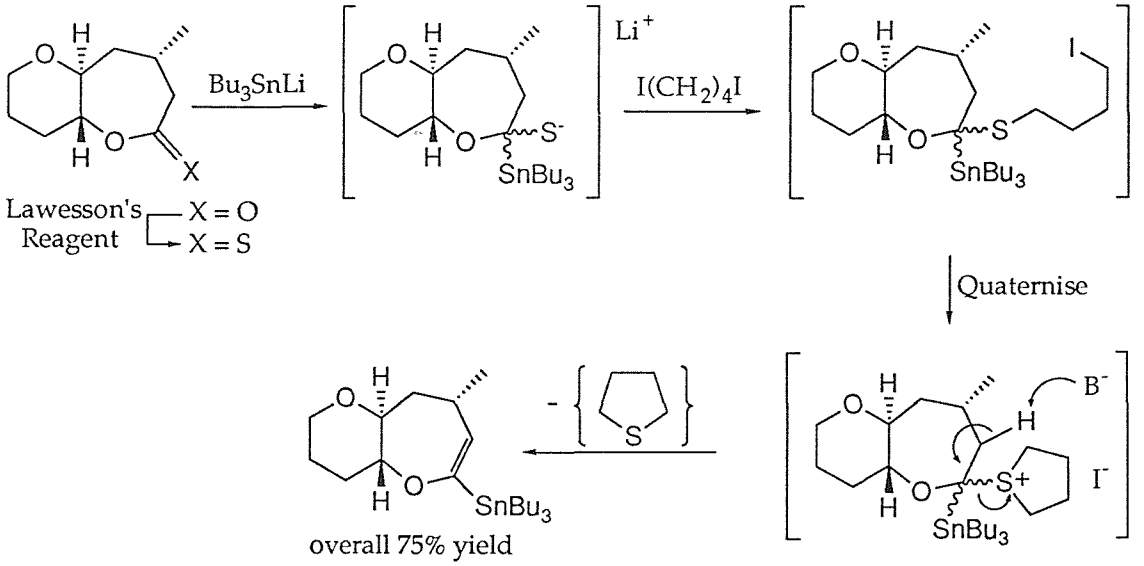


Figure 4.2

Trialkyltin functionalities are often introduced into compounds by quenching anionic intermediates with chloro-trialkyltin compounds. This method was unsuitable for the synthesis of (121), because we were unable to form the required anionic intermediate (117). We therefore required a method for the preparation of (121) which did not involve (117) as an intermediate. We initially hoped to make use of an excellent method which had been developed within our group

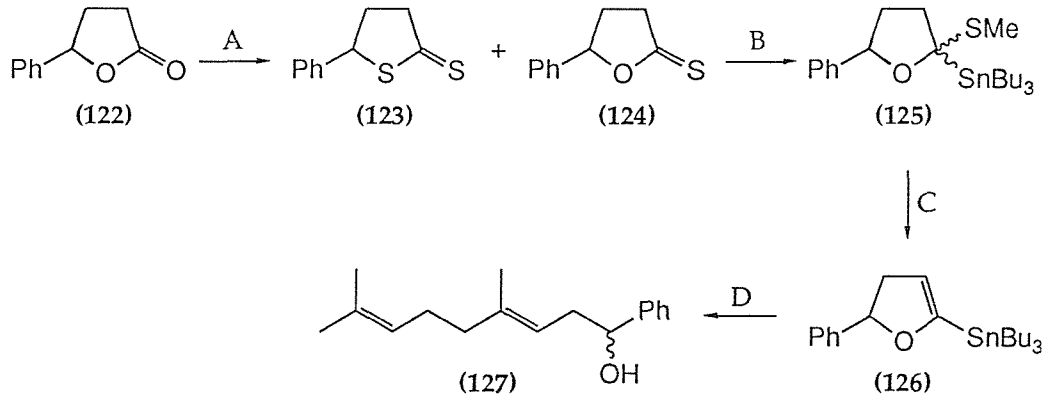
for the preparation of stannylated dihydropyrans.[146] Jarowicki and Barber, however, demonstrated that the method fails for dihydrofuran ring systems and as such another route had to be devised. A recent report by Nicolaou details the preparation of α-stannylated, medium-ring, cyclic enol ethers from lactone precursors.[147] The Nicolaou method, an example of which is shown in Scheme 4.12, relies on the conversion of lactone precusors to their analogous thionolactones *via* treatment with Lawesson's reagent.[148] The thionolactones, which are attacked by nucleophiles without the cleavage of the thionolactone ring, are then treated with Bu_3SnLi to produce a thiolate intermediate, which is alkylated with 1,4-diiodobutane. The resulting compound then undergoes an intramolecular quaternisation reaction at the sulphur centre, to produce an iodide salt, which on treatment with a hindered base such as 2,6-lutidine eliminates tetrahydrothiophene, to generate the stannylated enol-ether product.



Scheme 4.12: The Nicolaou preparation of α-stannylated cyclic enol-ethers

We hoped to use the Nicolaou method to produce our required stannylated dihydrofuran (**121**), which was to be the starting material for the copper (I)-catalysed coupling reaction. In order to test the applicability of our proposed route, we carried out a series of model studies based on the commercially available 5-phenyltetrahydrofuran-2-one (**122**) as summarised in Scheme 4.13. Treatment of (**122**) with Lawesson's reagent allowed the preparation of the thionolactone (**124**), along with small quantities of the dithionolactone (**123**). However, when we attempted to elaborate the thionolactone (**124**) to the stannylated dihydrofuran (**125**) *via* the one-pot reaction sequence reported by Nicolaou, none of the desired compound was obtained. Treatment of (**124**) with Bu_3SnLi did result

in the formation of the expected thiolate anion, however the subsequent diiodobutane quench and tetrahydrothiophene elimination processes were not observed. In their report, Nicolaou *et al.* only quote the application of the stannylation procedure to cyclic systems containing seven-membered rings and above. It is possible that the increased steric constaints of the five-membered ring present in our system, simply prevented the alkylation from taking place. Treatment of the thiolate derived from (**124**) with MeI did result in the preparation of the thiomethyl-substituted tetrahydrofuran (**125**). This compound was elaborated to the desired stannylated compound (**126**), by means of an alternative elimination procedure, which was again developed by Nicolaou.[149] The alternative procedure involved treating (**125**) with a mixture of 1,2,2,6,6-pentamethylpiperidine and copper (I) triflate,[150] which brought about the elimination of methanethiol to give the desired product (**126**). When we applied our copper (I)-catalysed reaction to this stannylated dihydrofuran we were delighted by the fact that the desired homoallylic product (**127**) was obtained in a 48% yield.



Reagents

A	6% (**123**) 55% (**124**)	Lawesson's Reagent / PhMe, Δ, 5 h, separate;
B	72%	i) Bu_3SnLi / THF, -80°C, 1 h; ii) MeI, -80° to r.t.;
C	44%	pentamethylpiperidine, $(CuOTf)_2 \bullet Ph$ / Ph, r.t., 1 h;
D	48%	(84), $CuBr \bullet SMe_2$ / Et_2O-SMe_2 (1:1), -80°C to r.t., 3 h.

Scheme 4.13

This result encouraged us to apply the whole procedure to the 'real' TMS-furanyl substituted system. One reservation remained, however, and this was as a result of the formation of the dithionolactone (**123**) through the reaction of (**122**) with Lawesson's reagent. The formation of (**123**) was possibly caused by the donation of electrons from the phenyl ring, which we believed caused (**124**)

to undergo a ring-opening/ring-closure rearrangement as shown in Fig. 4.3, to produce the thiolactone (**128**). Reaction of (**128**) with a further quantity of Lawesson's reagent would produce (**123**). The fact that this reaction took place was somewhat disquieting as we anticipated that the TMS-furanyl substituent of our 'real' system would be even more likely to favour the rearrangement process than the phenyl group, because of the donation of a lone pair by the furanyl-oxygen (*cf.* Fig. 4.3). We nevertheless decided to attempt the TMS-furanyl series of reactions.

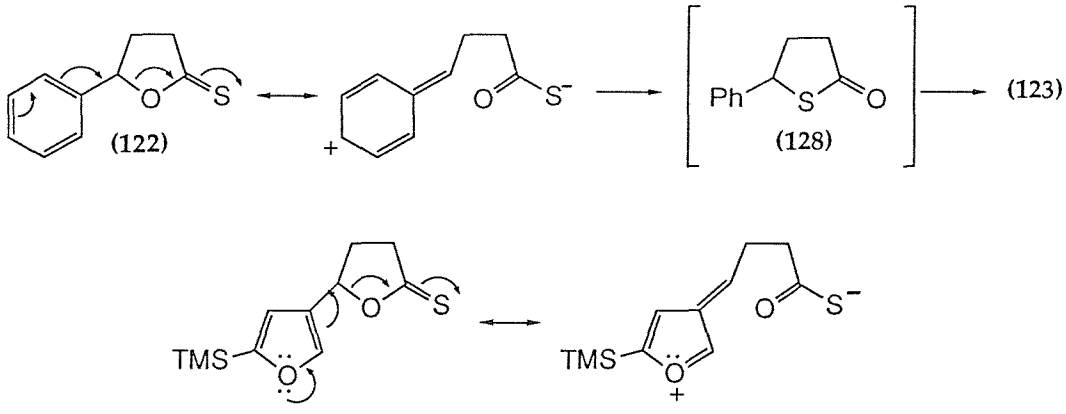
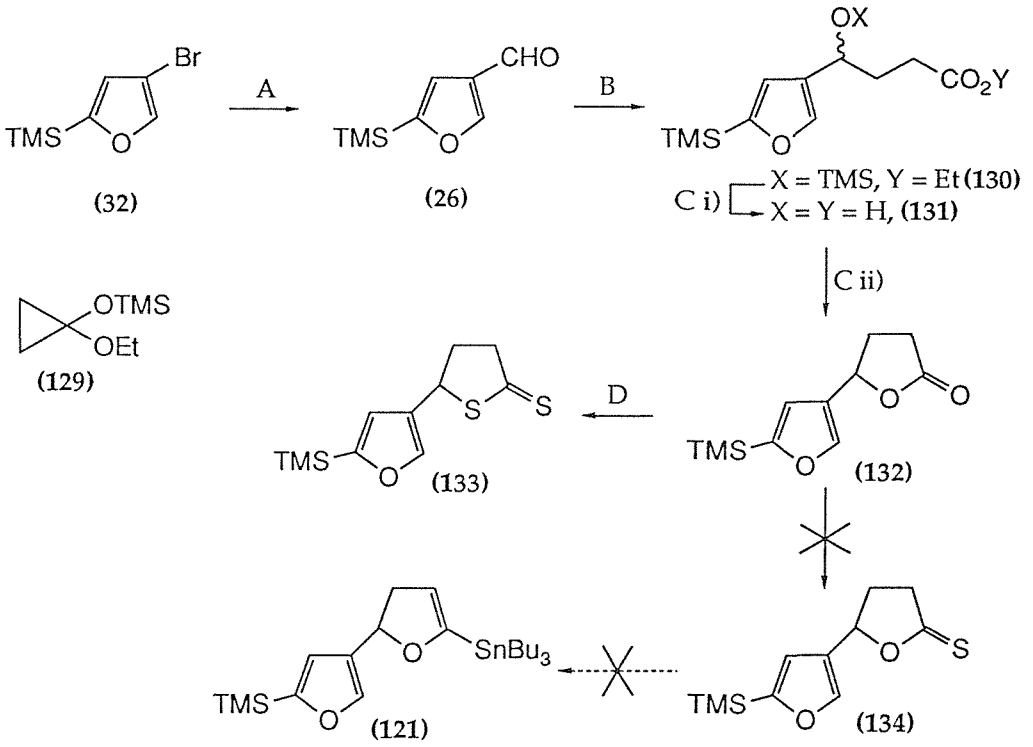


Figure 4.3

2-Trimethylsilyl-4-furancarboxaldehyde (**26**), was readily prepared from 5-bromo-2-trimethylsilylfuran (**32**) by treatment with ^{s}BuLi, followed by an N-methylformanilide quench.[129] The aldehyde functionality was then elaborated by means of the elegant homo-Reformatsky methodology developed by Kuwajima and co-workers, to give the remarkably stable TMS-protected hydroxy ester (**130**), which could be purified by column chromatography. The Kuwajima method employs commercially avaliable [(1-ethoxycyclopropyl)oxy]trimethylsilane (**129**) as the source of the ethyl propionate (homoenolate) anion.[151] The TMS-ether and ethyl ester groups of (**130**) were then removed by sequential base and acid hydrolysis, and the resulting hydroxy-acid intermediate (**131**) was lactonised by means of a Mitsunobu reaction to give the key lactone intermediate (**132**).[152]

This brought us up to the stage of converting the lactone (**132**) to its sulphur analogue (**134**). Unfortunately, the worries which ensued from the formation of the dithionolactone species (**123**) in the phenyl-sustituted series, proved to be entirely justified. A number of attempts were made to carry out the thionation of (**132**), using both Lawesson's reagent and the analogous compound, 2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulphide,[153] in the hope of preparing the key intermediate (**134**). The only product which we were able to

isolate from these thionation reactions, however, was the dithionlactone species (133).



A 78% i) *s*-BuLi / Et_2O, -70°C, 1 h;
ii) HCON(Me)Ph / Et_2O, -70°C to r. t., 1 h;
B 83% ZnI_2, **(129)** / DCM, r. t., 22 h;
C 73% i) 2M LiOH / MeOH-H_2O, r. t., 18 h, then AcOH, r. t. 24 h;
ii) DEAD, PPh_3 / THF, -80°C to r. t., 5 h;
D 30% Lawesson's reagent / PhMe, Δ, 5 h.

Scheme 4.14: The attempted preparation of the α-stannylated TMS-furanyl-2,3-dihydrofuran (**121**) *via* the Nicolaou methodology.

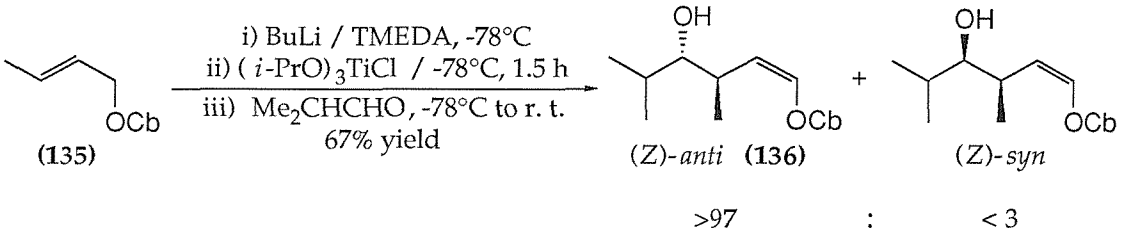
With this inability to prepare the crucial intermediate (**134**), our proposed synthetic route to manoalide broke down once again, and the route was therefore abandoned.

Chapter 5

Studies Towards The Synthesis Of Manoalide *via* A Copper(I)-Catalysed Reaction Of An Enol Carbamate.

5.1. The Copper (I)-Catalysed Coupling Of Enol-Carbamates With Alkyllithium Reagents.

The discovery of the copper (I)-catalysed reaction between organolithiums and α-lithiated cyclic enol-ethers, which we discussed in Chapter 3, inspired a number of investigations within our group, aimed at identifying similar reaction processes within alternative substituted enol systems. The most successful alternative which has been discovered to date involves the use of acyclic enol-carbamates rather than enol-ethers in analogous copper-catalysed coupling reactions, leading to the formation of homoallylic alcohol products.[154]

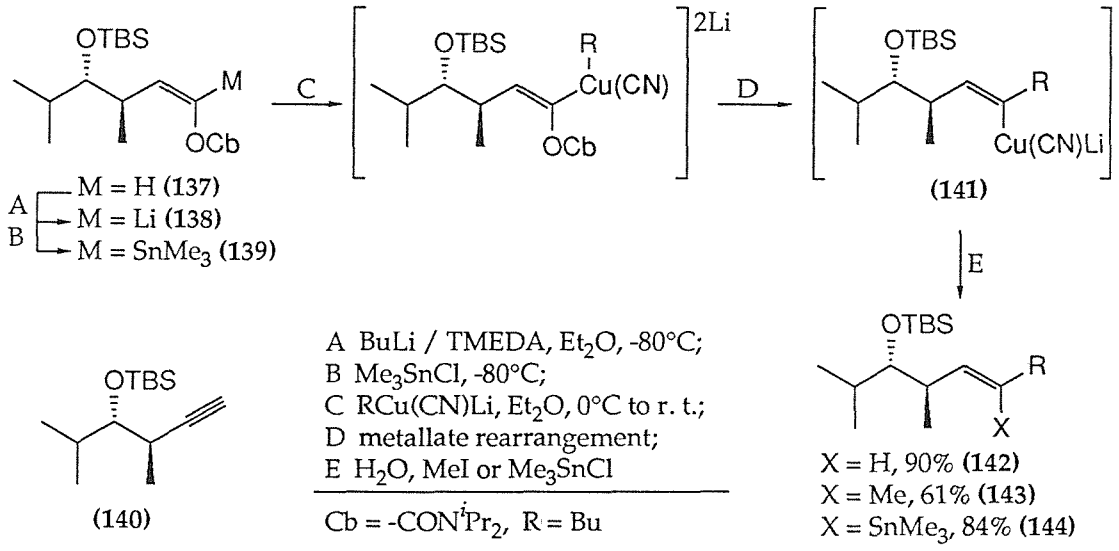


Scheme 5.1: The preparation of *anti* enol-carbamate (**136**).

The N,N-diisopropyl (*Z*)-*anti*-enol-carbamates used as the starting materials for the novel Cu(I)-catalysed coupling reactions were readily prepared on a substantial scale using the elegant homoaldol methodologies developed by Hoppe and co-workers.[155] The Hoppe procedures, which are exemplified in Scheme 5.1 for the preparation of (**136**), involve the reaction of aldehydes with σ-bonded allyltitanium species derived from substituted allyl carbamates such as the crotonyl carbamate (**135**). The reactions show very high diastereoselectivities for the formation of the *anti* aldol products as indicated in Scheme 5.1 above.

The actual application of the enol-carbamates to the copper (I)-catalysed rearrangement process is summarised in Scheme 5.2. The α-protons of enol-carbamates are acidic and deprotonation of (**137**), the TBS-ether derivative of (**136**), was readily achieved by treatment with butyllithium in the presence of TMEDA; resulting in the formation of the configurationally stable α-lithiated enol-carbamate (**138**). On warming to -40°C or above, however, (**138**) proved to be thermally labile, suffering a Fritsch-Buttenberg-Wiechell (FBW) rearrangement[156] to form the acetylene (**140**). All attempts to achieve a 1,2-metallate rearrangement by reacting (**138**) with cuprates were therefore unsuccessful, as the FBW reaction took place at a lower temperature than the desired 1,2-metallate rearrangement; the only product isolated from the reactions being the acetylene (**140**).[154] The thermal stability of the metallated derivative of (**137**) was increased

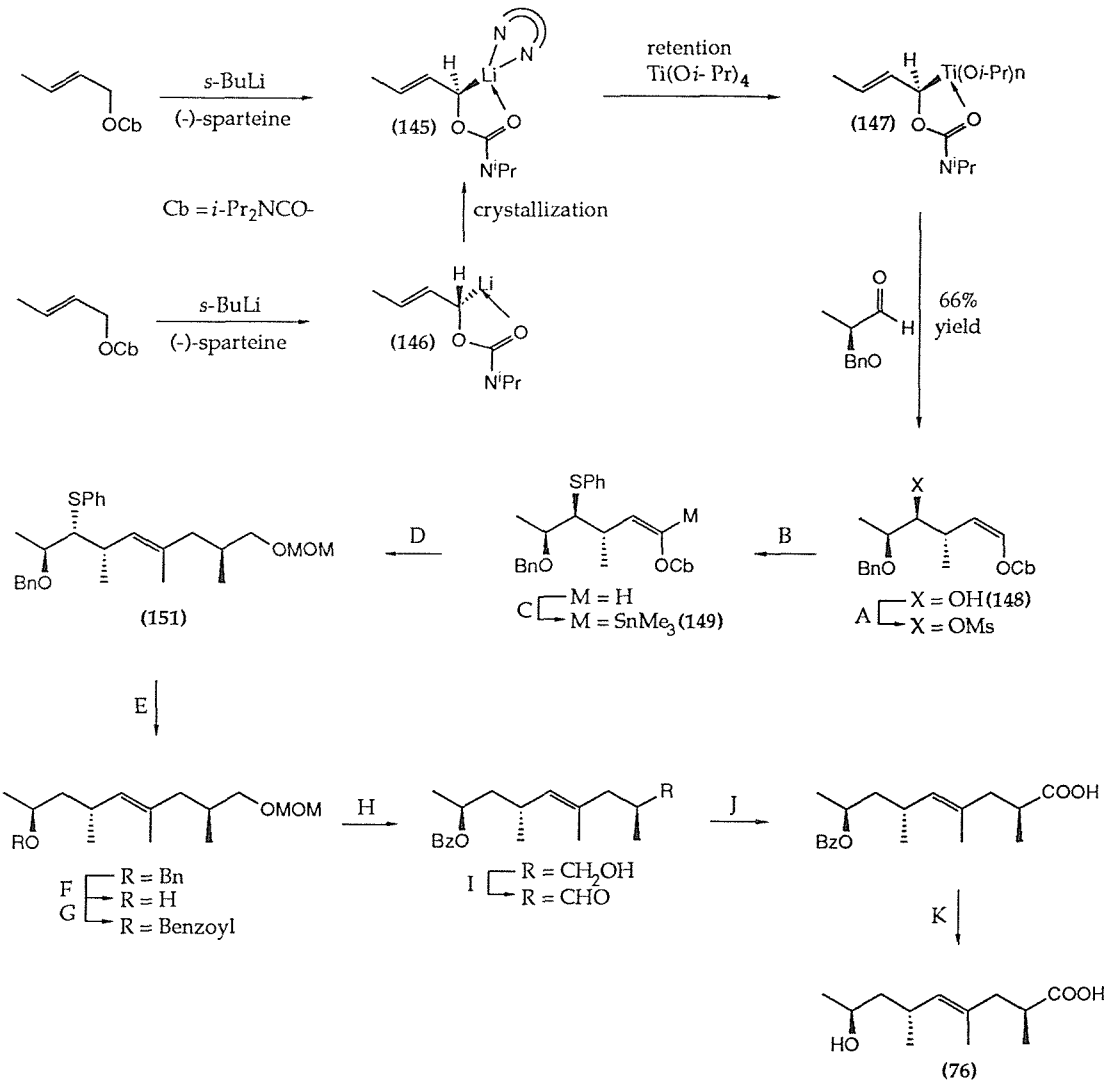
by transmetallation from lithium to tin; quenching the lithiated species (138) with trimethyltin chloride gave the vinylstannane product (139), which was stable at refrigerator temperatures. Treatment of (139) with a solution of BuCu(CN)Li in ether at 0°C resulted in transmetallation, giving an unstable higher-order cyanocuprate, which duly underwent the desired 1,2-metallate rearrangement to give the vinylcuprate (141). Protonolysis of (141) resulted in the formation of the homoallylic alcohol (142) in an overall yield of 90% from (137). The nascent double bond, created as a result of the rearrangement, had at least 97% *trans*-stereochemistry, as shown by high field ^{1}H and ^{13}C NMR analyses. The vinylcuprate intermediate (141) was also quenched with methyl iodide and trimethyltin chloride, to give the corresponding homoallylic alcohol products (143) and (144) respectively.[154]

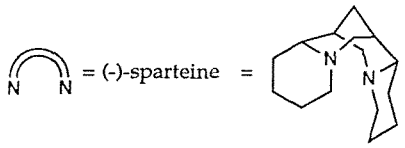


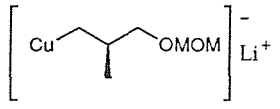
Scheme 5.2: The copper (I)-catalysed rearrangement of metallated enol-carbamates.

5.2. The Application Of 1,2-Metallate Rearrangements Of Enol-carbamates.

The most notable application of the copper (I)-catalysed 1,2-metallate rearrangement of α-stannylated enol-carbamates was seen in Pimm's preparation of the polyketide fragment (76) of the jaspamide and geodiamolide natural products.[157] The homochiral species (76) was prepared *via* the synthetic sequence detailed in Scheme 5.3 (*cf.* also Scheme 3.12). The initial preparation of the (*Z*)-*anti*-enol-carbamate (148) was noteworthy, as it was achieved by means of the extremely elegant enantioselective homoaldol chemistry developed by Hoppe and Zschage.[158]







(150)

Reagents

A 51% MsCl, NEt_3 / DCM, -30°C, 3 h;
B 80% NaH, PhSH / DCM, THF, 60°C, 12 h;
C 89% i) *t*-BuLi; ii) Me_3SnCl / THF, -70°C to r. t., 1 h;
D 46% i) cuprate (150) / Et_2O, SMe_2, 0°C, 1 h;
ii) HMPA, MeI, -70°C to r. t.;
E 83% Raney Ni / EtOH, 60°C, 15 min.;
F 97% Na / NH_3, THF, -70°C, 3 h;
G 100% PhCOCl / Pyr, DMAP, 30 min.;
H 85% *c.* H_2SO_4, MeOH, 2 h;
I 81% Dess Martin Periodinane / DCM, 30 min.;
J 84% $NaOCl_2$, H_2NSO_3H, 1-methylcyclohexanone in DCM, H_2O, 2 h;
K 85% LiOH (10%), MeOH, 48 h.

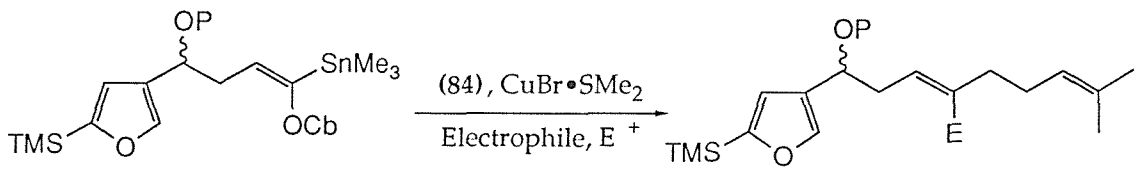
Scheme 5.3: Pimm's preparation of the polyketide fragment of Jaspamide.[157]

Lithiation of crotonyl N,N-diisopropyl carbamate was followed by the addition of the chiral diamine, (-)-sparteine, which resulted in the crystallization of the homochiral lithium complex (**145**). The isomeric α-lithiated enol-carbamate (**146**) was conformationally labile and was therefore converted by equilibration to (**145**), which was effectively removed from the reaction mixture by the crystallization process. The homochiral lithium complex was then transmetallated to the allyltitanium species (**147**), with retention of stereochemistry, by the addition of $Ti(O^iPr)_4$. Reaction of (**147**), which was configurationally stable, with (S)-2-benzyloxypropionaldehyde resulted in the formation of the homochiral carbamate (**148**), which was then converted to the stannylated sulphide intermediate (**149**). Treatment of (**149**) with the homochiral cuprate (**150**) resulted in the desired 1,2-metallate rearrangement taking place, to give after a methyl iodide quench, the homoallylic alcohol (**151**). The homochiral polyketide species (**76**) was then prepared from (**151**) in seven steps.

The main attraction of Pimm's reaction sequence was the fact that the cuprate coupling allowed the preparation of a key homochiral synthetic intermediate with complete control of the stereochemistry of the nascent trisubstituted double bond.

5.3. The Attempted Synthesis Of Manoalide *Via* The Copper (I)-catalysed Enol-Carbamate Rearrangement.

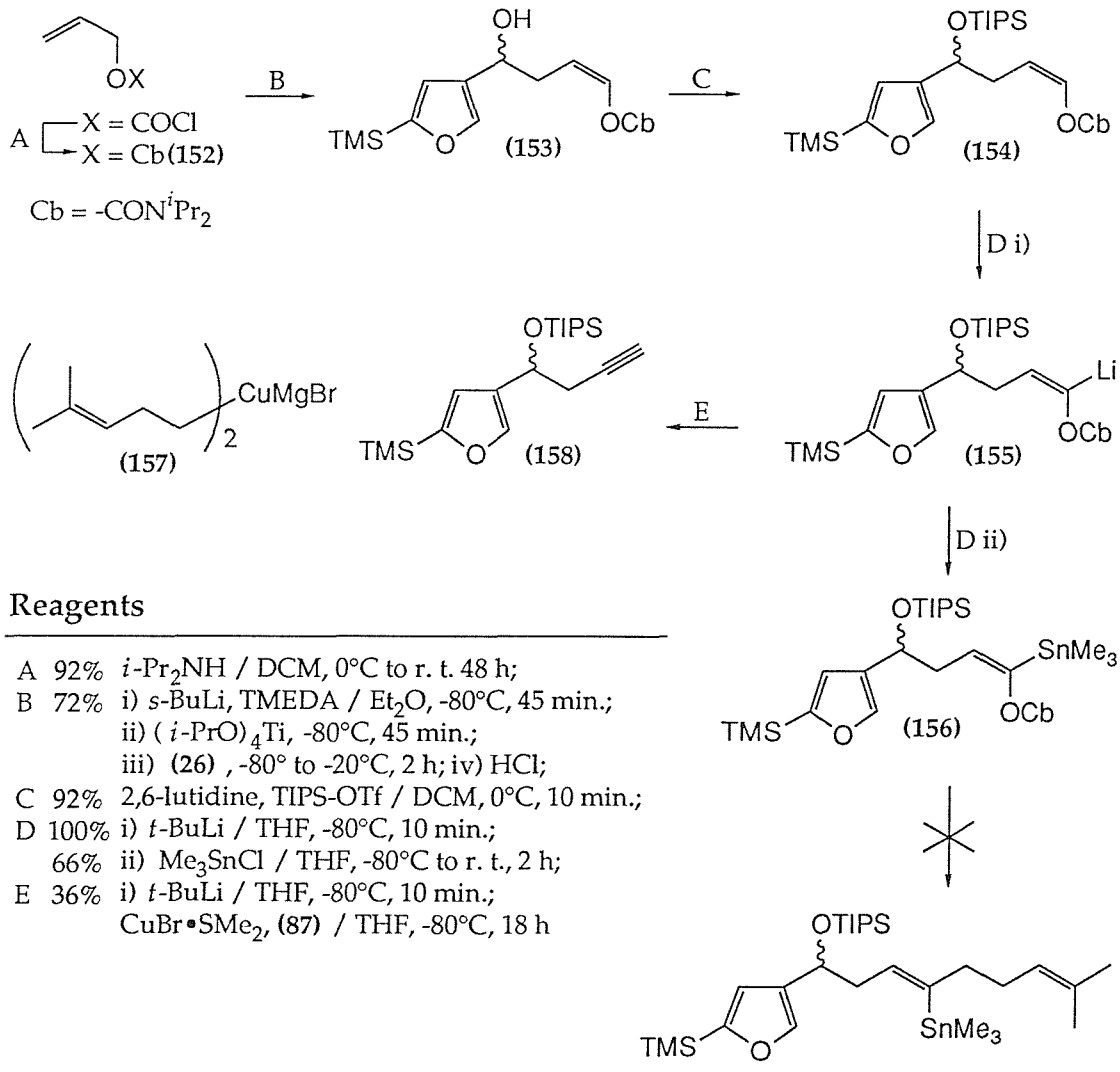
Following the successful application of the enol-carbamate coupling rearrangement to the synthesis of the polyketide (**76**), we were stimulated to try and apply the chemistry to the construction of the C6-C7 double bond of manoalide. Once again we wished to preserve our stocks of the 'real' system homoallylic bromide (**40**), and so we concentrated our attention on the reactions of the model homoallylic system of 1-bromo-4-methyl-3-pentene (**82**) and the analogous iodide (**83**). The key reaction in our proposed synthetic sequence was, therefore, the copper-catalysed coupling of the organolithium reagent (**84**) with a stannylated enol-carbamate as shown in Figure 5.1.



P = Bulky Protecting Group

Figure 5.1

By means of the use of the carbamate coupling with a suitable electrophilic quench, we hoped to introduce both the desired C6-C7 trisubstituted double bond and the TMS-substituted furan moiety of the model manoalide analogue simultaneously.



Scheme 5.4: Attempted synthesis of manoalide *via* the copper (I)-catalysed rearrangement of an enol-carbamate

The reaction sequence which we employed is summarised in Scheme 5.4. Allyl chloroformate was reacted with diisopropylamine to give the allyl carbamate (**152**). A Hoppe homoaldol reaction was then then carried out between (**152**) and 2-TMS-4-furancarboxaldehyde (**26**), resulting in the formation of the racemic enol-carbamate (**153**). Clearly, there was no need to worry about the diastereoselectivity of the homoaldol reaction, as there was only one stereogenic centre in our target compound. We envisaged a major difficulty in the next stage of the preparation of the enol-carbamate coupling precursor; namely the introduction

of the trimethyltin group. The presence of the acidic proton in the 5'-position of the furan moiety had the potential to interfere in the process of α-lithiation and Me_3SnCl quench. We hoped that the introduction of a very bulky protecting group onto the alcohol functionality of the homoaldol product would, as the result of steric hindrance, allow the selective α-lithiation of the carbamate. Consequently, the alcohol (**153**) was protected as its triisopropylsilyl ether. We were gratified to find that our protecting strategy was effective; the lithiation and stannylation of (**154**) proceeded smoothly, to generate the desired coupling precursor (**156**). We then attempted to bring about the coupling of (**156**) with (**84**). As in our earlier attempts to effect the coupling of (**84**) with 5-lithio-2,3-dihydrofuran (**63**), we once again encountered difficulties regarding the thermal instability of the homoallylic cuprate intermediate, which we already knew to be unstable at temperatures above -25°C. The standard reaction conditions for the enol-carbamate process developed by Pimm and Dixon, required the mixing of the stannylated enol-carbamates with the organocuprates at 0°C;[154, 157] we nevertheless hoped that at least some coupling would occur at lower temperatures. Unfortunately, all attempts to effect the coupling reaction between the stannylated carbamate (**156**) and the lithiocuprate derived from $CuBr \bullet SMe_2$ and (**84**) at -80°C, were unsuccessful. The only isolable product was the carbamate (**154**) generated by transmetallation and protonolysis of (**156**).

In the case of the Cu-catalysed coupling of lithiated cyclic enol-ethers with organometallics, we had established that the reaction based on the use of Grignard reagents took place at a much lower temperature than the corresponding organolithium based processes. We hoped that a similar pattern of reactivity would exist for the carbamate couplings, and consequently the reaction between (**156**) and the magnesio-cuprate (**157**) was investigated. Unfortunately, the coupling rearrangement did not occur in this case, simply because the magnesiocuprate reagent (**157**) was incapable of transmetallating the vinylstannane functionality. No literature precedent is available for the transmetallation of vinylstannanes with magnesio-cuprates, and so the lack of reactivity was not unexpected. When attempts were made to carry out the coupling between (**157**) and the vinyllithium (**155**), the only reaction observed was the FBW rearrangement to the acetylene (**158**).

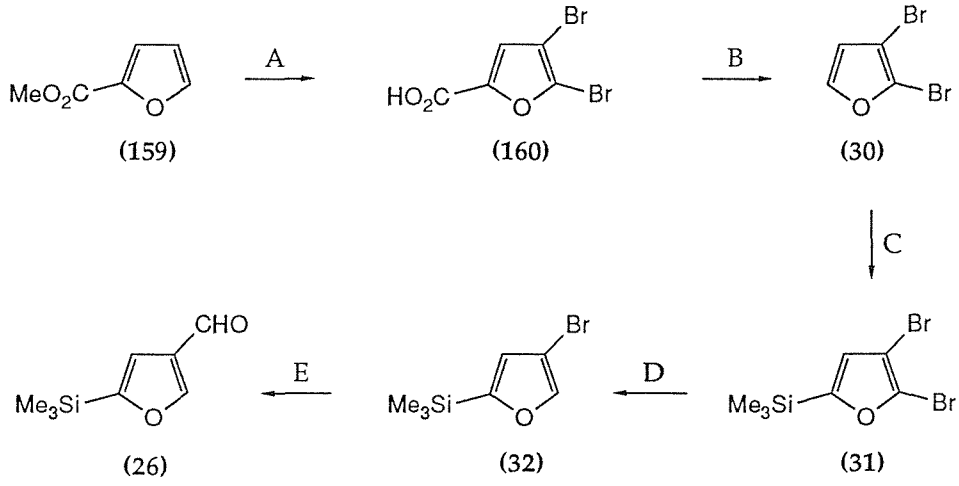
These disappointing results led us to abandon the attempts to construct the C6-C7 double bond of manoalide by means of a 1,2-metallate rearrangement. The alternative method which we employed is discussed in Chapter 7.

Chapter 6

The Preparation Of Furan Intermediates.

6.1. The Importance Of Furan Derivatives In The Synthesis Of Manoalide.

As we discussed in Chapter 2, furans bearing a trimethysilyl substituent in their 2-position played pivotal roles in the three published syntheses of Manoalide (**1**). The singlet-oxygen oxidation of 2-trimethylsilyl-4-alkyl-disubstituted furans allowed the regioselective preparation of the 5-hydroxy-4-alkyl-2(5H)-furanone moiety present in (**1**). In a similar way, the peracetic acid oxidation of 2-TMS-substituted furans has allowed the regioselective preparation of other furanone species.[159-161] As we wished to use the singlet-oxygen oxidation methodology in our own proposed syntheses of (**1**), we required several 2,4-disubstituted furan derivatives, the preparation of which are discussed below.



A 73% i) Br_2 / CCl_4, Δ, 24 h, then r. t. 48 h;
ii) 4M NaOH / H_2O, 60°C, 8 h, then r. t. 16 h;
B 51% Cu powder / quinoline, 180°C, 40 min.;
C 85% i) BuLi, Et_2NH / THF, -30°C, 20 min.;
ii) (30) / THF, -80°C, 90 min.; iii) Me_3SiCl, -80° C to r. t.;
D 65% BuLi / Et_2O, -80°C, 5 min.;
E 78% i) *s*-BuLi /Et_2O, -70°C, 1 h;
ii) N-Me-formanilide, -70°C to r. t., 1 h;

Scheme 6.1: The Katsumura preparation of 2-TMS-4-furancarboxaldehde (**26**).[57]

6.2. The Syntheses Of 2-Trimethylsilyl-4-Bromofuran (32) and 2-Trimethylsilyl-4-Iodofuran (113).

2-Trimethylsilyl-4-bromofuran (**32**) was a key intermediate in the syntheses of all of the different furan derivatives which we required throughout our work. We prepared (**32**) using the method summarised in Scheme 6.1, which was based on that reported by Katsumura *et al.* in their second synthesis of manoalide (*cf.* Scheme 2.2).[57] The starting point in the preparation of (**32**) was the inex-

pensive, commercially available precursor, methyl 2-furoate (**159**), which was converted to the intermediate 2,3-dibromofuran (**30**) using the method patented by Majoie.[162] The first step in the sequence was a dibromination reaction, achieved by treating a refluxing solution of (**159**) in CCl_4, with a solution of bromine. The resulting product was then saponified to give 4,5-dibromo-2-furoic acid (**160**) in a 73% overall yield, with a small amount of the tribrominated acid as an impurity. Decarboxylation of the acid functionality was then achieved by heating a mixture of (**160**) and copper powder in quinoline at 180°C, giving (**30**) in a 50% yield.

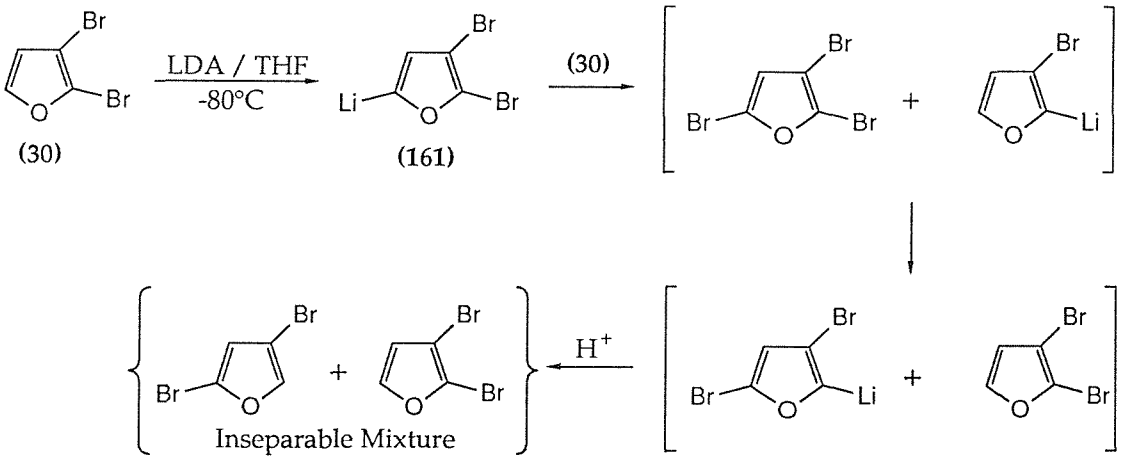


Figure 6.1: The 'halogen-dance' rearrangement of lithiated 2,3-dibromofuran.

Davies and Davies reported that the treatment of (**30**) with LDA, followed by chlorotrimethylsilane, resulted in the formation of 2-trimethysilyl-4,5-dibromofuran (**31**).[163] This observation was confirmed by Katsumura *et al.*, who prepared (**32**) by selectively debrominating (**31**) at the 5-position, using the method reported by Sornay and co-workers,[164] which involved the treatment of (**31**) with one equivalent of BuLi, followed by protonolysis. When we tried to repeat the transformation of (**30**) to (**32**), however, we invariably obtained an inseparable mixture, consisting mainly of the two isomeric products, 2-trimethysilyl-3-bromofuran and (**32**). The source of the isomerisation was the LDA deprotonation step; we found that the anion (**161**), formed on treatment of (**30**) with LDA, was undergoing a rearrangement, which scrambled the positions of the bromine substitution. This occurred even when we very carefully followed the method employed by Davies and Davies.[163b] We believe that the rearrangement was an example of a 'halogen dance' reaction. Exactly analogous processes have been observed in the LDA deprotonations of 2,3-dibromothiophene,[165] 2-bromo-3-methanethio-thiophene[166] and other halogenated heterocycles.[167] We believe that the rearrangement probably takes place *via*

an intermolecular metal-halogen exchange between the anion (**161**) and unreacted (**30**), as shown in Figure 6.1 above.

Our proposed mechanism infers that one possible cause of the rearrangement is a slow reaction between (**30**) and the LDA, resulting in the formation of a mixture of the protonated and metallated species, which subsequently undergoes the metal-halogen exchanges. Working on this assumption, we hypothesised that the use of a less hindered base would allow the more rapid deprotonation of (**30**), and hence stop the halogen dance by preventing the formation of mixtures of (**161**) and (**30**). We were delighted to find that our ideas proved effective, as the treatment of (**30**) with lithium diethylamide, rather than LDA, gave exclusively the unisomerised product (**31**), which debrominated cleanly to give the desired product (**32**).

In view of the consistant difficulties which we encountered with the LDA reaction, the author would like to express his surprise that the halogen rearrangement was not observed by either the Katsumura or the Davies groups.

As we discussed previously (*cf.* Chapter 4, Section 4.3) the iodofuran (**113**), which was required as the precursor to the furanyl-dihydrofuran (**115**), was prepared from (**32**) by means of a metal-halogen exchange, followed by an iodine quench (*cf.* Schemes 4.9).

6.3. The Synthesis Of 2-Trimethylsilyl-4-Furancarboxaldehyde (26).

The furan derivative, 2-trimethylsilyl-4-furancarboxaldehyde (**26**) was a key intermediate in our projected syntheses of manoalide (**1**) (*cf.* Sections 5.3. and 4.3.1. respectively). The compound was also an important intermediate in both the Garst[58] and Katsumura[56] syntheses of (**1**). A number of different strategies for the preparation of (**26**) have been published, each of which has its own merits and disadvantages.

The Garst route summarised in Scheme 2.3, which was based on a procedure reported by Florentin and co-workers,[168] involved the use of 3-furaldehyde as the starting material. The aldehyde (**26**) was prepared *via* a bromination, protection, metallation, and silylation sequence, which proceeded in an overall yield of 37%. The major detraction of this Garst route is the 3-furaldehyde starting material. This compound is expensive, photosensitive and unstable and as such commercial sources are often of variable quality. These factors reduce the attractiveness of the Garst route.

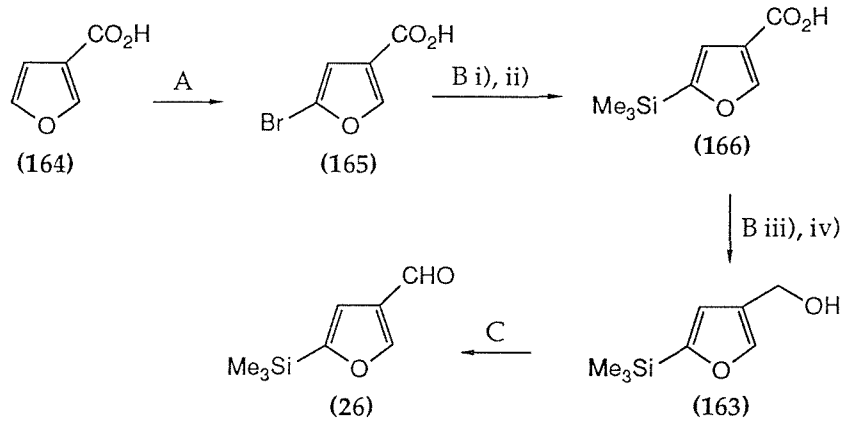
The method employed by Katsumura for the synthesis of (**26**) (*cf.* Scheme 2.1), was based on a procedure developed by Goldsmith and co-workers.[160] Treat-

ment of 3-furanmethanol with butyllithium, regioselectively deprotonated the alcohol and the 2-position of the furan ring. The metallated furan was then reacted with diphenyldisulphide, to form the intermediate species (**25**). Neither Goldsmith, nor Katsumura made any mention of the formation of the isomeric, 5-phenylthio-3-furanmethanol species (**162**) in the latter reaction. On the other hand, Tanis and Head reported that the metallation/PhSSPh process gave rise to a mixture of the two isomeric disubstituted-furan products (ratio of **25 : 162** = 4 : 1), which had to be separated by HPLC.[161] After the separation, a second dilithiation of (**25**), followed by silylation and desulphurisation, gave the intermediate 2-trimethylsilyl-4-furanmethanol (**163**), which was oxidised with barium permanganate to the aldehyde (**26**). As with the Garst procedure, the Goldsmith/Katsumura method had the major disadvantge of using an expensive starting material, 3-furanmethanol. In addition, the need for a difficult separation step led to us avoid the use of this particular method for our preparation of (**26**).

The first of the methods which we eventually chose for our own synthesis of (**26**), (*cf.* Scheme 6.1) was based on the use of the familiar starting material, 2-trimethysilyl-4-bromofuran (**32**). Treatment of (**32**) with ^{s}BuLi, to form the corresponding 4-furanyl anion, was followed by the addition of N-methylformanilide;[129] allowing the direct preparation of the desired aldehyde (**26**) in a 78% yield. This route had a number of distinct advantages, not least of which was the fact that it employed relatively cheap reagents throughout. The reactions could also be carried out on a large scale. The one major disadvantage of our reaction sequence, was the fact that it was time consuming. The initial bromination of the methyl 2-furoate (**159**) took a total of 72 hours to complete, and this was followed by a further 24 hour reaction for the saponification to prepare (**160**). The high temperatures required for the decarboxylation of (**160**), along with the rather unpleasant quinoline solvent, were also disadvantages of the route; albeit minor ones.

We also carried out the synthesis of (**26**) by the rather shorter route summarised in Scheme 6.2, which was based on the reaction sequence reported by Tanis and Head.[161] The commercially available starting material, 3-furoic acid (**164**), was brominated by treatment with pyridinium bromide perbromide, using the method of Ferraz and do Ameral,[169] to produce 2-bromo-4-furoic acid (**165**). Treatment of (**165**) with two equivalents of butyllithium formed a dianion, which was quenched with chlorotrimethylsilane to give the intermediate silylated acid. The acid was immediately reduced with lithium aluminium hydride, to give 2-trimethylsilyl-4-furanmethanol (**163**), which was then oxidised to the aldehyde (**26**) *via* the Swern technique.[131] Our latter method for the preparation

of (26) does have the advantage of being much faster than the one based on the elaboration of (32), although it suffers from the fact that the starting material, 3-furoic acid, is expensive.



A 57% Py.HBr.Br_2 / HOAc, 40-45°C, 2 h;
B 33% i) 2.5 BuLi / Et_2O, -60°C, 40 min.;
ii) Me_3SiCl, -60°C to r. t., 2 h;
iii) $LiAlH_4$ / THF, 0°C to r. t., 2 h;
iv) HCl / H_2O;
C 79% Swern oxidation

Scheme 6.2: The second preparation of 2-TMS-4-furancarboxaldehyde.

In a very recent report, Garst and co-workers have revealed an extremely short method for the preparation of (26).[42] Unfortunately, the details disclosed about the experimental procedure are virtually non-existant. The method, which is shown in Fig. 6.2, appears to be a one pot process involving the treatment of 3-furaldehyde with a mixture of morpholine and butyllithium, followed sequentially by ^{s}BuLi and chlorotrimethylsilane. This novel synthesis of (26) appears to be the most attractive method available for the preparation of the aldehyde, although the scant nature of the information disclosed makes it impossible to give an absolute judgement. Garst does state that a full report on the novel synthesis of (26) is in press.[42] In the absence of full details for the Garst methodology, we would suggest that either of our routes, as discussed above, are reasonable alternatives.

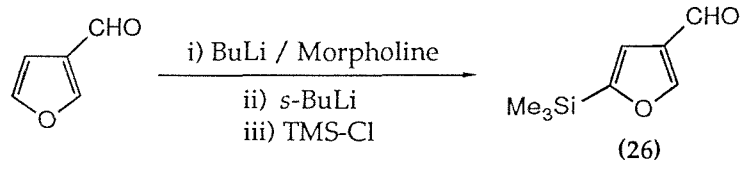


Figure 6.2: The novel Garst synthesis of (26).[42]

Chapter 7

The Formal Synthesis Of Manoalide

7.1. The Carbomagnesiation Of Acetylenes.

As we discussed in Chapter 2, one of the key structural features of manoalide which we needed to construct was the C6-C7 trisubstituted double bond. As we were unable to elaborate the products obtained *via* our novel copper (I)-catalysed reaction of metallated cyclic enol-ethers (*cf.* Chapters 3 and 4), we decided to employ a completely different method for the introduction of this crucial functionality; namely the carbometallation of an acetylene.
The addition of organometallics to carbon-carbon multiple bonds (*i.e.* the carbometallation reaction,[170] *cf.* Fig. 7.1), has been the focus of a huge amount of research over the past thirty years, with studies having been carried out based on a number of different metallic elements and a wide range of substrates. A comprehensive review of the carbometallation of alkenes and acetylenes is beyond the scope of this thesis, and the interested reader is directed to the reviews which are available in the literature.[171-173]

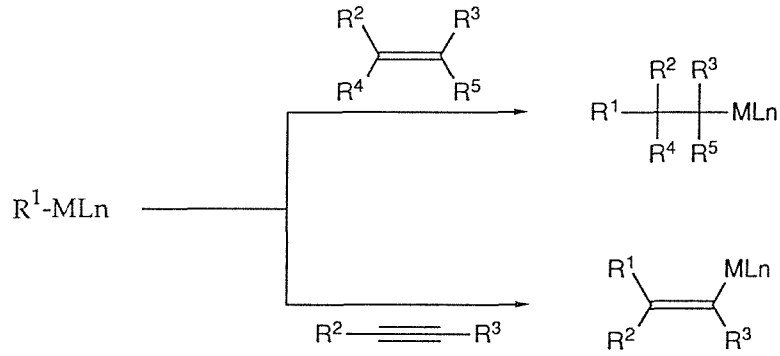
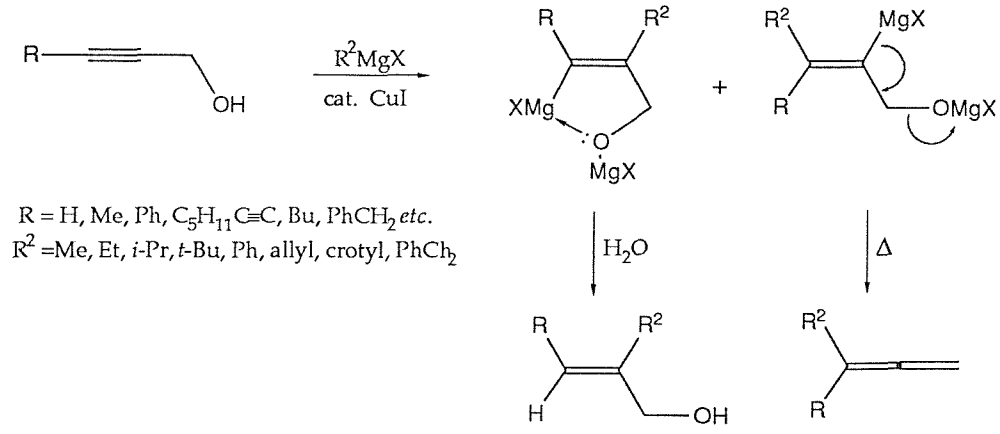


Figure 7.1: Carbometallation of alkenes and acetylenes

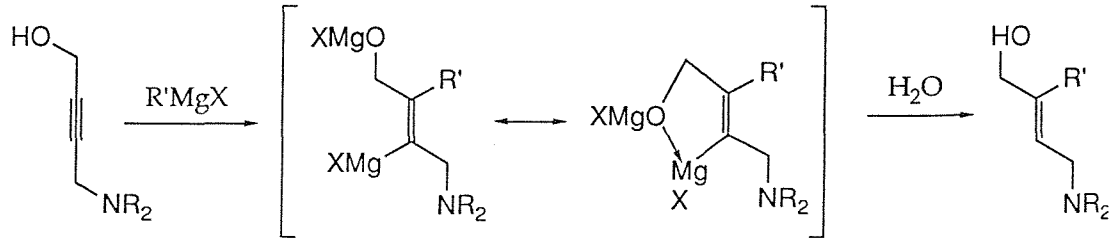
The carbomagnesiation of the π-systems of alkenes or acetylenes usually only takes place when the reactions are promoted by the presence of metal-coordinating functionalities in the unsaturated substrates, typically in the allylic or propargylic positions. Although the addition of highly reactive Grignard reagents to allylic[174] and propargylic[175] alcohols have been well documented, it was not until the development of a copper-catalysed process by Jousseaume and Duboudin, that carbomagnesiation could be achieved with a wide range of Grignard reagents (*cf.* Scheme 7.1).[176] The degrees of regio- and stereoselectivity observed in the acetylene carbometallation reactions are good; the additions normally proceed *anti* with respect to the Grignard reagent, and the nucleophilic alkyl group usually adds predominantly to one specific end of the acetylene; the exact centre of substitution being dictated by the nature of the promoting functionality. The reactions are not normally totally stereospecific, however,

and allenes are commonly obtained as a result of the thermal decomposition of the by-products resulting from the inverse addition of the Grignard reagents (*cf.* Scheme 7.1).[176]



Scheme 7.1: The Jousseaume and Duboudin carbomagnesiation of propargylic alcohols.[176]

The efficiency of the carbomagnesiation of acetylenes is improved when the reaction is carried out on substrates which bear two different groups capable of promoting the carbometallation process. The reactions of Grignard reagents with 1,4-dialkylamino-2-butynes,[177] 1-dialkylamino-4-alkylthio-2-butynes,[178] 1-dialkylamino-4-alkoxy-2-butynes,[179] and 2-butyne-1,4-diols[180] have been reported. The latter reaction in particular is normally highly stereoselective, giving good yields of 2-alkyl-2-buten-1,4-diol products. The carbometallation of 2-butyne-1,4-diol itself was employed within our group, in the preparation of a key intermediate required for the total synthesis of the natural product zoapatanol.[181]



Scheme 7.2: The Mornet and Gouin carbomagnesiation of 4-dialkylamino-2-butyn-1-ols.[182]

The carbometallation process which most caught our interest, with respect to the preparation of the C6-C7 double bond of manoalide, was the process developed by Mornet and Gouin, which involves the carbomagnesiation of 4-dialkylamino-2-butyne-1-ol substrates (*cf.* Scheme 7.2 above).[182] The reactions are very easy to carry out practically, and are essentially regio- and stereospecific; allowing the facile preparation of 4-dialkylamino-2-alkyl-2-buten-1-ol products, in which the elements of the Grignard reagents have been added to the C-C triple bond of the acetylene in a *trans* fashion as shown in Scheme 7.2. The very high degree of regioselectivity observed in the Mornet and Gouin reactions is achieved as a result of the additive effects of the two different propargylic heteroatom substituents (*cf.* Fig. 7.2). Propargylic alcohols direct the addition of the carbanions of Grignard reagents to the acetylene carbon closest to the alcohol, whereas propargylic dialkylamines direct the addition of the alkyl anions to the acetylene carbon atom furthest away from the nitrogen.[182] The summation of both of these effects in the difunctionalised acetylenes gives rise to the highly stereo- and regio-selective additions observed.

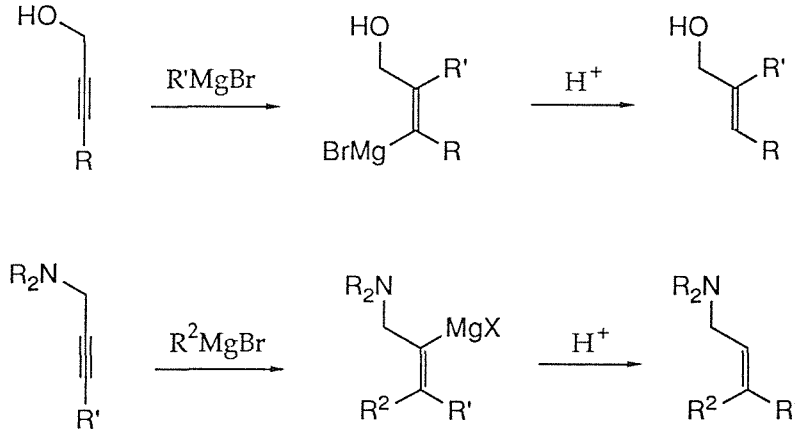


Figure 7.2: The complimentary directing properties of propargylic alcohols and dialkylamines in carbomagesiation reactions.[182]

Considering the virtues of the Mornet and Gouin carbometallation process, it is somewhat astonishing that there have been only two cases where the reaction has been applied to target syntheses; one example was seen in Mornet and Gouin's preparation of *trans*-zeatine,[183] and the other was exhibited in the preparation of the tetrasubstituted alkene precursors which were employed in the construction of 4-alkylidenecyclohexanones.[184]

7.2. The Development Of A New Synthetic Strategy For Manoalide.

Our new retrosynthetic strategy for the total synthesis of manoalide is summarised in Fig. 7.3. The first disconnection was made at the C5, allylic position, generating the two fragments, (E) and (F). We intended to prepare the fragment (E), a formyl anion equivalent,[185] from the familiar 2-trimethylsilyl-4-furancarboxaldehyde (**26**). Specifically, we decided to use a 1,3-dithiane derivative of (**26**) as the formyl anion equivalent, as a number of mild methods for the preparation, elaboration and removal of these species have been reported.[186]
We envisaged the fragment (F) as being derived *via* the Mornet and Gouin carbometallation procedure. The relevant disconnection revealed the two key precursors, 4-di-*n*-butylamino-2-butyn-1-ol (**166**) and the homoallylic Grignard reagent (**167**). We intended to prepare (**167**) from the homoallylic bromide (**40**).

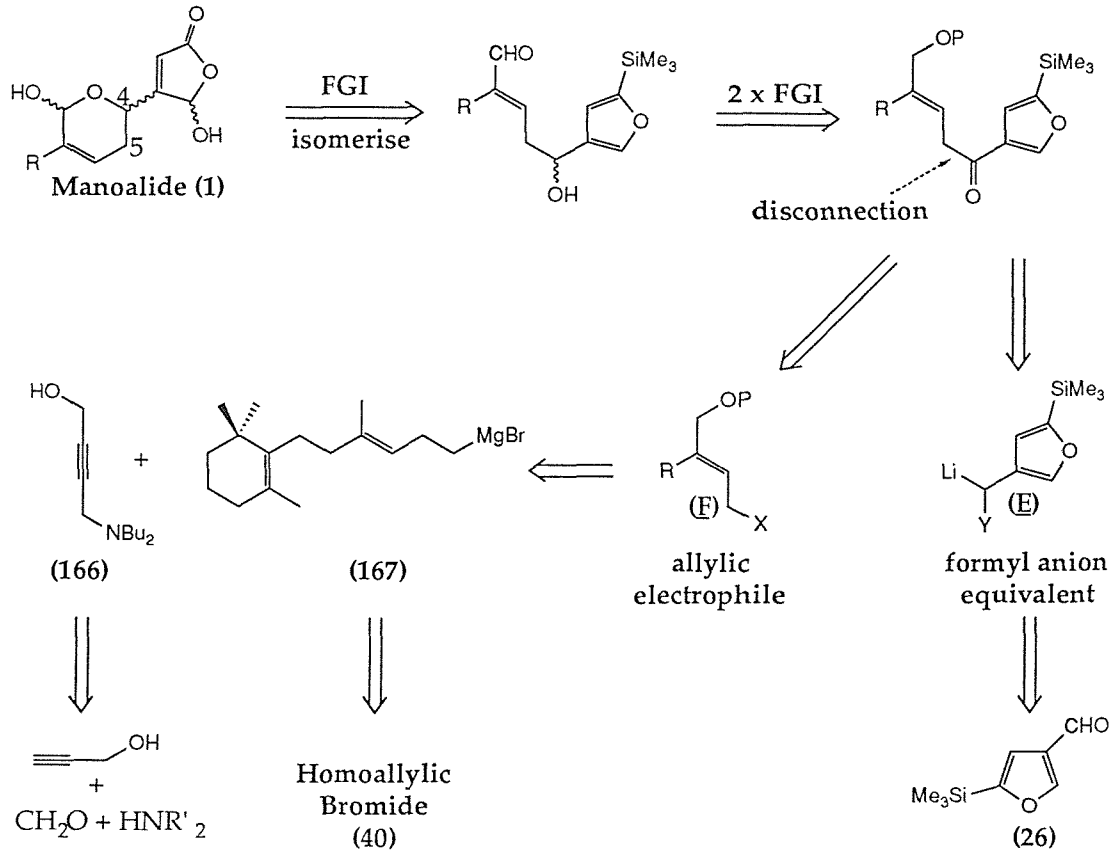


Figure 7.3: A Retrosynthetic analysis of manoalide based on the Mornet and Gouin carbomagnesiation of acetylenes.

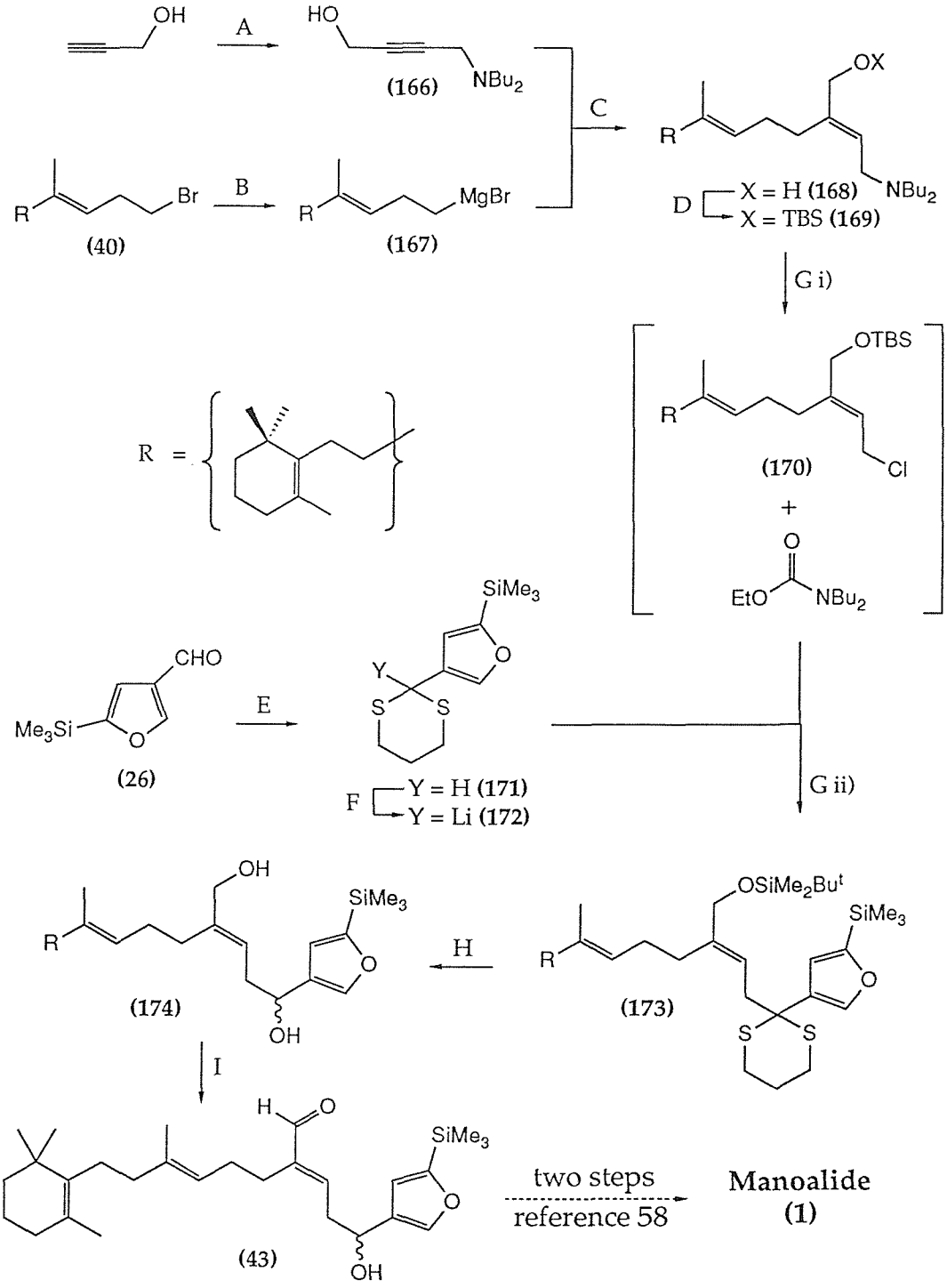
7.3. The Formal Synthesis Of Manoalide.

The actual synthetic route which we employed for the formal synthesis of Manoalide is summarised below in Scheme 7.3. The difunctionalised acetylene, 4-di-*n*-butylamino-2-butyn-1-ol (**166**) was readily prepared on a large scale from propargylic alcohol, using a method based on that reported by Salvador and Simon.[187] We have already discussed the preparation of the other key starting material, the homoallylic bromide (**40**) (*cf.* Section 3.3.2., Scheme 3.13).

With the starting materials in hand we set about the synthesis itself. The C-C triple bond of (**166**) was reacted with the Grignard reagent (**167**), using a variation of the experimental procedure described by Mornet and Gouin.[182] In their published procedure, the difunctionalised acetylene starting materials are reacted with only one Grignard reagent. As a full equivalent of the Grignard reagent is therefore destroyed in the initial deprotonation of the alcohol functionality, the procedure is inefficient for cases where the organomagnesium species is at all precious. As this was definitely true in our own case, we carried out the initial deprotonation using ethyl magnesium bromide as a sacrificial Grignard reagent. In all other respects, the carbometallation was carried out exactly as described in the literature. We were delighted to find that the use of the sacrificial Grignard reagent made no difference to the overall course of the carbometallation, with no interference being observed through side reactions between (**166**) and the EtMgBr.

The desired alkene product (**168**) was therefore obtained in an 85% chemical yield, with greater than 97% of the *E*-configuration; none of the *Z*-geometrical isomer was visible in the high-field ^{1}H and ^{13}C NMR spectra of the product. The alcohol group of (**168**) was protected as its TBS silyl ether (**169**), and the tertiary amine functionality of the resulting species transformed to an allylic chloride by means of a reaction with ethyl chloroformate.[188] This variation of the von Braun reaction resulted in the formation of an inseparable mixture of the allylic chloride (**170**) and ethyl di-*n*-butylcarbamate. In our case, that the addition of a source of chloride ions, Bu_4NCl, and the use of THF as the reaction solvent rather than benzene, gave improved yields of the desired product. The allylic chloride (**170**) proved to be quite unstable, and all attempts to purify the compound by either column chromatography or distillation resulted in its decomposition. As a consequence, the subsequent reaction between (**170**) and the formyl anion equivalent suffered from a competing reaction between the anion and the carbamate. This meant that a large excess of the anion had to be employed. As we stated above, the formyl anion equivalent which we used was the 1,3-dithiane derivative (**172**). This compound was readily prepared from the

aldehyde (**26**) *via* treatment with 1,3-propanedithiol in the presence of a catalytic quantity of $BF_3 \bullet Et_2O$. The 1,3-dithiane (**171**) was deprotonated with butyllithium, and the resulting anion (**172**) reacted with the impure allylic chloride (**170**), to give the alkylated dithiane species (**173**) in an overall 49% yield from (**169**).
The next step in the synthetic sequence, the removal of the dithiane to reveal an unprotected carbonyl functionality, proved to be extremely troublesome. A number of different reagent systems were tried, including treatment with methyl iodide,[189] $CuCl_2/CuO$[190] and $AgNO_3$/N-chlorosuccinimide.[191] The deprotection was finally achieved by treating the dithiane with $HgCl_2$ and $CaCO_3$,[191] resulting in the formation of a fully deprotected hydroxy-ketone intermediate. In order to avoid the migration of the double bond into conjugation with the ketone, a reduction was immediately carried out to yield the diol (**174**). The primary hydroxyl functionality of (**174**) was then selectively oxidised to an aldehyde by means of a TPAP oxidation.[137] In this manner the critical intermediate (**43**) was prepared.
The preparation of the compound (**43**) constitutes a formal synthesis of Manoalide, as the same species was the final intermediate in the Garst synthesis of the natural product. Unfortunately, the quantities of material which were available to us at this stage of our work were extremely small and the one attempt made to carry out the singlet-oxygen oxidation and photolytic rearrangement was unsuccessful; the compound decomposed during the photo-irradiation step. Simple lack of time prevented us from repeating the work and achieving the total synthesis.



A 90% Bu_2NH, CH_2O, $CuSO_4 \bullet 5H_2O$, pH 8/ H_2O, Δ, 18 h;
B 88% Mg turnings / THF, 50°C, 2 h;
C 85% i) **(166)** , EtMgBr / Et_2O, r. t.; ii) **(167)** / Et_2O, Δ, 8 h;
D 98% TBS-Cl, DMAP / DCM, r. t., 4 h;
E 84% 1,3-propanedithiol, *cat.* $BF_3 \bullet Et_2O$ / $CHCl_3$, -20°C to r.t., 7 h;
F 100% BuLi / THF, -40°C, 1 h;
G 49% i) Bu_4NCl, EtOCOCl / THF, r. t.; ii) **(170)** + **(172)** / THF, -80°C, 12 h;
H 25% i) 2.2 $HgCl_2$, 2.2 $CaCO_3$ / 80% CH_3CN (aq), Δ, 4 h;
ii) $NaBH_4$ / EtOH, 0°C to r.t., 2 h;
I 42% TPAP, mol. sieves, 4-Me-morpholine *N*-oxide / 10% CH_3CN in DCM, r. t., 3 h;

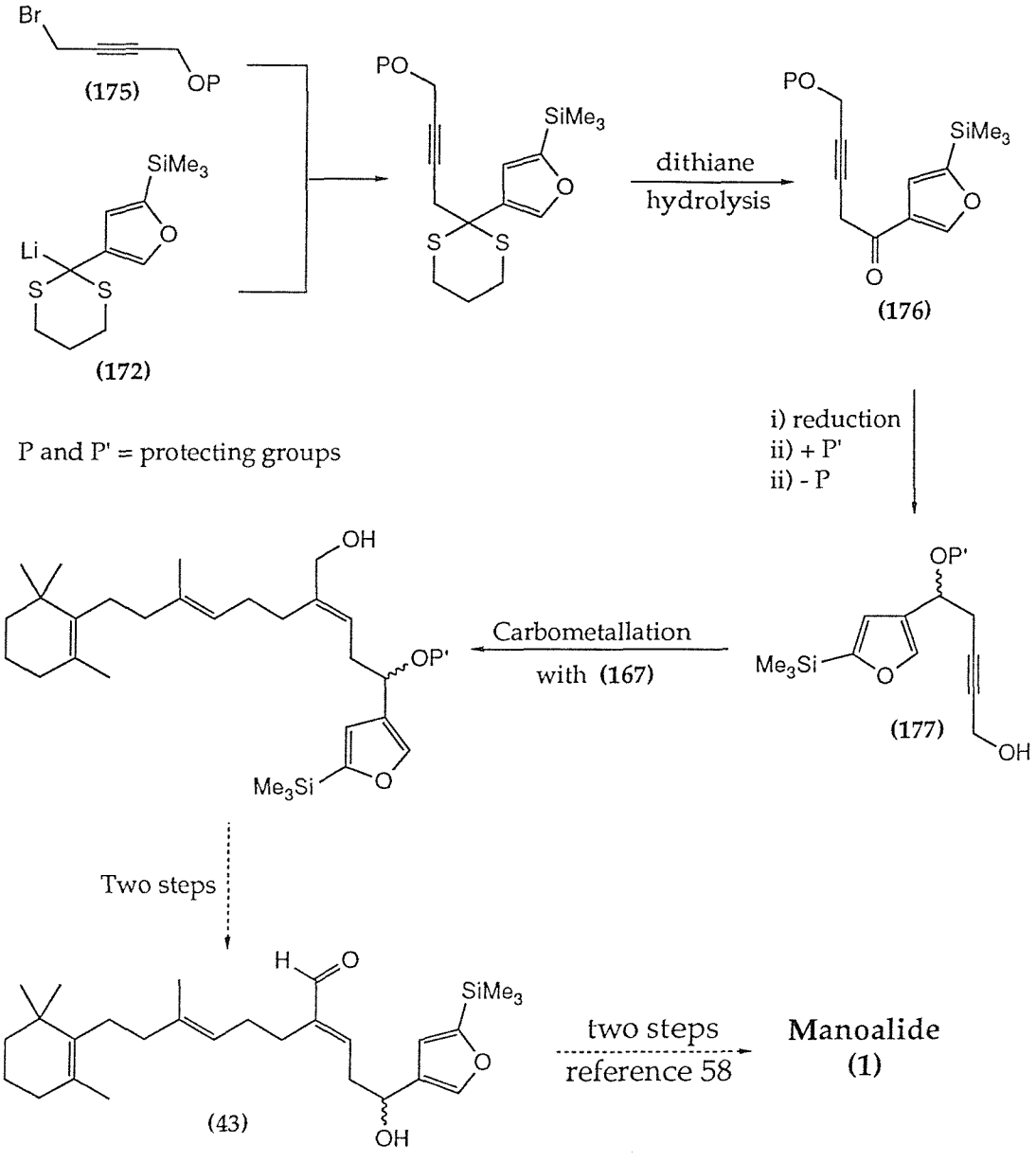
Scheme 7.3: The formal synthesis of manoalide

Chapter 8

Conclusions And Recommendations For Future Work.

8.1. Recommendations For Alternative Syntheses Of Manoalide.

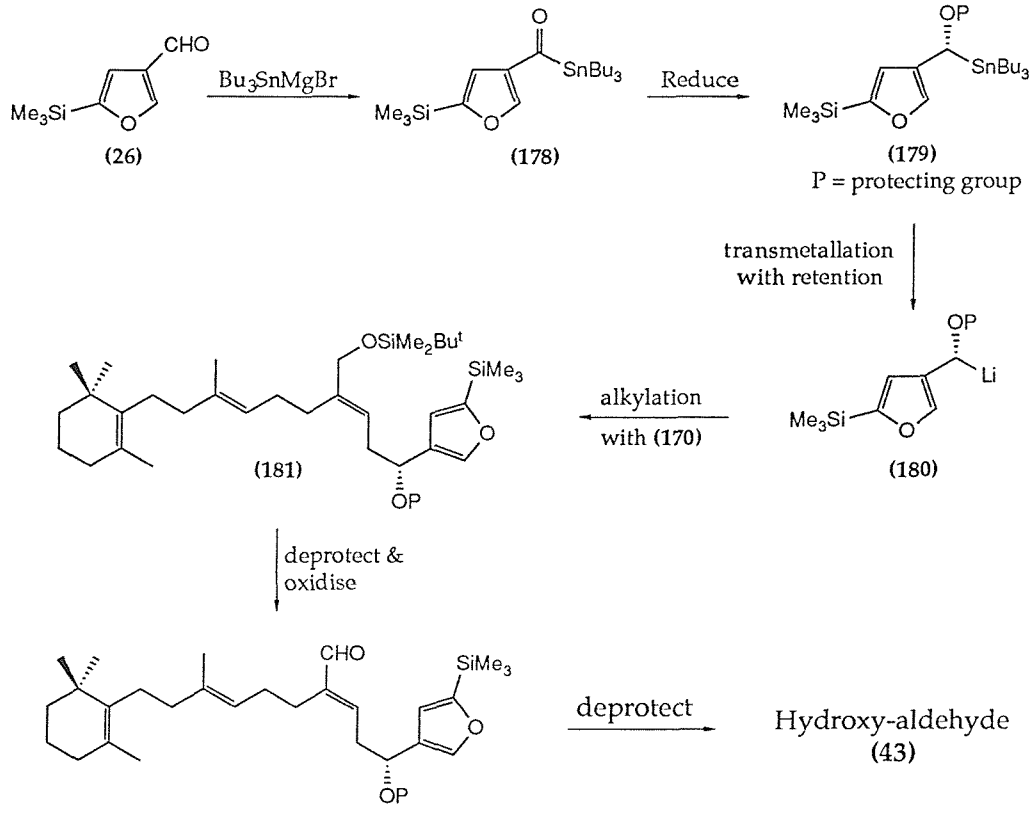
The formal synthesis of manoalide described in Section 7.3, possesses all of the major features which we identified in Chapter 2 as being essential to an efficient synthesis of the natural product. The principal feature of our route is that both of the key trisubstituted double bonds present in the natural product were constructed in good yield, and in a highly stereoselective (in fact essentially stereospecific) manner. The trimethylcyclohexenyl group and an immediate synthetic precursor to the 5-hydroxy-2(5H)-furanone moiety of the natural product were also introduced.



Scheme 8.1: A proposed alternative route for the synthesis of manoalide.

The reaction step which detracted most from the overall efficiency of our formal synthesis of (**1**) was the removal of the 1,3-dithiane moiety from the intermediate (**173**). In any future work on the synthesis of manoalide this step would clearly be one of the key areas where an improvement could be made.

One alternative synthetic route which would involve the removal of the 1,3-dithiane species at an early stage of the synthesis, and hence reduce the loss of precious advanced intermediates, is outlined above in Scheme 8.1. The key step of this proposed route would be the carbometallation of the mono-protected diol (**177**), using the methodology reported by Duboudin and Jousseaume.[176b] We envisage (**177**) as being ultimately derived from 2-butyne-1,4-diol *via* the protected bromo-alcohol (**175**), which may be prepared *via* a relatively trivial synthetic sequence. The alkylation of the 1,3-dithiane anion (**172**) with (**175**), followed by the hydrolysis of the 1,3-dithiane group, would generate the ketone (**176**). Reduction and protection of the nascent hydroxyl functionality, followed by a selective deprotection, would give (**177**). Carbometallation of (**177**) with the familiar Grignard reagent (**167**) would generate a mono-protected diol, which could then be transformed to the key intermediate (**43**) *via* oxidation and deprotection steps. Once again the intermediate (**43**) would be taken through to manoalide by the method reported by Garst *et al.*[136]



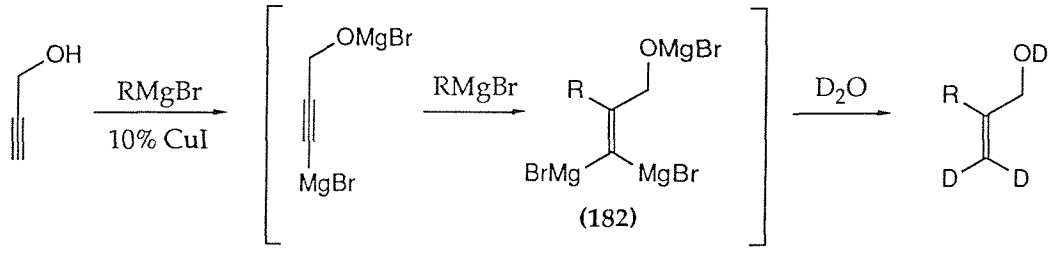
Scheme 8.2: A second alternative synthetic proposal for the synthesis of manoalide.

A second alternative approach to manoalide is summarised above in Scheme 8.2. Undoubtedly the most effective way to avoid the problems encountered with the hydrolysis of the 1,3-dithiane in (**173**), would be to avoid its use altogether. Our second proposed synthesis embraces this particular principle; the only major diversion from our own completed formal synthesis being found in the alkylation step used to introduce the TMS-substituted furan. In our proposal, the allylic chloride (**170**) would be reacted with an α-alkoxy organolithium reagent (**180**), which we envisage as being generated from an acylstannane, (**178**).

Acylstannanes, which are well documented in the literature[192] are readily prepared from aldehyde precursors *via* a reaction with trialkyltin magnesium halides.[192] The carbonyl functionalities of acyltins may be reduced with metal hydrides, furnishing α-hydroxystannane products. The key feature of these reduction reactions is that chiral reducing agents may be employed, allowing the preparation of highly enantioenriched α-hydroxy-stannanes.[193] Protection of the nascent alcohol functionalities, followed by the transmetallation of the tin group with retention of configuration by treatment with butyllithium, allows the preparation of configurationally stable α-alkoxy organolithium reagents in high enantiomeric excess.[193] We suggest therefore (*cf.* Scheme 8.2), that the aldehyde (**26**) might be reacted with $Bu_3SnMgBr$ to generate the acyltin (**178**). This might then be enantioselectively reduced and protected, to generate the α-alkoxystannane (**179**). This, in turn, may be transmetallated with retention of configuration, generating the organolithium reagent (**180**), which would be reacted with the allylic chloride (**170**), to produce the fully protected diol (**181**). Selective deprotection and oxidation of the primary allylic alcohol, followed by deprotection of the secondary alcohol, would generate the familiar species (**43**). The paramount feature of this second proposed route to (**1**), is that it has the potential to prepare the C4 stereogenic centre of manoalide in an enantioselective manner. No such asymmetric synthesis of (**1**) has ever been reported.

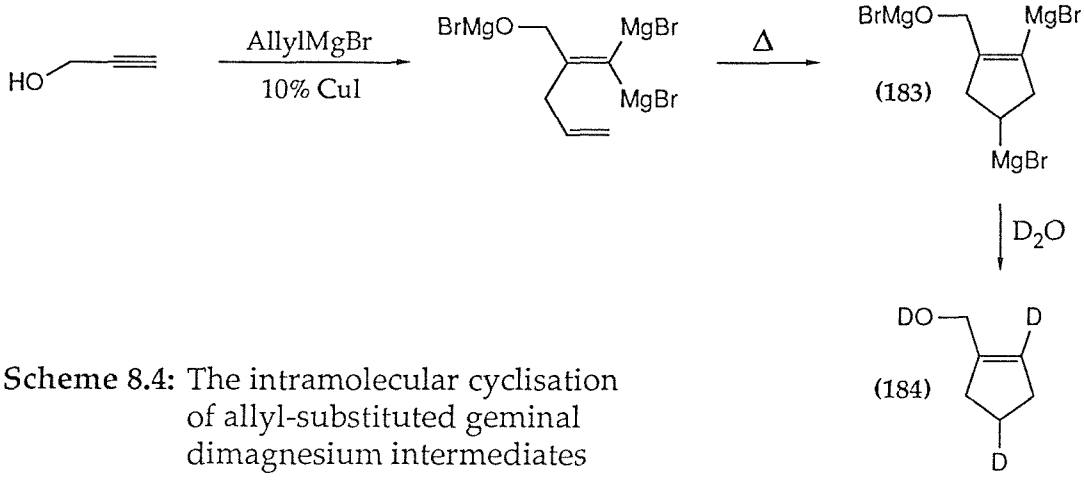
8.1.1. Future Possibilities For The Carbometallation Reaction.

In addition to making improvements to our synthetic route to manoalide as discussed above, other potential avenues for future work also exist in the investigation of the products of the acetylene carbometallation process.



Scheme 8.3

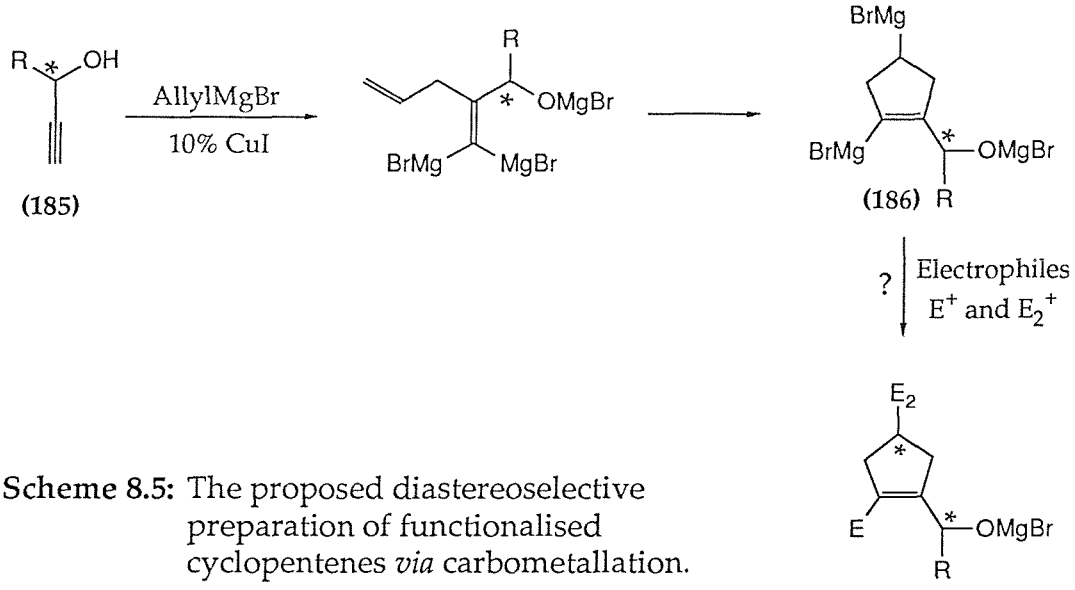
In 1979, Duboudin and Jousseaume reported that the copper (I)-catalysed addition of Grignard reagents to propargylic alcohol, resulted in the formation of geminal dimagnesium intermediates such as (**182**), which were reacted with electrophiles to form alkenes as shown in Scheme 8.3. In the case where allylmagnesium bromide was employed as the Grignard reagent, however, the geminal dimagnesium intermediate underwent an unusual intramolecular cyclisation reaction (*cf.* Scheme 8.4), to generate a metallated cyclopentene (**183**), which was subsequently quenched with deuterium oxide to produce (**184**).[194] Improved reaction conditions for the cyclisation process have since been developed within our group at Southampton.[195]



Scheme 8.4: The intramolecular cyclisation of allyl-substituted geminal dimagnesium intermediates

An interesting field of future study would involve carrying out the carbomagnesiation reaction on a substituted propargylic alcohol, (**185**) as shown in Scheme 8.5. The subsequent cyclisation process would generate a cyclopentene (**186**) containing two different stereogenic centres. Hopefully an examination of

the stereochemical outcome of the cyclisation reaction would reveal some degree of diastereoselectivity. Additionally, the intriguing possibility of achieving the chemoselective elaboration of the two different types of organomagnesium centre present within the putative intermediate (**186**), also warrants investigation. The carbomagnesiation and cyclisation of substituted propargylic alcohols therefore potentially allows the asymmetric synthesis of substituted cyclopentenes, which may find application to natural product synthesis.



Scheme 8.5: The proposed diastereoselective preparation of functionalised cyclopentenes *via* carbometallation.

8.2. Conclusions.

The majority of the work discussed within this thesis was centred upon the investigations which we carried out into the copper (I)-catalysed reaction of metallated cyclic enol-ethers. Our development of experimental procedures based upon readily prepared Grignard reagents, rather than their more elusive organolithium analogues, has provided a genuine extension to the reaction. Similarly, the study of the methods of elaborating the vinylmetallic intermediates will certainly prove useful in future applications of the reaction. Additionally, the problems encountered with the use of the homoallylic organolithium reagent (84) in the copper (I)-catalysed reaction, have highlighted a critical limitation of the reaction; underlining the important influence of the thermal stability of the higher-order lithio-cuprates believed to be intermediates in the process.

The copper (I)-catalysed reaction has a great deal of potential for extension into natural product synthesis. It allows the coupling of two nucleophilic organometallic species with a very high degree of stereocontrol. The reaction tolerates quite a narrow, but nevertheless synthetically useful, range of functionalities.

Additionally, our modification and refinement of the published methods for the preparation of 2,4-disubstituted furans, especially our development of a reliable route for the preparation of 2-lithio-4,5-dibromofuran, may have significant applications in the future use of the singlet-oxygen oxidation reactions discussed in Chapter 2.

The application of the heteroatom-promoted carbomagnesiation of 4-di-*n*-butylamino-2-butyne-1-ol, detailed in Chapter 7, is only the third example of the extension of the methodology into natural product synthesis. Our proposals for the future application of the carbometallations, as detailed above, serve to highlight the enormous potential of these processes. Their practical simplicity, combined with the fact that they allow the predictable, stereocontrolled, generation of alkene products containing potentially useful functionality, can only mean that they must find future applications in natural product synthesis.

Experimental

General Experimental.

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of dry oxygen-free nitrogen, or high purity argon where stated. Anhydrous solvents and reagents were prepared by distillation from the usual drying agent[196] prior to use: THF from sodium and benzophenone; pyridine, diisopropylamine, triethylamine, dihydrofuran, dimethyl sulphide and dichloromethane from calcium hydride. Diethyl ether ('ether'), benzene and toluene were stored over sodium wire. Commercial organometallic reagents were used as supplied by the Aldrich Chemical Company, and other commercial reagents were purified by standard methods.[196] Copper (I) bromide dimethylsulphide complex was purified by recrystallisation from anhydrous dimethylsulphide and pentane, and copper (I) cyanide was dried *in vacuo* at 100°C. All reactions were magnetically stirred unless otherwise stated.

Organic extracts were concentrated at aspirator pressure using a Büchi rotary evaporator. All reactions were monitored by TLC on Macherey-Nagel Duren Alugram Sil G/UV_{254} pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised with UV (254 nm), then I_2, followed by 2M H_2SO_4 in methanol and 0.2M vanillin in ethanol or by 5% w/w phosphomolybdic acid in ethanol. Flash column chromatography[197] was performed on May & Baker Colpak Sorbsil C60 (0.04-0.06 mm particle size) and run under low pressure. Light petroleum ether refers to distilled petroleum ether with a boiling point range of 40-60°C.

All IR spectra were recorded using a Perkin Elmer 1600 series FT-IR spectro-photometer, using a thin film supported on NaCl plates, or as solutions within sodium chloride cells where stated. Details are reported as ν_{max} in cm^{-1}, followed by a description using the following abbreviations: vs = very strong, s = strong, m = medium, w = weak or br = broad.

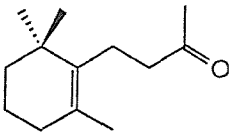
^1H NMR spectra were recorded in Fourier Transform mode on Jeol FX-90 (90 MHz), Jeol GX-270 (270 MHz), Bruker AM 360 (360 MHz) or Varian VXR 500 (500MHz) spectrometers. All spectra were obtained in $CDCl_3$ or CD_3OD solution in 5 mm diameter tubes, and the chemical shift values are reported as values on the δ scale, in p.p.m., relative to the residual signals of chloroform (δ = 7.27) or methanol (3.50) as the internal standard. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad. Coupling constants (J) are reported in parentheses in Hz.

^{13}C NMR spectra were recorded on Jeol FX-90 (22.5 MHz), Jeol GX-270 (67.9 MHz), or Bruker AM 360 (90 MHz) spectrometers in either $CDCl_3$ or

CD_3OD solution in 5 mm diameter tubes, and the chemical shift values are reported as values on the δ scale, in p.p.m., relative to the signals of deuterochloroform (δ = 77.2) or deuteromethanol (δ = 49.3) as the internal standards. The multiplicities, recorded in parentheses, refer to the signals in the off-resonance spectra and were elucidated using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are described using the following abbreviations: 0 = singlet (due to quarternary carbon), 1 = doublet (methyne), 2 = triplet (methylene), 3 = quartet (methyl).

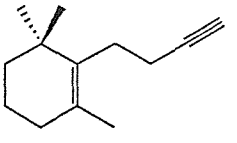
Low and high resolution mass spectra were run on a VG 70-250-SE spectrometer. Ion mass/charge (m/z) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%) and, where assigned, by the proposed identity of the peak. Signal patterns generated by compounds containing bromine or tin atoms, which have more than one isotope of significant natural abundance, are quoted as the signals derived from the ^{79}Br and ^{120}Sn isotopes.

4-(2',6',6'-Trimethyl-1'-cyclohexen-1'-yl)-2-butanone (38).



A mixture of β-ionone (**37**) (48.0 g, 0.25 mol), Adogen®464 (39.0 g, 87.5 mmol) and $NaHCO_3$ (105.0 g, 1.25 mol) in a two-phase solvent system of toluene and water (1:2, 1500 ml) was vigorously stirred under nitrogen. Sodium dithionite (49.0 g, 0.28 mol) was then added in one portion, and the mixture heated to gentle reflux for 30 min, after which time it was cooled and a further portion of $Na_2S_2O_4$ (49.0 g, 0.28 mol) added. The mixture was then heated under reflux for 3 h with vigorous stirring, cooled to r. t. and the organic and aqueous phases separated. The aqueous phase was extracted with ether (3 x 300 ml) and the combined organic phases washed with water (400 ml), dried ($MgSO_4$), and the concentrated *in vacuo*. Unreacted β-ionone (**37**) (*ca.* 5-10%) was removed from the residual pale yellow oil by flash column chromatography (SiO_2, 5% ether in light petroleum eluant) to give, after distillation, the *title compound* (29.4 g, 150 mmol, 60%) as a colourless oil: b.p. 47-49°C/0.01 mm Hg. Lit.[107] 60-64°C/0.2 mmHg; **^{1}H NMR** ($CDCl_3$, 360 MHz) δ = 2.47 (2H, m, J 8), 2.21 (2H, t, J 8), 2.11 (3H, s), 1.86 (2H, t with fine splitting, J 6), 1.53 (3H, s), 1.52 (2H, m), 1.38 (2H, m), 0.90 (6H, s); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ = 208.9 (0, C=O), 136.0 (0), 127.8 (0), 44.6 (2), 39.8 (2), 35.1 (0), 32.8 (2), 29.8 (3), 28.5 (2C, 3), 22.3 (2), 19.7 (3), 19.5 (2); **IR (film)**: 3412w, 2958s, 2928s, 2866s, 2830m, 1717s, 1676w, 1474m, 1458m, 1434m, 1411m, 1360s, 1305w, 1280w, 1261m, 1230w, 1204w, 1161s cm^{-1}; **LRMS** (70 eV EI) m/z: 194 (M^+, 14%), 179 (M^+-Me, 23), 176 (29), 161 (40), 136 (45),121 (100), 43 (55).

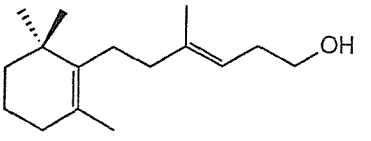
4-(2',6',6'-Trimethyl-1'-cyclohexen-1'-yl)-1-butyne (77).



A solution of lithium diisopropylamide (LDA) was prepared by the dropwise addition of butyllithium (2.5M in hexanes, 17.6 ml, 44 mmol) to a solution of N,N-diisopropylamine (4.45 g, 44 mmol) in dry THF (60 ml), under nitrogen, at -30°C. The resulting solution was stirred at this temperature for 30 min and then cooled to -80°C. A solution of 4-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-butanone (**38**) (7.76 g, 40 mmol) in dry THF (5 ml) was added dropwise, and the mixture stirred at -80°C for 1 h. Diethylchlorophosphate (7.64 g, 44 mmol) was then added to the reaction mixture and the solution allowed to warm slowly to r. t. The resulting crude enol phosphate was then added to a solution of LDA [prepared from N,N-diisopropylamine (9.10 g, 90 mmol) and butyllithium (2.5M in hexanes, 36.0 ml, 90 mmol) as above] in THF (60 ml) at -80°C, and the dark orange solution so formed was then allowed to warm to r. t. The reaction was quenched by the addition of water (60 ml) and the organic products extracted with light petroleum (4 x 200 ml). The extracts were combined, washed with 20% citric acid (100 ml), saturated aqueous $NaHCO_3$ (100 ml), and dried ($MgSO_4$). Af-

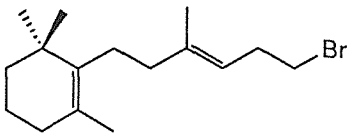
ter removal of the solvent *in vacuo,* the crude product was purified by flash column chromatography (SiO_2, light petroleum eluant), followed by kugelrohr distillation to give the *title compound* (4.82 g, 27.3 mmol, 70%) as a colouress mobile oil: b. p. 70°C (bath)/0.1 mm Hg. Lit.[107] 69-71°C/1.8 mmHg; **^{1}H NMR** ($CDCl_3$, 360 MHz) δ = 2.29 (2H, m), 2.21 (2H, m), 1.98 (1H, t, J 2.6 Hz), 1.90 (2H, bt, J 6 Hz), 1.61 (3H, s), 1.55 (2H, m), 1.41 (2H, m), 0.99 (6H, s). **^{13}C NMR** ($CDCl_3$, 90 MHz) δ = 136.1 (0), 128.7 (0), 85.1 (0), 68.1 (alkyne, 1), 39.8 (2), 34.8 (2), 32.8 (2), 28.6 (2C, 3), 28.4 (2), 20.0 (3), 19.6 (2), 19.4 (2). **IR** (film): 3310 s, 2120w, 625s cm^{-1}. **LRMS** (70 eV EI) m/z: 176 (M^+, 25%), 161 (40), 137 (100), 123 (35), 119 (57), 105 (43), 95 (77), 91 (35), 81 (50), 69 (43), 67 (33), 55 (30), 39 (25), 27 (15).

4-Methyl-6-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-hex-3-en-1-ol (39).



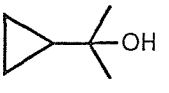
To a stirred slurry of zirconocene dichloride (1.46 g, 5 mmol) in dry CH_2Cl_2 (20 ml) at 0°C under argon, was added dropwise trimethylaluminium (3.5M in hexanes, 2.86 ml, 10.0 mmol). 4-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-1-butyne (**77**) (0.88 g, 5 mmol) in CH_2Cl_2 (5 ml) was added to the resulting lemon-coloured solution at r. t. After stirring for 3 h, volatile compounds were removed by evaporation at reduced pressure and the residue was extracted with dry pentane (4 x 20 ml). The combined extracts were transferred to a dry reaction vessel *via* cannula and butyllithium (2.5M in hexanes, 2.2 ml, 5.5 mmol) was added dropwise at -80°C under argon. The resultant white precipitate was dissolved by adding dry THF (5 ml). The reaction mixture was then warmed slowly to *ca* -30°C and oxirane (4M solution in ether, 2.5 ml, 10 mmol) added. The reaction was allowed to warm gradually to r. t. and stirring was continued for a total of 18 h, whereupon water (40 ml) was carefully added and the mixture acidified to pH 2 by adding 2M HCl. The products were then extracted into ether (4 x 50 ml) and the combined extracts washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was then purified by flash column chromatography (SiO_2, 10% light petroleum in CH_2Cl_2 eluant) to give the *title compound* (0.76 g, 3.21 mmol, 64%) as a colourless oil: **^{1}H NMR** ($CDCl_3$, 360 MHz) δ = 5.15 (1H, td, J 7, 1), 3.61 (2H, t, J 7), 2.29 (2H, q, J 7), 2.05 (4H, A_2B_2 system appearing as a single broad peak), 1.97 (1H, bs), 1.90 (2H, t, J 6), 1.68 (3H, d, J 1), 1.59 (3H, s), 1.55 (2H, m), 1.40 (2H, m), 0.98 (6H, s); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ = 139.7 (0), 137.1 (0), 127.1 (0), 119.3 (1), 62.5 (2), 40.4 (2), 40.0 (2), 35.1 (0), 32.9 (2), 31.6 (2), 28.7 (2C, 3), 28.0 (2), 19.9 (3), 19.6 (2), 16.3 (3); **IR** (film): 3331bs, 2928s, 2866s, 1666w, 1473m, 1457m, 1382m, 1360m, 1203w, 1154w, 1048s, 877w cm^{-1}. **LRMS** (70 eV EI) m/z: 236 (M^+, 20%), 221 (M-Me, 5), 137 (100), 121 (20), 107 (15), 95 (35), 81 (40).

1-Bromo-4-methyl-6-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-3-hexene (40).



To a solution of 4-methyl-6-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-hex-3-en-1-ol (**39**) (2.87 g, 12.15 mmol) and triethylamine (2.40 ml, 1.74 g, 17.2 mmol) in dry CH_2Cl_2 (40 ml) at -10°C, was added dropwise methanesuphonyl chloride (1.15 ml, 1.70 g, 14.9 mmol) at a rate sufficient to maintain the temperature between -10° and -5°C. After stirring for 30 min, the mixture was poured into saturated aqueous $NaHCO_3$ solution (100 ml), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (4 x 50 ml). The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude mesylate as a pale brown oil, which was immediately dissolved in acetone (150 ml) and LiBr (4.22 g, 48.6 mmol) added. The resulting mixture was gently refluxed for 2.5 h, whereupon the bulk of the acetone was removed by rotary evaporation and the residue taken up in water (100 ml). The product was then extracted into light petroleum (4 x 100 ml) and the combined extracts washed with 2M HCl (100 ml), $NaHCO_3$ (100 ml) and brine (2 x 100 ml). After drying ($MgSO_4$), the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2, light petroleum eluant) to give the *title compound* (3.26 g, 10.9 mmol, 90%) as a colouress mobile oil: **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.16 (1H, td, J 7, 1), 3.36 (2H, t, J 7), 2.58 (2H, q, J 7), 2.06 (4H, A_2B_2 system appearing as a single broad peak), 1.92 (2H, t, J 6), 1.68 (3H, d, J 1), 1.61 (3H, s), 1.58 (2H, m), 1.42 (2H, m), 1.00 (6H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 139.8 (0), 137.1 (0), 127.3 (0), 120.3 (1), 40.4 (2), 40.0 (2), 35.1 (0), 33.0 (2), 32.9 (2), 31.9 (2), 28.8 (2C, 3), 27.9 (2), 20.0 (3), 19.7 (2), 16.5 (3); **IR** (film): 3100-2800s, 1670m, 1385s, 1360s, 1270s, 1205s, 640s cm^{-1}; **LRMS** (70 eV EI): m/z = 298 (M^+, 7%), 283 (M-Me, 2), 219 (2), 137 (100), 95 (50), 81 (20), 67 (12), 55 (20), 41 (20), 28 (33); **HRMS** (CI, NH_3): Found: M+H 299.1374. $C_{16}H_{28}Br$. requires 299.1374.

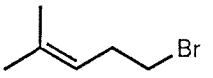
2-Cyclopropyl-2-propanol (81).



The *title compound* was prepared by the method of Julia *et al.*[115] A solution of iodomethane (126.6 g, 0.89 mol) in dry ether (200 ml) was added dropwise, under nitrogen, to vigorously stirred magnesium turnings (28.2 g, 1.16 mol) in dry ether (100 ml); the rate of addition being varied so as to maintain a gentle reflux. The reaction mixture was stirred at r. t. for 1 h, then the resulting Grignard solution was transferred to a dry reaction flask *via* cannula. Cyclopropylmethylketone (**80**) (33.9 g, 0.40 mol) was then added dropwise to the Grignard solution; the rate of addition being varied so as to maintain a gentle reflux. The reaction mixture was stirred for 1 h, then poured into a vigorously stirred mixture of crushed ice and saturated aqueous NH_4Cl (300 ml). The products

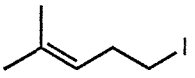
were extracted with ether (4 x 300 ml) and the organic extracts combined, washed with saturated aqueous $NaHCO_3$ (300 ml), brine (300 ml), and dried ($MgSO_4$).The ether was then removed by fractional distillation and the product distilled to give the *title compound* (25.8 g, 0.26 mol, 65%) as a colourless oil; b. p. 120-121°C at ambient pressure. Lit.[115] 121-122°C/760 mmHg; **^{1}H NMR** ($CDCl_3$, 360 MHz) δ = 1.98 (1H, s), 1.05 (6H, s), 0.81 (1H, m), 0.22 (4H, m); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ = 69.4 (0), 28.4 (3), 22.2 (1), 0.8 (2); **IR** (film): 3400bs, 1470m, 1380s, 1370s, 1160s, 1050m, 1020s, 960s, 920s, 850s cm^{-1}; **LRMS** (70 eV EI) m/z: 100 (M^+, 1%), 85 (M^+-Me, 55), 83 (5), 72 (35), 67 (15), 59 (30), 57 (23), 43 (100).

1-Bromo-4-methyl-3-pentene (82).



The *title compound* was prepared by the method of Julia *et al.*[115] An aqueous solution of HBr (47%, 34.9 ml, 300 mmol) was added dropwise to stirred 2-cyclopropyl-2-propanol (**81**) (15.0 g, 150 mmol) at 0°C. The resulting two-phase mixture was extracted into ether (4 x 40 ml) and the extracts combined, washed with $NaHCO_3$ (40 ml), brine (40 ml), and dried ($MgSO_4$). The ether was then removed by fractional distillation and the product short path distilled, the *title compound* (23.15 g, 0.142 mol, 95%) being collected as a colourless oil; b. p. 147-149°C at ambient pressure. Lit.[199] 152-154°C/mmHg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.14 (1H, tm, J 7 and 1), 3.35 (2H, t, J 7), 2.57 (2H, apparent q, J 7), 1.72 (3H, d, J 1), 1.64 (3H, apparent s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 135.1 (0), 121.0 (1), 33.0 (3), 31.9 (3), 25.8 (2), 18.0 (2); **IR** (film): 2980s, 2920s, 1675w, 1270s, 640s cm^{-1}, **LRMS** (70 eV EI) m/z: 162 (M^+, 25%), 83 (M^+-Br, 100), 69 (77), 55 (70), 41 (45), 27 (25).

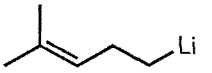
1-Iodo-4-methyl-3-pentene (83).



A mixture of 1-bromo-4-methyl-3-pentene (**82**) (8.15 g, 50 mmol) and sodium iodide (37.5 g, 250 mmol) in dry acetone (200 ml) was heated under gentle reflux for 2 h, the reaction mixture being kept in the dark. The acetone was then removed by rotary evaporation to give a pale yellow residue, which was partitioned between water (100 ml) and light petroleum (100 ml) and the organic layer separated. The aqueous layer was then extracted with light petroleum (3 x 50 ml) and the organic extracts combined, washed with 0.1M aqueous sodium sulphite solution (50 ml), brine (50 ml) and dried ($MgSO_4$). The solvent was removed by rotary evaporation to give a mobile oil which was kugelrohr distilled to give the *title compound* (6.5 g, 31.2 mmol, 62%) as a colourless oil; b. p. (bath) 85°C/0.4-0.5 mm Hg. Lit.[200] 65-66°C/7 mmHg; **^{1}H NMR** ($CDCl_3$, 90 MHz) δ = 5.11 (1H, tm, J 7.4 and 1.4), 3.12 (2H, t, J 7.4), 2.60 (2H, apparent q, J 7.4), 1.71 (3H, d, J 1.4), 1.63 (3H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 134.7 (0), 123.3 (1), 32.7

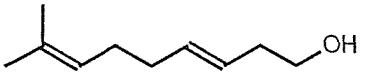
(2), 25.9 (3), 18.1 (3), 6.2 (2), **IR** (film): 2980s, 2935s, 2930s, 1670w, 1450s, 1380s, 1250s, 1170s cm^{-1}; **LRMS** (70 eV EI) m/z: 210 (M^+, 5%), 83 (M^+-I, 100), 67 (13), 41 (65), 39 (25), 28 (27).

4-Methyl-3-pentenyllithium (84).



The *title compound* was prepared by a method based on that reported by Bailey.[119] *t*-Butyllithium (1.7M solution in pentane, 2.50 ml, 4.25 mmol) was added dropwise, under argon, to a solution of 1-iodo-4-methyl-3-pentene (**83**) (0.52 g, 2.48 mmol) in pentane/ether (2.0 ml, 3:2 respectively), at -80°C. After stirring for 5 min, dry THF (0.5 ml) was added, the mixture warmed to 0°C and stirred for 2 h to ensure the complete destruction of any excess *t*-BuLi.[198] The resulting slightly cloudy, pale yellow, solution was then titrated against 1,3-diphenylacetone-*p*-toluenesulphonyl-hydrazone[120] in THF at 0°C, showing the molarity of the organolithium to be 0.48M. Thus the calculated yield of the lithiated product was 95%

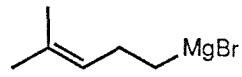
(3*E*)-8-Methyl-3,7-nonadien-1-ol (85).



t-Butyllithium (1.7M solution in pentane, 3.40 ml, 5.78 mmol) was added, under argon, to a stirred solution of 2,3-dihydrofuran (**60**) (0.40 ml, 0.37 g, 5.29 mmol) in THF (1 ml) at -50°C. The resulting yellow solution of 5-lithio-2,3-dihydrofuran (**63**) was warmed to 0°C and stirred for 30 min to destroy excess *t*-BuLi. In the meantime a solution of 4-methyl-3-pentenyllithium (**84**) (0.35M solution in ether and pentane, 15.0 ml, 5.25 mmol) was added, under argon, to a stirred suspension of copper (I) bromide dimethylsulphide complex (0.50 g, 2.43 mmol) in dry ether (2 ml) at -80°C. The resulting orange cuprate mixture was then warmed to 0°C, turning a very dark brown colour as the temperature rose above -25°C. The solution of (**63**) was then added to the cuprate and the resulting mixture stirred for a period of 2 h whilst warming to r. t. The mixture was then poured into a solution of saturated aqueous NH_4Cl and conc. NH_4OH (9:1, 30 ml) and the products extracted into ether (4 x 30 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash column chromatography (SiO_2, 10% EtOAc in light petroleum eluant) and the *title compound* (0.26 g, 1.69 mmol, 32%) isolated as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.52 (1H, dm, J 15), 5.35 (1H, dt, J 15 and 6.8), 5.07 (1H, m), 3.58 (2H, t, J 6.4), 2.22 (2H, apparent q, J 6.5), 2.16 (1H, bs, OH), 2.02 (4H, A_2B_2 system appearing as one broad peak), 1.66 (3H, d, J 1.3), 1.57 (3H, d, J 1.3); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 133.8 (1), 131.9 (0), 126.1 (1), 124.0 (1), 62.0 (2), 36.0 (2), 32.9 (2), 28.1 (2), 25.8 (3), 17.8 (3); **IR** (film): 3346bs, 2965s, 2918s, 1672w, 1439m, 1376m, 1188w, 1047s, 968s, 830m cm^{-1}; **LRMS** (70 eV EI) m/z: 154 (M^+, 1%), 139 (M-Me, 1), 136

(M-H2O, 2), 121 (1), 110 (11), 93 (5), 69 (100), 67 (13), 55 (16), 53 (13), 41 (60), 39 (22), 32 (12), 27 (13).

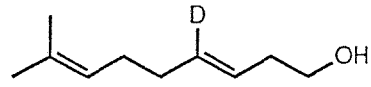
4-Methyl-3-pentenylmagnesium bromide (87).



A small crystal of iodine and three drops of iodomethane were added to a stirred mixture of flame-dried magnesium turnings (3.92 g, 0.16 mol) in dry THF (40 ml) and the mixture stirred for 10 min until the brown iodine colour had disappeared. The mixture was then warmed to 50°C and approximately 10 ml of a solution of 1-bromo-4-methyl-3-pentene (**82**) (13.04 g, 0.8 mol) in dry THF (120 ml) added rapidly. The remaining bromide solution was then added dropwise over a 2 h period maintaining the temperature between 50 and 55°C. The resulting mixture was stirred for a further 2 h, then the Grignard solution was cooled to r. t. and transferred to a clean dry storage vessel *via* cannula. The molar strength of the Grignard reagent was determined by making the triphenyltin derivative as described below. The cocentration was found to be 0.45M, which corresponded to a Grignard yield of 90%.

A 5 ml aliquot of the Grignard solution was added, under nitrogen, to a stirred solution of chlorotriphenyltin (1.10 g, 2.85 mmol) in THF (5 ml) at -50°C. The resulting mixture was stirred for 1 h whilst warming to r. t., then poured into saturated aqueous NH_4Cl (20 ml) and the products extracted into ether (4 x 20 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) and the Grignard's triphenyltin derivative, **1-triphenylstannyl-4-methyl-3-pentene (88)** (0.98 g, 2.26 mmol) isolated as a viscous oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.85-7.46 (15H, m), 5.32 (1H, tm, J 7.15 and 1.4), 2.57 (2H, apparent q with Sn satelites, J 7.7, J {Sn-H} 70), 1.75 (2H, t, J 7.8), 1.74 (3H, d, J 1), 1.59 (3H, s); **IR** (film): 3063s, 3048s, 3014m, 2987m, 2964m, 2926m, 2908s, 2854m, 1952w, 1875w, 1817w, 1672w, 1640w, 1579w, 1480m, 1428s, 1376m, 1332w, 1302w, 1257w, 1190w, 1141w, 1075s, 1022m, 997m, 727s, 699s, 658m cm^{-1}; **LRMS** (70 eV EI) m/z: 434 (M^+, 1%, Sn isotope pattern), 351 (Ph_3Sn, 100, Sn isotope pattern), 274 (351-Ph, 20, Sn isotope pattern), 197 (274-Ph, 38, Sn isotope pattern), 120 (197-Ph, 14, Sn isotope pattern), 77 (2), 55 (12), 41 (10).

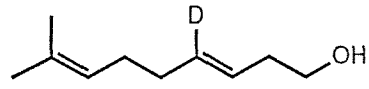
(3*E*)-4-Deutero-8-methyl-3,7-nonadien-1-ol (89).



4-Methyl-3-pentenylmagnesium bromide (**87**) (0.23M solution in THF, 10.0 ml, 2.30 mmol) was added, under argon, to a suspension of copper (I) cyanide (0.20 g, 2.24 mmol) in dry THF (5 ml) at -80°C, and the resulting mixture stirred at this temperature for 1 h. In the meantime *t*-butyllithium (1.7M solution in pentane, 1.60 ml, 2.72 mmol)

was added dropwise, under argon, to a solution of 2,3-dihydrofuran (**60**) (0.20 ml, 0.185 g, 2.64 mmol) in dry THF (5 ml) at -80°C. The resulting yellow coloured solution was then warmed to 0°C and stirred for 30 min in order to destroy excess *t*-BuLi. The resulting solution of 5-lithio-2,3-dihydrofuran (**63**) was then added to the cuprate mixture at -80°C, and the reaction mixture allowed to warm slowly to r. t. overnight. The mixture was then cooled to 0°C, deuterium oxide (0.5 ml) added and the mixture stirred for 1 h whilst warming to r. t. The resulting mixture was then poured into a 9:1 NH_4Cl / NH_4OH saturated aqueous solution (20 ml) and the two-phase system stirred until the aqueous layer took on a deep blue colouration. The aqueous phase was separated and extracted with ether (4 x 20 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 10% EtOAc in light petroleum eluant) and the *title compound* (0.27 g, 1.74 mmol, 75%) isolated as a colourless oil; **^{1}H NMR** ($CDCl_3$, 360 MHz) δ = 5.36 (1H, tm, J 6.95), 5.08 (1H, m), 3.58 (2H, t, J 6.4), 2.23 (2H, apparent q, J 6.6), 2.12 (1H, bs, OH), 2.0 (4H, A_2B_2 system appearing as a doublet), 1.66 (3H, s), 1.58 (3H, S); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ = 133.4 (CD, J {D-C} 23), 131.9 (0), 126.1 (1), 124.1 (1), 62.0 (2), 36.0 (2), 32.8 (2), 28.1 (2), 25.7 (3), 17.8 (3); **IR** (film): 3335bs, 2966s, 2922s, 2221w, 1673w, 1439m, 1376m, 1198w, 1046s, 885m, 829m cm^{-1}; **LRMS** (70 eV EI) m/z: 155 (M^+, 1%), 140 (M^+-Me, 1), 137 (M^+-H_2O, 2), 111 (8), 69 (100), 56 (7), 41 (45); **HRMS** (EI) Found: M^+ 155.1433.$C_{10}H_{17}DO$ requires M^+ 155.1420.

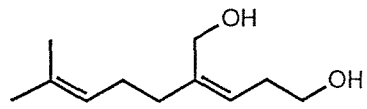
(3*E*)-4-Deutero-8-methyl-3,7-nonadien-1-ol (89).



4-Methyl-3-pentenylmagnesium bromide (**87**) (0.308M solution in THF, 10.0 ml, 3.08 mmol) was added, under argon, to a suspension of copper (I) bromide dimethylsulphide complex (0.47 g, 2.29 mmol, 75 mol%) in THF (5 ml) at -80°C. The resulting orange solution was stirred for 40 min warming slightly to -75°C. In the meantime *t*-butyllithium (1.7M solution in pentane, 2.0 ml, 3.40 mmol) was added dropwise, under argon, to a solution of 2,3-dihydrofuran (**60**) (0.25 ml, 0.23 g, 3.31 mmol) in dry THF (2 ml) at -80°C. The resulting yellow coloured solution was then warmed to 0°C and stirred for 30 min in order to destroy excess *t*-BuLi. The cuprate solution was then warmed to 0°C (the temperature rise causing the colour of the cuprate to change from orange to purple/blue) and the solution of 5-lithio-2,3-dihydrofuran (**63**) added rapidly. The resulting mixture was allowed to warm to r. t. over 2 h, then poured into a 9:1 NH_4Cl / NH_4OH saturated aqueous solution (30 ml) and stirred for 0.5 h until the aqueous phase had taken on a deep blue colouration. The product was then extracted into ether (4 x 30 ml) and the extracts combined, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash column chromatography

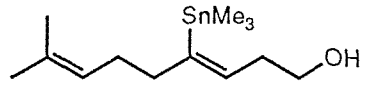
(SiO_2, 10% EtOAc in light petroleum eluant) and the *title compound* (0.28 g, 1.80 mmol, 58%) isolated as a colourless oil. The spectral data of the product so isolated were identical to those obtained for the sample of the *title compound* derived using copper (I) cyanide as the copper source, as described in the previous experimental procedure.

(3Z)-4-Hydroxymethyl-8-methyl-3,7-nonadien-1-ol (91).



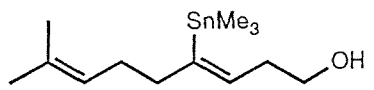
4-Methyl-3-pentenylmagnesium bromide (**87**) (0.23M solution in THF, 100 ml, 23.0 mmol) was added, under argon, to a suspension of copper (I) cyanide (2.0 g, 22.4 mmol) in dry THF (50 ml) at -80°C, and the resulting mixture stirred at this temperature for 1 h. In the meantime *t*-butyllithium (1.7M solution in pentane, 16.0 ml, 27.2 mmol) was added dropwise, under argon, to a solution of 2,3-dihydrofuran (**60**) (2.0 ml, 1.85 g, 26.4 mmol) in dry THF (20 ml) at -80°C. The resulting yellow coloured solution was then warmed to 0°C and stirred for 30 min in order to destroy excess *t*-BuLi. The resulting solution of 5-lithio-2,3-dihydrofuran (**63**) was then added to the cuprate mixture and the reaction mixture allowed to warm slowly to r. t. overnight. A 250 ml round bottomed flask containing dry paraformaldehyde (5.0 g, 0.17 mol) was connected to the cuprate reaction flask *via* a glass tube, which dipped under the surface of the cuprate solution. The cuprate mixture was cooled to 0°C and the paraformaldehyde pyrolysed by heating with a bunsen burner. The formaldehyde gas so produced was driven into the cuprate flask by a slow stream of argon. The resulting mixture was stirred at room temperature for 2 h, then poured into a 9:1 NH_4Cl / NH_4OH saturated aqueous solution (300 ml) and stirred for 1 h, the aqueous phase taking on a deep blue colouration. The product was extracted into ether (4 x 300 ml) and the combined extracts washed with brine, dried ($MgSO_4$) and the solvent removed by rotary evaporation. The product was purified by flash column chromatography (SiO_2, 1:1 ether and light petroleum eluant) and kugelrohr distillation; the *title compound* (3.37 g, 18.29 mmol, 79%) being isolated as a viscous colourless oil; b. p. (bath) 155°C/0.3 mm Hg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.30 (1H, t, J 7.9), 5.07 (1H, m), 4.02 (2H,s), 3.80 (2H,bs, OH), 3.57 (2H, t, J 5.9), 2.30 (2H, apparent overlapping dt, J 7.8 and 5.9), 2.11 (4H, A_2B_2 system appearing as a single broad peak), 1.65 (3H, S), 1.57 (3H, s); **^{13}C NMR** ($CDCl_3$, 68MHz) δ = 142.0 (0), 131.8 (0), 125.1 (1), 124.1 (1), 61.1 (2), 59.6 (2), 36.2 (2), 30.9 (2), 26.3 (2), 25.8 (3), 17.8 (3); **IR** (film): 3324bs, 2964s, 2925s, 2880s, 1672w,1441m, 1376m, 1240w, 1146w, 1106w, 1047s, 1003s, 882w, 831w, 735w cm^{-1}; **LRMS** (70 eV EI) m/z: 184 (M^+, 0.5%), 166 (M^+-H_2O, 5), 135 (12), 133 (12), 123 (10), 121 (11), 107 (22), 105 (21), 93 (38), 91 (26), 86 (22), 84 (34), 81 (16), 79 (30), 77 (17), 69 (100), 67 (28), 55 (20), 53 (18), 51 (15), 49 (47), 41 (92), 39 (26), 27 (17).

(3Z)-4-Trimethylstannyl-8-methyl-3,7-nonadien-1-ol (92).



4-Methyl-3-pentenylmagnesium bromide (**87**) (0.28M solution in THF, 10.0 ml, 2.80 mmol) was added, under argon, to a stirred suspension of copper (I) cyanide (0.25 g, 2.79 mmol) in dry THF (2 ml) at -80°C, and the resulting mixture stirred at this temperature for 2 h. In the meantime *t*-butyllithium (1.7M in pentane, 1.80 ml, 3.06 mmol) was added, under argon, to a solution of 2,3-dihydrofuran (**60**) (0.20 g, 2.91 mmol) in dry THF (2 ml) at -80°C. The resulting yellow solution was then warmed to 0°C and stirred for 25 min to destroy excess *t*-BuLi. The resulting solution of 5-lithio-2,3-dihydrofuran (**63**) was then added dropwise to the cuprate suspension at -80°C, and the reaction mixture warmed slowly to +10°C overnight. The temperature was then lowered to -80°C and a solution of trimethyltin chloride (1.12 g, 5.62 mmol) in dry THF (5 ml) added dropwise. After warming slowly to r. t., the reaction mixture was poured into a 9:1 NH_4Cl / NH_4OH saturated aqueous solution (50 ml) and the mixture stirred until the aqueous phase took on a deep blue colouration. The aqueous layer was separated, then extracted with ether (4 x 50 ml) and the combined organic phases washed with brine, dried ($MgSO_4$) and the solvent concentrated *in vacuo* to give the crude product as a pale yellow oil. The product was purified by flash column chromatography (SiO_2, 10% EtOAc in light petroleum eluant) to give the *title compound* (0.65 g, 2.05 mmol, 73%) as a colourless oil; **^{1}H NMR** ($CDCl_3$, 360 MHz) δ = 5.96 (1H, tm with Sn satellites, J 7.3 and 1.2, J {Sn-H} 140), 5.07 (1H, tm, J 7.1 and 1.4), 3.63 (2H, t, J 6.4), 2.30 (2H, apparent q, J 6.7), 2.23 (2H, t, J 7.6), 2.00 (2H, apparent q, J 7.4), 1.68 (3H, d, J 1.2), 1.59 (3H, s), 1.60-1.59 (1H, bs, OH), 0.19 (9H, s with Sn satellites, J {Sn-H} 54); **^{13}C NMR** ($CDCl_3$, 90 MHz) δ = 148.3 (0 , J {Sn-C} 355), 136.2 (1, J {Sn-C} 31), 131.8 (0), 124.2 (1), 62.4 (2), 40.6 (2, J {Sn-C} 45), 37.9 (2, J {Sn-C} 41), 29.3 (2, J {Sn-C} 12), 25.8 (3), 18.0 (3), -8.0 (3, J {Sn-C} 330); **IR** (film): 3334bs, 2967s, 2913s, 1620w, 1449m, 1376m, 1188m, 1046s, 858w, 769s cm^{-1}, **LRMS** (70 eV EI) m/z: 303 (M^+-Me, 100%, Sn isotope pattern), 163 (54, Sn isotope pattern), 217 (9, Sn isotope pattern), 195 (15, Sn isotope pattern), 151 (25, Sn isotope pattern), 135 (34), 107 (12), 93 (13), 79 (9), 69 (27), 53 (17), 41 (73), 27 (14); **HRMS** (CI) Found M+H 319.1093. $C_{13}H_{27}OSn$ requires 319.1084.

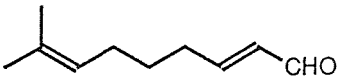
(3Z)-4-Trimethylstannyl-8-methyl-3,7-nonadien-1-ol (92).



A solution of 4-methyl-3-pentenylmagnesium bromide (**87**) in THF (100 ml) was prepared by the method described above from 1-bromo-4-methyl-3-pentene (**82**) (8.15 g, 50 mmol) and magnesium turnings (2.43 g, 100 ml). The Grignard solution was then added, under argon, to a stirred suspension of $CuBr{\bullet}SMe_2$ (9.25 g, 45 mmol) in dry THF/Me_2S (1:1, 80 ml) at -80°C, to form a deep red coloured

solution, which was stirred at this temperature for 0.5 h. In the meantime *t*-butyllithium (1.7M in pentane, 32.5 ml, 55.3 mmol) was added, under argon, to a solution of 2,3-dihydrofuran (**60**) (3.80 g, 54.2 mmol) in dry THF (20 ml) at -80°C. The resulting yellow solution was then warmed to 0°C and stirred for 30 min to destroy excess *t*-BuLi. The resulting solution of 5-lithio-2,3-dihydrofuran (**63**) was then added dropwise to the cuprate solution at -80°C, and the reaction mixture warmed slowly to r. t. The temperature was then lowered to -80°C and a solution of trimethyltin chloride (8.0 g, 40 mmol) in dry THF (20 ml) added dropwise. After warming slowly to r. t., the reaction mixture was poured into a 9:1 NH_4Cl / NH_4OH saturated aqueous solution (300 ml) and the mixture stirred until the aqueous phase took on a deep blue colouration. The aqueous layer was separated, then extracted with ether (4 x 100 ml) and the combined organic phases washed with brine, dried ($MgSO_4$) and the solvent concentrated *in vacuo* to give the crude product as a pale yellow oil. The product was purified by flash column chromatography (SiO_2, 5% EtOAc in light petroleum eluant) to give the *title compound* (4.81 g, 15 mmol, 30%) as a colourless oil. The spectral data for the product were identical to those detailed above.

(2*E*)-8-Methyl-2,7-nonadienal (95).

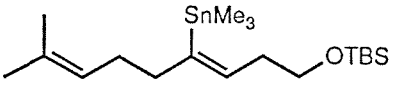


A solution of dimethylsulphoxide (0.50 ml, 0.55 g, 7.05 mmol) in CH_2Cl_2 (2 ml) was added dropwise to a vigorously stirred CH_2Cl_2 (3 ml) solution of oxalyl chloride (0.31 ml, 0.45 g, 3.55 mmol) at -50°C, a vigorous evolution of gas being observed. The resulting solution was then cooled to -60°C and a solution of (3Z)-4-trimethylstannyl-8-methyl-3,7-nonadien-1-ol (**92**) (1.0 g, 3.16 mmol) in CH_2Cl_2 (3 ml) added dropwise. The reaction mixture was stirred for *ca* 10 min, during which a white precipitate was formed. Triethylamine (1.35 ml, 0.98 g, 9.7 mmol) was then added, resulting in a partial re-dissolving of the precipitate, which was followed by the formation of a much thicker white precipitate. The resulting mixture was allowed to warm slowly to -5°C over 2.5 h, and was then poured into ice-cold 2M HCl (5 ml). The organic products were extracted into CH_2Cl_2 (4 x 10 ml), and the combined extracts washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. The product was purified by flash column chromatography (SiO_2, 5% EtOAc in light petroleum eluant) and the *title compound* (0.188 g, 1.23 mmol, 19%) isolated as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 9.48 (1H, d, J 7.9), 6.84 (1H, dt, J 15.5 and 6.8), 6.10 (1H, ddd, J 15.6, 7.9 and 1.4), 5.08 (1H, tm, J 7.1 and 1.4), 2.32 (2H, apparent qd, J 7.3 and 1.4), 2.02 (2H, m, J 7), 1.68 (3H, d, J 1.0), 1.58 (3H, s), 1.54 (2H, m, J 7); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 194.2 (1), 159.1 (1), 133.1 (1), 132.5 (0), 123.6 (1), 32.3 (2), 28.0 (2), 25.8 (3), 17.8 (2); **IR** (film): 2966s, 2926s, 2857s, 2729s, 1693vs, 1637m, 1449m, 1377m, 1160m, 1126s, 974s cm^{-1} ; **LRMS** (70 eV EI) m/z: 152 (M^+,

5%), 137 (M^+-Me, 33.5), 109 (13.5), 108 (10), 96 (9), 95 (11), 93 (8), 83 (20), 82 (33), 81 (17), 79 (8), 70 (14), 69 (52), 67 (33), 55 (57), 53 (18), 41 (100), 39 (35), 29 (14), 27 (21).

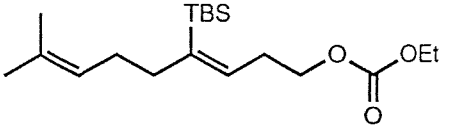
The *title compound* (0.062 g, 0.41 mmol, 40%) was also obtained *via* an essentially identical Swern oxidation procedure to that described above using (3Z)-4-trimethylstannyl-8-methyl-3,7-nonadien-1-ol (**92**) (0.32 g, 1.01 mmol), oxalyl chloride (0.10 ml, 0.146 g, 1.15 mmol), and dimethylsulphoxide (0.16 ml, 0.18 g, 2.25 mmol); with the triethylamine being substituted for *N*-methylmorpholine (0.33 ml, 0.30 g, 3.0 mmol).

(3Z)-1-(*t*-Butyldimethylsilyloxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (96).



A solution of *t*-butyldimethylchlorosilane (0.72 g, 4.8 mmol) in dry CH_2Cl_2 (2 ml) was added to a stirred solution of (3Z)-4-trimethylstannyl-8-methyl-3,7-nonadien-1-ol (**92**) (1.00 g, 3.2 mmol) and imidazole (0.43 g, 6.3 mmol) in CH_2Cl_2 (5 ml) at 0°C. A white precipitate was formed within 5 min and the resulting reaction mixture was stirred at 0°C for 1.5 h. The mixture was then poured into saturated brine (10 ml) and the organic products extracted into CH_2Cl_2 (3 x 20 ml). The extracts were combined, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a pale yellow oil. This was then purified by flash column chromatography (SiO_2, 5% ether in light petroleum eluant) to give the *title compound* (1.30 g, 3.01 mmol, 96%) as a colourless oil ; **^{1}H NMR** ($CDCl_3$, 90 MHz) δ = 5.99 (1H, t, J 7), 5.10 (1H, m), 3.60 (2H, t, J 7), 2.4-1.9 (6H, m), 1.68 (3H, s), 1.60 (3H, s), 0.91 (9H, s), 0.19 (9H, s with Sn satellites, J {Sn-H} 50), 0.07 (6H, s); **^{13}C NMR** ($CDCl_3$, 22.5 MHz) δ = 146.0 (0), 137.0 (1, J {Sn-C} 32), 131.4 (0), 124.4 (1), 63.6 (2), 40.7 (2, J {Sn-C} 47), 38.3 (2, J {Sn-C} 41), 29.6 (2, J {Sn-C} 14), 26.2 (3), 25.9 (3), 18.6 (0), 17.9 (3), -5.0 (3), -8.0 (3, J {Sn-C} 130); **IR** (film): 2957s, 2928s, 2857s, 1621w, 1472m, 1380m, 1255s, 1099s, 938m, 836s, 775s cm^{-1}; **LRMS** (CI, NH_3) m/z: 433 (M+H, 3%, Sn isotope pattern), 417 (M-Me, 72, Sn isotope pattern), 182 (100, Sn isotope pattern), 165 (20, Sn isotope pattern), 137 (30), 135 (14), 95 (24), 90 (10), 81 (22).

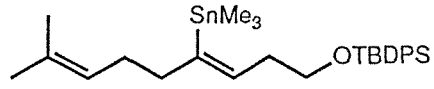
Ethyl (3Z)-4-*t*-butyldimethylsilyl-8-methyl-3,7-nonadienyl carbonate (100).



Butyllithium (1.6M solution in hexanes, 5.0 ml, 8.0 mmol) was added, under nitrogen, to a stirred solution of (3Z)-1-(*t*-butyldimethylsilyloxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (**96**) (3.0 g, 7.0 mmol) in THF (30 ml) at -80°C. The resulting solution was allowed to warm slowly to r. t. over a 2.5 h period, and then stirred at this temperature for 1.5 h. TLC at that stage showed the presence of unreacted stannane so the mixture was cooled to -80°C once

more, and a further volume of butyllithium (1.6M in hexanes, 4.0 ml, 6.4 mmol) added. The resulting mixture was allowed to warm rapidly to r. t. and stirred for a further 0.5 h. TLC at that stage showed that the stannane had been consumed, so the mixture was cooled to -80°C and ethyl chloroformate (2.80 ml, 3.18 g, 29.28 mmol) added. The resulting mixture was warmed to r. t. over a 2 h period, then stirred for 1 h at r. t. before being poured into a saturated aqueous NH_4Cl solution (100 ml). The product was extracted into ether (4 x 50 ml) and the combined extracts washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 1% ether in light petroleum eluant) and the *title compound* (1.86 g, 5.46 mmol, 78%) isolated as a colourless oil; **^{1}H NMR** ($CDCl_3$, 90 MHz) δ = 6.00 (1H, t, J 7.7), 5.05 (1H, bm), 4.45-4.00 (4H, m), 2.50 (2H, apparent q, J 7.7), 2.05 (4H, A_2B_2 system appearing as a single broad peak), 1.69 (3H, s), 1.59 (3H, s), 1.30 (3H, t, J 7), 0.90 (9H, s), 0.15 (6H, s); **^{13}C NMR** ($CDCl_3$, 22.5 MHz) δ = 155.4 (0), 140.5 (0), 137.7 (1), 131.6 (0), 124.5 (1), 67.7 (2), 64.1 (2), 38.2 (2), 32.4 (2), 29.4 (2), 27.2 (3), 25.9 (18.3 (0), 17.9 (3), 14.5 (3), -3.4 (3); **IR** (film): 2958s 2929s, 2857s, 1748s, 1613w, 1464m, 1401m, 1384m, 1366m, 1259s, 1097m, 1010m, 835m, 822m, 809m, 792m, 770m, 683w cm^{-1}; **LRMS** (CI, NH_3) m/z: 341 (M+H, 8%), 325 (M-Me, 16), 295 (33), 283 (91), 239 (35), 207 (27), 205 (35), 195 (18), 147 (25), 137 (20), 135 (100), 115 (57), 103 (39), 90 (45), 73 (51).

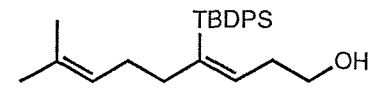
(3Z)-1-(*t*-Butyldiphenylsilyloxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (101).



t-Butyldiphenylchlorosilane (0.45 ml, 0.476 g, 1.73 mmol) was added to a stirred solution of imidazole (0.26 g, 3.82 mmol) and (3Z)-4-trimethylstannyl-8-methyl-3,7-nonadien-1-ol (**92**) (0.48 g, 1.51 mmol) in CH_2Cl_2 (5 ml) at 0°C, and the resulting solution stirred for 18 h whilst warming to r. t.; leading to the precipitation of a cream coloured solid. The mixture was then poured into brine (20 ml) and the products extracted into CH_2Cl_2 (4 x 20 ml). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The product was then purified by flash column chromatography (SiO_2, 5% ether in light petroleum eluant) and the *title compound* (0.75 g, 1.35 mmol, 89%) isolated as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.78-7.72 (4H, m), 7.52-7.39 (6H, m), 6.07 (1H, t with Sn satellites, J 7.1, J {Sn-H} 140), 5.15 (1H, tm, J 7 and 1.2), 3.73 (2H, t, J 6.8), 2.39 (2H, apparent q, J 6.8), 2.28-2.22 (2h, m), 2.04 (2H, apparent q, J 7.5), 1.72 (3H, d, J 1), 1.64 (3H, s), 1.12 (9H, s), 0.2 (9H, s with Sn satellites, J {Sn-H} 52); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 146.1 (0), 137.0 (1, J {Sn-C} 31), 135.8 (1), 134.1 (0), 131.6 (0), 129.7 (1), 127.8 (1), 124.3 (1), 64.3 (2), 40.8 (2, J {Sn-C} 45), 38.0 (2 J {Sn-C} 45), 29.6 (2), 27.0 (3), 25.9 (3), 19.4 (0), 18.0 (3), -8.1 (3, J {Sn-C} 340); **IR** (film): 3071w, 3050w, 2961s, 2930s, 1619w, 1590w, 1472m, 1428s, 1382m, 1361w, 1188w, 1112s, 1093s, 1008w, 939w,

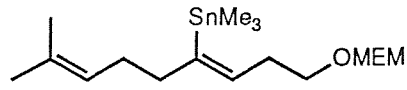
823s, 768s, 738s, 701s, 614s cm^{-1}; **LRMS** (CI, NH_3) m/z: 557 (M+H, 6%, Sn isotope pattern), 541 (M-Me, 62, Sn isotope pattern), 499 (13, Sn isotope pattern), 182 (100, Sn isotope pattern), 165 (7), 137 (11).

(3*Z*)-4-*t*-Butyldiphenylsilyl-8-methyl-3,7-nonadien-1-ol (102).



Butyllithium (1.6M solution in hexanes, 0.15 ml, 0.24 mmol) was added, under nitrogen, to a solution of (3*Z*)-4-trimethylstannyl-8-methyl-1-(*t*-butyldiphenylsilyloxy)-3,7-nonadiene (**101**) (0.11 g, 0.20 mmol) in THF (5 ml) at -80°C, and the resulting mixture stirred for a 2 h period, whilst warming to r. t. The mixture was poured into saturated aqueous NH_4Cl solution (10 ml) and the products extracted into ether (4 x 20 ml). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 20% EtOAc in light petroleum eluant) and the *title compound* (0.052 g, 0.132 mmol, 66%) isolated as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.70-7.64 (4H, m), 7.43-7.31 (6H, m), 6.30 (1H, t, J 7.4), 5.05 (1H, tm, J 7 and 1.3), 3.34 (2H, t, J 6.7), 2.44-2.34 (2H, distorted t, J 8), 2.10-2.01 (2H, distorted t, J 8), 1.96 (2H, apparent q, J 6.9), 1.68 (3H, d, J 1), 1.50 (3H, s), 1.15 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 142.9 (1), 138.1 (0), 136.2 (1, 2C), 131.7 (0), 129.1 (1), 127.8 (1), 124.4 (1), 62.4 (2), 39.0 (2), 37.1 (2), 29.8 (2), 28.9 (3), 25.9 (3), 19.4 (0), 17.9 (3); **IR** (film): 3336bs, 3070s, 3049m, 2965s, 2929s, 2858s, 1602w, 1472m, 1427s, 1391m, 1362m, 1260m, 1191w, 1103s, 1048, 818m, 740m, 702s, cm^{-1}; **LRMS** (CI, NH_3) m/z: 410 ($M+H+NH_3$, 100%), 393 (M+H, 2), 257 (9), 216 (8), 137 (10), 35 (42).

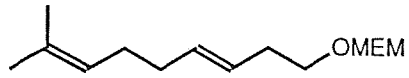
(3*Z*)-1-(Methoxyethoxymethoxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (103).



2-Methoxyethoxymethyl chloride (MEM chloride, 0.50 g, 4.01 mmol) was added to an ice cold solution of (3*Z*)-4-trimethylstannyl-8-methyl-3,7-nonadien-1-ol (**92**) (0.83 g, 2.62 mmol) and N,N-diisopropylethylamine (0.70 ml, 0.52 g, 4.02 mmol) in dry CH_2Cl_2 (10 ml), and the resulting solution stirred at 0°C for 0.5 h. The mixture was then warmed to r. t. and stirred for a further 6 h, then poured into 2M aqueous HCl (20 ml) and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml) and the organic fractions combined, washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a mobile yellow oil. This was purified by flash column chromatography (SiO_2, 5% ether in light petroleum eluant) to give the *title compound* (0.915 g, 2.26 mmol, 86%) as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.99 (1H, t with Sn satellites, J 7.15, J {Sn-H} 140), 5.08 (1H, t, J 6.9), 4.72 (2H, s), 3.70 (2H, m), 3.55 (4H, m), 3.40 (3H, s), 2.32 (2H, apparent q, J 6.9), 2.20 (2H, t, J 7.1), 1.97 (2H, apparent q, J 7.1), 1.68 (3H,

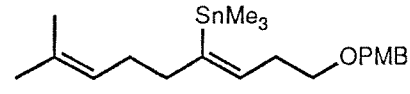
s), 1.59 (3H, s), 0.18 (9H, s with Sn satellites, J {Sn-H} 53). **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 146.6 (0, J {Sn-C} 440), 136.2 (1, J {Sn-C} 215), 131.4 (0), 124.1 (1), 95.5 (2), 71.9 (2), 67.9 (2), 59.1 (3), 40.5 (2, J {Sn-C} 46), 35.0 (2, J {Sn-C} 42), 29.4 (2, J {Sn-C} 14), 25.8 (3), 17.8 (3), -8.2 (3, J {Sn-C} 330); **IR** (film): 2968s, 2915s, 2890s, 1621w, 1452m, 1377m, 1243w, 1200m, 1173m, 1116s, 1100s, 1070s, 1040s, 984m, 936w, 855w, 769s, 712m cm^{-1}; **LRMS** (70 eV EI) m/z: 391 (M^+-Me, 28% with Sn isotope pattern), 301 (17, with Sn isotope pattern), 225 (31, with Sn isotope pattern), 181 (9), 165 (44, with Sn isotope pattern), 151 (15, with Sn isotope pattern), 135 (11), 89 (60), 69 (23), 59 (100), 41 (21), 31 (10).

(3*E*)-1-(Methoxyethoxymethoxy)-8-methyl-3,7-nonadiene (104).



Butyllithium (1.6M in hexanes, 0.45 ml, 0.72 mmol) was added dropwise, under nitrogen, to a stirred solution of (3*Z*)-1-(methoxyethoxymethoxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (**103**) (0.16 g, 0.398 mmol) in dry THF (2 ml) at -75°C. The resulting mixture was allowed to warm slowly to r. t. and was then poured into saturated aqueous NH_4Cl (10 ml), and the organic products extracted into ether (4 x 10 ml). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. The product was then purified by flash column chromatography (SiO_2, 10% ether in light petroleum eluant) and the *title compound* (0.025 g, 1.03 mmol, 25%) isolated as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.60-5.35 (2H, m), 5.11 (1H, bm), 4.72 (2H, s), 3.75-3.65 (2H, m), 3.55-3.60 (4H, m), 3.40 (3H, s), 2.28 (2H, apparent q, J 6.6), 2.10-1.95 (4H, A_2B_2 system appearing as a single broad peak), 1.68 (3H s), 1.60 (3H, s); **^{13}C NMR** ($CDCl_3$, 22.5 MHz) δ = 127.6 (1), 126.9 (0), 122.3 (1), 120.2 (1), 93.9 (2), 72.3 (2), 68.6 (2), 67.7 (2), 60.4 (3), 36.7 (2), 36.5 (2), 32.2 (2), 29.8 (3), 22.6 (3); **IR** (film): 2924s, 2880s, 1672w, 1452m, 1377m, 1283w, 1243m, 1200m, 1173m, 1117s, 1099s, 1047s, 970s, 935m, 850m cm^{-1}; **LRMS** (70 eV EI) m/z: 242 (M^+, 1%), 166 (5), 151 (4), 136 (5), 121 (7), 107 (7), 95 (10), 89 (71), 82 (13), 81 (13), 69 (94), 68 (28), 67 (25), 59 (100), 41 (48), 31 (11), 29 (12).

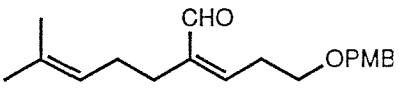
(3*Z*)-1-(*p*-Methoxybenzyloxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (105).



Sodium hydride (60% dispersion in mineral oil, 0.25 g, 6.25 mmol) was added in small portions, under nitrogen, to an ice-cold solution of (3*Z*)-4-trimethylstannyl-8-methyl-3,7-nonadien-1-ol (**92**) (1.28 g, 4.04 mmol) in dry DMF (40 ml) and the resulting mixture allowed to warm to r. t. After stirring for 10 min, *p*-methoxybenzyl chloride (0.60 ml, 0.69 g, 4.4 mmol) was added and the mixture stirred at r. t. for 18 h. After this time the mixture was poured into saturated aqueous NH_4Cl solution (200 ml) and the organic products extracted into ether (4 x 100 ml). The combined extracts were washed with

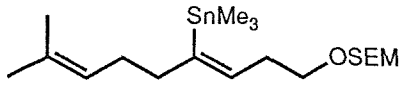
brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (SiO_2, 1% ether in light petroleum eluant), followed by kugelrohr distillation to give the *title compound* (1.22 g, 2.79 mmol, 67%) as a colourless oil: b. p. 250°C (bath)/1.5 mm Hg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.24 (2H, dm, J 8.6), 6.87 (2H, dm, J 8.6), 5.98 (1H, t with Sn satellites, J 7.25, J {Sn-H} 140), 5.07 (1H, tm, J 7 and 1), 4.41 (2H, s), 3.77 (3H, s), 3.42 (2H, t, J 7), 2.30 (2H, apparent q, J 7), 2.22-2.16 (2H, m), 2.01-1.93 (2H, m), 1.65 (3H, d, J 1), 1.57 (3H, d, J 0.7), 0.15 (9H, s with Sn satellites, J {Sn-H} 50); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 159.3 (0), 146.5 (0 with Sn satellites, J {Sn-C} 450), 136.4 (1 with Sn satellites, J {Sn-C} 31), 131.5 (0), 130.7 (0), 129.4 (1), 124.2 (1), 113.9 (1), 72.7 (2), 70.2 (2 with Sn satellites, J {Sn-C} 9), 55.4 (3), 40.5 (2 with Sn satellites, J {Sn-C} 45), 35.2 (2 with Sn satellites, J {Sn-C} 43), 29.5 (2 with Sn satellites, J {Sn-C} 12), 25.9 (3), 18.0 (3), -8.1 (3 with Sn satellites, J {Sn-C} 327); **IR** (film): 2965s, 2910s, 2853s, 1614s, 1586w, 1513s, 1464m, 1454m, 1442m, 1376w, 1360m, 1302m, 1248s, 1208s, 1172m, 1097s, 1039s, 821m, 768s, 710m, 524s cm^{-1}; **LRMS** (CI, NH_3) m/z: 439 (M+H, 1%, Sn isotope pattern), 423 (M-Me, 24, Sn isotope pattern), 301 (M+H-$MeOC_6H_4OH$, 7, Sn isotope pattern), 122 (16), 121 (100), 83 (12), 49 (15), 30 (28).

(2Z)-2-(4'-Methyl-3'-pentenyl)-5-*para*-methoxybenzyloxy-2-pentenal (106).



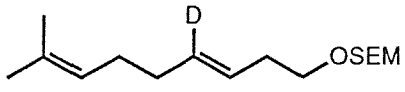
Butyllithium (1.6M in hexanes, 1.25 ml, 2.0 mmol) was added, under nitrogen, to a stirred solution of (3Z)-1-(*p*-methoxybenzyloxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (**105**) (0.45 g, 1.03 mmol) in dry ether (10 ml) at -80°C. The resulting mixture was allowed to warm slowly to r. t. over a 3 h period, then cooled to -35°C. N -Methylformanilide (0.50 ml, 0.55 g, 4.05 mmol) was then added, the mixture again allowed to warm to r. t. and then stirring continued at r. t. for 2 h. The reaction mixture was then poured into 2M HCl (30 ml) and the product extracted into ether (4 x 30 ml). The combined extracts were washed with saturated $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash column chromatography (SiO_2, 10% ether in light petroleum eluant) to give the *title compound* as a colourless oil (0.14 g, 0.46 mmol, 44%); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 10.12 (1H, s), 7.27 (2H, dm, J 8.6), 6.90 (2H, dm, J 8.6) 6.50 (1H, t, J 8), 5.10009 (1H, tm, J 7 and 1.3), 4.48 (2H, s), 3.82 (3H, s), 3.57 (2H, t, J 6.4), 2.87 (2H, apparent q, J 7), 2.27-2.18 (2H, m, J 7), 2.09 (2H, apparent q, J 7.6), 1.68 (3H, d, J 1), 1.59 (3H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 191.1 (1), 159 33 (0), 145.5 (1), 141.0 (0), 132.3 (0), 130.2 (0), 129.3 (1), 123.6 (1), 113.9 (1), 72.8 (2), 68.8 (2), 55.3 (3), 30.5 (2), 27.4 (2), 27.3 (2), 25.7 (3), 17.8 (3); **IR** (film): 2922s, 2924s, 2856s, 1676vs, 1613s, 1586m, 1513s, 1463m, 1455m, 1443m, 1361m, 1302m, 1248s, 1173m, 1100s, 1036s, 821m cm^{-1}; **LRMS** was not recorded for this compound.

(3Z)-1-(2'-Trimethylsilylethoxymethoxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (107).



To a solution of (3Z)-4-trimethylstannyl-8-methyl-3,7-nonadien-1-ol (**92**) (0.83 g, 2.62 mmol) and N,N-diisopropylethylamine (1.80 ml, 1.34 g, 10.33 mmol) in dry CH_2Cl_2 (5 ml) was added β-trimethysilylethoxymethyl chloride (SEM chloride, *ex* Aldrich, 0.70 ml, 0.66 g, 3.96 mmol). The resulting solution was stirred at r. t. for 3 h, then poured into 2M aqueous HCl (20 ml). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated *in vacuo* to give a mixture of a waxy yellow solid and a colourless oil. The product was purified by flash column chromatography (SiO_2, 1% ether in light petroleum eluant) to give the *title compound* as a colourless oil (1.10 g, 2.46 mmol, 94%); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 6.00 (1H, t with Sn satellites, J 7.2, J {Sn-H} 150), 5.09 (1H, tm, J 7.0 and 1.4), 4.68 (2H, s), 3.65-3.57 (2H,m), 3.54 (2H, t, J 7.15), 2.33 (2H, apparent q, J 7.15), 2.21 (2H, t, J 7.15), 1.98 (2H, apparent q, J 7.2), 1.68 (3h, d, J 1.4), 1.60 (3H, s), 0.95 (2H, m), 0.19 (9H, s with Sn satellites, J {Sn-H} 50), 0.03 (9H, s), **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 146.7 (0), 136.3 (1, J {Sn-C} 31), 131.5 (0), 124.2 (1), 94.9 (2), 67.9 (2, J {Sn-C} 8), 65.1 (2), 40.6 (2, J {Sn-C} 46), 35.1 (2, J {Sn-C} 43), 29.5 (2 J {Sn-C} 14), 25.9 (3), 18.3 (2), 17.9 (3), -1.2 (3), -8.1 (3, J {Sn-C} 327); **IR** (film): 2953s, 2916s, 1621w, 1449w, 1376m, 1249s, 1189m, 1151m, 1110s, 1064s, 1029s, 938m, 921m, 860s, 836s, 767m, 710w, 694w cm^{-1}; **LRMS** (70 eV EI) m/z : 433 (M^+-Me, 5%, Sn isotope pattern), 403 (1, Sn isotope pattern), 375 (M^+-TMS, 9, Sn isotope pattern), 301 (4, Sn isotope pattern), 239 (15, Sn isotope pattern), 165 (21, Sn isotope pattern), 147 (8), 103 (17), 101(13), 73 (TMS^+, 100), 69 (22), 41 (12).

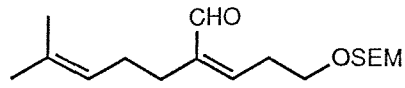
(3*E*)-1-(2'-Trimethylsilylethoxymethoxy)-4-deutero-8-methyl-3,7-nonadiene (108).



Butyllithium (1.6M solution in hexanes, 0.45 ml, 0.72 mmol) was added, under nitrogen, to a solution of (3Z)-1-(2'-trimethylsilylethoxymethoxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (**107**) (0.22 g, 0.49 mmol) in anhydrous ether (2 ml) at -35°C. The resulting solution was allowed to warm to r. t. over a 1.5 h period, then stirred at this temperature for 1 h. Deuterium oxide (0.2 ml) was then added and the mixture stirried for 30 min, then poured into saturated aqueous NH_4Cl (10 ml). The products were extracted into ether (4 x 10 ml), and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) and kugelrohr distillation to give the *title compound* (0.10 g, 0.35 mmol, 70%) as a colourless oil: b. p 120 (bath)/0.9 mm Hg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.42 (1H, t, J 7), 5.10 (1H, m), 4.68 (2H, s), 3.65-3.58 (2H, m), 3.55 (2H, t, J 6.8), 2.29 (2H, apparent q, J 6.8), 2.03-2.01 (4H, A_2B_2

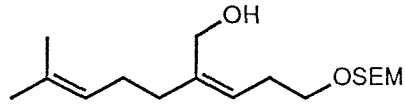
system appearing as a single broad peak), 1.69 (3H, s), 1.60 (3H, s), 0.98-0.88 (2H, m), 0.03 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 132.4 (CD), 131.7 (0), 126.5 (1), 124.2 (1), 94.9 (2), 67.8 (2), 65.1 (2), 33.2 (2), 32.9 (2), 28.2 (2), 25.8 (3), 18.2 (2), 17.9 (3), -1.2 (3); **IR** (film): 2953s, 2921s, 2874s, 2220w, 1440m, 1377m, 1249s, 1192m, 1153m, 1111s, 1063s, 938m, 921m, 860s, 836s, 758m, 693m cm^{-1}; **LRMS** (70 eV EI) m/z: 270 (M^+-Me, 0.5%), 185 (3), 103 (45), 101 (28), 82 (13), 75 (22), 72 (100), 70 (12), 69 (79), 41 (34).

(2Z)-2-(4'-Methyl-3'-pentenyl)-5-(2"-trimethylsilylethoxymethoxy)-2-pentenal (109).



Butyllithium (1.6M in hexanes, 0.90 ml, 1.44 mmol) was added, under nitrogen, to a stirred solution of (3Z)-1-(2'-trimethylsilylethoxymethoxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (**107**) (0.33 g, 0.74 mmol) in dry ether (10 ml) at -80°C. The resulting mixture was allowed to warm slowly to r. t. over a 3 h period, then cooled to -35°C. N -Methylformanilide (0.45 ml, 0.49 g, 3.65 mmol) was then added, the mixture again allowed to warm to r. t. and then stirring continued at r. t. for 4 h. The reaction mixture was then poured into 2M HCl (20 ml) and the product extracted into ether (4 x 20 ml). The combined extracts were washed with saturated $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash column chromatography (SiO_2, 5% EtOAc in light petroleum eluant) to give the *title compound* as a colourless oil (0.14 g, 0.44 mmol, 59%); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 10.11 (1H, s), 6.49 (1H, t, J 8), 5.07 (1H, tm, J 7 and 1.3), 4.68 (2H, s), 3.66 (2H, t, J 6.4), 3.61 (2H, m), 2.85 (2H, apparent q, J 6.9), 2.21 (2H, distorted t, J 7), 2.07 (2H, apparent q, J 7), 1.67 (3H, d, J 1), 1.56 (3H, s), 0.94 (2H, m), 0.02 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 191.0 (1), 145.2 (1), 141.2 (0), 132.3 (0), 123.6 (1), 95.0 (2), 66.7 (2), 65.3 (2), 30.6 (2), 27.4 (2), 27.3 (2), 25.8 (3), 18.2 (2), 17.8 (3), -1.31 (3); **IR** (film): 2954s, 2922s, 2874s, 1679vs, 1448m, 1410w, 1376m, 1249s, 1195m, 1153m, 1112s, 1064s, 1030s, 937m, 920m, 860s, 836s, 758w, 694m cm^{-1}; **LRMS** (CI, NH_3) m/z: 330 (M+H+NH_3, 7%), 313 (M+H, 0.5), 285 (6), 267 (6), 255 (25), 237 (7), 195 (15), 177 (12), 165 (100), 147 (13), 107 (13), 90 (46), 35 (47).

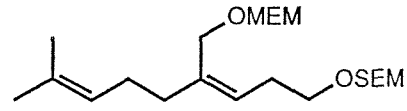
(3Z)-1-(2'-Trimethylsilylethoxymethoxy)-4-hydroxymethyl-8-methyl-3,7-nonadiene (110).



Butyllithium (1.6 M in hexanes, 13.6 ml, 21.8 mmol) was added, under nitrogen, to a stirred solution of (3Z)-1-(2'-trimethylsilylethoxymethoxy)-4-trimethylstannyl-8-methyl-3,7-nonadiene (**107**) (6.50 g, 14.5 mmol) in dry THF (100 ml) at -80°C. The resulting mixture was allowed to warm slowly to r. t. over a 2.5 h period, then paraformaldehyde (1.30 g, 43 mmol) was then added and the resulting solution stirred for 2 h at r. t.. The mixture was then poured into 2M HCl (150 ml) and the product extracted into

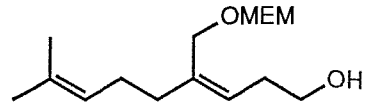
ether (4 x 150 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 20% EtOAc in light petroleum eluant), the *title compound* being isolated as a colourless oil (3.99 g, 12.69 mmol, 87%); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.34 (1H, t, J 7.9), 5.13-5.08 (1H, m), 4.66 (2H, s), 4.05 (2H, bs), 3.63-3.55 (2H, m), 3.55 (2H, t, J 5.9), 2.43-2.34 (3H, overlapping bs and apparent q, J 6.6), 2.14-2.12 (4H, A_2B_2 system appearing as a single broad peak), 1.68 (3H, s), 1.60 (3H, s), 0.96-0.89 (2H, m), 0.02 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 142.0 (0), 131.8 (0), 124.7 (1), 124.1 (1), 94.8 (2), 66.7 (2), 65.3 (2), 60.0 (2), 36.3 (2), 28.4 (2), 27.0 (2), 25.8 (3), 18.1 (2), 17.8 (3), -1.3 (3); **IR** (film): 3422bs, 2954s, 2922s, 2873s, 1670w, 1439m, 1377m, 1249s, 1191m, 1153m, 1112s, 1065s, 1027s, 938m, 921m, 860s, 836s, 758m, 694m cm^{-1}; **LRMS** (CI, NH_3) m/z: 332 ($M+H+NH_3$, 39%), 315 (M+H, 10), 297 (6), 285 (14), 269 (34), 257 (8), 239 (15), 214 (16), 197 (78), 179 (100), 167 (56), 149 (46), 90 (61), 35 (12).

(3Z)-1-(2'-Trimethylsilylethoxymethoxy)-4-(methoxyethoxymethoxymethyl)-8-methyl-3,7-nonadiene (111).



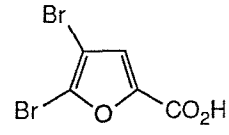
A solution of (3Z)-1-(2'-trimethylsilylethoxymethoxy)-4-hydroxymethyl-8-methyl-3,7-nonadiene (**110**) (0.205 g, 0.65 mmol), and N,N-diisopropylethylamine (0.30 ml, 0.22 g, 1.72 mmol) in dry CH_2Cl_2 (5 ml) was treated with MEM-chloride (0.15 ml, 0.16 g, 1.31 mmol) and the resulting solution stirred at r. t. for 4.5 h. The mixture was then poured into 2M HCl (20 ml) and the product extracted into CH_2Cl_2 (4 x 20 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 10% EtOAc in petrol eluant), and the *title compound* isolated as a colourless oil (0.196 g, 0.49 mmol, 75%); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.44 (1H, t, J 7.1), 5.1-5.07 (1H, bm), 4.71 (2H, s), 4.66 (2H, s), 4.09 (2H, s), 3.73-3.68 (2H, m), 3.65-3.55 (4H, m), 3.53 (2H, t, J 6.8), 3.40 (3H, s), 2.39 (2H, apparent q, J 7), 2.12-2.08 (4H, A_2B_2 system appearing as a single broad peak), 1.67 (3H, s), 1.59 (3H, s), 0.97-0.85 (2H, m), 0.02 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 137.4 (0), 131.6 (0), 125.7 (1), 124.2 (1), 94.8 (2), 94.8 (2), 71.9 (2), 67.6 (2), 66.9 (2), 65.1 (2), 64.7 (2), 59.1 (3), 35.6 (2), 28.4 (2), 26.8 (2), 25.8 (3), 18.2 (2), 17.8 (3), -1.3 (3); **IR** (film) 2923s, 2879s, 1452m, 1377m, 1249s, 1200m, 1172m, 1111s, 1045s, 938m, 921m, 860s, 836s, 758w, 734w, 694m cm^{-1}; **LRMS** (CI, NH_3) m/z: 420 ($M+H+NH_3$, 100%), 327 (3), 299 (3), 285 (2), 269 (11), 209 (21), 195 (5), 179 (29), 165 (13), 149 (8), 90 (23), 30 (10).

(3Z)-4-(Methoxyethoxymethoxymethyl)-8-methyl-3,7-nonadien-1-ol (112).



Tetrabutylammonium fluoride (1M solution in THF, 5.00 ml, 5.0 mmol) was added to (3Z)-1-(2'-trimethylsilylethoxymethoxy)-4-methoxyethoxymethoxymethyl-8-methyl-3,7-nonadiene (**111**).(0.403 g, 1.0 mmol) and the THF removed *in vacuo*, keeping the mixture free from moisture at all times. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (0.50 ml) was then added, and the resulting mixture stirred at 80°C for 3 h. The mixture was then diluted with ether (20 ml) and poured into water (20 ml). The product was extracted into ether (3 x 20 ml), and the combined extracts then washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 1:1 EtOAc and petrol eluant), to give the *title compound* (0.215 g, 0.^^8 mmol, 79%) as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.38 (1H, t, J 7.7), 5.10-5.00 (1H, m), 4.67 (2H, s), 4.05 (2H, s), 3.70-3.65 (2H, m), 3.60-3.50 (4H, m), 3.56 (3H, s), 2.54 (1H, bs), 2.32 (2H, apparent q, J 6.8), 2.08 (4H, A_2B_2 system appearing as a single broad peak), 1.63 (3H, s), 1.55 (3H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 138.1 (0), 131.8 (0), 126.4 (1), 124.0 (1), 94.5 (2), 71.8 (2), 66.8 (2), 64.4 (2), 61.9 (2), 59.0 (3), 35.8 (2), 31.3 (2), 26.7 (2), 25.7 (3), 17.7 (3); **IR** (film) 3424bs, 2926s, 2881s, 1670w, 1451m, 1376m, 1243m, 1200m, 1172m, 1108s, 1045s, 985m, 941m, 849m cm^{-1} ; **LRMS** (CI, NH_3) m/z: 290 (M+H+NH_3, 50%), 273 (M+H, 10), 214 (25), 197 (100), 179 (99), 167 (46), 149 (12), 135 (10), 122 (7), 109 (7); **HRMS** Found: M+H+NH_3 290.2331, $C_{15}H_{32}O_4N$ (M+H+NH_3) requires 290.2339.

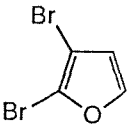
4,5-Dibromo-2-furoic acid (160).



A solution of bromine (25.0 ml, 0.49 mol) in dry CCl_4 (20 ml) was added dropwise over 4 h to a mechanically stirred, gently refluxing, solution of methyl 2-furoate (**159**) (20.0 g, 0.16 mol) in CCl_4 (50 ml); a vigorous evolution of gas was observed during the addition. After complete addition of the bromine, the mechanical stirrer was replaced with a magnetic stirrer and the mixture heated under gentle reflux for 24 h, and then stirred at r. t. for a further 48 h. Nitrogen gas was then bubbled through the mixture to remove HBr and most of the excess bromine. The mixture was then poured into saturated aqueous Na_2CO_3 (100 ml) and the product extracted into CH_2Cl_2 (4 x 50 ml). The extracts were combined, washed with saturated aqueous sodium sulphite (2 x 100 ml), a further portion of saturated aqueous Na_2CO_3, brine, and dried (Na_2SO_4). The solvent was then removed by rotary evaporation to give a yellow viscous oil which solidified to a solid mass when refrigerated. This mixture of methyl bromofuroates was hydrolysed by heating with mechanical stirring for 8 h at 60-65°C in 4M aqueous sodium hydroxide (250ml). The resulting mixture was then cooled and allowed to stand at r. t. for 16 h, whereupon a thick white precipitate of water-insoluble

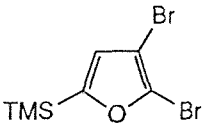
sodium dibromofuroates formed. The precipitate was filtered off and washed with ether to remove any organic impurities. It was then recombined with the aqueous reaction liquors and ether (300 ml) added. The mixture was acidified by adding ice (90 g) and concentrated HCl (90 ml) with vigorous stirring. The ether layer was separated and the aqueous phase extracted with ether (5 x 200 ml). The combined ether phases were then washed with water until the aqueous phase was *ca* pH 4. The ether solution was dried ($MgSO_4$) and the solvent removed by rotary evaporation to give a waxy, cream-coloured solid consisting mainly of the *title compound* along with minor amounts of a tribromo derivative (detected by LRMS) (31.9 g, *ca.* 0.12 mol, *ca.* 73%): **^{1}H NMR** (CD_3OD, 270MHz) δ = 7.47 (1H, s), 5.26 (1H, bs); **^{13}C NMR** (CD_3OD, 68MHz) δ = 159.9 (0), 148.5 (0), 129.5 (0), 123.0 (1) 104.9 (0); **IR** (nujol mull): 3000-2500bs, 1680vs, 1581s, 1418s, 1341s, 1299vs, 1191vs, 1089w, 985s, 952m, 852w, 761m, 618w, 570s; **LRMS** (70 eV EI) m/z: 270 (M^+, 100%), 253 (M-OH, 15), 226 (14), 197 (18), 119 (16), 118 (17), 117 (18), 116 (17), 44 (22), 37 (26).

2,3-Dibromofuran (30).



A stirred mixture of crude 4,5-dibromo-2-furoic acid (**160**) (20.2 g, 75 mmol) and copper bronze (8.60 g, 0.135 mol) in quinoline (100 ml) was heated to 180°C for 40 min during which time a vigorous evolution of gas was observed. The resulting dark coloured mixture was cooled and poured into a mixture of ice cold 6M aqueous HCl (300 ml) and ether (200 ml). The mixture was stirred for 1 h and then filtered through celite covered with a layer of sand in order to remove copper residues. The resulting heterogeneous mixture was separated and the aqueous phase extracted with ether (4 x 200 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and decolourised with activated charcoal. The solvent was then removed by distillation to give the crude product as a pale brown oil which was purified by short path distillation to give the *title compound* (8.6 g, 38.1 mmol, 51%) as a colourless oil: b.p. 58-59°C/13 mmHg. Lit.[201] b.p. 55-56°C/12 mmHg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.43 (1H, d, J 2.1), 6.48 (1H, d, J 2.1); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 144.8 (1), 123.3 (0), 115.7 (1), 101.8 (0); **IR** (film): 3156w, 3130w, 1684w, 1552m, 1484s, 1349m, 1192s, 1155s, 1107w, 1039s, 956s, 909w, 881s, 842w, 728s, 612m, 592s; **LRMS** (70 eV, EI) m/z: 226 (M^+, 100%), 197 (M-CHO, 12), 145 (M-Br, 2), 117 (48), 38 (25), 37 (23), 28 (12). The mass spectrum also showed that a trace of a tribromofuran was present.

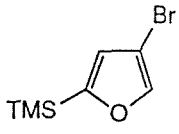
2-Trimethylsilyl-4,5-dibromofuran (31).



Butyllithium (1.6M in hexanes, 50 ml, 80 mmol) was added dropwise, under nitrogen, to a stirred solution of diethylamine (8.80 ml, 6.22 g, 85.1 mmol) in dry THF (140 ml) at -30°C, and the mixture stirred for 20 min.

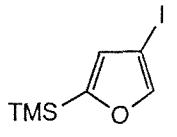
The temperature was then lowered to -80°C and a solution of 2,3-dibromofuran (**30**) (13.0 g, 57.6 mmol) in THF (150 ml) added dropwise. The resulting solution was stirred for 90 min, whereupon chlorotrimethylsilane (17.4 ml, 14.9 g, 137 mmol) was added and the mixture allowed to warm slowly to r. t. The mixture was then poured into saturated aqueous NH_4Cl solution and the products extracted into ether (4 x 100 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated*in vacuo* to a dark yellow oil which was purified by distillation to give the *title compound* (14.6 g, 49 mmol, 85%) as a colourless oil: b.p. 134-140°C/12-15 mm Hg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 6.34 (1H, s), 0.35 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 160.2 (0), 126.3 (0), 114.9 (1), 111.8 (0), -1.5 (3). **IR** (film): 3141w, 2960s, 2899w, 1537s, 1463s, 1410w, 1317s, 1252s, 1192w, 1164s, 1064m, 971s, 929s, 844s, 791m, 760s, 701w, 634m; **LRMS** (70eV EI) m/z: 300, 298, 296 (M^+, 24, 50, 23%), 285, 283, 281 (M^+-Me, 54, 100, 53), 257, 255, 253 (9, 16, 8), 229, 227, 225 (18, 36, 18), 205, 203, 201 (21, 41, 20), 139, 137 (62, 61), 73 (30), 43 (20).

2-Trimethylsilyl-4-bromofuran (32).



To a magnetically stirred solution of 2-trimethylsilyl-4,5-dibromofuran (**31**) (12.51 g, 42.0 mmol) in dry ether (150 ml) at -80°C under nitrogen, was added dropwise a solution of butyllithium (1.7M in hexanes, 26.0 ml, 44.2 mmol). After the addition was complete, the mixture was stirred for 5 min and then poured into saturated aqueous NH_4Cl. The product was extracted into ether (4 x 100 ml) and the combined extracts washed with brine, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was purified by kugelrohr distillation to give the *title compound* (6.01 g, 27.4 mmol, 65%) as a colourless oil: b.p. 140°C(bath)/10 mm Hg; **^{1}H NMR** (270 MHz) δ = 7.62 (1H, d, J 0.6), 6.63 (1H, d, J 0.6), 0.28 (9H, s); **^{13}C NMR** (68 MHz) δ = 162.3 (0), 145.0 (1), 122.7 (1), 99.7 (0), -1.7 (3); **IR** (film): 3147w, 2960m, 2900w, 1527w, 1464w, 1409w, 1321m, 1252s, 1204s, 1139w, 1110s, 1062s, 998w, 951w, 923m, 904m, 843s, 759m, 700w, 632w, 588s cm^{-1}; **LRMS** (70eV EI) m/z: 218 (M^+, 42%), 203 (M-Me, 98), 173 (2), 147 (12), 137 (73), 123 (5), 109 (6), 95 (6), 73 (14), 43 (15).

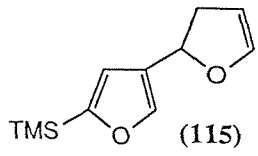
2-Trimethylsilyl-4-iodofuran (113).



To a solution of 2-trimethylsilyl-4-bromofuran (**32**) (2.18 g, 9.95 mmol) in dry ether (50 ml), under nitrogen, was added dropwise a solution of *s*-butyllithium (1.3M in cyclohexane, 8.0 ml, 10.4 mmol) at -80°C, and the resulting solution stirred for 30 min. Iodine (7.60 g, 29.9 mmol) was then added in small portions over 5 min and the solution stirred for 1h whilst warming to -50°C. The mixture was poured into 0.5M citric acid solution (50 ml) and the product extracted into ether (4 x 50 ml). The combined extracts were washed with saturated aqueous sodium sulphite, brine and dried ($MgSO_4$). The solvent was then removed by rotary evaporation and the prod-

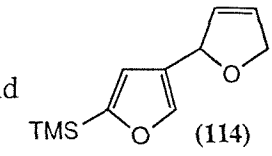
uct kugelrohr distilled from copper powder to give the *title compound* (2.07 g, 7.8 mmol, 78%) as a very pale yellow oil, b. p. (bath) 150°C/12 mmHg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.61 (1H, d, J 0.6), 6.68 (1H, d, J 0.6), 0.28 (9H, s). **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 162.8 (0), 149.6 (1), 126.4 (1), 63.9 (0), -1.6 (3). **IR** ($CDCl_3$): 2962m, 1309w, 1252s, 1204m, 1106s, 844s, 772m, 632m, 589m cm^{-1}. **LRMS** (70 eV EI) m/z: 266 (M^+, 89%), 251 (M-Me, 100), 185 (75), 124 (9), 84 (12), 73 (15), 43 (10).

2-(2'-Trimethylsilylfuran-4'-yl)-2,3-dihydrofuran (115) and 2-(2'-Trimethylsilylfuran-4'-yl)-2,5-dihydrofuran (114).



(115)

and

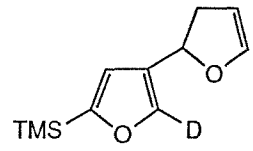


(114)

A solution of triphenylphosphine (0.060 g, 2.28 mmol) and palladium (II) acetate (0.050 g, 2.23 mmol) in dry DMF (10 ml) was stirred at 80°C under nitrogen for 20 min to produce a dark brown solution. Potassium acetate (2.20 g, 22.4 mmol), anhydrous *tetra-n*-butylammonium chloride (2.08 g, 7.48 mmol), 2-trimethylsilyl-4-iodofuran (**113**) (1.99 g, 7.48 mmol) and 2,3-dihydrofuran (**60**) (4.0 ml, 3.71 g, 52.9 mmol) were then added, and the resulting mixture stirred at 80°C, under reflux, for 24 h. The mixture was then poured into water (50 ml) and the products extracted into ether (4 x 50 ml). The combined extracts were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The products were then purified by flash column chromatography (SiO_2, 1% ether in light petroleum eluant) to give the *title compounds* as colourless oils in the respective order of elution; *2-(2'-trimethylsilylfuran-4'-yl)-2,3-dihydrofuran* (**115**) (0.345 g, 1.66 mmol, 22%): **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.63 (1H, s), 6.67 (1H, s), 6.39-6.36 (1H, apparent q, J 2.5), 5.49 (1H, dd, J 10.4 and 8.5), 4.98 (1H, apparent q, J 2.5), 2.95 (1H, ddt, J 15.0, 10.4 and 2.5), 2.64 (1H, ddt, J 15.0, 8.5 and 2.5), 0.26 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 162.1 (0), 145.2 (1), 143.8 (1), 126.9 (0), 118.9 (1), 99.4 (1), 75.5 (1), 36.3 (2), -1.5 (3); **IR** (film): 3106s, 2958s, 2899s, 2861m, 1619s, 1597m, 1478w, 1454w, 1408w, 1376w, 1340w, 1251s, 1136s, 1079s, 1051s, 941m, 912s, 844s, 758s, 706s, 631s cm^{-1}; **LRMS** (CI, NH_3): m/z = 226 ($M+H+NH_3$, 17%), 209 (M+H, 100), 179 (5), 119 (11), 90 (27), 73 (6);

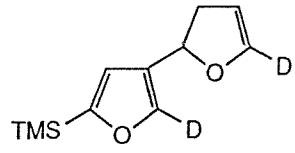
and *2-(2'-trimethylsilylfuran-4'-yl)-2,5-dihydrofuran* (**114**) (0.51 g, 2.47 mmol, 33%): **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.10759 (1H, s), 6.58 (1H, s), 6.06-6.01 (1H, m), 5.90-5.85 (1H, m), 5.82-5.76 (1H, m), 4.84-4.65 (2H, m), 0.26 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 161.7 (0), 143.9 (1), 128.9 (1), 127.3 (1), 126.3 (0), 118.9 (1), 79.8 (1), 75.1 (2), -1.6 (3); **IR** (film): 2985s, 2897m, 2851m, 1677w, 1592w, 1565w, 1251s, 1074s, 1020m, 911m, 845s, 786m, 758s, 699w, 631m cm^{-1}; **LRMS** (70 eV EI) m/z: 208 (M^+, 56%), 207 (24), 193 (M-Me, 14), 180 (18), 167 (89), 165 (23), 91 (30), 75 (41), 73 (TMS, 100).

2-(2'-Trimethylsilyl-5'-deuterofuran-4'-yl)-2,3-dihydrofuran (116)



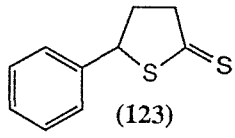
t-Butyllithium (1.7M solution in hexanes, 0.60 ml, 1.02 mmol) was added dropwise, under argon, to a THF (5 ml) solution of 2-(2'-trimethylsilylfuran-4'-yl)-2,3-dihydrofuran (**115**) (0.10 g, 0.50 mmol) at -80°C. The resulting yellow solution was stirred at this temperature for 1 h, then treated with deuterium oxide (1 ml) and allowed to warm to r. t. The mixture was then poured into saturated aqueous NH_4Cl (20 ml) and the products extracted into ether (4 x 20 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. The product was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) and the *title compound* collected as a colourless oil (0.084 g, 0.41 mmol, 80%), which contained small quantities of decomposition products: **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 6.67 (1H, s), 6.37 (1H, apparent q, J 2.5), 5.48 (1H, dd, J 10.4 and 8.5), 4.98 (1H, apparent q, J 2.5), 2.95 (1H, ddt, J 15, 10.4 and 2.5), 2.64 (1H, ddt, J 15, 8.5 and 2.5), 0.26 (9H, s); **LRMS** (70 eV EI) m/z: 209 (M^+, 55%), 194 (M-Me, 9), 180 (13), 177 (15), 166 (11), 150 (6), 135 (5), 124 (5), 119 (8), 92 (22), 75 (34),73 (100), 59 (12), 45 (12).

2-(2'-Trimethylsilyl-5'-deuterofuran-4'-yl)-5-deutero-2,3-dihydrofuran (118).

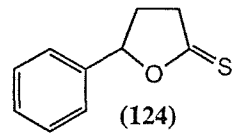


t-Butyllithium (1.7M solution in hexanes, 2.0 ml, 3.4 mmol) was added dropwise, under argon, to a solution of 2-(2'-trimethylsilylfuran-4'-yl)-2,3-dihydrofuran (**115**) (0.072 g, 0.35 mmol) in THF (5 ml) at -80°C. The resulting yellow solution was stirred for 20 min, then treated with deuterium oxide (1 ml) and allowed to warm to r. t. The reaction mixture was poured into saturated aqueous NH_4Cl (20 ml) and the products extracted into ether (4 x 20 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. The product was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) and the *title compound* collected as a colourless oil (0.056 g, 0.27 mmol, 76%); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 6.67 (1H, s), 5.49 (1H, dd, J 10.2 and 8.5), 4.98 (1H, t, J 2.4), 2.95 (1H, ddd, J 15, 10.2 and 2.4), 2.63 (1H, ddd, J 15, 8.5 and 2.4), 0.27 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 161.9 (0), 145.0 (CD, J ^{13}C-D 29), 143.5 (CD, J 13C-D 30), 126.7 (0), 118.5 (1), 99.1 (1), 75.5 (1), 36.3 (2),
-1.6 (3); **IR** ($CHCl_3$): 2961s, 2900w, 2252m, 1539s, 1455w, 1408w, 1315w, 1252s, 1162w, 1138m, 1090s, 1041s, 964s, 845s cm^{-1}; **LRMS** (70 eV EI) m/z: 210 (M^+, 30%), 195 (M-Me, 5), 180 (8), 167 (7), 149 (6), 120 (6), 105 (6), 93 (16), 83 (7), 75 (22), 73 (TMS, 100), 57 (19), 45 (9), 41 (16).

5-Phenyltetrahydrothiophen-2-thione (123) and 5-Phenyltetrahydrofuran-2-thione (124).


(123)

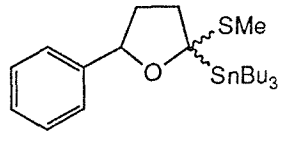
and


(124)

Lawesson's reagent (0.27 g, 0.67 mmol) was added, under nitrogen, to a stirred solution of 5-phenyltetrahydrofuran-2-one (**122**) (0.20 g, 1.23 mmol) in dry toluene (5 ml) and the mixture heated, under gentle reflux for 5 h. The mixture was cooled to r. t. and any solid by-products removed by filtration through a celite pad; the residues being washed with toluene. The filtrate was then concentrated *in vacuo* and the crude product purified by flash column chromatography (SiO_2, 5% EtOAc in light petroleum eluant) to give the *title compounds* in their respective order of elution; *5-phenyl-tetrahydrothiophen-2-thione* (**123**) (0.014 g, 0.072 mmol, 6%), a yellow foul smelling wax: **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.51-7.31 (5H, m), 5.30 (1H, dd, J 10.2 and 5.6), 3.40 (1H, ddd, J 17.5. 6.8 and 3), 3.09 (1H, ddd, J 17.5, 11.2 and 6.5), 2.81 (1H, m); **LRMS** (70 eV EI) m/z: 194 (M^+, 62%), 149 (28), 117 (100), 115 (12), 91 (15), 77 (9);

and *5-phenyl-tetrahydrofuran-2-thione* (**124**) (0.121 g, 0.62 mmol, 55%) a viscous yellow oil which solidified on refrigeration: **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.50-7.30 (5H, m), 5.87-5.81 (1H, dd, J 8.5 and 6.8), 3.29 (1h, ddd, J 18.7, 8.7 and 4.2), 3.15 (1H, ddd, J 18.7, 9.5, and 8.7), 2.78-2.62 (1H, m), 2.33-2.18 (1H, m). **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 222.1 (0), 138.0 (0), 128.9 (1), 128.8 (1), 125.8 (1), 90.9 (1), 45.0 (2), 32.4 (2). **IR** ($CHCl_3$) 3017m, 1496w, 1454w, 1419w, 1337s, 1276m, 1236s, 1164s, 1139s, 996w, 920m, 870m cm^{-1}; **LRMS** (70 eV EI) m/z: 178 (M^+, 76%), 123 (17), 122 (11), 118 (37), 117 (100), 103 (10), 91 (25), 77 (11).

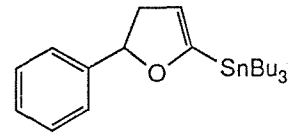
5-Phenyl-2-(*tri-n*-butylstannyl)-2-methanethiotetrahydrofuran (125).



n-Butyllithium (1.7M in hexanes, 4.60 ml, 7.82 mmol) was added dropwise, under nitrogen, to a stirred solution of N,N-diisopropylamine (1.10 ml, 0.79 g, 7.85 mmol) in THF (15 ml) at -30°C. The resulting solution was stirred at this temperature for 20 min, then *tri-n*-butyltin hydride (2.10 ml, 2.27 g, 7.81 mmol) was added and the solution stirred for a further 10 min. The temperature was then lowered to -80°C and a solution of 5-phenyltetrahydrofuran-2-thione (**124**) (0.76 g, 4.28 mmol) in THF (10 ml) added. The resulting mixture was stirred for 1 h, then iodomethane (0.60 ml, 1.37 g, 9.64 mmol) was added and the mixture allowed to warm slowly to r. t. The resulting mixture was poured into water (100 ml) and the products extracted into ether (4 x 500 ml). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 0.5% ether in light petroleum eluant) and the resulting mixture of diasterisomers collected as a colourless oil (1.50 g, 3.10 mmol, 72%);.**^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.54-7.24 (5H,

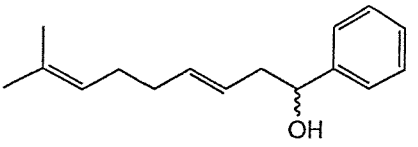
m), {5.17 (0.28H, dd, J 7 and 7.7), 4.94 (0.72H, dd, J 10.2 and 6.2)}, 2.62-2.40 (2H, m), 2.38-2.21 (1H, m), 2.21-2.07 (4H, overlapping s and m), 1.68-1.54 (6H, m), 1.46-1.36 (6H, sextet, J 7.3), 1.12-1.03 (6H, m), 1.00-0.91 (9H, two overlapping t, J 7.3); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = {142.9 (0), 142.5 (0)}, {128.4 (1), 128.4 (1)}, {127.4 (1), 127.3 (1)}, {126.9 (1), 126.2 (1)}, {91.2 (0), 90.2 (0)}, {84.2 (1), 79.1 (1)}, {39.7 (2), 38.8 (2)}, {35.3 (2), 34.5 (2)}, 29.2 (2, J {Sn-C} 20), 27.7 (2, J {Sn-C} 57),13.9 (3), 13.1 (3), 10.7 (2, J {Sn-C} 300); **IR** (film): 3063w, 3029w, 2956s, 2923s, 2870s, 2853s, 1742w, 1604w, 1493w, 1457w, 1376m, 1340w, 1292w, 1240w, 1180w, 1073m, 1013s, 962m, 932m, 898w, 896m, 781w, 755m, 698s, 659w cm^{-1}; **LRMS** (70 eV ei) m/z: 484 (M^+, 0.2%), 469 (M-Me, 23), 437 (M-SMe, 9), 427 (M-Bu, 20), 379 (37), 351 (10), 324 (15), 291 (40), 281 (17), 235 (47), 193 (100), 179 (57), 177 (57), 145 (91), 121 (28), 119 (22), 117 (78), 104 (25), 91 (25), 75 (24), 47 (17), 29 (18).

2-Phenyl-5-(*tri-n*-butylstannyl)-2,3-dihydrofuran (126).



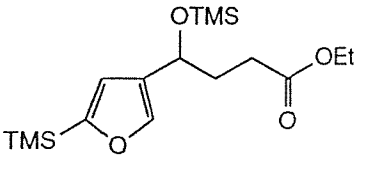
1,2,2,6,6-Pentamethylpiperidine (1.34 ml, 1.15 g, 7.41 mmol) was added, under argon, to a suspension of copper (I) trifluoromethanesulfonate•benzene complex (1.84 g, 7.32 mmol) in anhydrous benzene (20 ml) at r. t. A solution of 5-phenyl-2-*tri*-n-butylstannyl-2-methanethio-tetrahydrofuran (**125**) (0.88 g, 1.82 mmol) in benzene (20 ml) was then added, and the mixture stirred for 1 h. The resulting suspension was poured into a 1:1 NH_4Cl / NH_4OH saturated aqueous solution (50 ml) and the mixture stirred until the aqueous phase took on a deep blue colouration. A small amount of a yellow-green precipitate was also formed. The product was extracted into ether (4 x 50 ml) and the combined extracts washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (neutral activated Al_2O_3 *ex* Aldrich, partially deactivated with 5% w/w water; 0.5% ether in light petroleum eluant) to give the *title compound* as a colourless oil (0.35 g, 0.80 mmol, 44%): **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.36-7.20 (5H, m), 5.48 (1H, dd, J 10.8 and 8), 5.03 (1H, t, J 2.4, J {Sn-H} 11), 3.08 (1H, ddd, J 15.2, 10.8 and 2.4), 2.55 (1H, ddd, J 15.2, 8 and 2.4), 1.66-1.46 (6H, m), 1.42-1.28 (6H, sextet, J 7.2), 1.08-0.99 (6H, m), 0.91 (9H, t, J 7.2); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 162.6 (0), 144.5 (0), 128.5 (1), 127.3 (1), 125.8 (1), 110.8 (1, J {Sn-C} 62), 83.0 (1, J {Sn-C} 23), 39.3 (2, J {Sn-C} 27), 29.2 (2, J {Sn-C} 21), 27.4 (2, J {Sn-C} 58), 13.9 (3), 9.9 (2, J {Sn-C} 345); **IR** (film): 3029s, 2956s, 2927s, 2871s, 2853s, 1585m, 1493w, 1457m, 1418w, 1376wm 1340w, 1292w, 1259w, 1194w, 1151w, 1056s, 938m, 860m, 756m, 723m, 697s, 665m cm^{-1}; **LRMS** (CI, NH_3) m/z: 437 (M+H, 100%, Sn), 396 (20, Sn isotope pattern), 379 (3, Sn isotope pattern), 352 (5, Sn isotope pattern), 308 (13, Sn isotope pattern), 145 (11), 35 (22); **HRMS** (CI): Found: M+H 437.1856, $C_{22}H_{36}OSn$ requires M+H 437.1866.

(±)-(3*E*)-1-Phenyl-8-methyl-3,7-nonadien-1-ol (127).



t-Butyllithium (1.7M solution in hexanes, 1.0 ml, 1.7 mmol) was added, under argon, to a stirred solution of 1-iodo-4-methyl-3-pentene (**83**) (0.21 g, 0.999 mmol) in anhydrous pentane / ether (3:2, 5 ml) at -80°C, and the resulting solution stirred at this temperature for 10 min. A small amount of THF (0.5 ml) was then added, and the resulting yellow solution of 4-methyl-3-pentenyllithium (**84**) warmed to 0°C and stirred for 20 min to destroy excess *t*-BuLi. The mixture was then added to a solution of copper (I) bromide•dimethyl sulphide complex (10 mgs, 0.049 mmol, *ca* 19 mol%) in ether: dimethylsulphide (1:1, 5 ml) and the resulting cuprate mixture stirred for 10 min. A solution of 2-phenyl-5-(*tri-n*-butylstannyl)-2,3-dihydrofuran (**126**) (0.11 g, 0.25 mmol) in ether (2 ml) was then added, resulting in the formation of a pale yellow solution which turned deep orange whilst warming to r. t. over a 3 h period. The solution was poured into 5:1 aqueous NH_4Cl / NH_4OH (30 ml) and stirred for 10 min, the aqueous phase taking on a deep blue colouration. The product was extracted into ether (4 x 30 ml) and the combined extracts washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 10% ether in light petroleum eluant) to give the *title compound* (0.028 g, 0.12 mmol, 48%) as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.40-7.20 (5H, m), 5.63-5.54 (1H, dm, J 15.3), 5.42 (1H, ddd, J 15.3, 7.5 and 6.4), 5.11 (1H, bm), 4.68 (1H, dd, J 7.9 and 4.8), 2.55-2.34 (2H, m), 2.20 (0.4H, bs, O<u>H</u>), 2.10-2.00 (4H, A_2B_2 system, m), 1.71 (3H, d, J 1), 1.61 (3H, d, J 1.1); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 144.1 (0), 135.1 (1), 132.1 (0), 128.5 (1), 127.5 (1), 126.0 (1), 125.9 (1), 124.1 (1), 73.4 (1), 43.0 (2), 33.0 (2), 28.04 (2), 25.9 (3), 17.9 (3); **IR** (film): 3378s, 3029m, 2965s, 2923s, 2854s, 1723w, 1672w, 1604w, 1494m, 1453s, 1736m, 1320m, 1250m, 1199m, 1043s, 970s, 912w, 878w, 830w, 757s, 731m, 700s cm^{-1}; **LRMS** (CI, NH_3) m/z: 248 (M+H+NH_3, 45%), 231 (M+H, 20), 230 (248-H_2O, 100), 213 (29), 35 (27).

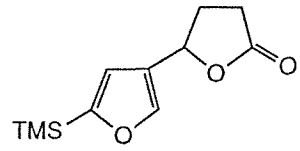
Ethyl 4-(2'-trimethylsilylfuran-4'-yl)-4-trimethylsilyloxybutanoate (130).



A solution of zinc iodide (6 mgs, 19 µmol), 2-trimethylsilyl-4-furancarboxaldehyde (**26**) (0.303 g, 1.80 mmol) and [(1-ethoxycyclo-propyl)oxy]-trimethylsilane (**129**) (0.65 ml, 0.626 g, 3.23 mmol) in dry CH_2Cl_2 (15 ml) was stirred at r. t., under nitrogen, for 22 h. Two drops of pyridine were then added and the solution stirred for 10 min, then poured into 0.5M citric acid solution. The product was then extracted into CH_2Cl_2 (2 x 50 ml) and the combined extracts washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) and the *title compound* (0.51 g, 1.49 mmol, 83%) isolated as a colourless oil;

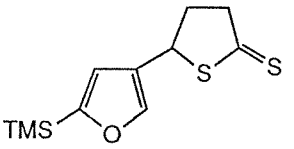
^{1}H NMR ($CDCl_3$, 270 MHz) δ = 7.47 (1H, s), 6.54 (1H, s), 4.71 (1H, t, J 6.2), 4.10 (2H, q, J 7.15), 2.40 -2.31 (2H, m), 2.03-1.93 (2H, apparent q, J 7.1), 1.25 (3H, t, J 7.15), 0.24 (9H, s), 0.06 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 173.8 (0), 161.1 (0), 143.2 (1), 129.0 (0), 118.6 (1), 66.6 (1), 60.4 (2), 34.2 (2), 30.4 (2), 14.4 (3), 0.2 (3), -1.5 (3); **IR** (film) 2959s, 2901s, 1737s, 1593w, 1446m, 1374m, 1335m, 1303m, 1251s, 1174s, 1079s, 974m, 941m, 912m, 844s, 757s, 697m, 666m, 630m cm^{-1}; **LRMS** (70 eV EI) m/z: 342 (M^+, 23%), 327 (M-Me, 3), 297 (M-OEt, 4), 241 (70), 73 (100); **HRMS** (EI): found: M^+ 342.1695, $C_{16}H_{30}O_4Si_2$ requires M^+ 342.1683.

5-(2'-Trimethylsilylfuran-4'-yl)-tetrahydrofuran-2-one (132).



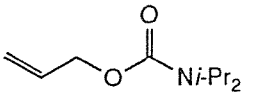
A solution of ethyl 4-(2'-trimethylsilylfuran-4'-yl)-4-trimethylsilyloxybutanoate (**130**) (0.17 g, 0.5 mmol) and lithium hydroxide (2M aqueous, 5 ml, 10 mmol) in methanol (20 ml) was stirred at r. t. for 18 h. The mixture was then acidified to pH 3 by the addition of glacial acetic acid and the resulting solution stirred at r. t. for 24 h. The methanol and the acetic acid were then removed by rotary evaporation, and the residues partitioned between 2M HCl (50 ml) and ethyl acetate (50 ml). The organic products were extracted into ethyl acetate (4 x 50 ml) and the combined extracts washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting hydroxy-acid mixture was then dissolved in dry THF (5 ml). Diethyl azodicarboxylate (0.09 ml, 0.10 g, 0.57 mmol) was added to a solution of triphenylphosphine (0.15 g, 0.57 mmol) in dry THF (2 ml) at -80°C under nitrogen and the resulting solution stirred for 10 min, a thick white precipitate being formed. The hydroxy-acid solution was then added and the resulting suspension stirred for 30 min, then warmed to r. t.. and stirred for 5 h. The THF was then removed *in vacuo* and the product purified by flash column chromatography (SiO_2, 20% EtOAc in petrol eluant), to give the *title compound* (81mgs, 0.36 mmol, 73%) as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.63 (1H, s), 6.61 (1H, s), 5.47 (1H, apparent t, J 6.9), 2.65-2.51 (3H, m), 2.29-2.16 (1H, m), 0.24 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 176.9 (0), 162.5 (0), 144.0 (1), 124.2 (0), 118.0 (1), 75.0 (1), 29.4 (2), 29.0 (2), -1.7 (3); **IR** (film) 2985m, 1777s, 1598w, 1460w, 1422w, 1329w, 1296w, 1251s, 1219m, 1183s, 1138m, 1079m, 1016m, 979w, 922m, 844s, 758m, 681w, 630w cm^{-1}; **LRMS** (70 eV EI) m/z: 224 (M^+, 89%), 209 (M-Me, 100), 191 (8), 181 (19), 165 (16), 153 (19), 151 (21), 91 (21), 75 (93), 73 (32), 59 (16); **LRMS** (CI, NH_3) m/z: 242 (M+H+NH_3, 100%), 225 (M+H, 47); **HRMS** (CI) found: M+H+NH_3 242.1216, $C_{11}H_{20}NO_3Si$ requires M+H+NH_3 242.1212.

5-(2'-Trimethylsilylfuran-4'-yl)-tetrahydrothiophen-2-thione (133).



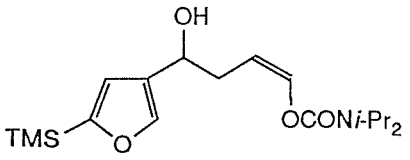
Lawesson's reagent (1.27 g, 3.14 mmol) was added, under nitrogen, to a solution of 5-(2'-trimethylsilylfuran-4'-yl)-tetrahydrofuran-2-one (**132**) (0.673 g, 3.00 mmol) in toluene (25 ml) and the resulting mixture heated under gentle reflux for 5 h. TLC showed the development of only one major product during that time. Chromatography grade silica gel-60 was then added to the the reaction mixture and the solvent evaporated *in vacuo*. The resulting silica-bound, pre-absorbed product, was then purified by flash column chromatography (SiO_2, 5% EtOAc in light petroleum eluant) to give the *title compound* as a yellow coloured wax (0.23 g, 0.90 mmol, 30%); **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.64 (1H, s), 6.65 (1H, s), 5.24 (1H, dd, J 9.4 and 5.7), 3.32 (1H, ddd, J 17.9, 6.7 and 3.8), 3.08 (1H, ddd, J 17.9, 10.4 and 6.7), 2.75 (1H, dddd, J 12.7, 6.7, 5.7 and 3.8), 2.50 (1H, dddd, J 12.7, 9.4, 10.4 and 6.7), 0.27 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 245.5 (C=S, 0), 162.7 (0), 144.0 (1), 123.3 (0), 119.0 (1), 55.7 (2), 52.2 (1), 38.7 (2), -1.6 (3); **IR** (nujol mull): 1587w, 1408w, 1295s, 1250s, 1192s, 1138s, 1075s, 1039s, 980m, 910m, 843s, 816s, 758s, 678m, 625s cm^{-1}; **LRMS** (70 eV EI) m/z: 256 (M^+, 90%), 241 (M-Me, 8), 223 (49), 179 (43), 165 (11), 151 (15), 123 (17), 91 (16), 83 (11), 75 (16), 73 (TMS, 100), 59 (18), 45 (12).

Allyl N, N-diisopropylcarbamate (152).



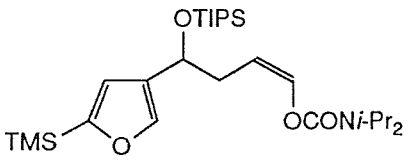
Allyl chloroformate (10.6 ml, 12.04 g, 99.9 mmol) was added dropwise, with stirring, to an ice-cold solution of N, N-diisopropylamine (30.0 ml, 21.7 g, 214 mmol) in CH_2Cl_2 (100 ml). The resulting mixture was warmed to r. t. and stirred for 48 h, then poured into water (200 ml) and the products extracted into CH_2Cl_2 (2 x 200 ml). The combined extracts were washed with 0.5M citric acid solution, saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The *title compound* (17.43 g, 94.1 mmol, 92%) was purified by kugelrohr distillation, and collected as a colourless oil; b. p. (bath) 150°C/1 mm Hg; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 5.92 (1H, ddt, J 17.2, 10.4 and 5.5), 5.26 (1H, apparent dq, J 17.2 and 1.5), 5.15 (1H, apparent dq, J 10.4 and 1.5), 4.56 (2H, apparent dt, J 5.5 and 1.5), 4.0-3.7 (2H, bm), 1.18 (12H, d, J 6.8); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 155.4 (0), 133.5 (1), 117.0 (2), 65.3 (2), 44.6-45.7 (rotamers, broad, 1), 21.1-21.0 (rotamers, broad, 3); **IR** (film): 3085w, 2971s, 2877m, 1696s, 1649m, 1544w, 1441s, 1368s, 1311s, 1219s, 1158s, 1135s, 1053s, 996m, 928m, 771m cm^{-1}; **LRMS** (CI, NH_3) m/z: 203 ($M+H+NH_3$, 11%), 186 (M+H, 100), 170 (6), 102 (5), 58 (5), 52 (12).

(±)-(1Z)-4-Hydroxy-4-(2'-trimethysilylfuran-4'-yl)-1-butenyl N, N-diisopropylcarbamate (153).



s-Butyllithium (1.3M solution in cyclohexane, 4.50 ml, 5.85 mmol) was added, under argon, to a dry ether (20 ml) solution of TMEDA (0.90 ml, 0.69 g, 6.0 mmol) at -80°C. The solution was stirred at this temperature for 20 min, then a solution of allyl N, N-diisopropylcarbamate (**152**) (1.0 g, 5.4 mmol) in ether (50 ml) was added and the resulting mixture stirred at -80°C for a further 45 min. Titanium (IV) isopropoxide (6.0 ml, 5.7 g, 20.0 mmol) was then added and the resulting solution stirred at -80°C for 45 min, turning deep orange in colour. 2-Trimethylsilyl-4-furancarboxaldehyde (**26**) (0.841 g, 5.0 mmol) was then added and the mixture allowed to warm to -20°C over a 2 h period. The mixture was then poured into 2M HCl (100 ml) and the products extracted into ether (4 x 100 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The product was purified by flash column chromatography, (SiO_2, 20% EtOAc in light petroleum eluant) to give the *title compound* (1.27 g, 3.58 mmol, 72%) as a colourless wax; m. p. 50-53°C; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.59 (1H, s), 7.14 (1H, dt, J 6.6 and 1.4), 6.63 (1H, s), 4.83-4.74 (1H, apparent q, J 7), 4.77-4.69 (1H, m), 4.10 (1H, bm, NC<u>H</u>Me_2), 3.82 (1H, bm, NC<u>H</u>Me_2), 2.74-2.54 (2H, m), 1.97 (1H, d, O<u>H</u>), 1.35-1.15 (12H, bm), 0.26 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 161.4 (0), 152.9 (0), 143.3 (1), 137.4 (1), 128.6 (0), 118.4 (1), 106.2 (1), 66.5 (1), 47.0-45.8 (rotamers, broad, 1), 33.9 (2), 21.6-20.5 (rotamers, broad, 3), -1.6 (3) ; **IR** (film): 3449bs, 3103w, 2967s, 1705vs, 1592w, 1473s, 1440s, 1371s, 1308s, 1250s, 1212s, 1188s, 1157s, 1134s, 1079s, 1055vs, 972w, 912m, 844s, 760s, 736m, 699w, 631m cm^{-1}; **LRMS** (CI, NH_3) m/z: 354 (M+H, 4%), 336 (M+H-H_2O,100), 185 (6), 128 (35), 102 (13), 35 (11); **HRMS** (CI): Found: M+H 354.2092. $C_{18}H_{32}NO_4Si$ requires M+H 354.2101.

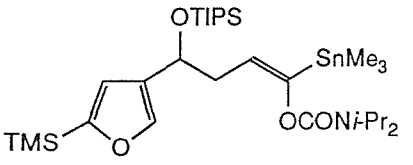
(±)-(1Z)-4-Triisopropylsilyloxy-4-(2'-trimethysilyl-furan-4'-yl)-1-butenyl N, N-diisopropylcarbamate (154).



2,6-Lutidine (0.10 ml, 0.092 g, 0.86 mmol) was added, under nitrogen, to an ice-cold solution of 4-hydroxy-4-(2'-trimethysilylfuran-4'-yl)-1-butenyl N, N-diisopropylcarbamate (**153**) (0.11 g, 0.30 mmol) in CH_2Cl_2 (10 ml), and the solution stirred for 5 min. Triisopropylsilyl trifluoromethane-sulphonate (0.12 ml, 0.14 g, 0.45 mmol) was then added and the mixture stirred for 10 min before being poured into 0.5M citric acid solution (30 ml). The product was extracted into CH_2Cl_2 (4 x 30 ml) and the combined extracts washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) to give the *title compound*

(0.14 g, 0.28 mmol, 92%) as an extremely viscous oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.49 (1H, s), 7.03 (1H, apparent dt, J 6.6 and 1.6), 6.59 (1H, s), 4.82 (1H, dd, J 7.1 and 5.4), 4.77-4.68 (1H, apparent dt, J 8.0 and 6.6), 4.06 (1H, bm, NC<u>H</u>Me_2), 3.81 (1H, bm, NC<u>H</u>Me_2), 2.75-2.64 (1H, dddd, J 14.3, 8.0, 5.4 and 1.6), 2.56-2.44 (1H, dddd, J 14.3, 7.1, 6.6 and 1.6), 1.25-1.22 (12H, m), 1.06-1.00 (21H, m), 0.24 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 160.6 (0), 152.9 (0), 143.0 (1), 136.3 (1), 129.4 (0), 119.0 (1), 106.5 (1), 67.3 (1), 46.8-45.8 (broad, rotamers, 1), 35.6 (2), 21.6-20.5 (broad, rotamers, 3), 18.2 (3), 18.1 (3), 12.5 (1), -1.5 (3); **IR** (film): 2961s, 2867s, 1711vs, 1465m, 1438m, 1370m, 1308s, 1289s, 1250s, 1213m, 1158m, 1133s, 1087s, 1061s, 1014w, 997w, 911m, 883m, 844s, 758m, 735m, 680m, 629m cm^{-1}; **LRMS** (CI, NH_3) m/z: 527 (M+H+NH_3, 3%), 510 (M+H, 2), 494 (M-Me, 0.5), 466 (M-Pr, 1), 398 (3), 353 (3), 336 (100), 325 (16), 128 (13), 102 (9), 90 (5), 35 (100); **HRMS** (CI): Found: M+H+NH_3 527.3655. $C_{27}H_{55}N_2O_4Si_2$ requires M+H+NH_3 527.3701.

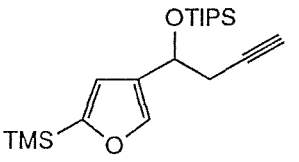
(±)-(1*E*)-1-Trimethylstannyl-4-triisopropylsilyloxy-4-(2'-trimethysilylfuran-4'-yl)-1-butenyl N, N-diisopropylcarbamate (156).



tert-Butyllithium (1.7M solution in pentane, 0.97 ml, 1.65 mmol) was added, under argon, to a solution of 4-triisopropylsilyloxy-4-(2'-trimethysilylfuran-4'-yl)-2-butenyl N, N-diisopropylcarbamate (**154**) (0.42 g, 0.83 mmol) in dry THF (20 ml) at -80°C, and the resulting yellow solution stirred at this temperature for 10 min. A solution of trimethyltin chloride (0.34 g, 1.71 mmol) in THF (10 ml) was then added, and the resulting solution allowed to warm to r. t. over a 2 h period. The mixture was then poured into water (50 ml) and the products extracted into ether (4 x 50 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 1% ether in light petroleum eluant) to give the *title compound* (0.37 g, 0.55 mmol, 66%) as an extremely viscous oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.50 (1H, s), 6.60 (1H, s), 5.00 (1H, dd, J 7.4 and 6.5), 4.86 (1H, t with Sn satellites, J 6.2, J {Sn-H} 32), 4.05 (1H, bm, NC<u>H</u>Me_2), 3.85 (1H, bm, NC<u>H</u>Me_2) 2.74 (1H, ddd, J 14.3, 7.4 and 6.2), 2.55 (1H, apparent dt, J 14.3 and 6.4), 1.22 (12H, d, J 6.8), 1.10-0.95 (21H, m), 0.25 (9H, s), 0.13 (9H, s with Sn satellites, J {Sn-H} 56); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 160.4 (0), 156.3 (0), 155.0 (0), 142.8 (1), 130.0 (0), 120.1 (1), 119.3 (1), 67.6 (1), 46.7-45.7 (rotamers, broad, 1), 37.3 (2), 21.6-20.6 (rotamers, broad, 3), 18.3 (3). 18.2 (3), 12.6 (1), -1.5 (3), -6.2 (3 with Sn satellites, J {Sn-C) 374); **IR** (film): 2963s, 2867s, 1690vs, 1532w, 1464m, 1437s, 1380m, 1370m, 1333s, 1287s, 1250s, 1212m, 1158m, 1135m, 1059s, 1013m, 911m, 883m, 843s, 766s, 680m, 630m, 607m cm^{-1};

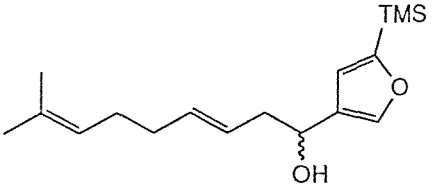
LRMS (CI, NH_3) m/z: 674 (M+H, 14%, Sn isotope pattern), 500 (100, Sn isotope pattern), 336 (46), 325 (37), 191 (11), 128 (15), 102 (26); **HRMS** (CI): Found: M+H 674.3075. $C_{30}H_{60}NO_4Si_2Sn$ requiresM+H 674.3083.

(±)-4-Triisopropylsilyloxy-4-(2'-trimethysilylfuran-4'-yl)-1-butyne (158).



4-Methyl-3-pentenyl magnesium bromide (0.41M solution in THF, 1.83 ml, 0.75 mmol) was added, under argon, to a stirred suspension of copper (I) bromide•dimethylsulphide complex (0.15 g , 0.75 mmol) in dry THF (10 ml) at -80°C, and the resulting cuprate mixture stirred for 0.5 h. In the meantime, *t*-butyllithium (1.7M solution in pentane, 0.90 ml, 1.53 mmol) was added, under argon, to a solution of 4-triisopropylsilyloxy-4-(2'-trimethysilylfuran-4'-yl)-2-butenyl N, N-diisopropylcarbamate (**154**) (0.38 g, 0.75 mmol) in dry THF (10 ml) at -80°C and the resulting yellow solution stirred for 10 min. The lithiated carbamate solution so produced was then added dropwise to the cuprate mixture at -80°C, and the resulting orange coloured mixture allowed to warm to r. t. over a 5 h period, taking on an orange/brown colouration. The reaction mixture was poured into a saturated aqueous 9:1 NH_4Cl / NH_4OH solution (30 ml) and stirred for 10 min until the aqueous phase took on a deep blue colouration. The products were extracted into ether (4 x 30 ml) and the combined extracts washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, light petroleum to 1% ether in light petroleum graduated eluant) to give the *title compound* (0.11 g, 0.27 mmol, 36%) as a colourless oil; **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.50 (1H, s), 6.68 (1H, s), 5.0-4.9 (1H, dd, J 7.3 and 5.4), 2.67 (1H, ddd, J 16.4, 5.4 and 2.7), 2.59-2.48 (1H, ddd, J 16.4, 7.3 and 2.7), 1.98 (1H, t, J 2.7), 1.15-0.95 (21H, m), 0.26 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 160.8 (0), 143.3 (1), 128.8 (0), 118.8 (1), 81.5 (1), 70.4 (0), 66.8 (1), 30.4 (2), 18.2 (3), 18.1 (3), 12.5 (1), -1.5 (3); **IR** (film): 3314m, 2944s, 2867s, 1593w, 1464m, 1384w, 1338w, 1251s, 1093s, 1014m, 911m, 883s, 844s, 757m, 680m, 626s cm^{-1}; **LRMS** (CI, NH_3) m/z: 365 (M+H, 47%), 321 (45), 292 (22), 275 (23), 208 (66), 191 (100), 90 (77), 35 (91).

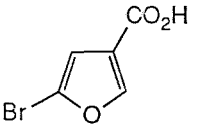
Attempted Synthesis of (±)-(3*E*)-1-(2'-trimethylsilylfuran-4'-yl)-8-methyl-3,7-nonadien-1-oL



t-Butyllithium (1.7M in pentane, 2.20 ml, 3.74 mmol) was added, under argon, to a solution of 1-iodo-4-methyl-3-pentene (**83**) (0.46 g, 2.19 mmol) in pentane / ether (3:2, 3.0 ml) at -80°C, and the resulting solution stirred for 10 min. Dry THF (0.5 ml) was then added and the yellow solution warmed to 0°C and stirred for 20 min to destroy excess *t*-BuLi. The resulting solu-

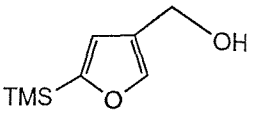
tion of 4-methyl-3-pentenyllithium (**84**) was then added to a suspension of copper (I) bromide•dimethylsulphide complex (0.05 g, 0.24 mmol) in ether (1 ml) at -80°C, and the resulting cuprate mixture stirred for 1.5 h. A solution of 1-trimethylstannyl-4-triisopropylsilyloxy-4-(2'-trimethysilylfuran-4'-yl)-2-butenyl N,N-diisopropylcarbamate (**156**) (0.37 g, 0.55 mmol) in ether (2 ml) was then added, and the mixture then stirred at -80°C for 18 h. The mixture was then poured into saturated aqueous 9:1 NH_4Cl / NH_4OH solution (30 ml) and stirred until the aqueous layer took on a deep blue colouration. The products were then extracted into ether (4 x 30 ml) and the combined extracts washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then dissolved in dry THF (10 ml) and treated, under argon, with tetrabutylammonium fluoride (1M solution in THF, 0.55 ml, 0.55 mmol) at r. t. The resulting mixture was stirred for 0.5 h then poured into water (50 ml) and the products extracted into ether (4 x 50 ml). The combined extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and the product purified by flash column chromatography (SiO_2, 10% EtOAc in light petroleum eluant). The product (Rf 0.42) was isolated as a colourless oil and was identified as 4-hydroxy-4-(2'-trimethysilylfuran-4'-yl)-2-butenyl N,N-diisopropylcarbamate (**153**) (0.11 g, 0.31 mmol, 57%).

2-Bromo-4-furoic acid (165).



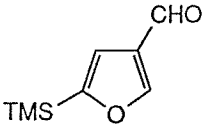
The *title compound* (15.2 g, 80 mmol, 64%) was prepared from 3-furoic acid (**164**) (14.1 g, 0.125 mol) and pyridinium hydrobromide perbromide (42.1 g, 0.132 mol) in glacial HOAc (60 ml) by the method of Ferraz and do Amaral.[169] To a solution of freshly prepared pyridinium hydrobromide perbromide (42.1 g, 0.132 mol) in glacial acetic acid (60 ml) was added portionwise 3-furoic acid (**164**) (14.1 g, 0.125 mol) with magnetic stirring. The resulting solution was heated at 40-45°C for 2 h, nitrogen being swept over the reaction mixture to remove liberated HBr. The bulk of the acetic acid was then removed by rotary evaporation at *ca.* 50°C and water (400 ml) added with efficient stirring to the residue. The crude *title compound* (15.2 g, 79.6 mmol, 57%) was collected by suction filtration, dried *in vacuo*, and used in the next step without further purification. The crude product was contaminated with approximately 5% of an isomeric bromofuroic acid.

2-Trimethylsilyl-4-furanmethanol (166).



Crude 2-bromo-4-furoic acid (**165**) (5.07 g, 26.5 mmol) in dry ether (200 ml) was cooled to -80°C and butyllithium (1.6M in hexanes, 42 ml, 67 mmol) added dropwise, with mechanical stirring. After the addition was complete the temperature was allowed to rise to -60°C and stirring continued for a further 40 min, whereupon chlorotrimethylsilane (9.4 g, 11.0 ml, 87 mmol) was added. The cooling bath was removed and the mixture allowed to warm to r. t. over 2 h and stirring continued at r. t. for a further 30 min. The mixture was poured into saturated aqueous NH_4Cl (200 ml) and the the product extracted into EtOAc (4 x 200 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$, brine and dried ($MgSO_4$). The residue obtained on concentration *in vacuo* was then dissolved in dry THF (50 ml) and added to a stirred suspension of $LiAlH_4$ (2.0 g, 53 mmol) in dry THF (30 ml) at 0°C, under nitrogen. After addition was complete the mixture was allowed to warm to r. t. and stirred for a further 2 h. The mixture was then carefully poured into iced water (200 ml) and acidified to pH 1 by adding conc. HCl. The products were extracted into EtOAc (4 x 100 ml) and the combined extracts washed with brine and dried ($MgSO_4$). The residue obtained on concentration *in vacuo* was purified by flash column chromatography (SiO_2, 20% EtOAc in light petroleum) to give the *title alcohol* (1.50 g, 8.80 mmol, 33% overall) as a colourless oil: **^{1}H NMR** ($CDCl_3$, 270 MHz) δ = 7.59 (1H, m, J 0.8), 6.66 (1H, broadened s), 4.53 (2H, d, J 0.96), 2.33 (1H, broad s), 0.26 (9H, d, J 0.8); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 161.8 (0), 144.2 (1), 125.2 (0), 119.9 (1), 56.5 (2), -1.6 (3); **IR** (film): 3331bs, 2958s, 2899s, 1709w, 1594w, 1409m, 1251s, 1160w, 1121m, 1077s, 1019s, 980s, 911s, 844s, 757s cm^{-1}; **LRMS** (CI, NH_3) m/z: 171 (M+H, 37%), 1710(M+H+NH_3-$H_2$0, 37), 153 (M+H-$H_2$0, 16), 132 (100), 115 (15), 98 (14), 90 (14), 81 (17), 35 (44).

2-Trimethylsilyl-4-furancarboxaldehyde (26).

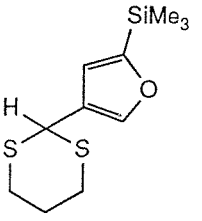


To a solution of 2-trimethylsilyl-4-bromofuran (**32**) (1.03 g, 4.7 mmol) in dry ether (25 ml) was added *s*-butyllithium (1.3M solution in cyclohexane, 4.3 ml, 5.6 mmol) at -70°C. The resulting solution stirred for 1 h, then freshly distilled N-methylformanilide (1.2 ml, 1.3 g, 9.7 mmol) was added and the stirring continued at -70°C for 20 min followed by 1 h at r. t. The mixture was poured into 0.5M citric acid solution and the organic products extracted into ether. The combined extracts were washed with 0.5M citric acid, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 2% ether in hexane eluant) to give the *title compound* (0.62 g, 3.68 mmol, 78%) as a colourless oil: **^{1}H NMR** (270 MHz) δ = 9.91 (1H, d, J 0.4), 8.22 (1H, d, 0.7), 6.94 (1H, apparent t, J 0.5), 0.24 (9H, s); **^{13}C NMR** (68 MHz) δ = 184.6 (1), 164.1 (0), 155.6 (1), 129.0 (0), 116.2 (1), -1.9 (3); **IR** (film): 3359w, 3105w, 2961s, 2901m, 2823m, 2780w, 2731w,

1734w, 1692s, 1568s, 1398m, 1372m, 1253s, 1137s, 1061s, 898s, 843s, 759s, 701m, 632m, 600s cm^{-1}; **LRMS** (70eV EI) m/z: 168 (M^+, 32%), 153 (M-Me, 100), 125 (39), 97 (24), 59 (10), 43 (14).

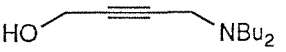
The *title compound* (2.05 g, 12.2 mmol, 79%) was also obtained by Swern oxidation[131] of 2-trimethylsilyl-4-furanmethanol (**163**) (2.63 g, 15.4 mmol, 79%) using the normal procedure.

2-Trimethysilyl-4-(1',3'-dithian-2'-yl)-furan (171).



To a magnetically stirred solution of 2-trimethylsilyl-4-furancarboxaldehyde (**26**) (0.84 g, 5.0 mmol) and 1,3-propanedithiol (0.50 ml, 0.53 g, 5.0 mmol) in $CHCl_3$ (10 ml) at -20°C, was added $BF_3 \cdot Et_2O$ (0.05 ml, 0.06 g, 0.4 mmol, 8 mol%). The cooling bath was removed and the mixture allowed to stir at ambient temperature for 7 h. The mixture was then washed with water (20 ml), 10% w/w aqueous KOH (20 ml), water (20 ml) and the organic layer dried over K_2CO_3. The residue obtained on evaporation of the solvent was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) to give the *title compound* (1.09 g, 4.22 mmol, 84%) as a white solid. A sample recrystallised from EtOH gave m.p. 92-93°C; **^{1}H NMR** ($CDCl_3$, 360 MHz): δ = 7.70 (1H, apparent t, J 0.6), 6.70 (1H, apparent d, J 0.6), 5.14 (1H, m), 2.99 (2H, ddd, J 14.5, 11.5, 2.7), 2.88 (2H, ddd, J 14.5, 5, 3.2), 2.15 (1H, dtt, J. 14.1, 4.2, 2.6), 1.92 (1H, m), 0.25 (9H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz): δ = 161.5 (0), 144.5 (1), 124.0 (0), 119.6 (1), 41.5 (1), 31.3 (2), 25.3 (2), -1.6 (3); **IR** ($CHCl_3$): 1960s, 2902s, 1585w, 1423m, 1359w, 1252s, 1216s, 1171m, 1125s, 1076s, 987m, 911s, 841s cm^{-1}; **LRMS** (70 eV, EI): m/z = 258 (M^+, 97%), 243 (7), 225 (8), 211 (9), 193 (19), 184 (73), 169 (100), 73 (64), 45 (17). **Elemental Analysis**: Found: C, 50.97; H, 6.92%. $C_{11}H_{18}OS_2Si$ requires C, 51.12; H, 7.02%.

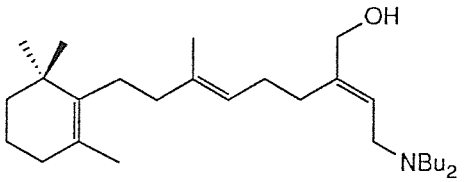
4-Di-n-butylamino-2-butyn-1-ol (166).



The *title compound* was prepared by the method of Salvador and Simon.[187] To a water (40 ml) solution of di-*n*-butylamine (100 ml, 76.7 g, 0.59 mol), adjusted to pH 9 by the addition of 50% H_2SO_4, was added formaldehyde (37-41% aqueous solution, 65 ml, *ca* 0.87 mol) followed by propargyl alcohol (28.0 g, 0.50 mol). After adding $CuSO_4 \cdot 5H_2O$ (3.0 g, 16 mmol) in water (25 ml), the pH was adjusted to *ca* 8 by the addition of triethylamine and the mixture refluxed for 18 h. The resultant brown suspension containing suspended Cu(0) was cooled to r. t. and poured into conc. NH_4OH (150 ml). The product was extracted into EtOAc (6 x 100 ml) and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give an orange oil which was distilled to give the *title compound* (88.6 g, 0.45 mol, 90%) as a pale yellow oil: b. p. 100-108°C/0.05 mmHg. Lit.[182] b. p. 125-126°C/0.5 mm Hg);

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 4.21 (3H, overlapping bs and t, J 1.7), 3.38 (2H, t, J 1.7), 2.41 (4H, m), 1.40 (4H, m), 1.27 (4H, m), 0.88 (6H, t, J = 7.1); **^{13}C NMR** ($CDCl_3$, 68 MHz) δ = 83.9 (0), 79.1 (o), 53.5 (2), 50.5 (2), 42.1 (2), 29.4 (2), 20.8 (2), 14.1 (3); **IR (film)**: 3376bs, 2958s, 2864s, 1655w, 1459s, 1377s, 1359s, 1325s, 1235m, 1176m, 1106s, 1024s, 949m, 902m, 839m, 786m, 735; **LRMS** (CI, NH_3): m/z = 198 (M+H, 100%), 180 (5), 154 (72), 112 (15).

(2*E*,6*E*)-9-(2',6',6'-Trimethyl-1'-cyclohexen-1'-yl)-7-methyl-3-hydroxymethyl-1-(N,N-di-*n*-butylamino)-2,6-nonadiene (168).

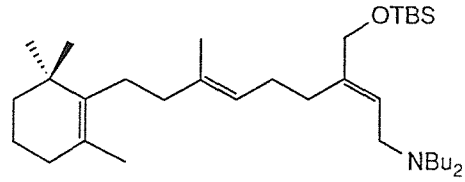


(3E)-4-Methyl-6-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-3-hexenylmagnesium bromide (**167**). To magnesium turnings (0.50 g, 20.6 g atom) and a small crystal of iodine covered with dry THF (5 ml), at 50°C, were added 3 drops of methyl iodide and approximately 1 ml of a solution of (3*E*)-1-bromo-4-methyl-6-(2',6',6'-trimethyl-1'-cyclohexenyl)-3-hexene (**40**) (2.99 g, 10.0 mmol) in dry THF (15 ml). The remaining homoallylic bromide solution was added dropwise over a 2.5 h period. After complete addition the solution was stirred under reflux at 50°C for a further 2 h. The Grignard solution was then transferred to a clean, dry storage vessel *via* cannula. The titer of the Grignard solution, (determined by reaction with triphenyltin chloride in THF and isolation of the (3*E*)-4-methyl-6-(2',6',6'-trimethyl-1'-cyclohexenyl)-3-hexenyl-triphenyltin) indicated that the desired Grignard reagent was formed in *ca* 88% yield.

To a magnetically stirred solution of 4-di-*n*-butylamino-2-butyn-1-ol (**166**) (0.90 g, 4.6 mmol) in ether (5 ml) was added dropwise, at r. t., EtMgBr (1.5M solution in ether, 3.1 ml, 4.6 mmol). Vigorous gas evolution was accompanied by the formation of a gelatinous white precipitate. After stirring for 5 min, (3*E*)-4-methyl-6-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-3-hexenylmagnesium bromide (**167**) (0.22 M, 26 ml, 5.7 mmol) was added. The precipitate dissolved and the resulting solution was refluxed for 8 h and then poured into cold saturated aqueous NH_4Cl with vigorous stirring. The organic layer was separated and the aqueous layer extracted with EtOAc (4 x 50 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 10% EtOAc in light petroleum) to give the *title compound* (1.63 g, 3.9 mmol, 85%) as a colourless oil: **^{1}H NMR** ($CDCl_3$, 360 MHz): δ = 5.56 (1H, t, J 6.6), 5.14 (1H, apparent t, J 6.0), 4.06 (2H, d, J 0.7), 3.14 (2H, d, J 6.6), 2.7 (1H, bs), 2.43 (4H, m), 2.12 (4H, m), 2.02 (4H, m), 1.89 (2H, t, J 6.2), 1.64 (3H, d, J 1.5), 1.60 (3H, s), 1.56 (2H, m), 1.42 (6H, m), 1.29 (4H, sextet, J 7.3), 0.99 (6H, s), 0.90 (6H, distorted t, J 7.3); **^{13}C NMR** ($CDCl_3$, 68 MHz): δ = 141.6 (0), 137.2 (0), 136.7 (0), 127.1 (0), 123.4 (1), 123.3 (1), 66.6 (2), 53.8 (2), 51.3 (2), 40.4 (2), 40.0 (2), 35.1 (0), 32.9 (2), 29.0 (2), 28.7 (3), 28.6 (2), 27.9 (2), 27.05 (2),

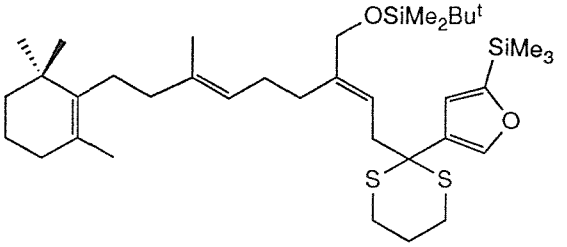
21.0 (2), 19.9 (3), 19.7 (2), 16.2 (3), 14.2 (3); **IR** (film): 3348bs, 2957s, 2931s, 2864s, 1664w, 1458m, 1379m, 1360m, 1302w, 1276w, 1204w, 1177w, 1154w, 1088m, 1068m, 1015m, 787m, 764m; **LRMS** (70 eV, EI): m/z = 417 (M^+, 47%), 386 (32), 374 (18), 280 (100), 224 (5), 210 (11), 137 (40), 95 (24), 86 (38), 81 (19), 55 (11), 41 (14); **HRMS** (EI): Found: M^+ 417.3965. $C_{28}H_{51}NO$ requires M^+ 417.3971.

(2*E*,6*E*)-9-(2',6',6'-Trimethyl-1'-cyclohexen-1'-yl)-7-methyl-3-[(*t*-butyldimethyl-silyloxy)-methyl]-1-(N,N-di-*n*-butylamino)-2,6-nonadiene (169).



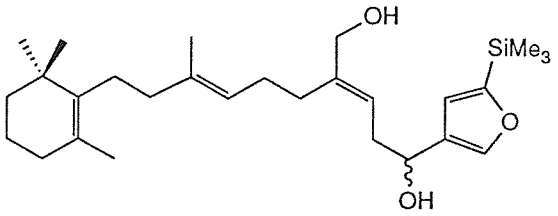
A solution of (2*E*, 6*E*)-9-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-7-methyl-3-hydroxymethyl-1-(N,N-di-*n*-butylamino)-2, 6-nonadiene (**168**) (1.41 g, 3.37 mmol), DMAP (20 mg), imidazole (0.57 g, 8.37 mmol), and *tert*-butyldimethylchlorosilane (0.76 g, 5.04 mmol) in dry CH_2Cl_2 (40 ml), was stirred at r. t. for 4 h. The mixture was then poured into water (50 ml) and the product extracted into CH_2Cl_2 (4 x 40 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*and the product purified by flash column chromatography (SiO_2, 10-20% EtOAc in light petroleum graduated eluant) to give *the title compound* (1.76 g, 3.30 mmol, 98%) as a colourless oil: **^{1}H NMR** ($CDCl_3$, 500 MHz) δ = 5.53 (1H, tt, J 6.6, 1.5), 5.14 (1H, m), 4.08 (2H, apparent q, J 1.5), 3.14 (2H, d, J 6.6), 2.40 (4H, m), 2.08 (4H, A_2B_2 system appearing as a single broad peak), 2.02 (4H, m), 1.90 (2H, t, J 6.4), 1.64 (3H, d, J 1.5), 1.60 (3H, s), 1.56 (2H, m), 1.42 (6H, m), 1.28 (4H, sextet, J 7.3), 0.99 (6H, s), 0.90 (9H, s), 0.895 (6H, t, 7.3), 0.06 (6H, s); **^{13}C NMR** ($CDCl_3$, 68 MHz): δ = 140.6 (0), 137.2 (0), 136.5 (0), 127.1 (0), 123.5 (1), 122.6 (1), 67.0 (2), 53.95 (2), 51.3 (2), 40.4 (2), 40.0 (2), 35.1 (0), 32.9 (2), 29.5 (2), 28.8 (3), 28.5 (2), 28.0 (2), 27.2 (2), 26.1 (3), 21.0 (2), 20.0 (3), 19.7 (2), 18.6 (0), 16.2 (3), 14.3 (3), -5.1 (3); **IR** (film): 2956s, 2929s, 2859s, 1666w, 1462m, 1380m, 1360m, 1302w, 1254m, 1099m, 1062m, 1006w, 939w, 837s, 775m; **LRMS** (CI, NH_3) m/z = 532 (M+H, 100%), 394 (11), 387 (9), 312 (3), 142 (4), 137 (5), 130 (5), 129 (4), 86 (3), 35 (31); **HRMS** (EI): Found: M^+ 531.4843. $C_{34}H_{65}NOSi$ requires M^+ 531.4835.

2-[(2*E*,6*E*)-9-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-7-methyl-3-[(t-butyldimethylsilyloxy)methyl]-2,6-nonadienyl]-2-[2"-trimethylsilylfuran-4"-yl]-1,3-dithian (173).



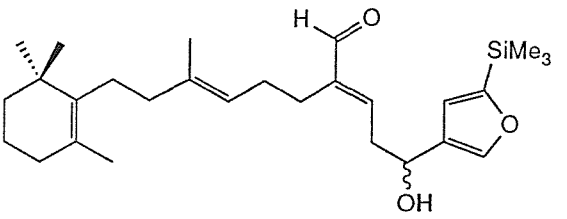
To a magnetically stirred mixture of *tetra-n*-butylammonium chloride (2.98 g, 10.7 mmol), K_2CO_3 (0.14 g, 1.01 mmol), and ethyl chloroformate (1.13 g, 1.0 ml, 10.5 mmol) in THF (20 ml), was added a solution of the allylic amine (**169**) (0.57 g, 1.07 mmol) in THF (30 ml) and the mixture stirred at r. t. for 20 min. The mixture was then poured into water (100 ml), the organic layer separated, and the aqueous layer extracted with ether (4 x 50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue, containing *(2E,6E)-9-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-7-methyl-3-[(t-butyldimethylsilyloxy)methyl]-1-chloro-2,6-nonadiene* (**170**) and ethyl di-*n*-butylcarbamate could not be separated by flash column chromatography owing to decomposition of the allylic chloride (**170**) and so the crude product was used immediately in the next step. To a magnetically stirred solution of 2-trimethysilyl-4-(1',3'-dithian-2'-yl)-furan (**171**) (1.39 g, 5.4 mmol) in THF (20 ml) at -40°C was added *n*-BuLi (1.6M in hexanes, 3.6 ml, 5.8 mmol), and the resultant yellow solution was stirred for 1 h. The temperature was then reduced to -80°C and a solution of the crude allylic chloride (**170**) in THF (50 ml) added over 10 min. After stirring for a further 12 h at -80°C, the mixture was poured into saturated aqueous NH_4Cl and the organic layer separated. The aqueous layer was extracted with ether (4 x 100 ml) and the combined organic phases washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) to give the *title compound* (0.35 g, 0.53 mmol, 49% overall from the allylic amine) along with recovered dithiane (**171**) (0.18 g, 0.69 mmol). The *title compound* gave: **^{1}H NMR** ($CDCl_3$, 360 MHz): δ = 7.65 (1H d, J 0.7), 6.65 (1H, d, J 0.7), 5.41 (1H, tm, J 7.1), 5.14 (1H, m), 4.06 (2H, d, J 1.3), 2.87 (2H, ddd, J 14.4, 11.4 and 2.9), 2.77 (2H, d, J 7.1), 2.69 (2H, ddd, J 14.4, 5.0 and 3.3), 2.1-1.96 (10H, m), 1.91 (2H, t, J 6.3), 1.64 (3H, d, J 1.3), 1.61 (3H, s), 1.58 (2H, m), 1.42 (2H, m), 1.00 (6H, s), 0.89 (9H, s), 0.26 (9H, s), 0.04 (6H, s); **^{13}C NMR** ($CDCl_3$, 90 MHz): δ = 161.7 (0), 146.8 (1), 141.6 (0), 137.3 (0), 136.4 (0), 128.7 (0), 127.0 (0), 123.5 (1), 120.6 (1), 117.9 (1), 66.6 (2), 51.3 (0), 41.7 (2), 40.3 (2), 40.0 (2), 35.1 (0), 32.9 (2), 28.8 (3), 28.6 (2), 27.9 (2), 27.7 (2), 27.0 (2), 26.1 (3), 25.4 (2), 20.0 (3), 19.7 (2), 18.5 (0), 16.2 (3), -1.5 (3), -5.2 (3). **IR** (film): 2954s, 2982s, 2857s, 1664w, 1573w, 1472m, 1462m, 1423m, 1382m, 1360m, 1250s, 1124m, 1074s, 1006m, 939w, 911m, 842s, 776s, 758s, 735m, 699w, 631m; **LRMS** (70eV, EI) m/z: 660 (M^+, 5%), 257 (100), 185 (3), 137 (6), 95 (6), 73 (21), 55 (2), 45(2); **HRMS** (EI): Found: M^+ 660.3887, $C_{37}H_{64}O_2S_2Si_2$ requires M^+ 660.3886.

2-Trimethylsilyl-4-[(3'*E*,7'*E*)-10'-(2",6",6"-trimethy-1"-cyclohexen-1"-yl)-8'-methyl-4'-hydroxymethyl-1'-hydroxy-3',7'-decadien-1'-yl]-furan (174).



A mixture of dithian (**173**) (0.35 g, 0.53 mmol), $HgCl_2$ (0.31 g, 1.14 mmol), and $CaCO_3$ (0.115 g, 1.15 mmol) in 80% aqueous acetonitrile (70 ml) was heated under gentle reflux, under argon, for 4 h. After cooling to r. t., the mixture was filtered through Celite and the filter cake washed with 1:1 CH_2Cl_2 / light petroleum (200 ml). The filtrate was then washed successively with saturated aqueous NH_4OAc and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude unstable ketone product (0.28 g) as a colourless oil. This ketone was then dissolved in EtOH, cooled to 0°C and $NaBH_4$ (0.05 g, 1. 3 mmol) added. The mixture was allowed to warm to r. t. and then stirred for 2 h. The reaction mixture was then diluted with water (100 ml) and the product extracted into CH_2Cl_2 (2 x 100 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The product was then purified by flash column chromatography (SiO_2, 25% EtOAc in light petroleum eluant) to give the *title compound* (0.060 g, 0.13 mmol, 25%) as a colourless, viscous oil: **^{1}H NMR** ($CDCl_3$, 360 MHz): δ = 7.57 (1H, tm J 0.7), 6.63 (1H, d, J 0.7), 5.51 (1H, t, J 7), 5.18 (1H, tm, J 7), 4.69 (1H, dd, J 7.9 and 5), 4.06 (2H, s), 2.62-2.38 (2H, m), 2.40 (2H, bs), 2.24-2.04 (4H, m), 2.02 (4H, A_2B_2 system apearing as a doublet, J 1.9), 1.91 (2H, t, J 6.2), 1.64 (3H, d, J 1.2), 1.60 (3H, s), 1.58-1.54 (2H, m), 1.44-1.39 (2H, m), 0.99 (6H, s), 0.26 (9H, s); **^{13}C NMR** ($CDCl_3$, 90 MHz): δ = 161.6 (0), 143.3 (1), 142.2 (0), 137.2 (0), 136.9 (0), 128.7 (0), 127.1 (0), 123.2 (1), 122.2 (1), 118.5 (1), 66.9 (2), 66.9 (1), 40.4 (2), 40.0 (2), 36.4 (2), 35.1 (0), 32.9 (2), 28.8 (3), 28.5 (2), 28.0 (2), 27.0 (2), 20.0 (3), 19.7 (2), 16.2 (3), -1.5 (3); **IR** ($CHCl_3$): 3607bs, 3027m, 2960s, 2931s, 2867s, 1593w, 1458w, 1382w, 1360w, 1252s, 1118w, 1077s, 1050m, 1005m, 912m, 845s; **LRMS** (70eV, EI) m/z = 458 (M^+, 8%), 440 (M-$H_2$0; 4), 272 (10), 169 (46), 153 (8), 137 (100), 123 (15), 121 (16), 120 (11), 109 (10), 107 (10), 95 (40), 81 (29), 73 (51), 55 (23), 41 (23) **HRMS** (EI): Found: M^+ 458.3216, $C_{28}H_{46}O_3Si$ requires M^+ 458.3216.

2-Trimethylsilyl-4-[(3'*E*,7'*E*)-10'-(2",6",6"-trimethyl-1"-cyclohexen-1"-yl)-8'-methyl-4'-formyl-1'-hydroxy-3',7'-decadien-1'-yl]-furan (175).



A solution of *tetra-n*-propylammonium perruthenate (TPAP, 1.6 mgs, 4.56 μmol) in CH_2Cl_2 (1 ml) was added to a mixture of crushed 4Å molecular sieves (80 mgs), 4-methyl morpholine *N*-oxide (12.0 mgs, 102 μmol) and 2-trimethylsilyl-4-[(3'*E*, 7'*E*)-10'-(2",6",6"-trimethyl-1"-cyclohexen-1"-yl)-8'-methyl-4'-hydroxymethyl-1'-hydroxy-3',7'-decadien-1'-yl]-furan. (**174**) (38 mgs, 73.68 μmol) in 10% acetonitrile in CH_2Cl_2 (10 ml) at r. t. under argon. The mixture was stirred for 1.5 h then further amounts of 4-methyl morpholine *N*-oxide (6 mgs, 51 μmol) and TPAP (0.8 mgs, 0.28 μmol) were added and stirring continued for a further 1.5 h. The mixture was then passed through a plug of silica gel; the products being eluted with ethyl acetate (100 ml) to remove the molecular sieves and the TPAP residues. The products were concentrated *in vacuo* then purified by flash column chromatography (SiO_2, 10-20% EtOAc in light petroleum graduated eluant) to give in order of elution, unreacted starting diol (**174**) (11 mgs, 24 μmol, 28%) and the *title compound* (16 mgs, 35 μmol, 42%) as a colourless oil: **^{1}H NMR** ($CDCl_3$, 360 MHz): δ = 9.40 (1H, s), 7.61 (1H, apparent t, J 0.7), 6.64 (1H, d, J 0.7), 6.57 (1H, t, J 7.2), 5.14 (1H, tm, J 7.2 and 1.2), 4.87 (1H, dd, J 7.3 and 5.6), 2.85 (1H, dt, J 15.4 and 7.3), 2.79 (1H, ddd, J 15.4, 7.2 and 5.6), 2.31 (2H, t, J 7.7), 2.10-1.94 (6H, m), 1.91 (2H, t, J 6.3), 1.62-1.53 (2H, m), 1.61 (3H, d, J 1.2), 1.60 (3H, s), 1.42 (2H, m), 1.27 (1H, bs), 1.0 (6H, s), 0.27 (9H, s); **^{13}C NMR** ($CDCl_3$, 90 MHz): δ = 195.1 (1), 162.3 (0), 150.0 (1), 145.1 (0), 143.4 (1), 137.3 (0), 137.2 (0), 128.3 (0), 127.1 (0), 122.8 (1), 118.0 (1), 66.1 (1), 40.4 (2), 40.0 (2), 37.5 (2), 35.1 (0), 32.9 (2), 28.8 (3), 27.9 (2), 26.9 (2), 24.6 (2), 19.9 (3), 19.7 (2), 16.2 (3), -1.6 (3); **IR** (film): ; **LRMS** (70eV, EI) m/z = 456 (M^+, 5%), 438 (M-H_20, 4), 302 (5), 169 (40), 153 (21), 137 (100), 136 (42), 123 (10), 121 (12), 95 (40), 81 (30), 73 (36), 55 (16), 41(15); **HRMS** (EI): Found: M^+ 456.3055, $C_{28}H_{44}O_3Si$ requires M^+ 456.3060.

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