SYNTHETIC APPROACHES TOWARDS PHORBOLS

A thesis submitted to the Board of the Faculty of Physical Sciences

in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

by

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" To All My Relations "

That which does not kill us
makes us stronger

- Friedrich Nietzsche

ASLIB ABSTRACT

SYNTHETIC APPROACHES TOWARDS PHORBOLS

M. C. Bagley **D. Phil.**
Linacre College, Oxford **Trinity Term 1994**

The work described herein is concerned with the synthesis of phorbol natural products. The approach to these biological derivatives explored in this study utilised an intramolecular Diels-Alder reaction of a furan diene (IMDAF) precursor to establish the tigliane hydrocarbon skeleton and an intramolecular aldol cyclisation to construct the functionalised A-ring. Additionally, the subsequent elaboration of the phorboid cycloadducts could access highly functionalised ingenane analogues by Wagner-Meerwein rearrangement.

Chapter 1 contains a review of the biological activity and biosynthesis of some naturally occuring phorbols. A literature survey on approaches to tigliane, daphnane, and ingenane analogues is described as well as a report on the previous success of the IMDAF strategy.

Chapter 2 describes the development of an intramolecular aldol condensation to establish IMDAF precursors containing both a cyclopentenone A-ring and unactivated dienophilic moiety. A strategy to introduce benzylthiofuryl diene activation was developed. The cycloaddition of 3-furyl-2-pentenylcyclopent-2-enones bearing an unactivated dienophile was found to be unsuccessful.

Chapter 3 describes a model study of the C-ring tigliane-ingenane rearrangement in a 7-oxabicyclo[2.2.1]heptyl system. The successful isolation of a hydrogenated cycloadduct suitable for migration studies is reported. The biomimetic carbocyclic rearrangement of phenylthio- activated model substrates was not observed.

Chapter 4 describes an approach towards IMDAF precursors that contain mono- and di-activated dienophiles. Elaboration of the dienophile was investigated both before and after the intramolecular cyclisation of the A-ring and a synthetic route to (benzylthiofuryl)cyclopentenones containing an oxopentenyl dienophilic tether established. Direct introduction of tigliane C-4 oxygenation into IMDAF substrates was prevented by an unfavourable aldol cyclisation equilibrium. The observation of an IMDAF cycloadduct was facilitated by subjecting 3-[(5-(2-benzylthio)furyl]-2-(3-oxopent-4-enyl)cyclopent-2-enone to 19 kbar pressure but isolation of phorboid analogues containing unsaturation at the A-B ring junction was not possible.

ACKNOWLEDGEMENTS

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Finally I should like to thank Helen, Nicki and Jules who have been so very caring, patient and understanding and made me very happy, and my brothers and sisters in Malvern, for they shall always be in my thoughts.

ABBREVIATIONS

Ac	Acetate
acac	2, 4-Pentanedione
AIDS	Acquired Immunodeficiency Syndrome
atm.	atmospheres
AIBN	2, 2'-azobis*iso*butyronitrile
aq	aqueous
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
b.p.	boiling point
Bu	Butyl
cat.	catalytic
C.I.	Chemical ionisation
Cp	Cyclopentadienyl
D	Deuterium (^{2}H)
Δ	heat
DBA	Dibenzanthracene
DBU	1, 8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2, 3-Dichloro-5, 6-dicyano-1,4-benzoquinone
DIBAH or DIBAL	Di-*iso*butylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N, N*-Dimethylformamide
DMPU	1, 3-Dimethyl-3, 4, 5, 6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl sulphoxide
DNA	Deoxyribose nucleic acid
eq. or equiv.	equivalents

Et	Ethyl
Ether	Diethyl ether
Fu	Furyl
Fu'	2-(5-Substituted-furyl) (C_4H_2O)
G. C.	Gas chromatography
gem	*geminal*
gp.	group
h	hours
HIV	Human Immunodeficiency Virus
HMPA	Hexamethylphosphoramide
hν	photochemical irradiation
HOMO	Highest occupied molecular orbital
i	*iso*
Im	Imidazole
IMDA	Intramolecular Diels-Alder reaction
IMDAF	Intramolecular Diels-Alder reaction of furan
i.r.	infra-red
L	Leaving group
LAH	Lithium aluminium hydride
LDA	Lithium di-*iso*propylamide
L HMDS	Lithium hexamethyldisilazide
liq.	liquid
LUMO	Lowest unoccupied molecular orbital
m	*meta*
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
min	minutes
m.p.	melting point
Ms	Methanesulphonyl

n	*normal*
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
n.m.r.	nuclear magnetic resonance
o	*ortho*
[O]	Oxidation
p	*para*
P'	Protecting group
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
Piv	Pivaloate
PKC	Protein kinase C
PP	Pyrophosphate
PPTS	Pyridinium *para*-toluenesulphonate
Pr	Propyl
Py	Pyridine
quant.	quantitative
R	Alkyl
R_f	Retention factor
RNA	Ribose nucleic acid
r.t.	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
SM	Starting material
t or *tert*	*tertiary*
THF	Tetrahydrofuran
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tertiary*-butyldiphenylsilyl
TBS or TBDMS	*tertiary*-Butyldimethylsilyl

TEA	Triethylamine
Tf	Trifluoromethanesulphonyl
TFA	Trifluoroacetate
t.l.c.	thin layer chromatography
TMEDA	*N, N, N', N'* - Tetramethylethylenediamine
TMS	Trimethylsilyl
Tolyl	Methylphenyl
TPAP	Tetrapropylammonium perruthenate
Ts	toluenesulphonyl
v/v	volume ratios
vic	*vicinal*
X or Y	Unspecified substituent

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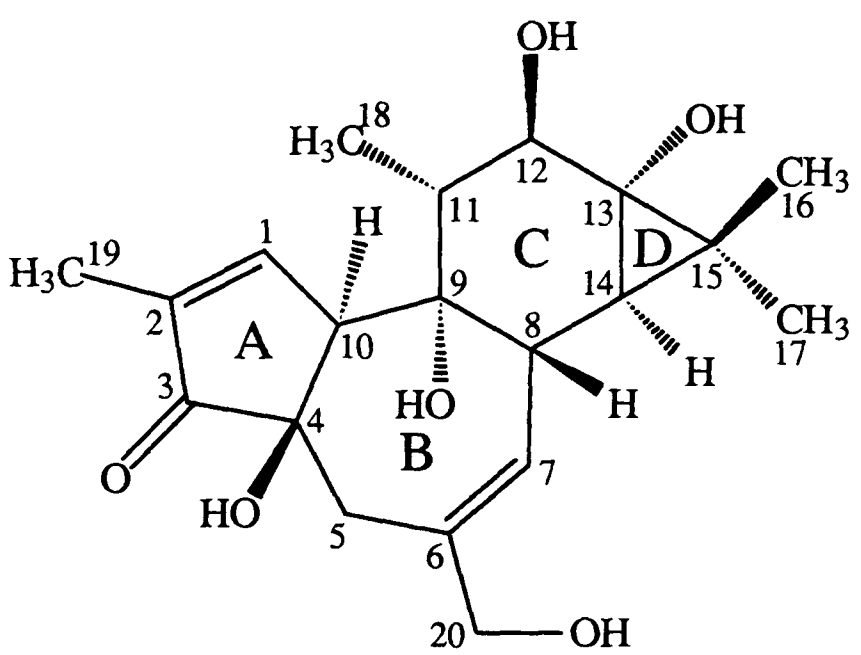
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CHAPTER ONE

CHAPTER 1 - INTRODUCTION

1.1. Phorbol Natural Products.

The phorbols are a family of tetracyclic diterpene natural products found in the milky sap of plants in the genus *Euphorbiaceae*.[1] The parent alcohol, phorbol (**1**), was first isolated by Bohm in 1935 in the hydrolysis of *Croton tiglium* oil,[2] but it was not until 1967 that the structure was determined by X-ray crystallographic studies.[3]

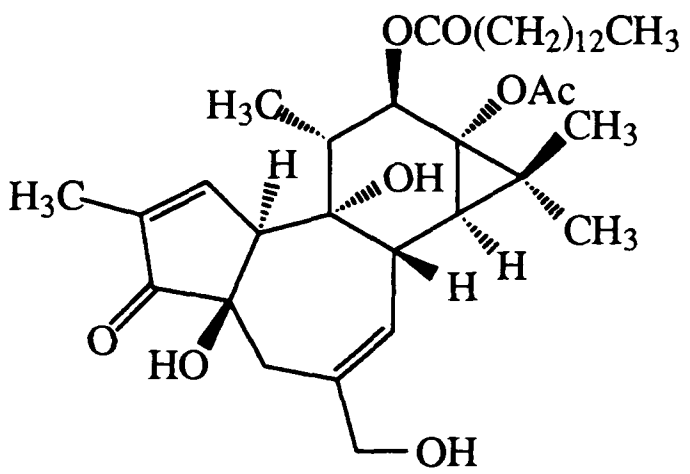


Phorbol (**1**)

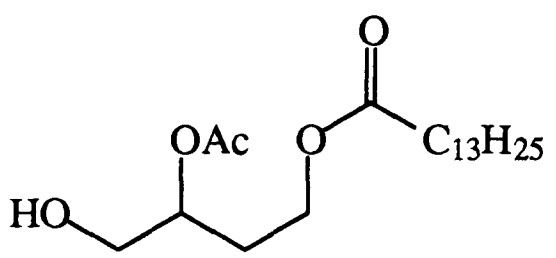
Phorbol (**1**) consists of a tetracyclic tigliane hydrocarbon framework based upon a perhydroazulene skeleton *trans* fused to a trihydroxylated cyclohexane C-ring *cis* fused to dimethylcyclopropane D. The net amphilic structure, that contains hydrophilic and hydrophobic regions, elicits a wide range of tissue responses and so is of considerable biological interest.[1]

In the 1930's it was demonstrated by Berenblum that the action of several noncarcinogenic compounds, now known as tumour promoters, amplified the effect of carcinogens on mouse skin.[4] The most potent of these agents, tetradecanoyl phorbol acetate (TPA) (**2**) or phorbol myristate acetate (PMA) as it was previously known, is the most active tumour promoter known. It was demonstrated that exposure of cells to these derivatives rendered them susceptible to otherwise sub-threshold concentrations of carcinogens.[5] As a

consequence of this discovery, the phorbol esters have become central in the study of carcinogenesis[6] and the proposal of a two-stage carcinogenesis mechanism.[7]



TPA (PMA) (**2**)
Tetradecanoyl phorbol acetate

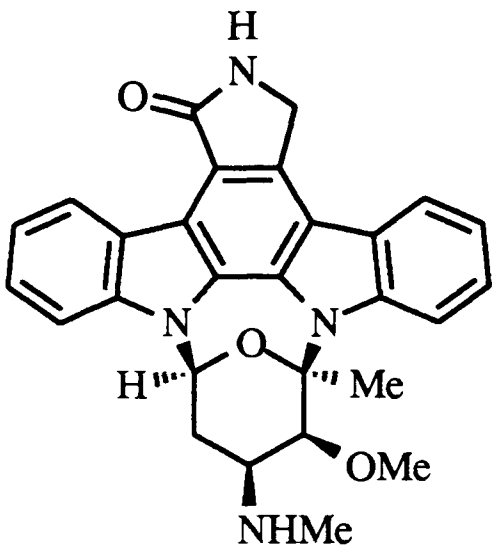


1-Oleoyl-2-acetyl glycerol (**3**)
(a diacyl glycerol)

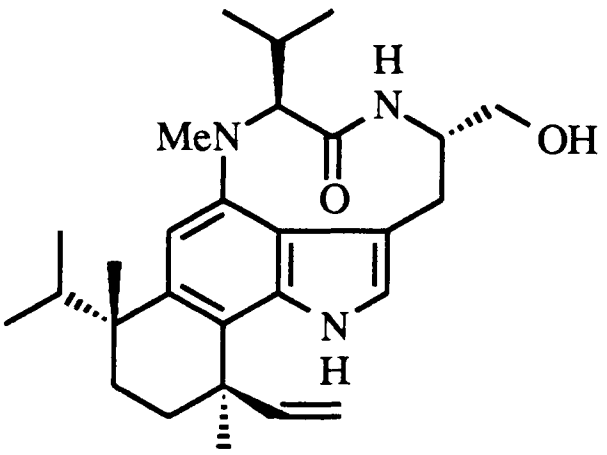
Recently Nishizuka identified the receptor for tumour promoting agents as protein kinase C,[8] a serine and threonine phosphorylating enzyme of great organomedicinal interest that plays a ubiquitous role in regulatory hormonal signal transduction in cells.[9] It has been shown that phorbol esters substitute for diacyl glycerol (**3**), the natural activator of the enzyme and a product of signal induced inositol phospholipid breakdown, thereby increasing the affinity of the enzyme for calcium ions. This results in permanent activation and a cascade effect that has far reaching implications, as illustrated by Castagna.[10] The importance of reversible phosphorylation as a major intercellular regulatory mechanism has only been recognised fully within the last decade, the neural and hormonal regulation of the enzyme being mediated in a wide variety of metabolic processes. As a result of the wide range of responses induced by protein kinase C activation,[11] the development of inhibitors of the enzyme could lead to the discovery of therapeutic agents of value in the treatment of chronic inflammatory and proliferative diseases.[12]

As a consequence of their tumour promoting activity, the phorbol esters have become probes of considerable importance in establishing a pharmacophore model for PKC activation and in understanding tumour proliferation in mammalian systems.[13] There is an important requirement for non-natural analogues of these agents to determine the structural requirements for diterpene recognition at the PKC regulatory domain and to design rational agonists and antagonists for the enzyme. Even over the past year, synthetic studies have been

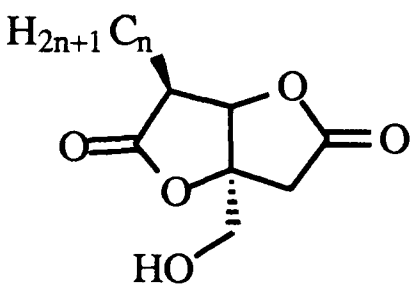
directed towards targets such as staurosporine (**4**),[14] bis-γ-butyrolactones (**5**),[15] and indolactam V (ILV (**6**)) benzenoid analogues (**7**)[16] in order to understand the structural determinants for PKC activation and in the search for effective agonists and antagonists of this ubiquitous enzyme.



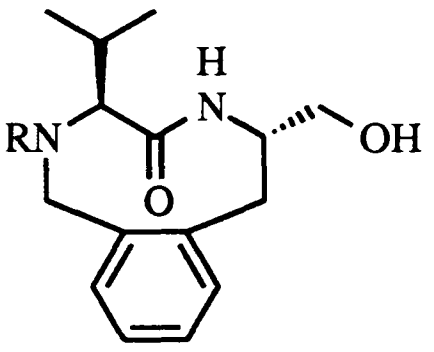
Staurosporine (**4**)



ILV (**6**)



(**5**)

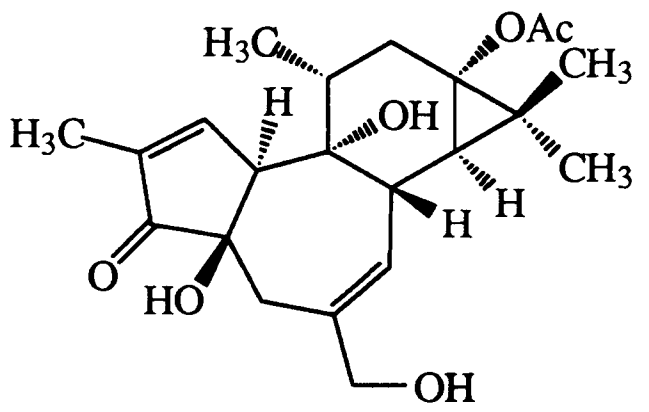


(**7**)

The phorbol esters elicit a wide variety of other biological responses, participating in cell proliferation and differentiation, ion transport and DNA, RNA and protein synthesis,[1] thus providing new opportunities for research on cancer, inflammation, cardiovascular disease, cystic fibrosis, AIDS, and memory development.[17] Of relevance to their therapeutic value, short-chain substituted 12-deoxyphorbol derivatives have been found only to be weakly tumour promoting or non-promoting.[18,19]

Homalanthus nutans, a small indigenous tree of the genus *Euphorbiaciae* from the islands of Samoa, has long been an important component of the native ethnopharmacology.[20] Recently, it was demonstrated that extracts of *Homalanthus nutans*, containing the 12-deoxy phorbol acetate prostratin (**8**) as the active component, had a potent cytoprotective effect in

human lymphocytic cells infected with the human immunodeficiency virus (HIV-I). At non-cytotoxic concentrations, this agent was found capable of preventing HIV-I reproduction in lymphocytic and monocytoid target cells and to fully protect susceptible cells from the lytic effects of HIV-I.[18]



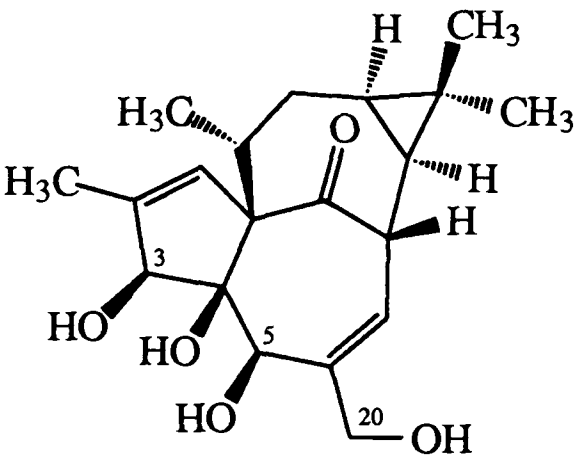
Prostratin (**8**)

The phorbol esters are part of a larger family of natural products, collectively entitled "phorbols", comprising daphnane and ingenane diterpenes, the constituents of plants in the genus *Euphorbiaceae* and *Thymelaeaceae*. The ingenanes are structurally related tetracyclic diterpenes that are only encountered in the *Euphorbiaceae* plant family and that contain a *trans* linked bicyclo[4.4.1]undecanone BC-ring system. X-ray crystallographic studies on the 3, 5, 20-triacetate[21,22] determined the presence of tetrol and olefinic sub-structures and an "inside-outside" B-C ring junction stereochemistry in the parent alcohol, ingenol (**9**).[23]

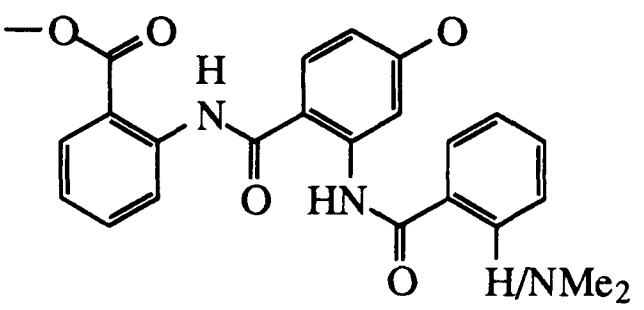
The ingenanes exhibit remarkably similar biological properties to tigliane natural products. They constitute the largest class of skin irritants in the genus, and elicit an inflammatory response on mammalian skin - a reaction that has been employed in the development of a mouse ear irritancy assay to monitor plant extract fractionation.[24] Constituents of *Euphorbia cotinifolia* exhibit piscidal activity,[25] and mixtures of ingenol esters display tumour promoting capabilites although their structural homogeneity prevents a systematic study of carcinogenic activity.[26]

Paradoxically ingenol-3, 20-dibenzoate, isolated from *Euphorbia esula L* by Kupchan, has been shown to display anti-leukaemic properties as well as an inhibitory action against rodent tumour proliferation.[27] C-3, C-5, or C-20 anthraniloyl tripeptide ingenol esters

inhibit the development of P-388 lymphocytic leukaemia in mice whilst appearing to lack any tumour promoting activity.[28]



Ingenol (**9**)

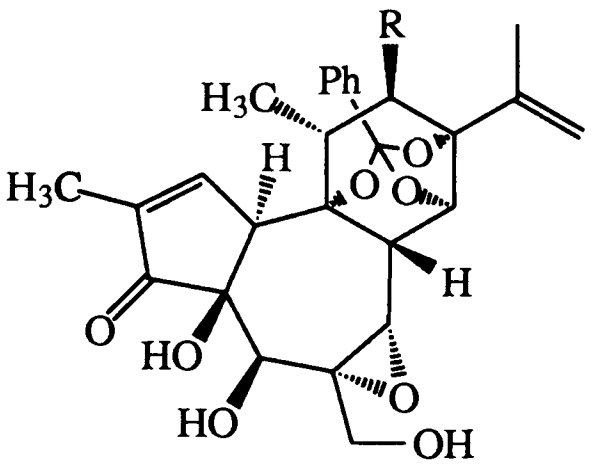


Anthraniloyl tripeptide ester sub-structure

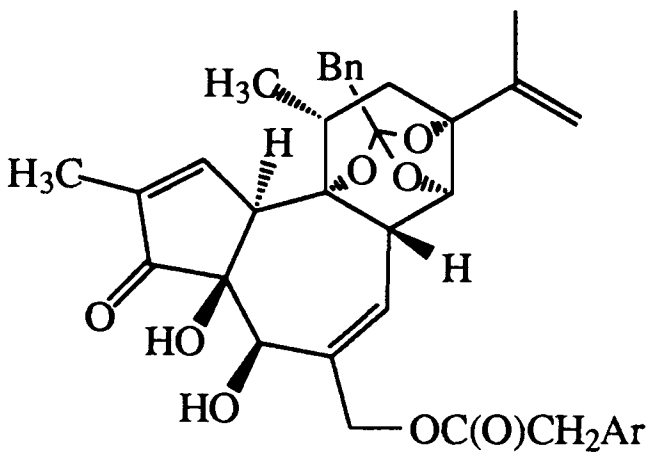
The structurally related daphnanes, predominantly isolated containing the rather unique *ortho* ester function, display interesting and diverse biological properties. Daphnetoxin (**10**), the poisonous principle of the bark of *Daphne mezereum L*, was the first identified daphnane isolated in 1970.[29] However, species of the genus *Daphne* have been recognised since at least the 11th century as virulent poisons,[30] *Schoenobiblus* actually being used as the basis of a Peruvian arrow poison. In addition to their toxicity, resiniferols (**11**) and other daphnane esters are amongst the most potent pro-inflammatory agents known to man.[31]

Conversely, plants of the genus *Euphorbiaceae* have long been recognised in folk-lore medicine as potential purgatives of cancers or warts.[32] Many of the 6-7 epoxy compounds display piscidal activity,[33] whilst daphnanes extracted from *Gnidia* such as Gnididin (**12**) have been shown to exhibit significant anti-leukaemic properties against P-388 lymphocytic leukaemia in *in vivo* tests in mice.[34]

Thus, it is evident that a great variety of tissue responses can be induced by relatively small changes in molecular structure. This illustrates the biological diversity of these natural products and demands structure-activity mapping and further analogue study in order to understand more comprehensibly their interesting mode of action.



Daphnetoxin (**10**) R = H,
Gnididin (**12**) R = $OCO(CH{=}CH)_2C_5H_{11}$

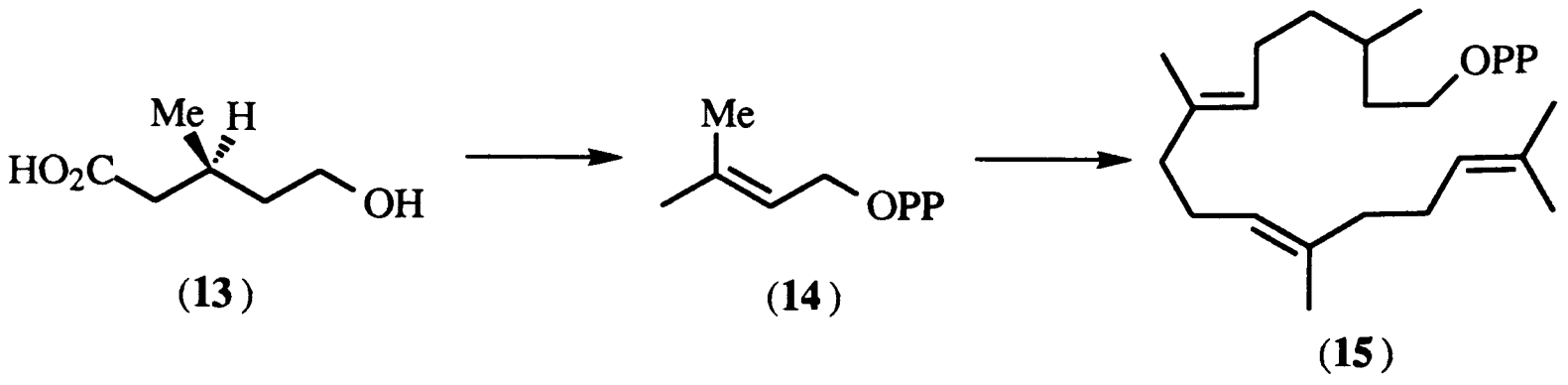


Resiniferol (**11**)

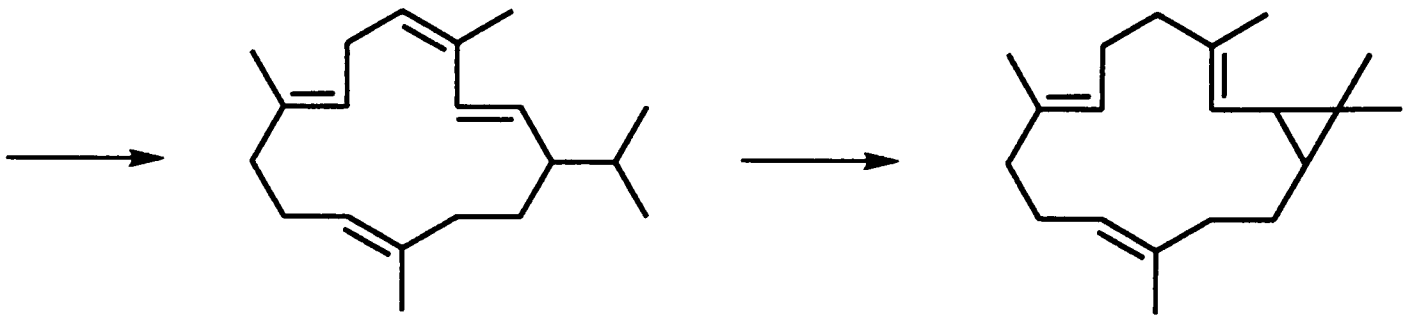
1.2. The Biosynthesis of Phorbols.

It is believed that the biosynthesis of phorbol diterpenes follows a classic acetate-mevalonate pathway.[35] Based on this concept, the phosphorylation-decarboxylation of 3*R*-mevalonic acid (MVA) (**13**) and subsequent head-to-tail condensation of dimethylallyl pyrophosphate (**14**) could establish geranyl-geranyl pyrophosphate (**15**) (**Scheme 1**), a recognised parent in diterpene biosynthesis.[36]

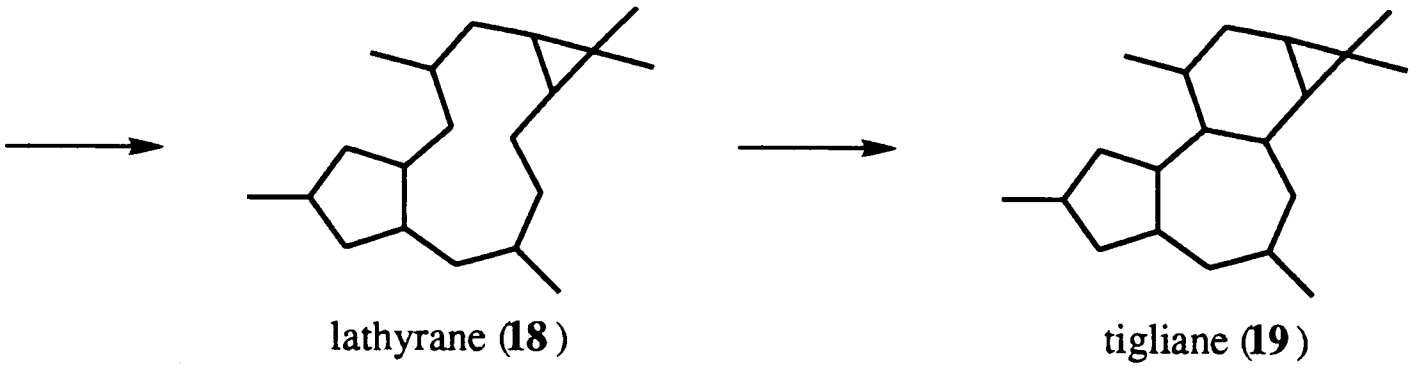
Adolf and Hecker postulated, based on the biosynthesis of a number of similar natural products,[37,38] that all diterpenes in the *Euphorbiaceae* genus could be derived from the head-to-tail condensation of the geranyl-geranyl precursor (**15**) that would proceed through a cembrene (**16**) cation intermediate.[39] The isolation of cembrene (**16**)[37] and casbene (**17**)[40] from plants in the *Euphorbiaceae* or *Thymelaeaceae* family supported this hypothesis, an observation reinforced by examples of tigliane and daphnane, and of tigliane and ingenane, natural product co-occurence in the phytochemical literature.[1]



(**13**) (**14**) (**15**)



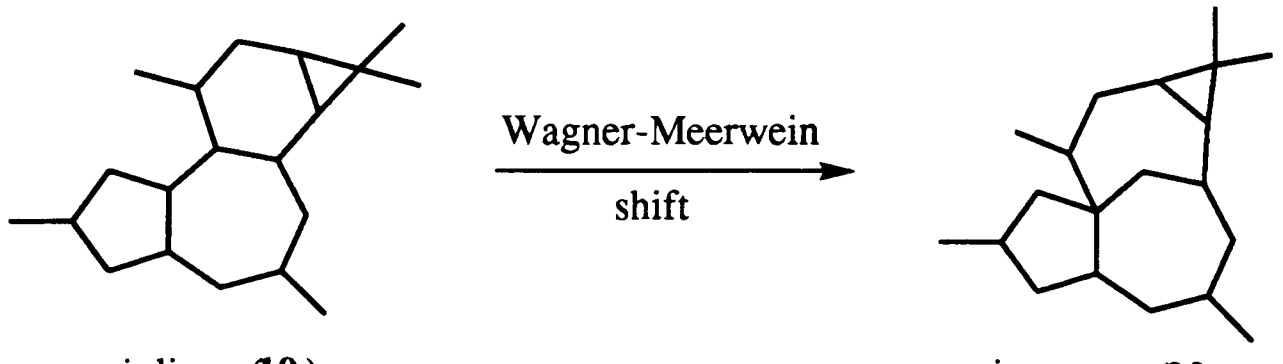
cembrene (**16**) casbene (**17**)



lathyrane (**18**) tigliane (**19**)

Scheme 1

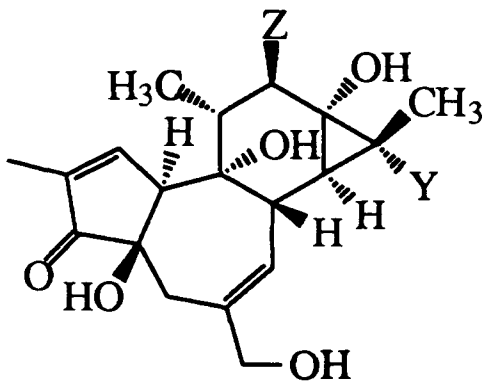
Additional evidence for the biosynthesis of ingenanes from tigliane precursors has been provided by Hecker[41] who has demonstrated that the reverse transformation is possible. A Wagner-Meerwein rearrangement of the tigliane hydrocarbon skeleton (**19**) could provide the ring expansion necessary to access the 7,7 fused B-C ingenane framework (**20**) (**Scheme 2**) although a biomimetic transformation of this nature has not been published.



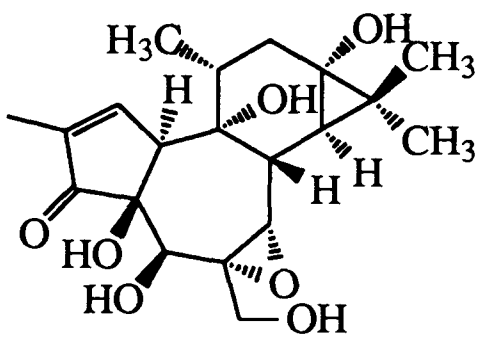
tigliane (**19**) ingenane (**20**)

Scheme 2

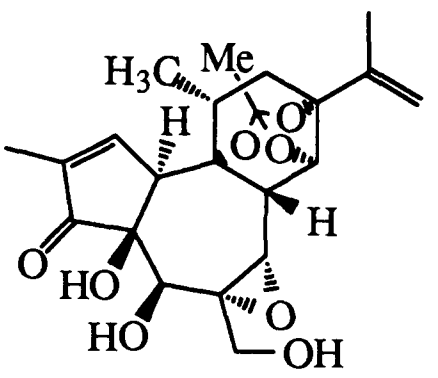
Adolf and Hecker's proposition on daphnane biogenesis from the tiglianes[39] has been supported by isolation of diterpenes (**21**) and (**23**) from a single plant species, along with an intermediate oxidation state (**22**).[42]



(**21**) Y = CH_3, Z = H,
(**24**) Y = CH_2OH, Z = H,
(**25**) Y = CH_2OH, Z = OH

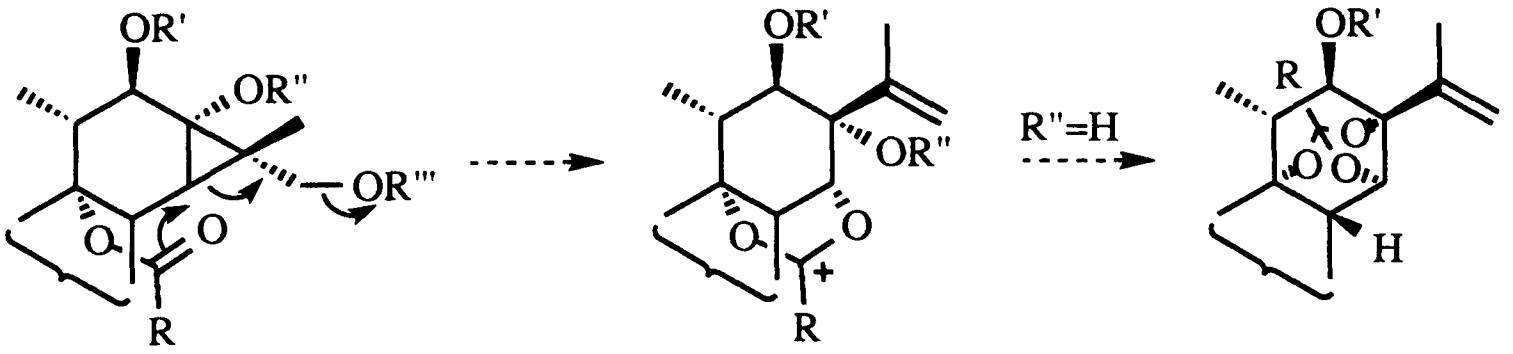


(**22**)



(**23**)

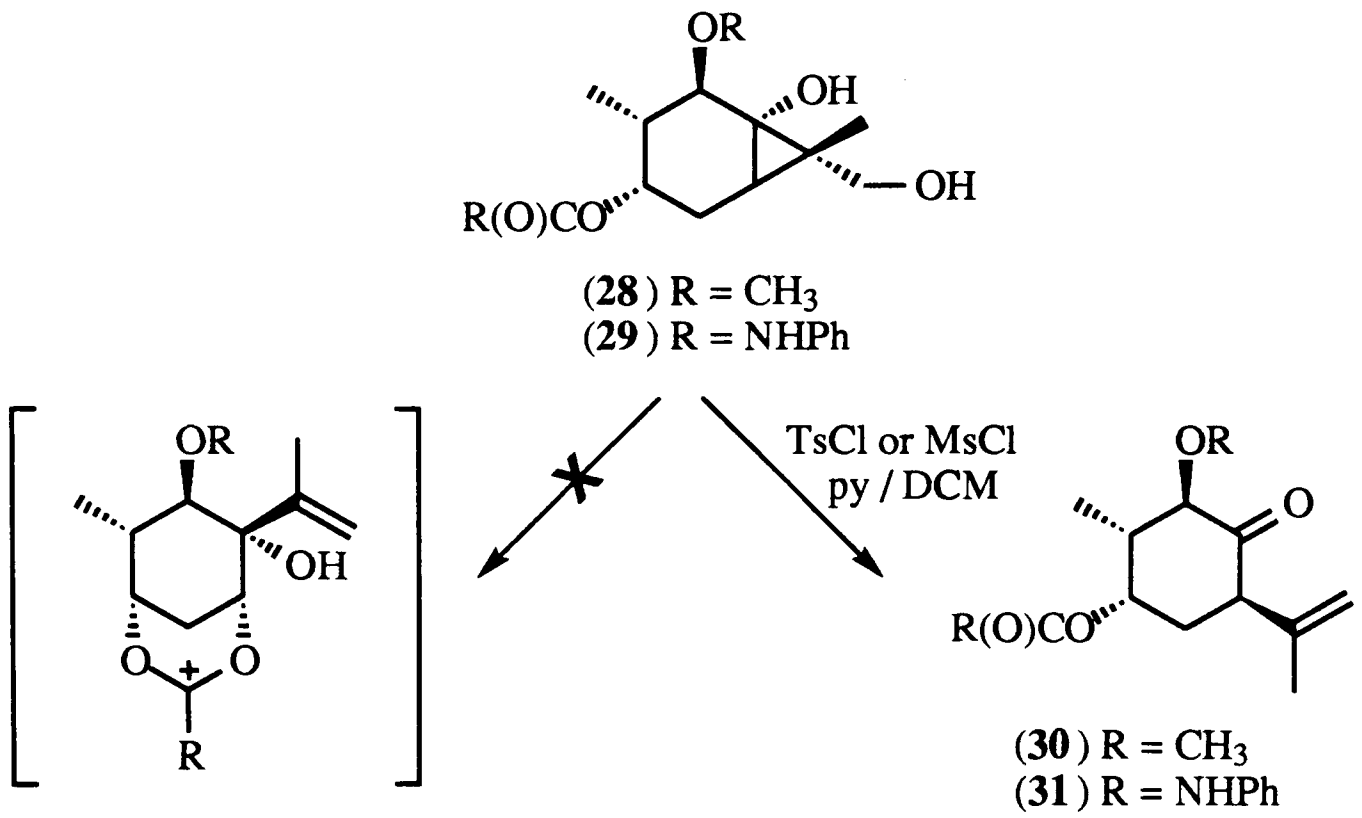
Observation that the C-16 hydroxylated species (**24**) and (**25**) co-occur[43,44] indicated that a C-16 methyl oxidation could induce an anchimerically assisted cyclopropyl carbinyl rearrangement in (**26**) to derive the daphnane skeleton (**27**) (**Scheme 3**) in the biosynthetic conversion.



(**26**) (**27**)

Scheme 3

Despite recent success in laboratory studies in *ortho* ester synthesis (see section 1.3.),[45] a biomimetic investigation of the cyclopropinyl rearrangement failed to support the biogenetic theory.[46] The anchimerically assisted rearrangement of model diacetate (**28**) and dicarbamate ester (**29**) precursors formed only β,γ-unsaturated ketones (**30**) and (**31**) respectively. Thus, lone pair assistance by the tertiary hydroxyl led to cleavage of the wrong cyclopropane bond in generation of the ketone π-system (**Scheme 4**).



Scheme 4

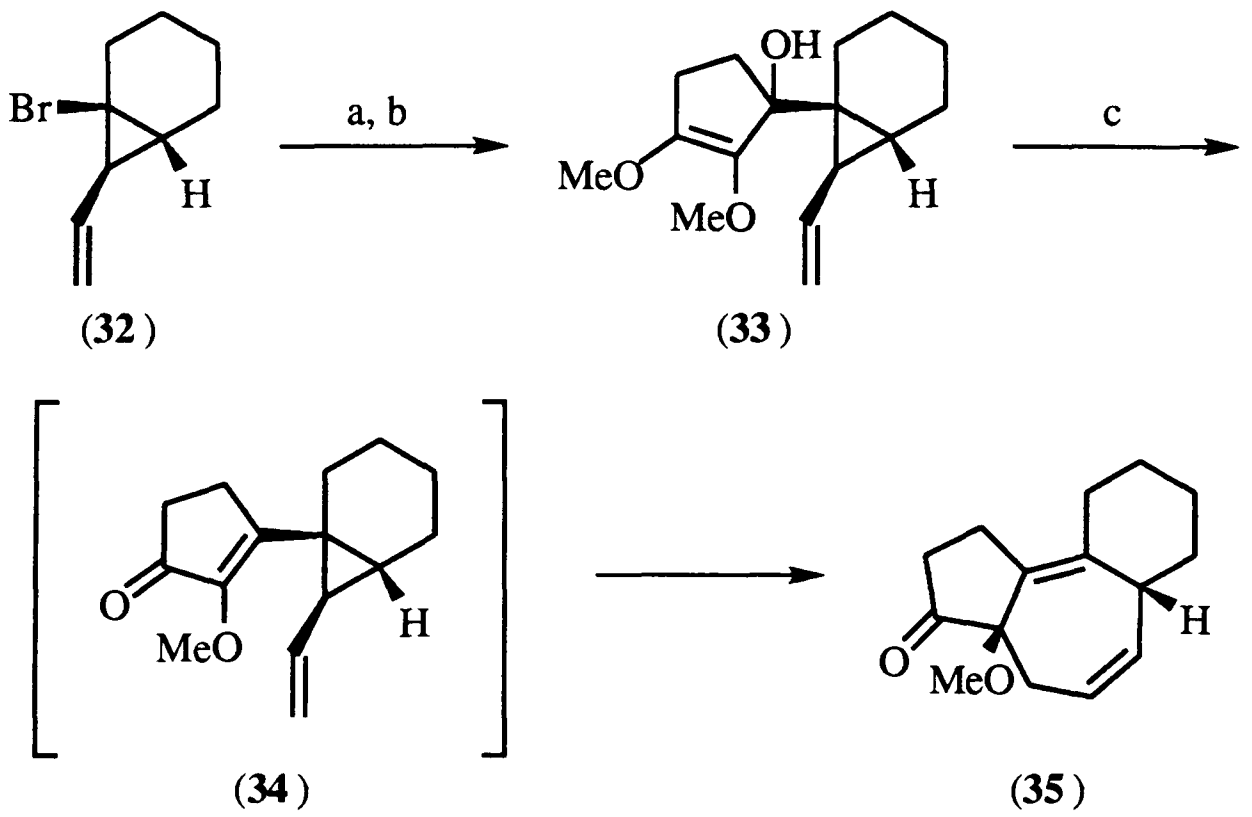
Similar problems have manifested in other phorboid systems. Cleavage of the alternative cyclopropyl bond has been observed in both the acid and base catalysed skeletal rearrangement of tiglianes (**24**) and (**25**).[44,47] Consequently a biomimetic tigliane-daphnane transformation has still not been effected and the hypothesis of Adolf and Hecker for ingenane and daphnane biogenesis remains largely unsupported.

1.3. The Synthesis of Phorbols.

The synthesis of phorbol natural products has been the focus of much literature attention in recent years. Since the first generation of phorbol (**1**) by Wender in 1989,[48] interest in the field has expanded dramatically. The synthetic challenge in constructing tigliane, ingenane, and daphnane derivatives, the search for more biologically active analogues, and an effort to provide biomimetic evidence for natural product biogenesis has demanded a continued interest from a number of groups that continue to publish in this area.

1.3.1. Routes to the Tiglianes.

Wender's first approach to the tigliane hydrocarbon framework utilised a divinyl cyclopropane rearrangement of (**34**) to establish the ABC-ring system.[49] 1, 2-Addition of the lithio derivative of allylbromocyclopropane (**32**) to cyclopentenone (**36**) established an allylic alcohol (**33**) that was readily hydrolysed in dilute acid to the rearrangement precursor (**34**). The reorganisation of carbocycle (**34**) spontaneously occured under the reaction conditions to afford the phorboid product (**35**) in 51 % overall yield and with specification of stereochemistry at two asymmetric centres (**Scheme 5**).

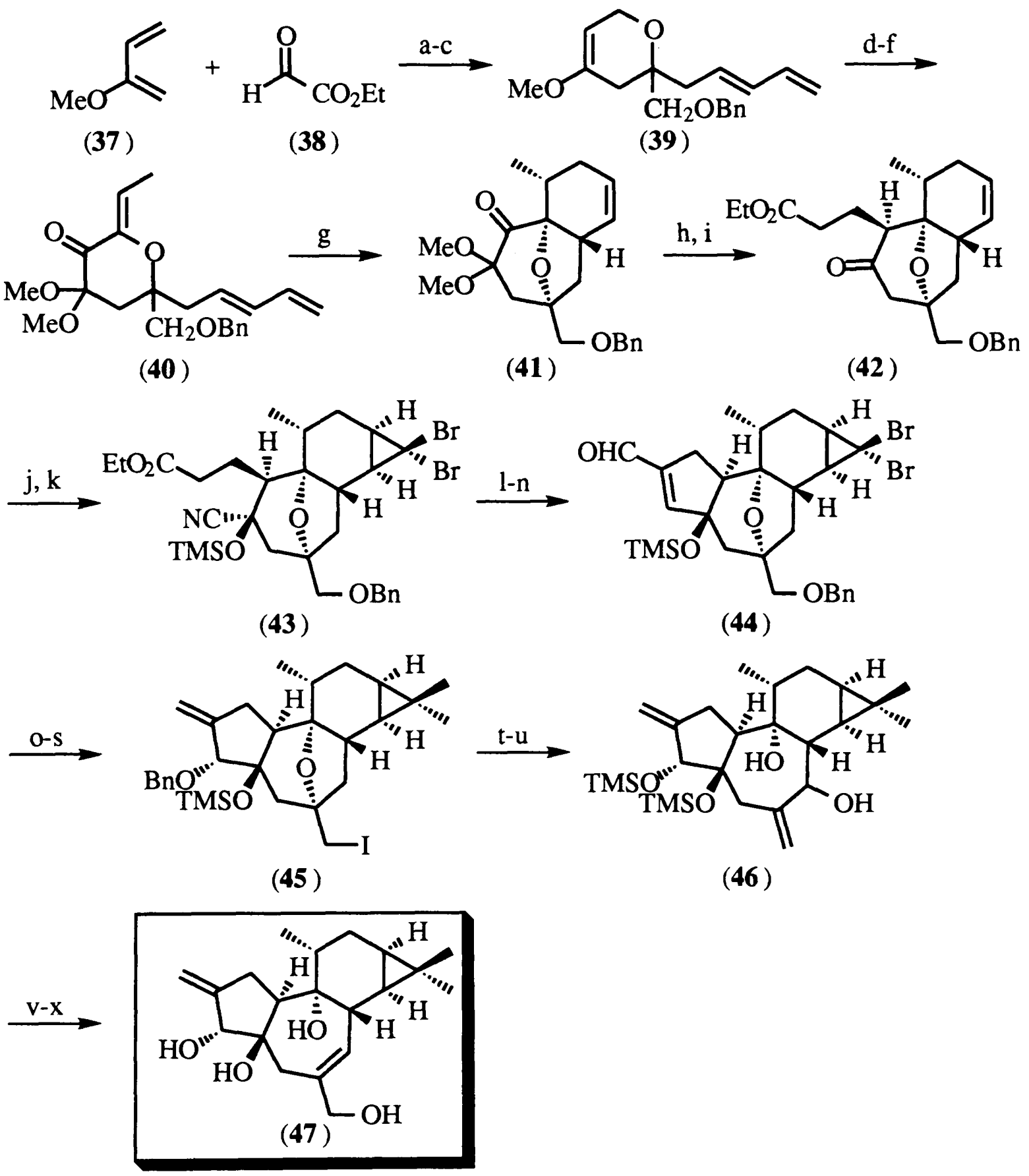


(**32**) (**33**) (**34**) (**35**)

(a) ^{t}BuLi / ether / -78°C to 0°C; (b) 2, 3-dimethoxycyclopent-2-enone (**36**); (c) 0.01 N H_2SO_4-acetone (1 : 1 v/v) / r.t. / 7 min.

Scheme 5

Despite the initial success of a cyclopropane rearrangement, Wender neglected this strategy of phorbol synthesis in favour of an intramolecular Diels-Alder approach (**Scheme 6**).[50] The cycloaddition of triene (**40**), prepared by an intermolecular hetero-Diels-Alder addition of 2-methoxybutadiene (**37**) with ethyl gloxylate (**38**), proceeded with *exo* selectivity. Exclusive formation of oxatricycle (**41**) was a consequence of steric congestion between the diene and C-4 methoxy substituent in the *endo* transition state. The oxygen

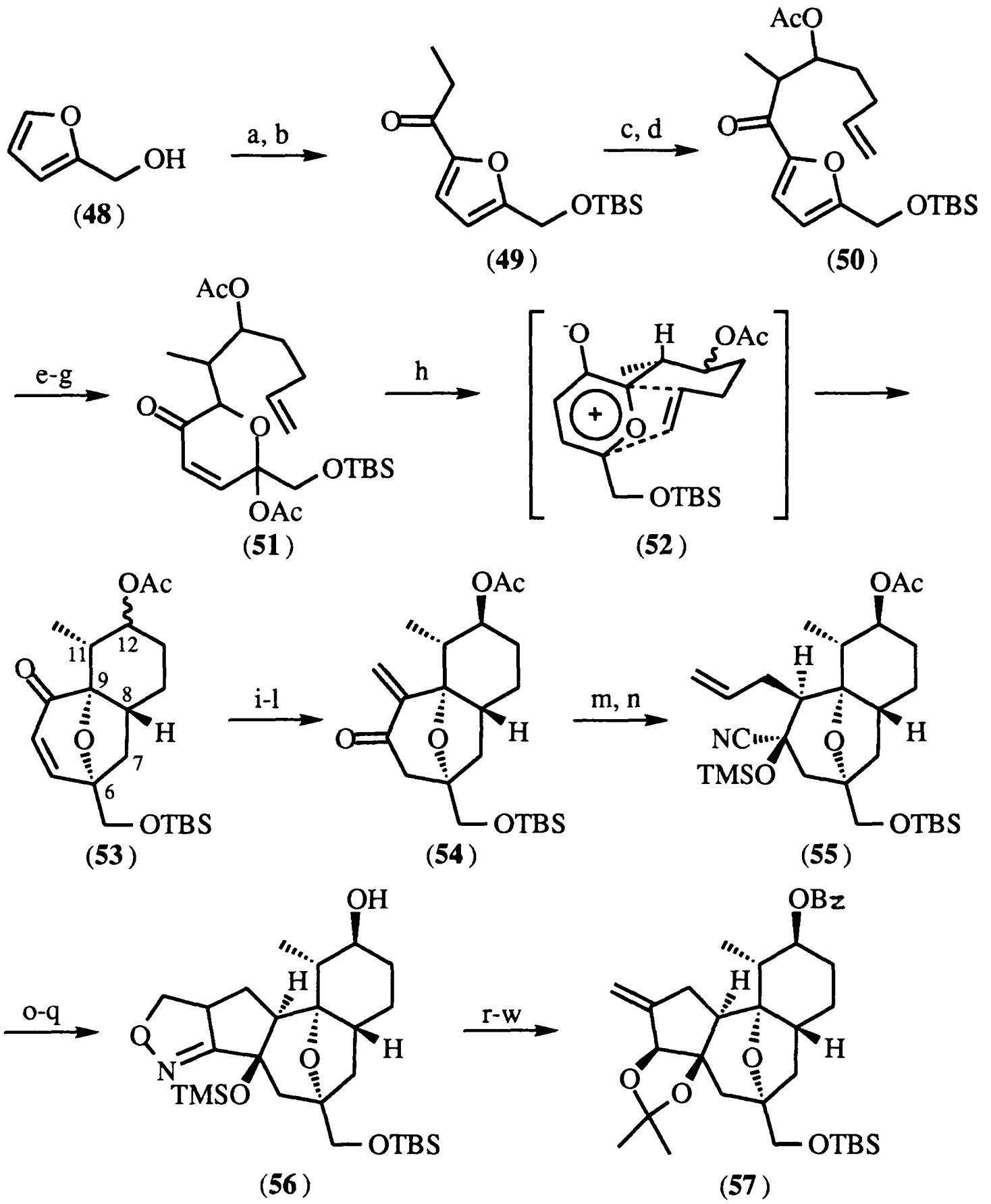


(a) 110°C / toluene; (b) (i) LDA / THF / -78°C / CH_2=CHCH=CHCH_2Br; (ii) LAH / THF / 0°C; (c) BnBr / Bu_4NI / NaH / THF / r.t.; (d) (i) *m*-CPBA / MeOH / 0°C; (ii) $(COCl)_2$ / DMSO / DCM / -60°C; Et_3N; (e) $LiN(TMS)_2$ / LiBr / THF / -78°C; CH_3CHO; (f) (i) MsCl / Et_3N / DCM; (ii) DBU / THF; (g) 145°C / xylene; (h) (i) Ph_3P=CH_2 / toluene / 105°C (ii) $(COOH)_2$ / SiO_2 / DCM (i) CH_2=C(OTBS)OEt / ZnI_2 / DCM; HF / CH_3CN; (j) $PhHgCBr_3$ / benzene / 80°C; (k) TMSCN / ZnI_2 / DCM; (l) DIBAH / toluene / -78 to 0°C; (m) $(COCl)_2$ / DMSO / DCM / -60°C; Et_3N; (n) $Bn_2NH_2CF_3CO_2$ / benzene; (o) DIBAH / toluene / -78°C; (p) $Me_2CuCNLi_2$ / ether / -20°C; MeI; (q) (i) *o*-NO_2PhSeCN / Bu_3P / pyridine; (ii) H_2O_2 / THF; (r) (i) Bn_2O / DMAP / Et_3N / DCM; (ii) ZnI_2 / TMSCN; (s) (i) Tf_2O / pyridine / DCM; (ii) Bu_4NI / HMPA; (t) *t*-BuLi / THF / -78°C; (u) (i) TMS-Im / DCM; (ii) SeO_2 / Me_3COOH / DCM / 0°C; (v) $SOCl_2$ / Et_2O / 0°C; (w) KOAc-TMEDA / AgOAc / CH_3CN; (x) TBAF / THF.

Scheme 6

bridge in the cycloadduct (**41**) served to protect the C-9 hydroxyl and enforce a structural rigidity on the conformationally flexible system, improving the stereocontrol of the synthesis. Addition to the less hindered convex face of the C-ring of (**42**) by Seyferth's reagent ($PhHgCBr_3$) established the *gem*-dimethylcyclopropane D-ring of (**43**). Finally, closure of the cyclopentenone A-ring by the base catalysed intramolecular aldol condensation of (**43**) and subsequent functional group manipulation produced the first route to the tigliane hydrocarbon skeleton (**47**) (**Scheme 6**) and signified an important landmark in the synthesis of the natural product, the stereochemistry at 7 of the 8 phorbol stereogenic centres being specified correctly.

In order to derive a general route to the structurally homologous daphnane, ingenane, and tigliane families, Wender altered his synthetic strategy and generated polycycle (**57**), delaying the introduction of the tigliane D-ring.[51] Preparation of a cycloaddition precursor (**52**) containing C-12 oxygenation was achieved by condensation of the enolate of ethylfurylketone (**49**), prepared from furfuryl alcohol (**48**). The subsequent oxidation of diastereomeric (**50**) furnished the required pyranones (**51**) as a mixture of stereoisomers. Heating to 150°C or stirring (**51**) in the presence of DBU at ambient temperature effected an oxidopyrilium-alkene cycloaddition to form oxatricycle (**53**) with specification of relative stereochemistry at the C-8, C-9, and C-11 stereogenic centres. The induction was a consequence of a chair-like transition state conformation (**52**) in which the C-11 methyl substituent adopted an equatorial environment in order to minimise steric interaction with C-10 oxygen functionality. The product (**53**) was formed as a mixture of C-12 epimers that were converged later in the synthetic sequence. The subsequent attachment of an allyl tether at C-10 was effected with total stereocontrol as a result of the stereochemical bias enforced by the convex polycycle (**54**). Finally, the closure of the A-ring was achieved by an internal nitrile oxide cycloaddition to furnish a general synthetic precursor (**57**) that possessed the basic ABC-ring structure of the tigliane skeleton (**Scheme 7**).



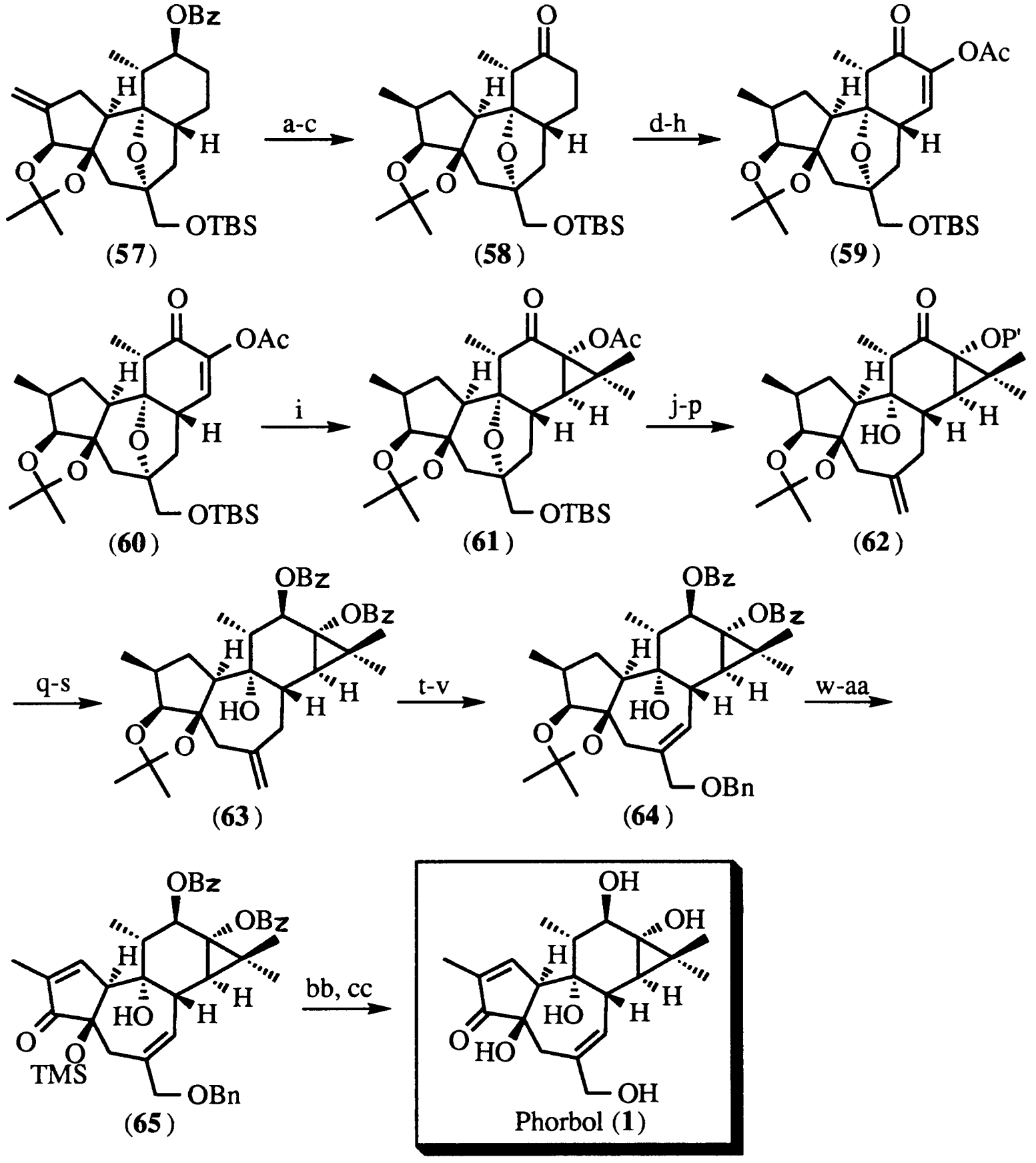
(a) TBSCl / DMF; (b) *n*-BuLi; EtCOOLi / THF; (c) $Li(TMS)_2$ / -78°C / 15 h / THF; 4-pentenal; (d) AcCl / py / DCM; $NaBH_4$ / MeOH; (e) *m*-CPBA / THF; (g) Ac_2O / pyridine / DMAP; (h) DBU / DCM / r.t.; (i) Separation; H_2 / Pd-C / EtOAc; (j) Ph_3PCH_2; (k) SeO_2 / ^tBuOOH / DCM; (l) MnO_2 / DCM; (m) $(CH_2{=}CH)_2CuCNLi_2$ / THF; (n) TMSCN / ZnI_2; (o) DIBAH / toluene; (p) NH_2OH / py; (q) NaOCl / THF; (r) H_2 / Raney Ni / acetone / H_2O (4 : 1); (s) Bz_2O / DMAP / py / DCM; (t) DBU / THF; (u) $NaBH_4$ / $CeCl_3$ / MeOH; (v) TBAF / ether; (w) 2-Methoxypropene / PPTS / DCM.

Scheme 7

Elaboration of Wender's synthetic precursor (**57**) allowed the first total synthesis of phorbol (**1**) to be effected in 1989.[48] α-Acyloxyenone (**60**) was generated to facilitate the

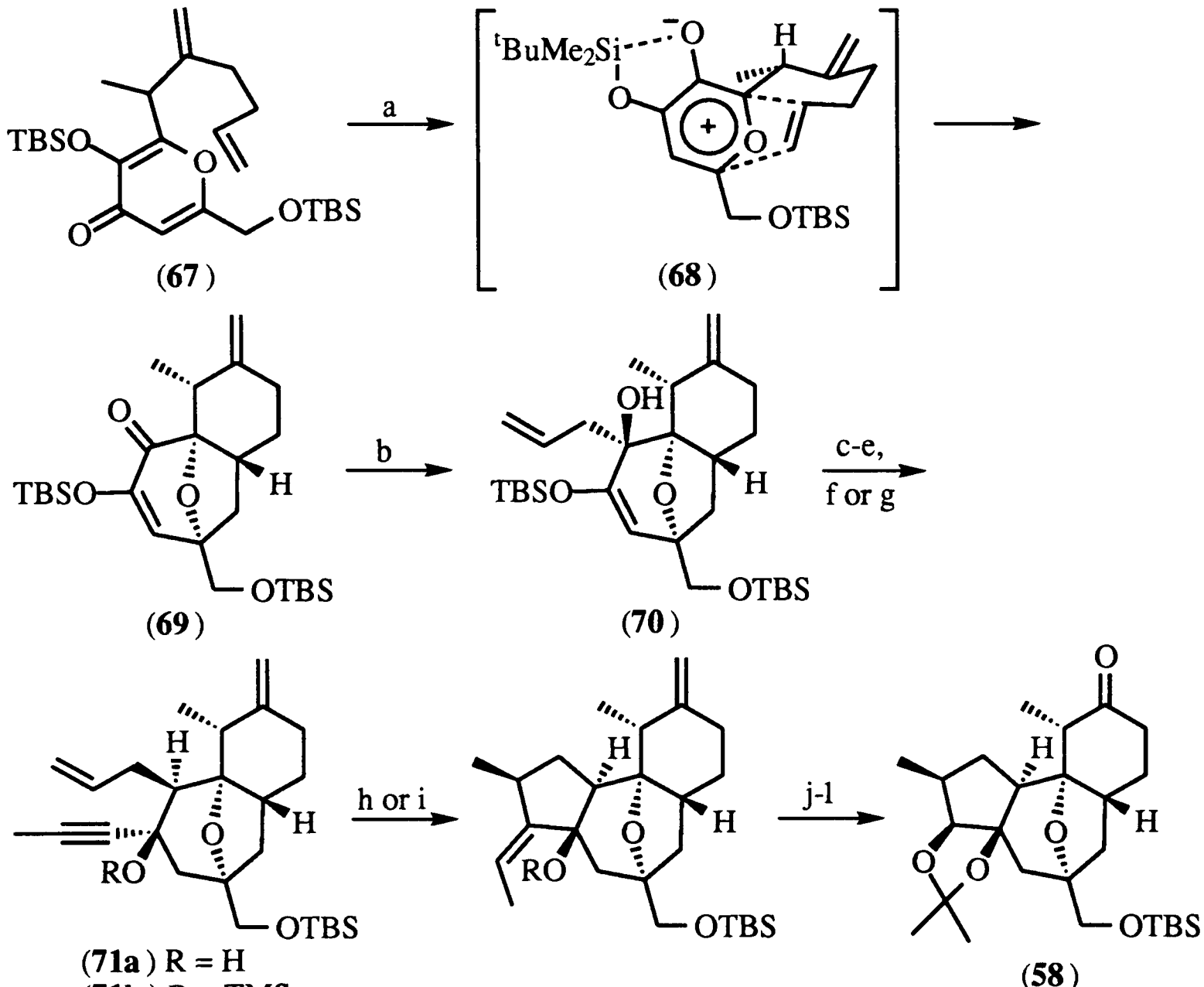
attachment of the D-ring, attack of the diphenylsulphide ylid (**66**) occuring exclusively from the more accessible β-face, to form *gem*-dimethylcyclopropane (**61**) in 85 % yield. Problems in the reduction of ketone (**61**), generating incorrect C-12 stereochemistry, were overcome by an internal hydride delivery that was directed by the C-9 hydroxyl in the oxygen bridge opened product (**62**). The structural manipulation of the more reactive A-ring sub-unit was delayed until the end of the sequence to complete the first total synthesis of the natural product phorbol (**1**) (**Scheme 8**).

The first generation phorbol (**1**) synthesis has since been improved upon by Wender.[52] Implementation of an unprecedented internal silicon transfer induced oxidopyrilium cycloaddition in silyloxy-γ-pyrone (**67**) generated the internally protected BC-skeleton of (**69**). Minimisation of 1, 3- interactions between the C-10 and C-11 substituents forced the methyl group to adopt an equatorial orientation in the chair-like transition state (**68**), allowing simultaneous specification of relative stereochemistry at 4 chiral centres. Latent C-4 oxygenation in the product (**71**) facilitated a new metal-mediated A-ring annelation, the stereocontrol in attachment of the allyl and propynyl side chains induced by the convex rigidity of the oxabicyclic B-ring. Standard transformations unveiled the phorboid intermediate (**58**) (**Scheme 9**), previously accessed by Wender's alternative route,[48] and had achieved an increase in versatility and reduction in length of the synthetic strategy.



(a) H_2 / $RhCl(PPh_3)_3$ / benzene; (b) DIBAH / toluene / -78°C; (c) PCC / DCM; (d) LDA / THF; TMSCl; (e) PhSCl / DCM; (f) $Pb(OAc)_4$ / benzene; (g) *m*-CPBA / DCM; (h) 60°C / $P(OEt)_3$ / benzene; (i) Ph_2SCMe_2 (**66**) / -78°C / THF / DCM; (j) DIBAH / $PhCH_3$; (k) $CO(Im)_2$ / DCM; (l) TBAF / THF; (m) Tf_2O / Et_3N / py / DCM; (n) Bu_4NI / HMPA / 55°C; (o) ^{t}BuLi / ether / -78°C; (p) PCC / DCM; (q) $NaBH(OAc)_3$ / THF / 60°C; (r) DIBAH / $PhCH_3$; (s) Bz_2O / DMAP / py / DCM; (t) SeO_2 / ^{t}BuOOH / DCM / 0°C; (u) $SOCl_2$ / propylene oxide / ether; (v) AgOBz / KOBz / TMEDA / CH_3CN; (w) $HClO_4$ / MeOH / Montmorillonite clay (K10) / $(CH_2OH)_2$; (x) SO_3.py.Et_3N / DMSO; (y) $CF_3CON(Me)TMS$ / DMAP / CH_3CN; (z) $KN(TMS)_2$ / -78°C; TMSCl / -78°C to r.t.; NBS / THF; (aa) LiBr / Li_2CO_3 / DMF / 130°C / 3 h; (bb) TsOH / MeOH; (cc) KCN / MeOH.

Scheme 8

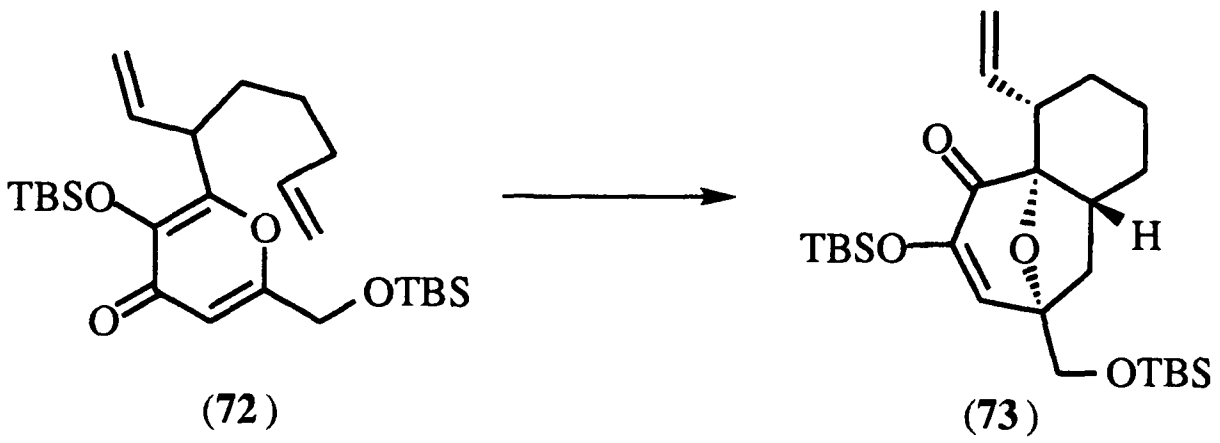


(a) 200°C / toluene / sealed tube / 48 h; (b) CH_2=$CHCH_2MgBr$ / THF (c) $SOCl_2$ / py / ether / 0°C; (d) TBAF / THF / 0°C; (e) Bu_3SnH / catalyst AIBN / toluene / 80°C; (f) 1-Lithio-propyne / 4 eq. of LiBr / THF / -78°C to 20°C; (g) 1-Lithio-propyne / 4 eq. of LiBr / THF / -78°C to 20°C; then TMSCl; (h) 0.1 eq. of $Pd_2(dba)_3.CHCl_3$ / 0.2 eq. of tri(*o*-tolyl)phosphine / 2 eq. of HOAc / 2 eq. of $(Me_2SiH)_2O$ / toluene; (i) Cp_2ZrBu_2 / -78°C to 20°C; then HOAc quench; (j) O_3 / DCM / MeOH / -78°C; $NaBH_4$ / -78°C to 20°C; (k) 2-Methoxypropene / catalyst PPTS / DCM; (l) PCC / NaOAc / DCM.

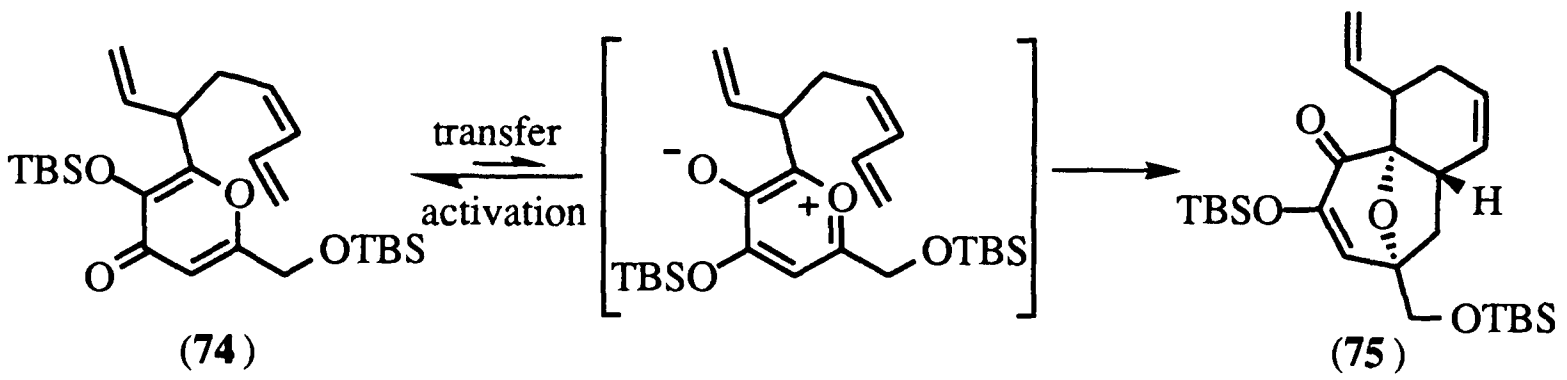
Scheme 9

Further study by Wender towards the derivation of a new general tigliane, ingenane, and daphnane precursor (**75**) expanded the technology of the [5+2] oxidopyrilium cycloaddition approach.[53] Silyloxy-γ-pyrone (**74**), bearing a synthetically more versatile diene tether, was synthesised. Despite the successful cycloaddition of dihydro (**72**), forming oxatricycle (**73**) as a single diastereoisomer (**Scheme 10**), attempts to effect the transformation on the required substrate (**74**) only afforded a trace of product (**75**) (**Scheme 11**). It was postulated by Wender that this was a consequence of the rate-limiting

silyl transfer - the slow substrate activation facilitating degradation to isomerised products and the poor reaction yield.

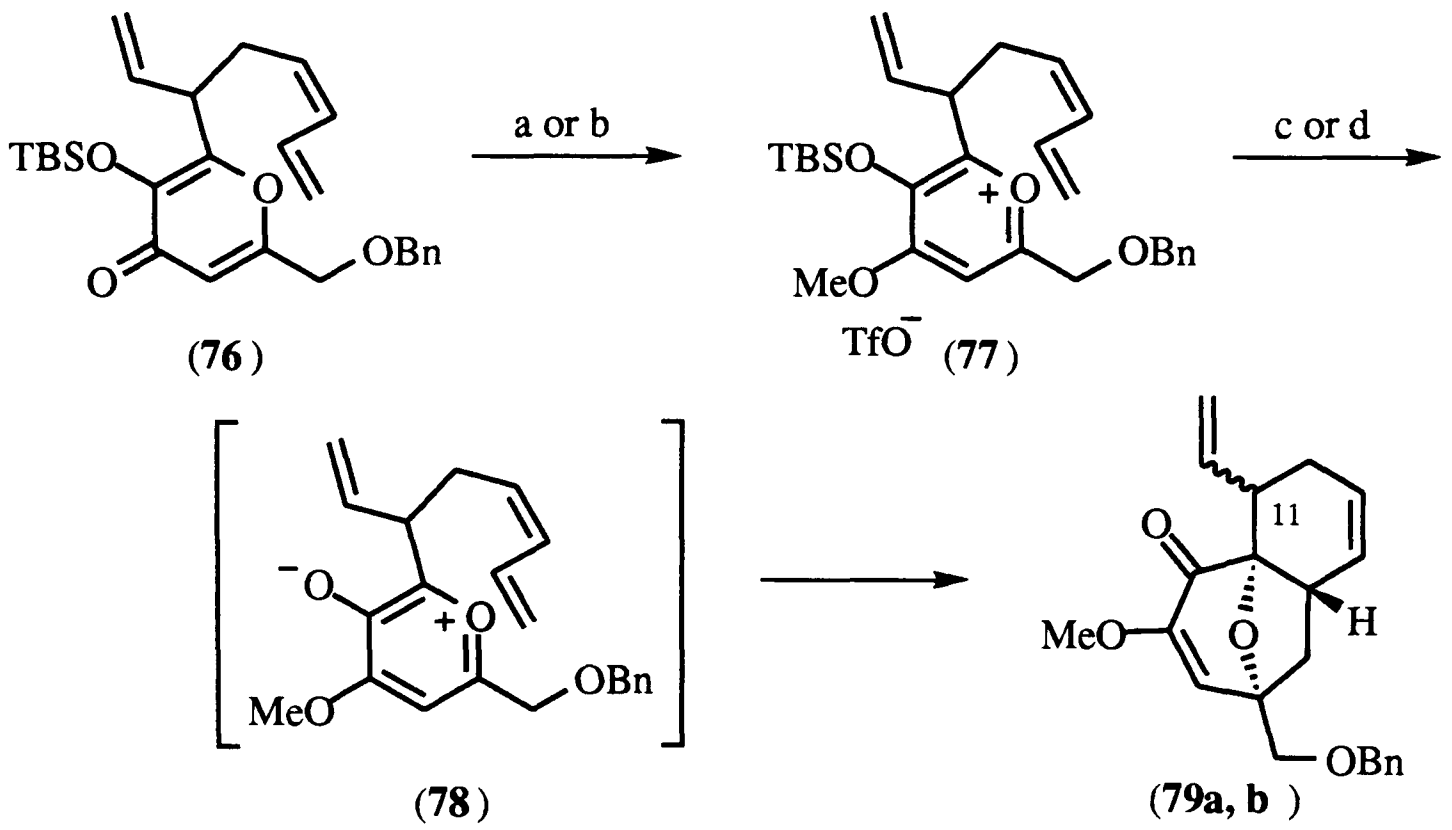


Scheme 10



Scheme 11

An effort was made to repeat the cycloaddition with an alternative substrate (**78**), in which a 4-alkoxy substituent had already been introduced by (**76**) alkylation. Treatment with cesium fluoride desilylated (**77**) and induced a spontaneous cyclisation of the oxidopyrilium intermediate (**78**) to form (**79a, b**) as a mixture of diastereoisomers (**Scheme 12**). Thus, opportunities for cycloaddition under these milder conditions permitted generation of a more versatile and synthetically useful phorbol precursor (**79**), although stereocontrol at the C-11 centre had been lost, giving rise to a 3.8 : 1 mixture of epimeric products.

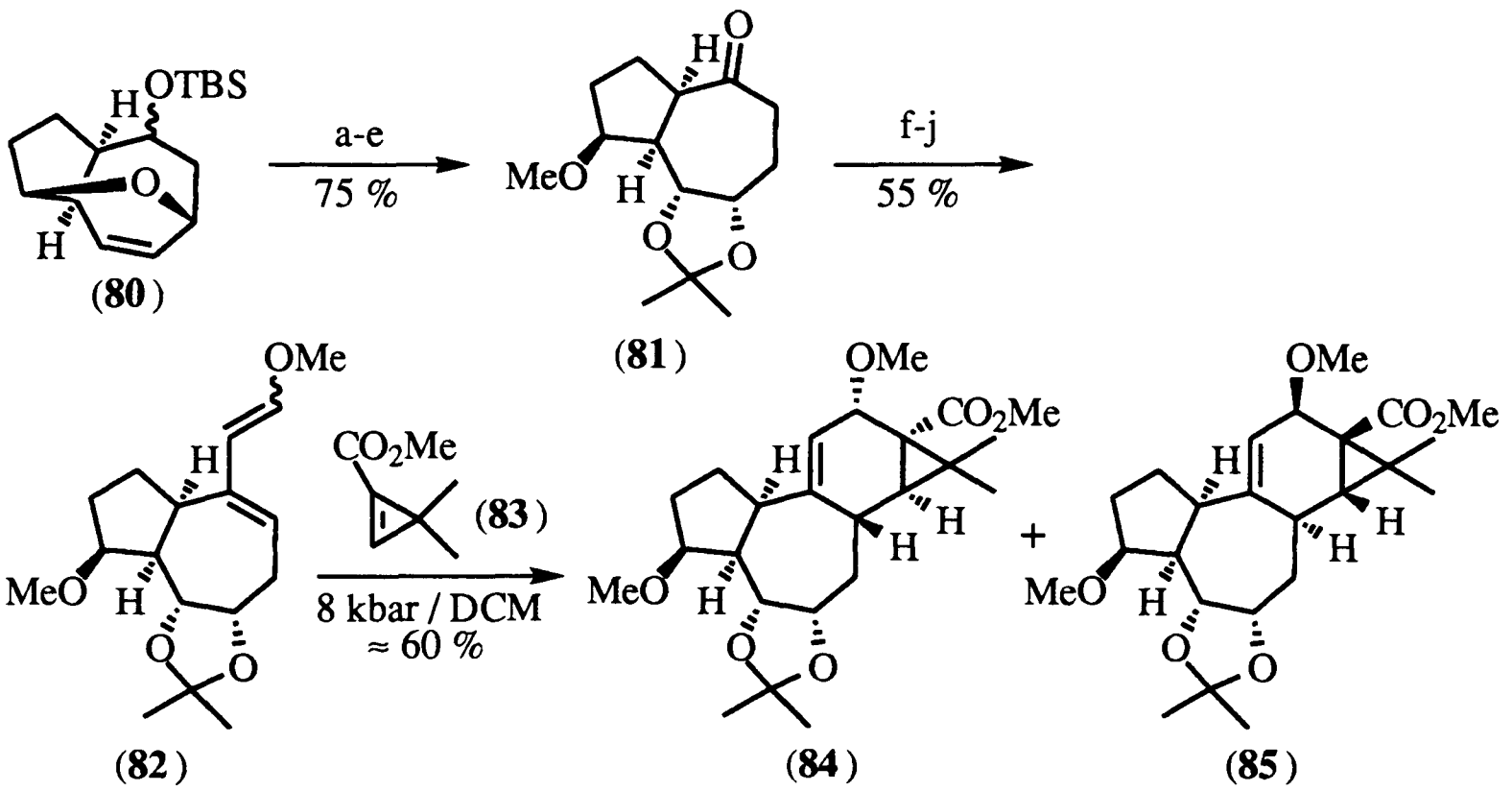


(a) 1.7 eq. of MeOTf / DCM / 40°C / 11 h; (b) 2 eq. of MeOTf / DCM / 20°C / 14 h; (c) 2 eq. of 2, 2, 6, 6, -tetramethylpiperidine / DCM / 20°C / 10 h; (d) excess CsF / DMF-DCM (1 : 1) / 10 h.

Scheme 12

Other groups have embarked upon synthetic studies directed towards phorbol natural products although, as yet, no other derivation of the complete tigliane skeleton has been published. Rigby has constructed the basic tetracyclic tigliane framework from a hydroazulene precursor (**81**),[54] that was derived from the readily available tricycle (**80**).[55] The C- and D-rings were introduced in a single step by the high pressure intermolecular cycloaddition of an activated cyclopropene (**83**) and a substrate bearing a methoxy activated diene tether (**82**) (**Scheme 13**).

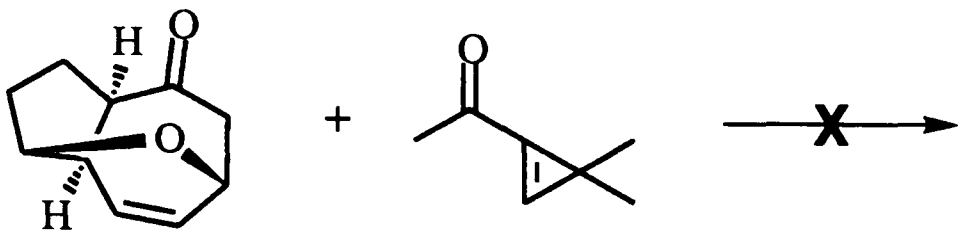
Although the methoxydiene (**82**) was obtained as a 2 : 1 *E/Z* mixture of geometrical isomers, cyclopropene dienophiles fail to react with *Z* dienes at any appreciable rate under high pressure conditions.[56] Hence, subjecting a solution of diene (**82**) and *gem*-dimethylcyclopropenecarboxylate (**83**) in dichloromethane to 8 kbar pressure generated a 2 : 1 mixture of tigliane products, (**84**) and (**85**), the required isomer (**84**) predominating. Cycloaddition stereoselectivity was attributed to the facial bias of the convex *cis*-fused hydroazulene ring, although the influence of the acetonide function undoubtedly altered the high degree of stereocontrol often inherent in these systems.[55]



(a) Li / $MeNH_2$; (b) MeI / NaH / THF / 0°C; (c) TBAF / THF / r.t.; (d) Swern oxidation; (e) OsO_4 / Me_3NO; $Me_2C(OMe)_2$ / H^+; (f) Lithium tetramethyl piperidine / Tf_2NPh; (g) $Pd(OAc)_2$ / CO / Ph_3P / Et_3N / MeOH; (h) DIBAL / -78°C; (i) Swern oxidation; (j) $Ph_3P^+CH_2OMe\ Cl^-$ / *n*-BuLi / 0°C.

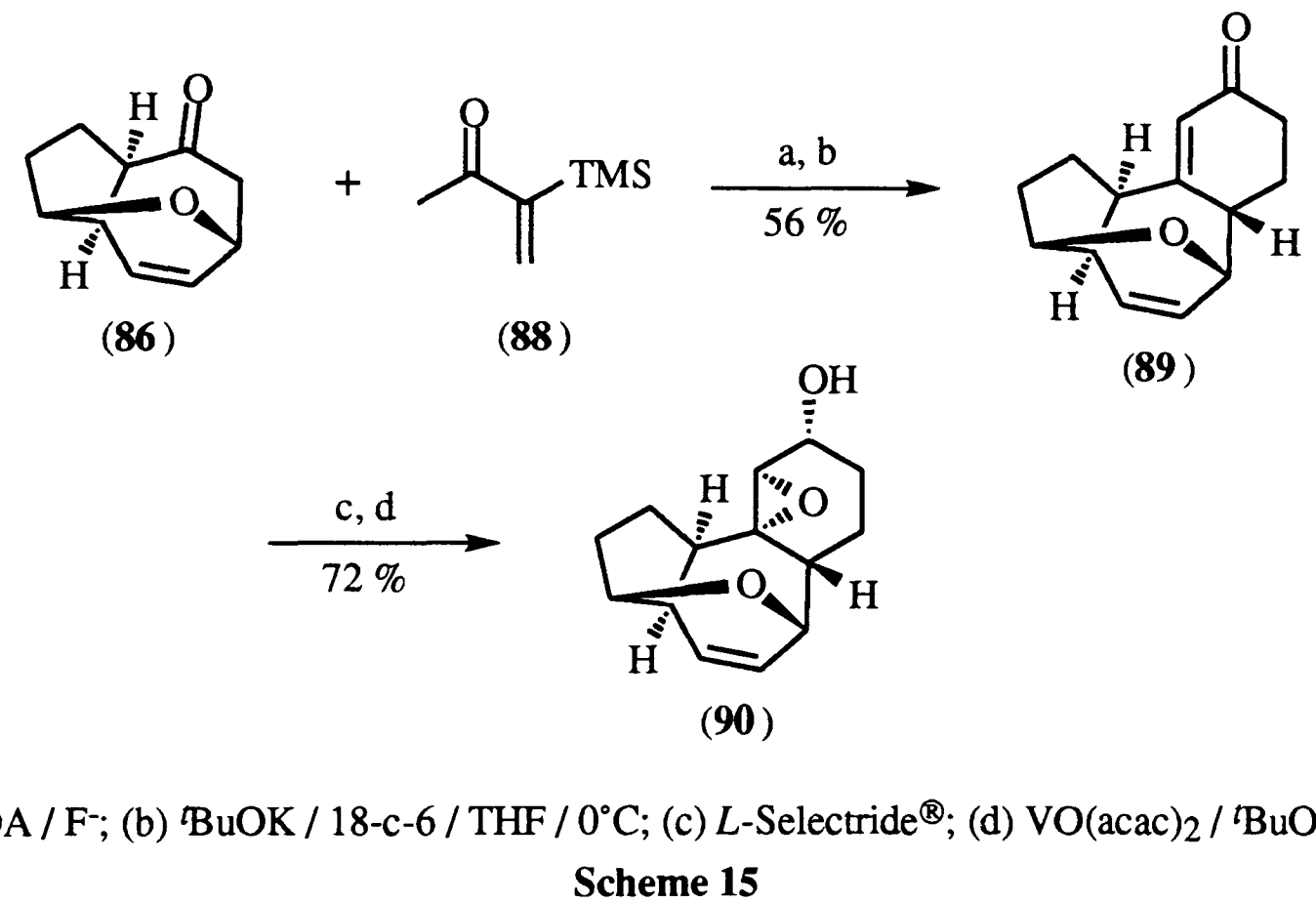
Scheme 13

Rigby has also investigated an alternative approach to the phorbols from hydroazulene precursors that utilised Robinson annulative protocol.[54] Although simultaneous assembly of the C- and D-rings was no longer viable due to the lack of an effective preparative route to the requisite acetylcyclopropene (**87**) (**Scheme 14**),[56] the construction of the C-ring with a view to subsequent D-ring formation was possible by condensation of (**86**) with the trimethylsilyl substituted methylvinylketone (**88**) (**Scheme 15**).[57] Conformational rigidity in the tricyclic precursor (**86**) conveyed the annelative stereocontrol and allowed formation of a single product (**89**) in 56 % yield. C-ring architectural features were then introduced by *L*-Selectride® reduction, that preferentially formed the desired pseudoaxial alcohol (3 : 1), and a directed epoxidation to furnish the highly substituted phorboid product (**90**).



(**86**) (**87**)

Scheme 14



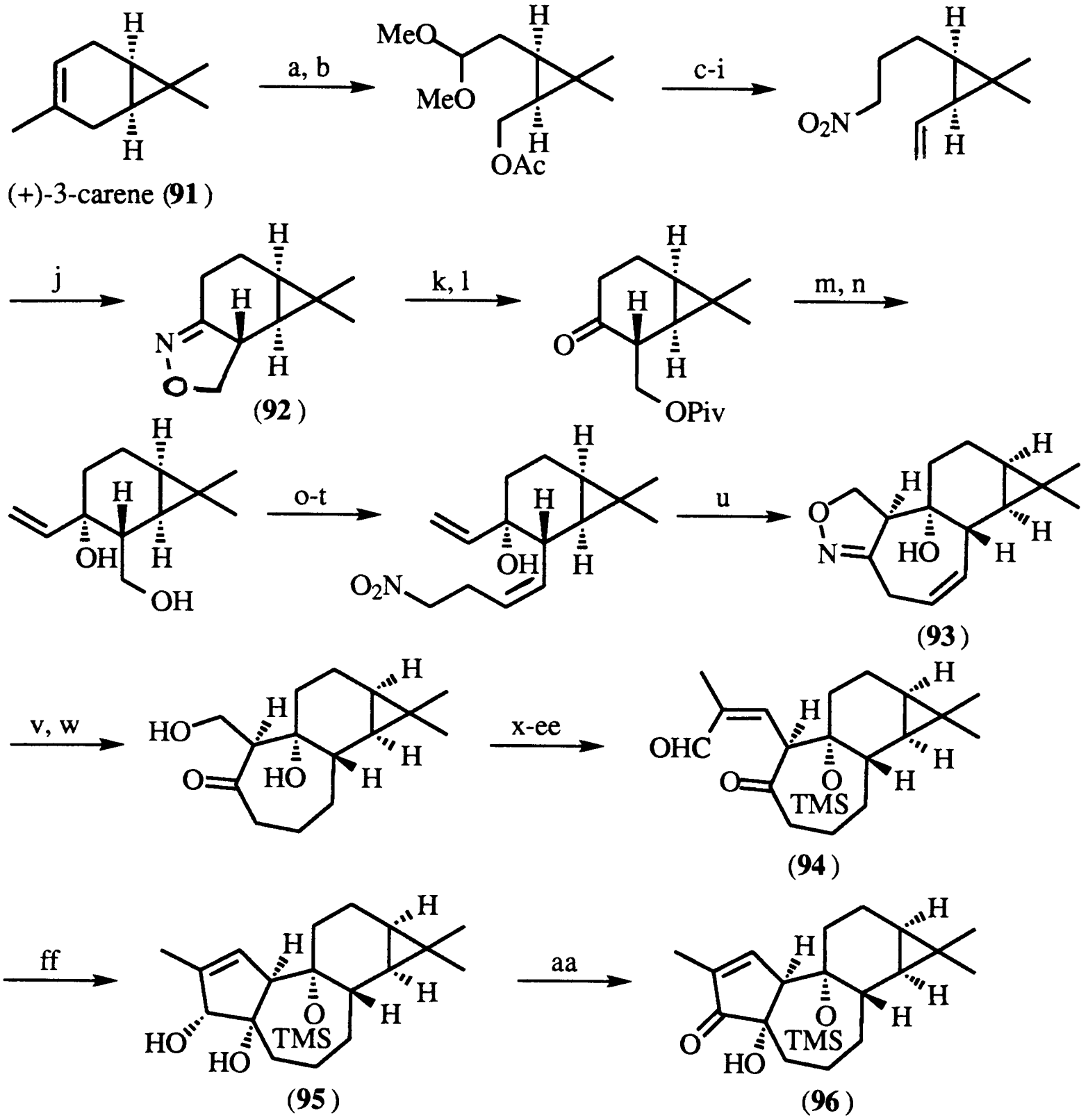
(**86**) (**88**) (**89**)

(**90**)

(a) LDA / F^-; (b) ^{t}BuOK / 18-c-6 / THF / 0°C; (c) *L*-Selectride®; (d) $VO(acac)_2$ / ^{t}BuOOH.

Scheme 15

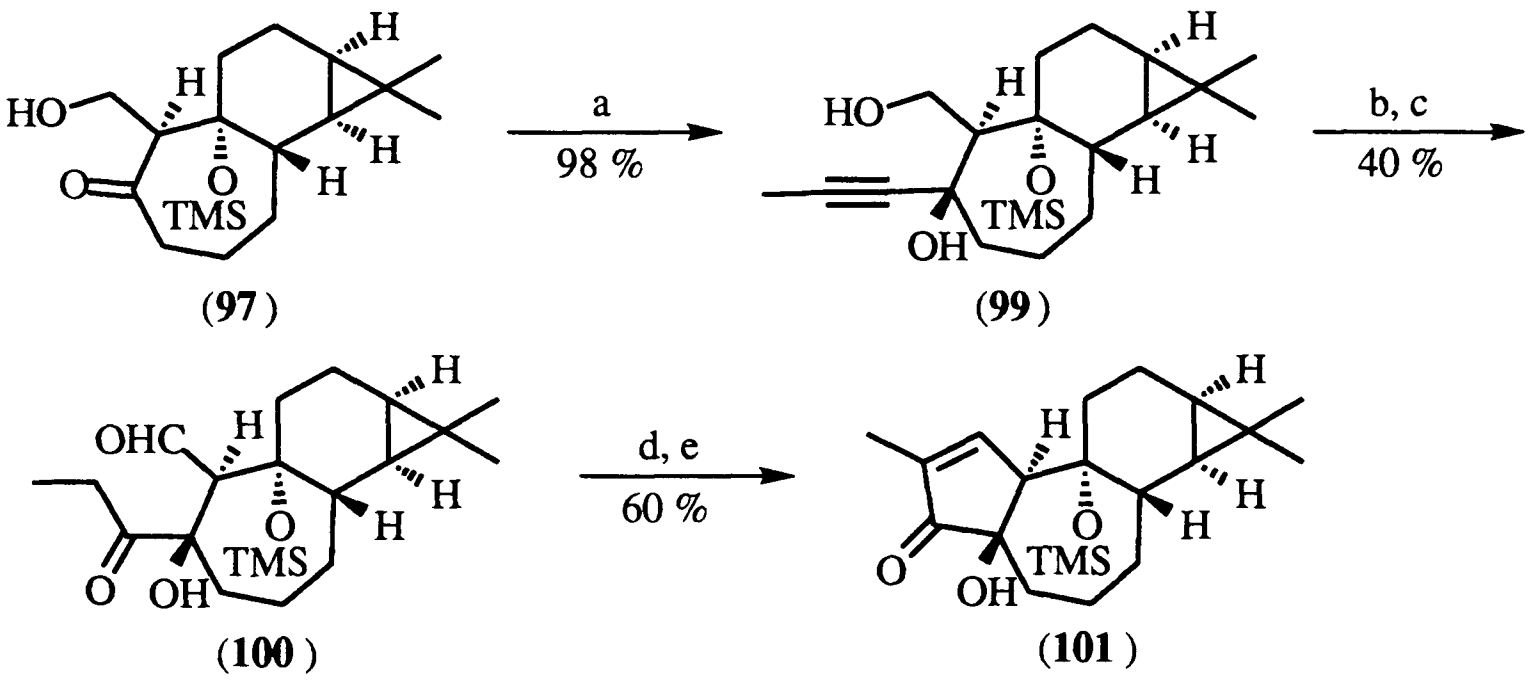
Shibasaki adopted a very different approach to the problem, establishing the tetracyclic phorbol framework from (+)-3-carene (**91**) that already contained the *gem*-dimethylcyclopropane D-ring.[58] The cyclohexene ring of (**91**) was oxidatively cleaved by ozonolysis and reclosed to (**92**) by intramolecular nitrile oxide cycloaddition. The 7 membered B-ring was introduced by a second cycloaddition, stereospecifically accessing the required oxazoline (**93**). Unfortunately, the intramolecular McMurry coupling of dicarbonyl (**94**) closed the A-ring exclusively to the undesired *cis*-diol (**95**), resulting in the formation of carbocycle (**96**) that possessed a *cis* A-B ring junction (**Scheme 16**).



(a) O_3 / MeOH / -78°C; Me_2S / r.t.; (b) *m*-CPBA / $CHCl_3$ / r.t.; (c) 10 % NaOH / MeOH / 0°C; (d) $(COCl)_2$ / DMSO / Et_3N / -78°C to r.t.; (e) $Ph_3P^+MeBr^-$ / BuLi / THF / -78°C to r.t.; (f) 30 % $HClO_4$ / THF / 0°C; (g) $MeNO_2$ / KF / Bu_4NCl / toluene / r.t.; (h) Ac_2O / py / DMAP / DCM / r.t.; (i) $NaBH_4$ / EtOH / 0°C; (j) MeNCO / Et_3N / benzene / r.t.; (k) aq. $TiCl_3$ / MeOH / r.t.; (l) PivCl / py / DCM / r.t.; (m) CH_2=$CHMgBr$ / THF / -78 to -55°C; (n) $LiAlH_4$ / ether / 0°C; (o) SO_3.py / Et_3N / DMSO / r.t.; (p) $Ph_3P(CH_2)_3OC(OMe)Me_2Br^-$ / $KN(TMS)_2$ / THF / HMPA / -78°C to r.t.; (q) 50 % AcOH / THF / r.t.; (r) *p*-TsCl / py / DMAP / DCM / r.t.; (s) NaI / 2-butanone / r.t.; (t) $AgNO_2$ / ether / r.t.; (u) *p*-ClC_6H_4NCO / Et_3N / benzene / 55°C; (v) H_2 / Raney Ni (W-2) / $B(OH)_3$ / MeOH / H_2O / r.t.; (w) H_2 / 10 % Pd-C / AcOEt / r.t.; (x) TMSCl / im / DMF / r.t.; (y) TBSOTf / Et_3N / DCM / 0°C; (z) K_2CO_3 / MeOH / 0°C; (aa) SO_3.py / Et_3N / DMSO / r.t.; (bb) $(CF_3CH_2O)_2P(O)CH(Me)COOMe$ / DBU / LiCl / MeCN / r.t.; (cc) DIBAH / toluene / -78°C; (dd) TBAF / THF / -45°C; (ee) MnO_2 / pentane / r.t.; (ff) $CpTiCl_3$ / $LiAlH_4$ / THF / 50°C.

Scheme 16

Shibasaki's procedure was later elaborated to specify correctly the stereochemistry of the C-4 hydroxyl.[59] Treatment of monosilyl protected (**97**) with the alkynyl cerium reagent (**98**) resulted in delivery of the nucleophile from the α-face to afford the required tertiary alcohol (**99**) in 98 % yield. Sequential intramolecular aldol cyclisation/elimination of the oxidised product (**100**) furnished tigliane (**101**) with a fully substituted and correctly specified A-ring (**Scheme 17**).

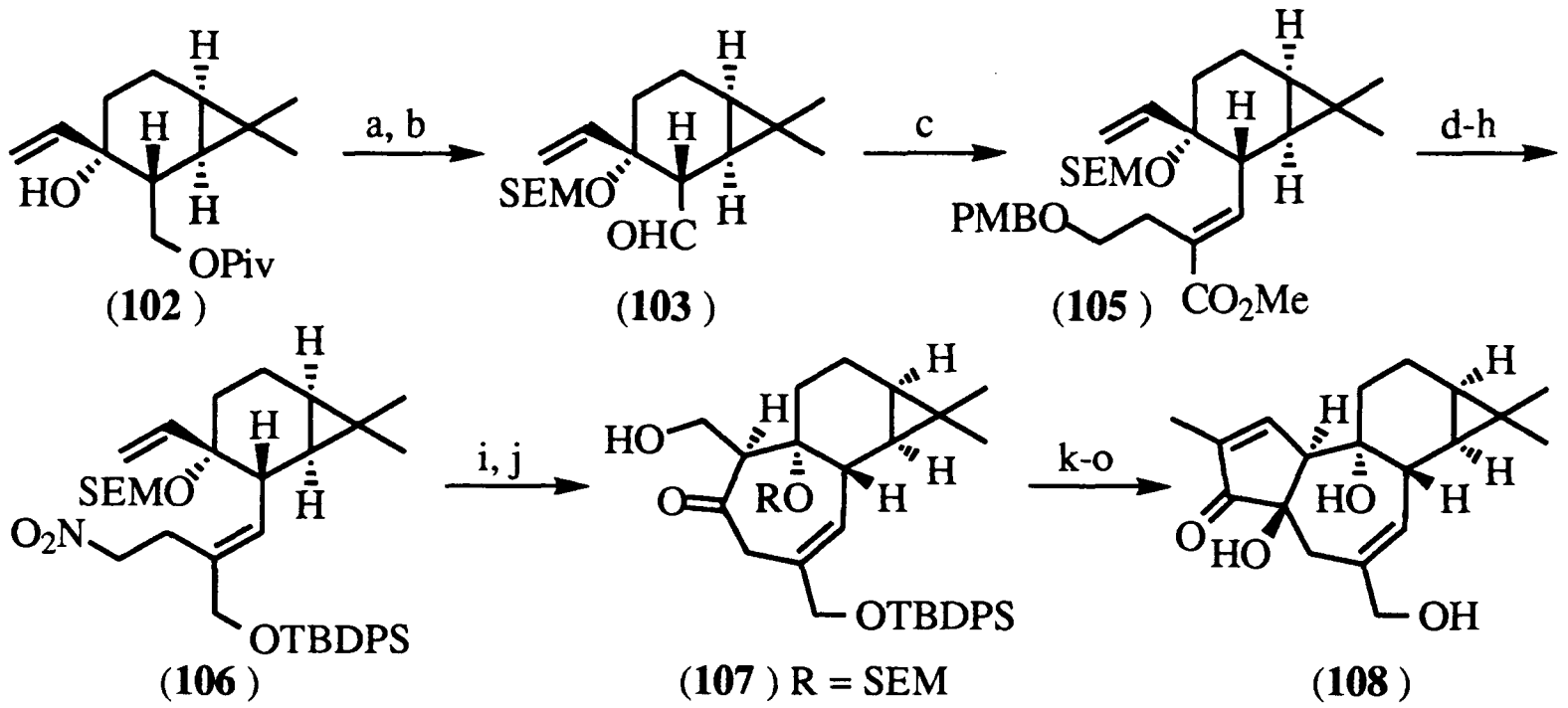


(**97**) (**99**) (**100**) (**101**)

(a) $(MeC{\equiv}C)_2CeCl$ (**98**) / THF / -78 to -30°C; (b) SO_3.py / Et_3N / DMSO / r.t.; (c) $HgSO_4$ / 1 % H_2SO_4 / THF / r.t.; (d) *tert*-BuOK / THF / -78 to -65°C; (e) MsCl / Et_3N.

Scheme 17

The successful introduction of the B-ring allylic alcohol sub-structure has also been demonstrated by Shibasaki[60] by use of an alternative chiral starting material (**102**) derived from (+)-3-carene (**91**). Nucleophilic addition of phosphonate carbanion (**104**) to aldehyde (**103**), followed by submission to the intramolecular aldol condensation protocol, succeeded in the stereoselective synthesis of a phorbol (**108**) containing an allylic alcohol function (**Scheme 18**).

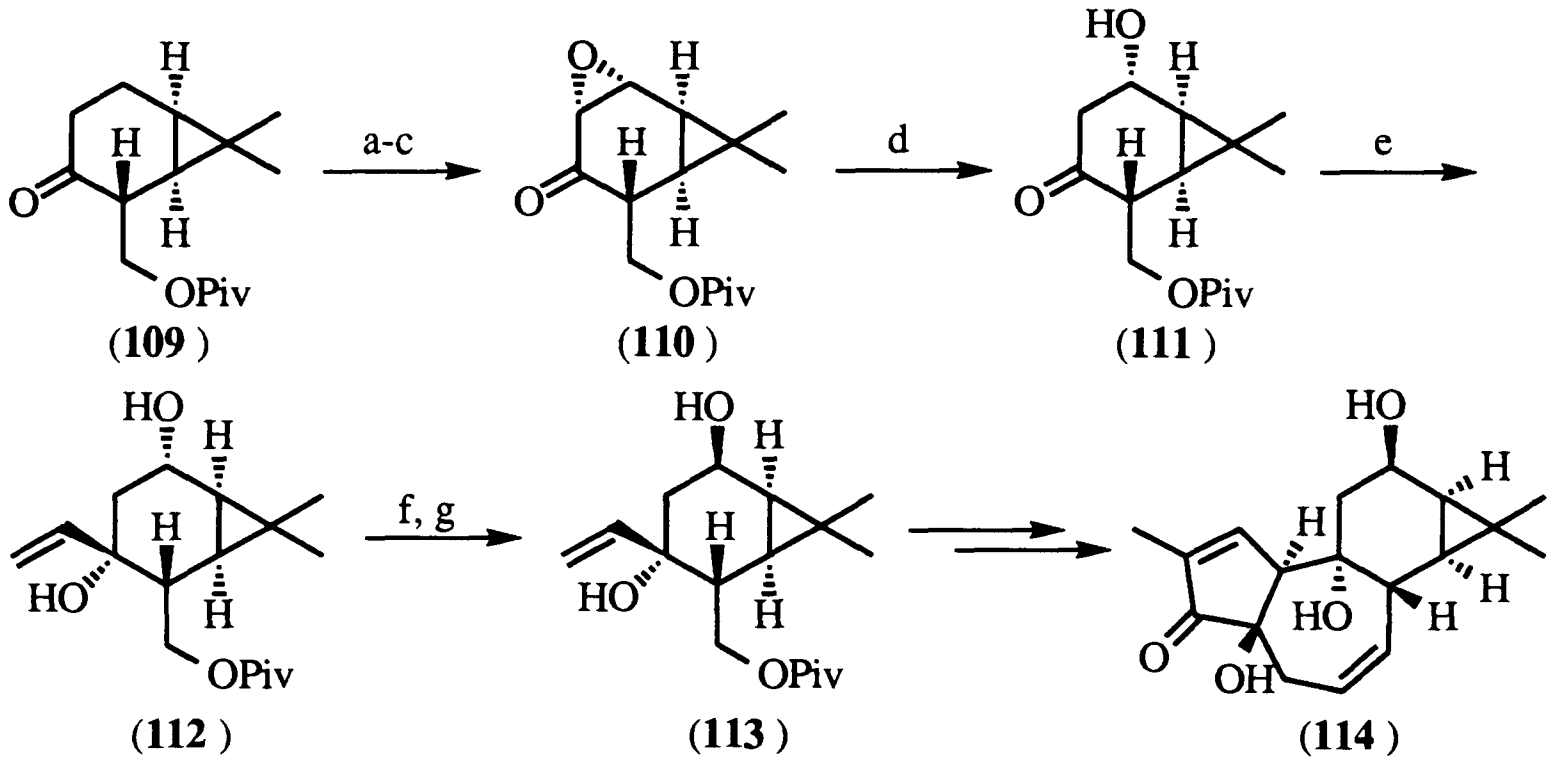


(a) 2.0 eq. of SEMCl / 3.0 eq. of $^{i}Pr_2NEt$ / DCM / 35°C / 17 h; (b) 1.5 eq. of $LiAlH_4$ / Et_2O / -78°C / 1 h; 5 mol% of TPAP / 1.5 eq. of NMO / 4Å molecular sieves / DCM-MeCN (10 : 1) / 0 to 25°C / 1 h; (c) 5.0 eq. of $(MeO)_2P(=O)C^{-}(CO_2Me)C_2H_4OPMB$ (**104**) / 4.8 eq. of LHMDS / 10.0 eq. of LiBr / toluene / 0 to 25°C / 1 h; then (**103**) / 0 to 25°C / 18 h; (d) 3.0 eq. of DIBAH / toluene / -78°C / 2 h; (e) 2.0 eq. of TBDPSCl / 3.0 eq. of Im / DMF / 25°C / 18 h; (f) 1.5 eq.of DDQ / DCM-H_2O (10 : 1) / 25°C / 3 h; (g) 2.0 eq. of TsCl / 10.0 eq. of py / DMAP (cat.) / DCM / 25°C / 24 h; 5.0 eq. of NaI / 2-butanone / 25°C / 24 h; (h) 2.0 eq. of $AgNO_2$ / ether / 25°C / 17 h; (i) 12 eq. of *p*-chlorophenylisocyanate / 1.25 eq. of Et_3N / benzene / 50°C / 96 h.

Scheme 18

Oxidation of Shibasaki's chiral substrate, cyclohexanone (**109**), would provide an obvious means of access to the C-12 oxygenated substituent, functionality that is of vital importance to the PKC regulatory activity of the natural product.[60] The reductive opening of the α-epoxide (**110**) with aluminium amalgam regiospecifically generated the C-12 α-hydroxy (**111**) in 92 % yield. Conversion to the C-9 allylic alcohol (**112**) allowed an epimerisation at C-12 to be effected, by successive oxidation/sodium borohydride reduction, to form (**113**) with the oxygenated C-12 stereogenic centre correctly specified. Submission of this customised chiral starting material to the elaborative protocol generated a C-11 demethylated tigliane (**114**) (**Scheme 19**).

Additional Reagents for **Scheme 18**; (j) H_2 / Raney Ni (W2) / $B(OH)_3$ / MeOH-H_2O (5 : 1) / 25°C / 2 h; (k) 20 eq. of lithium propyn-1-ide / 10 mol eq. of $CeCl_3$ / -78 to -60°C / 1 h; then (**107**) / -78 to -50°C / 3 h; (l) 5 mol% of TPAP / 1.5 eq. of NMO / 4Å molecular sieves / DCM-MeCN (10 : 1) / 0 to 25°C / 1 h; (m) 0.2 eq. of $HgSO_4$ / 1 % aq. H_2SO_4-acetone (1 : 10) / 0 to 25°C / 30 min; (n) 6.0 eq. of LDA / THF / -78 to -60°C / 1 h; then 30 eq. of MsCl / 50 eq. of TEA / -78 to 0°C / 3 h; (o) HF.py-THF (2 : 5) / 0 to 25°C / 2.5 h.



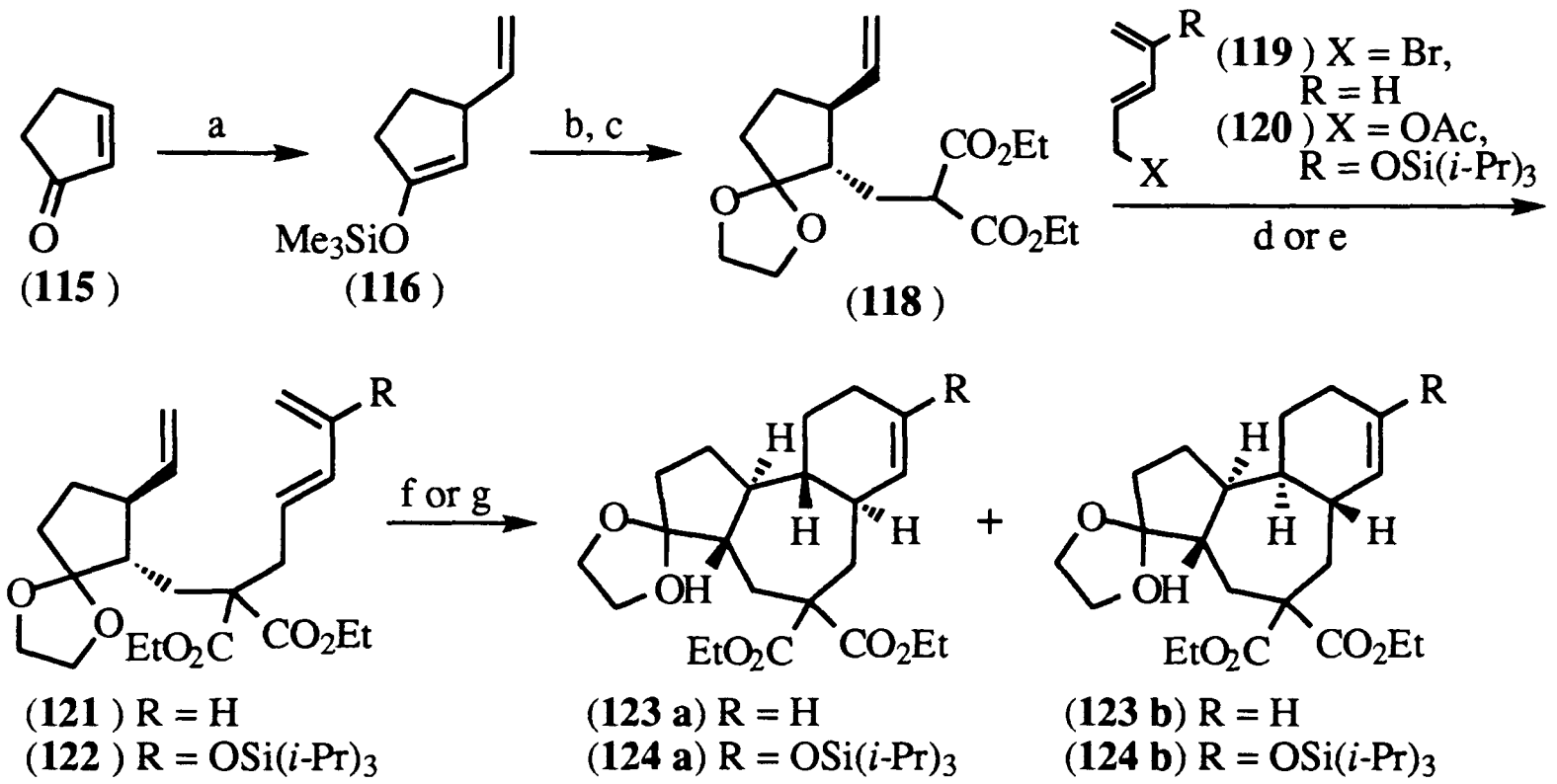
(109) (110) (111)

(112) (113) (114)

(a) 1.3 eq. of LDA / THF / -78°C / 1 h; 1.3 eq. of Cp_2ZrCl_2 / -78°C / 1 h; then 1.1 eq. of PhSeBr / -78 to 0°C / 2 h; (b) 1.2 eq. of *m*-CPBA / DCM / 0°C / 1 h; (c) 2.5 eq. of dimethyldioxirane / acetone / -78 to 25°C / 17 h; (d) 5.0 eq. of Al-Hg / THF-EtOH-H_2O (11 : 4 : 3) / -30°C / 36 h; (e) 5.0 eq. of CH_2=CHMgBr / THF / -78 to -30°C / 3 h; (f) 3.0 eq. of SO_3.py / 3.0 eq. of Et_3N / DMSO / 25°C / 10 min; (g) 1.5 eq. of $NaBH_4$ / MeOH / 0°C / 1.5 h.

Scheme 19

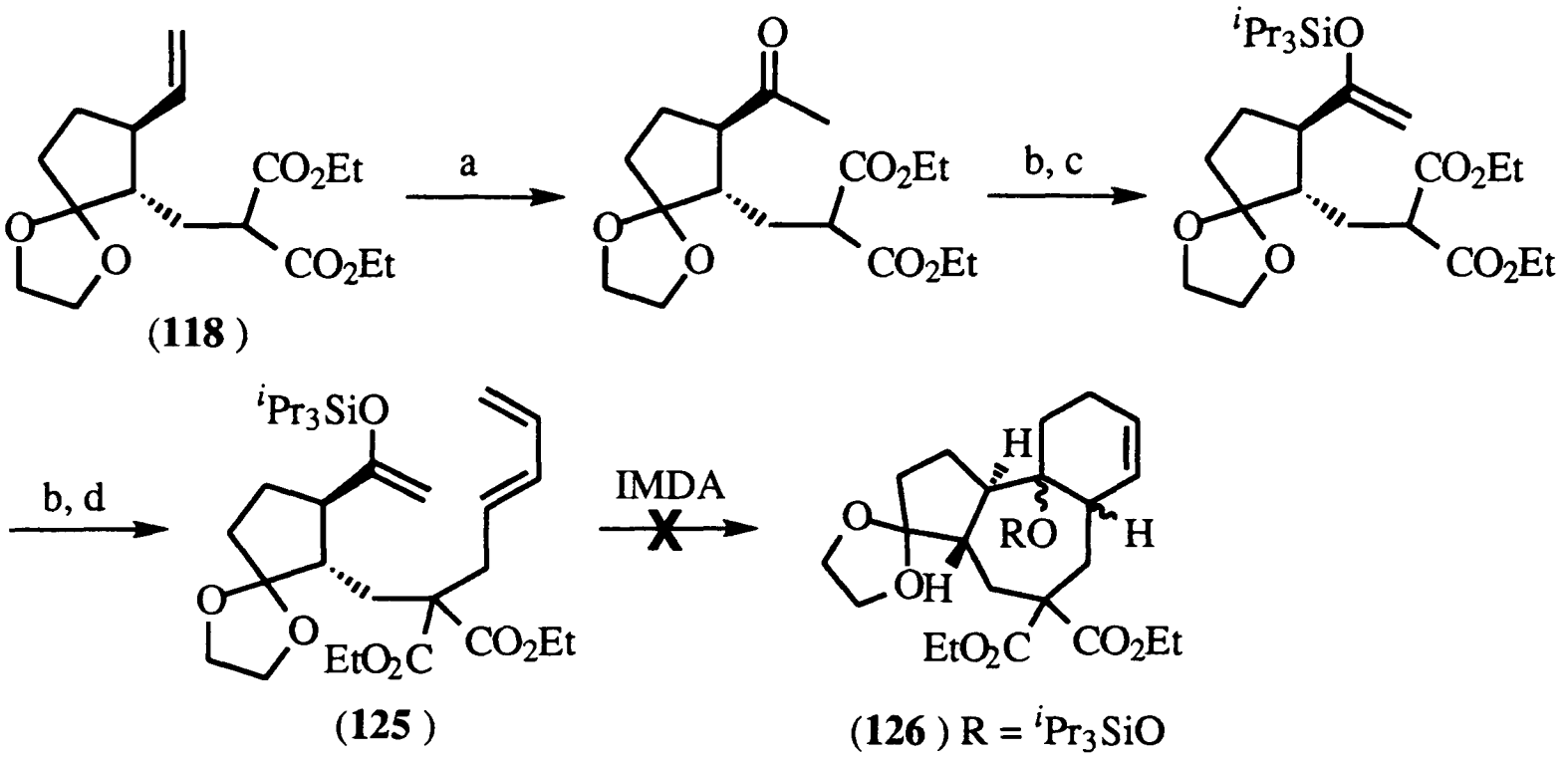
Page has adopted an IMDA approach to the construction of the B- and C-rings of daphnane and tigliane polycyclic systems.[61,62] Starting with the A-ring cyclopentenone (**115**), a conjugate vinylic addition introduced the dienophile and permitted the enolate to be trapped as a trimethylsilyl ether (**116**). Alkylation with the functionalised diethyl malonate (**117**) generated a *trans* A-B ring junction and established the precursor (**118**) that was capable of sustaining an anion. Simple nucleophilic halogen displacement[61] or a palladium catalysed coupling reaction[62] with pre-formed dienes, (**119**) or (**120**), provided a route to the triene IMDA substrates possessing either unactivated (**121**) or activated (**122**) diene sub-units. The intramolecular cycloaddition of trienes, (**121**) and (**122**), provided diastereomeric products, (**123a, b**) and (**124a, b**) respectively, that could not be separated (**Scheme 20**). A considerable increase in reactivity had been observed in cycloaddition of the activated diene (**122**) that successfully introduced C-13 oxygenation into the tigliane products (**124a, b**).[62]



(a) CH_2=CHMgBr / CuBr.DMS / Me_3SiCl / DMPU / Et_3N / THF / -78°C; (b) diethyl methylenemalonate (**117**) / $SnCl_4$ / DCM / -78°C / (c) ethylene glycol / TsOH / PhH / heat; (d) (X = Br, R = H) LDA / THF / -78°C; (e) (X = OAc, R = OSi(*i*-Pr)$_3$) [$Pd_2(dba)_3$.$CHCl_3$] / $CHCl_3$ / Ph_3P / THF; LHMDS / THF; (f) (X = Br, R = H) toluene / sealed tube / 160°C / 14 days; (g) (X = OAc, R = OSi(*i*-Pr)$_3$) toluene / sealed tube / 150 to 160°C / 3 days.

Scheme 20

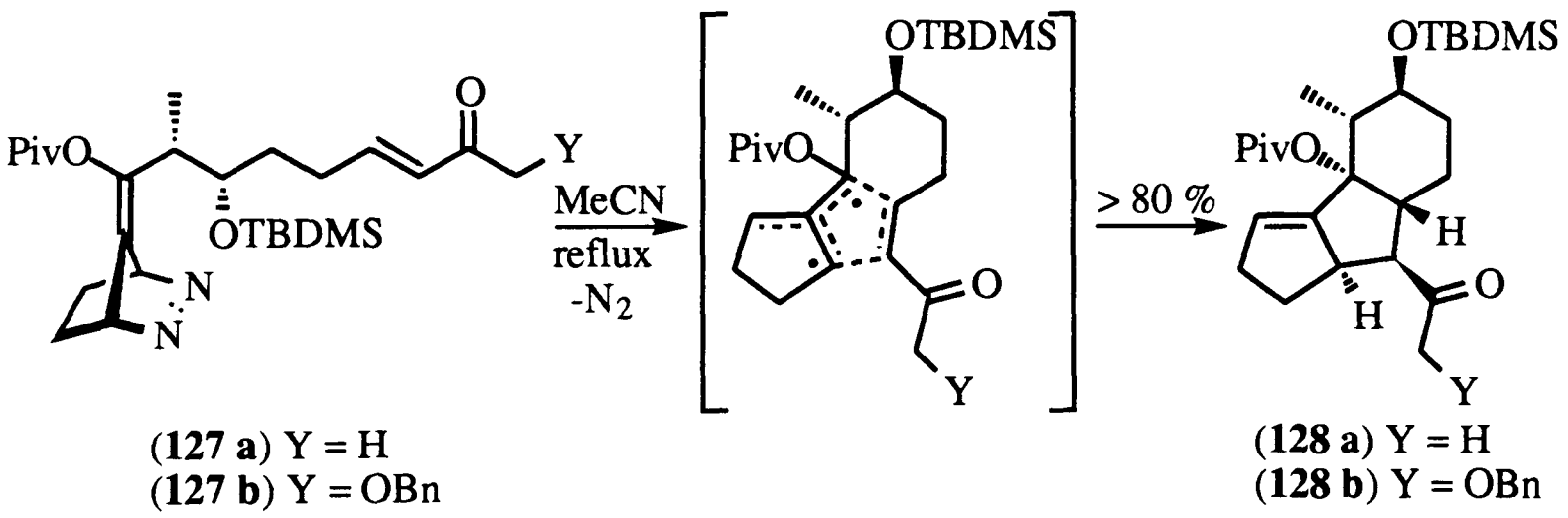
Further efforts to improve on the applicability of this approach have focused on successful incorporation of C-9 oxygenation in the cycloadducts (**126**) by dienophilic functionalisation. However in a preliminary communication it was reported that IMDA of silylenol ether (**125**), formed by similar alkylative protocol, was unsuccessful - the substrate being unstable under the cycloaddition reaction conditions (**Scheme 21**).[63]



(a) $PdCl_2$ / CuCl / O_2 / DMF / H_2O; (b) LDA / -78°C; (c) $^iPr_3SiCl$; (d) (**119**).

Scheme 21

Investigations by Little into the design of simpler PKC activators/inhibitors looked at the application of an intramolecular diyl trapping reaction to the problem.[64] Heating diazene (**127**) to reflux in a solution of acetonitrile effected closure to tricycle (**128**), predicted to be an active PKC modulator based on phorbol pharmacophore models.[13] The transformation proceeded in high yield and with control of relative and absolute stereochemistry at six asymmetric centres (**Scheme 22**).



Scheme 22

The asymmetric induction in this kinetically controlled process was attributed to the adoption of a *pseudo*-equatorial environment by the methyl, silyl ether, and diyl ring functionality in the lowest energy transition state (**Figure 1**). Thus the stereocontrol was a

consequence of substitution in the diylophilic tether, a phenomenon that explained the lack of stereoselectivity evident in the intramolecular diyl trapping reaction of a related diazene (**129**).[65]

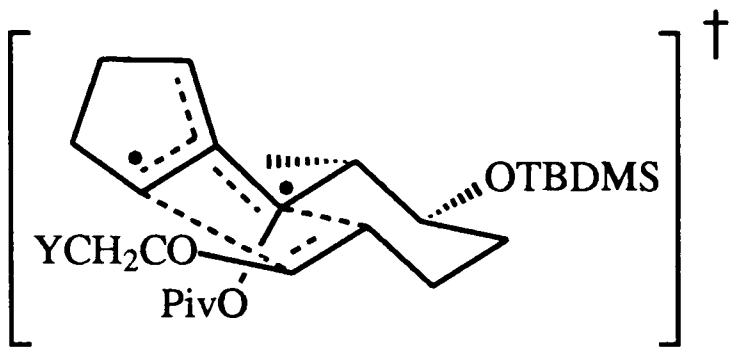
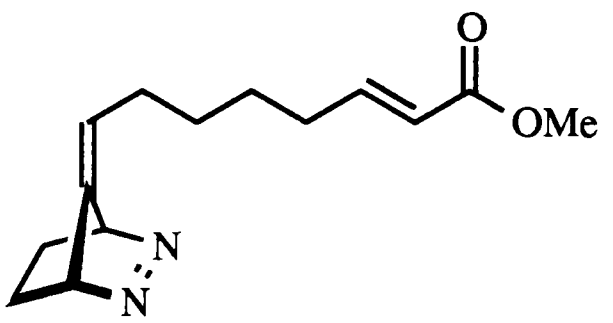


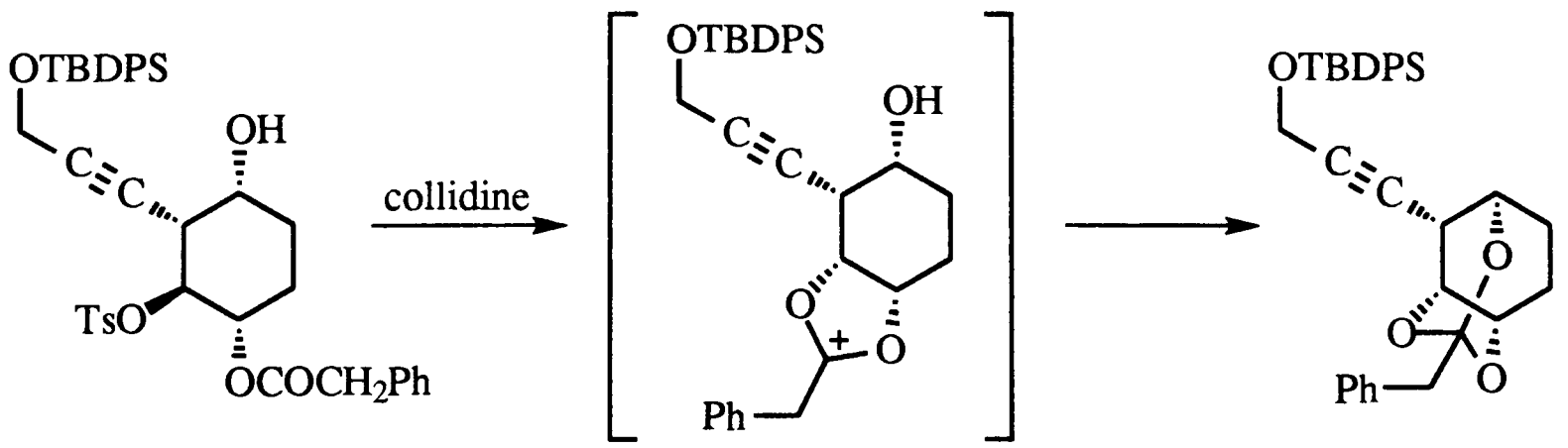
Figure 1



(**129**)

1.3.2. Routes to the Daphnanes.

In order for approaches towards phorbols to be applicable to the synthesis of daphnane natural products, the challenge of establishing the key 2, 9, 10-trioxatricyclo[4.3.1.$0^{3,8}$]decane system must be addressed. Construction of the 1, 2, 4-*ortho* ester daphnetoxin substructure (**132**) has been recently achieved in laboratory studies. The bicyclic dioxolenium ion (**131**) was generated by anchimerically assisted tosylate expulsion in (**130**), an intramolecular hydroxyl capture establishing (**132**) by closure of the ortho ester (**Scheme 23**).[45]



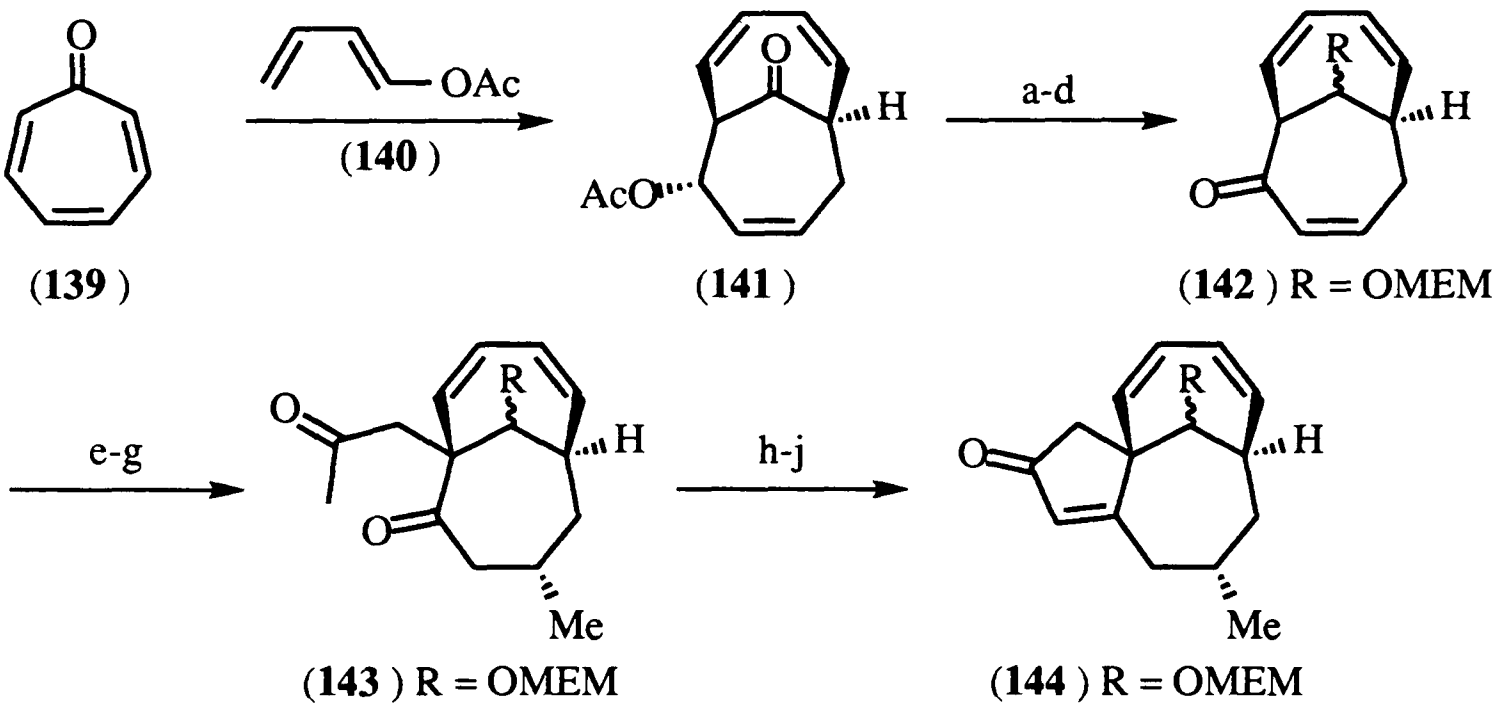
(**130**) (**131**) (**132**)

Scheme 23

1.3.3. Routes to the Ingenanes.

Although ingenanes are structurally related to the daphnanes and tiglianes, the development of routes to these natural products must address very different problems in both bond connectivity and stereochemistry. Not only is there an unusually dense *cis* array of

ring precursor (**143**). Intramolecular aldol condensation of dione (**143**) and subsequent deprotection and oxidation furnished (**144**) as a tricyclic ingenane analogue with functionality present for future elaboration (**Scheme 25**). Since this report, tricycle (**144**) has been synthesised by Mehta using a similar approach.[70]



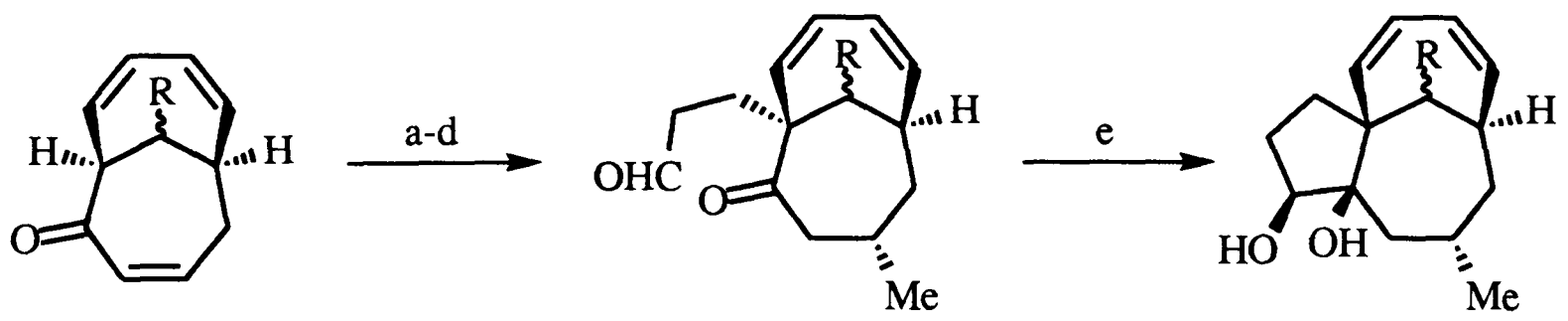
(**139**) (**141**) (**142**) R = OMEM

(**143**) R = OMEM (**144**) R = OMEM

(a) $NaBH_4$ / MeOH / r.t.; (b) MEMCl / $(i\text{-}Pr)_2EtN$; (c) K_2CO_3 / MeOH; (d) PDC / DCM; (e) LDA / -78°C / $CH_2{=}C(OMe)CH_2Br$ / HMPA / THF; (f) Me_2CuLi / 0°C; (g) H_3O^+; (h) NaH / toluene / reflux; (i) TMSCl / NaI; (j) PDC.

Scheme 25

Further studies by Rigby appended the bridgehead enolate alkylation technology of enone (**142**) and described a route to the tricyclic diol (**144a**) by Corey pinacolic coupling of the dicarbonyl (**143a**) (**Scheme 26**).[71] Correct specification of the C-4 stereogenic centre was imposed by the rigidity of the bicyclic array that precluded β-facial ketone carbonyl alkylation.

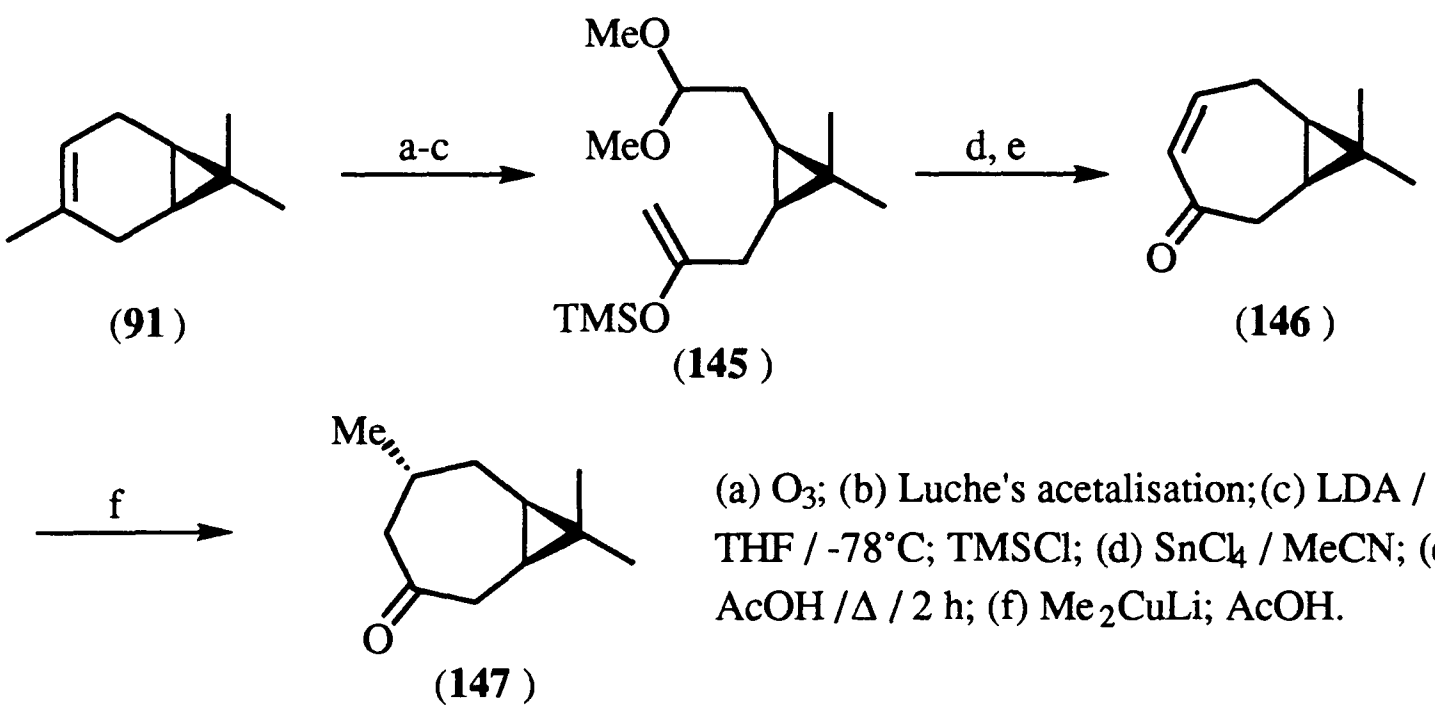


(**142**) R = OMEM (**143a**) R = OMEM (**144a**) R = OMEM

(a) LDA / THF / -78°C; (b) 2-(2-iodoethyl)-1, 3-dioxolane; (c) Me_2CuLi; (d) H_3O^+; (e) $CpTiCl_3$ / $LiAlH_4$.

Scheme 26

An approach to the CD-ingenane sub-structure has been published by Yamakawa starting from commercially available (+)-3-carene (**91**).[72] This chiral substrate has also been utilised by Paquette to derive nucleophilic 2- and 3-carene ingenane precursors.[73] Yamakawa's strategy involved oxidative cleavage of the preformed cyclohexene (**91**) followed by Lewis acid-promoted directed Mukaiyama aldol condensation of silyl enol ether (**145**) to perform the requisite ring expansion and furnish the bicyclo[5.1.0]octenone (**146**). 1, 4-Addition of lithium dimethylcuprate from the α-face of the enone (**146**) afforded trimethylbicyclo[5.1.0]octan-3-one (**147**) as a chiral ingenol ester synthetic intermediate (**Scheme 27**).

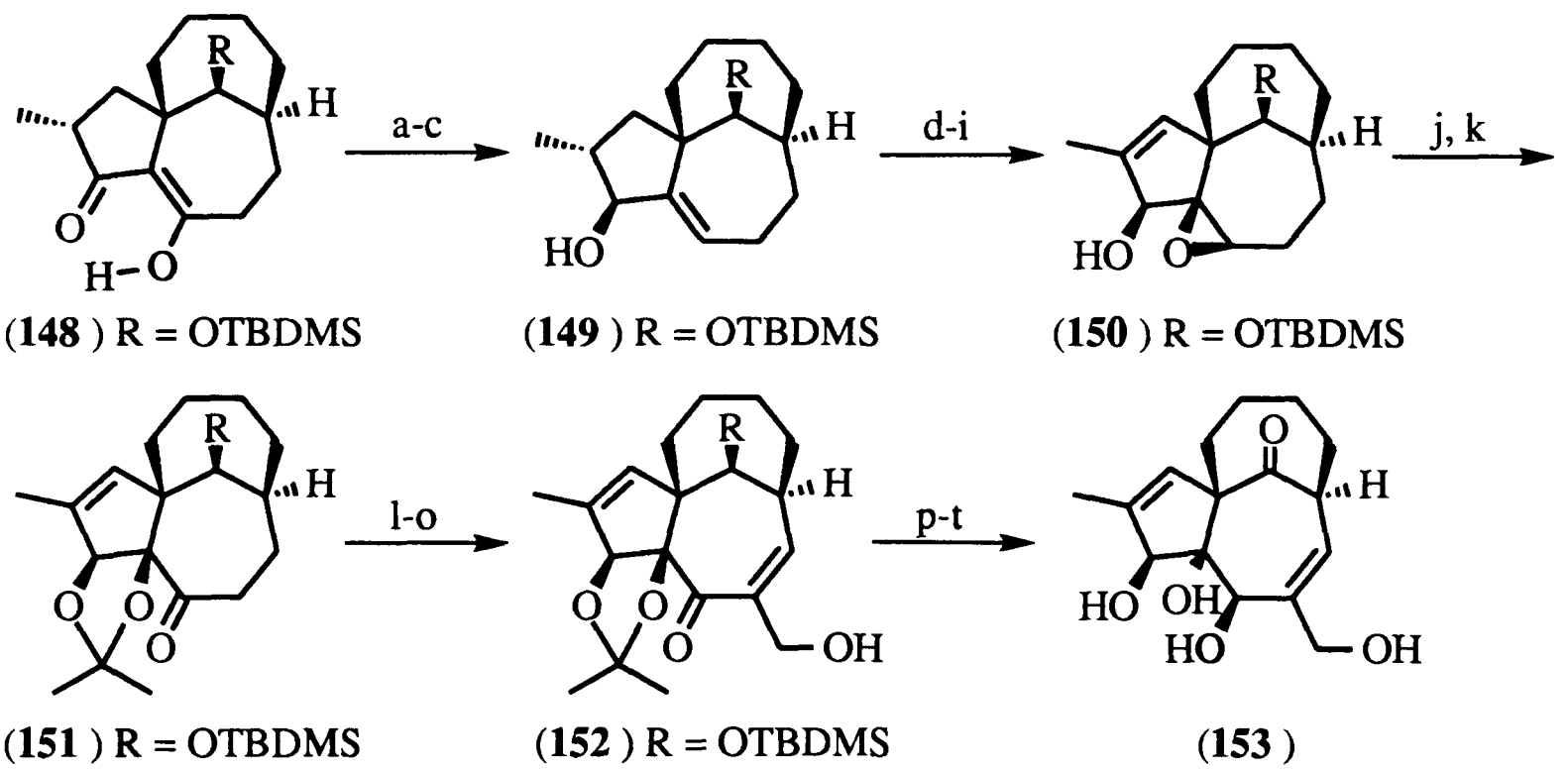


(**91**) (**145**) (**146**) (**147**)

(a) O_3; (b) Luche's acetalisation; (c) LDA / THF / -78°C; TMSCl; (d) $SnCl_4$ / MeCN; (e) AcOH / Δ / 2 h; (f) Me_2CuLi; AcOH.

Scheme 27

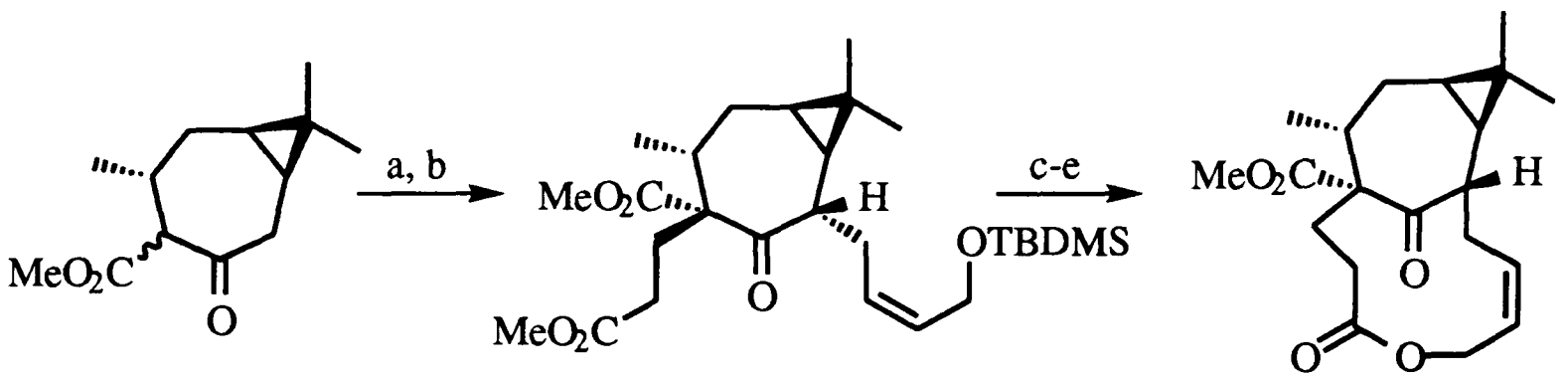
Perhaps the most functionalised *iso*ingenol analogue synthesised to date is the highly oxygenated ketotetraol (**153**) generated by Paquette[74] from the readily available β-diketone (**148**).[22] The kinetic preference for α-facial reagent delivery was overrided in the Sharpless epoxidation[75] of allylic alcohol (**149**), to specify the stereochemistry of the oxygenated C-4 stereogenic centre in (**150**). Selenation of the enolate derived from (**151**), followed by base-promoted condensation with aqueous formaldehyde and subsequent oxidative elimination further functionalised the B-ring of (**152**) and permitted access to the highly functionalised tetraol (**153**) (**Scheme 28**).



(a) KH; DIBAL; (b) H_3O^+; (c) $LiAlH_4$ / toluene-ether / -78°C; (d) *tert*-BuOOH / $VO(acac)_2$ / benzene / Δ; (e) CrO_3.py; (f) LDA / TMSCl; (g) NBS; (h) DBU; (i) $LiAlH_4$ / toluene-ether / -78°C; (j) KOH / MeOH; (k) PCC / Celite®; (l) LDA / TMSCl; (m) PhSeCl; (n) CH_2O (aq) / KOH / MeOH; (o) H_2O_2 / py / DCM; (p) $NaBH_4$ / $CeCl_3$ / MeOH; (q) acetone / TsOH / sieves; (r) TBAF / THF; (s) NCS / Me_2S / Et_3N; (t) $HClO_4$ / MeOH.

Scheme 28

Although the synthesis of ketotetraol (**153**) has facilitated derivation of analogues that possess much of the ABC-ingenane structure, correct specification of the C-8 stereogenic centre has been neglected in the majority of approaches. To address this central issue of bicyclic topological isomerism, Funk adopted an alternative strategy, forming the ABC-ingenane skeleton by a Claisen rearrangement-mediated ring contraction of macrocyclic lactone (**156**).[66] The *in-out* bridged bicycle (**156**) was constructed by *trans* di-alkylation of cycloheptanone (**154**), the stereoselectivity being dictated by the steric influence of ring substituents (**Scheme 29**). Without the presence of bending strain inherent in smaller bicyclo[4.4.1]undecanones, no stereoisomerisation was observed.

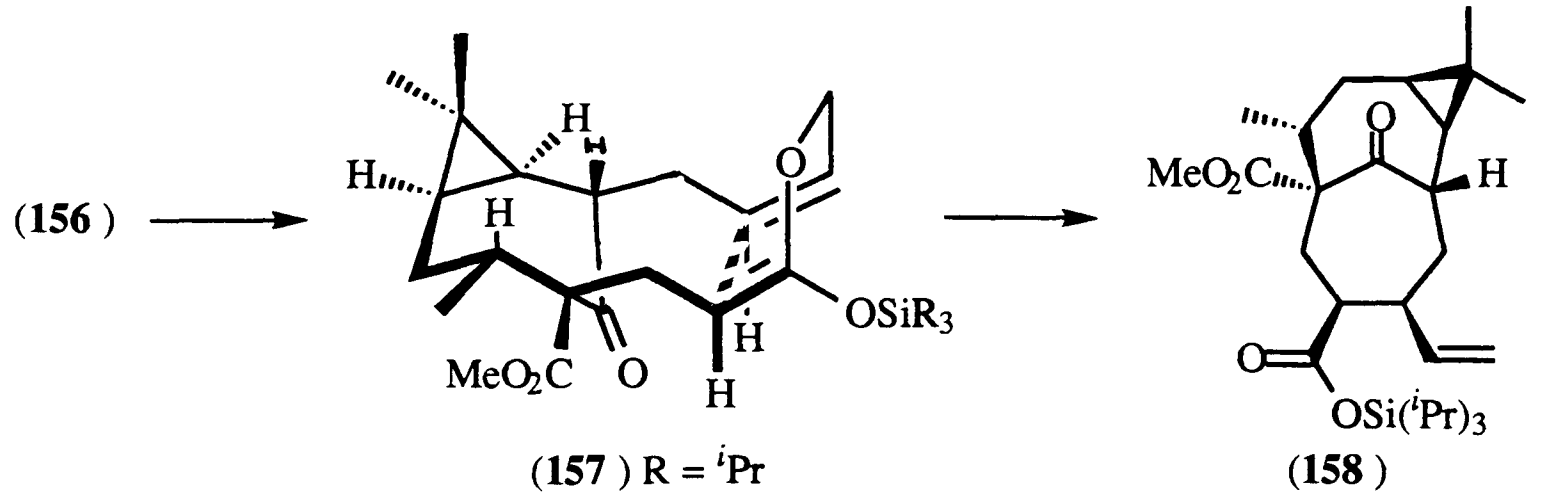


(154) **(155)** **(156)**

(a) 2.25 eq. of LDA / 1 eq. of HMPA / THF / -78°C to 30°C / 3 h; 2 eq. of *cis*- 1-(*tert*-butyldimethylsilyloxy)-4-chloro-2-butene / -78 to 30°C / 4 h; (b) 10 eq. of CH_2=$CHCO_2Me$ / 1 eq. of Triton-B® / dioxane / 10°C / 30 min; (c) 1.2 eq. of TBAF / THF / 0°C / 2 h; (d) 2 eq. of K_2CO_3 / MeOH / H_2O / 25°C / 48 h; (e) 6 eq. of *N*-methyl-2-chloropyridinium iodide / 8 eq. of Et_3N / MeCN.

Scheme 29

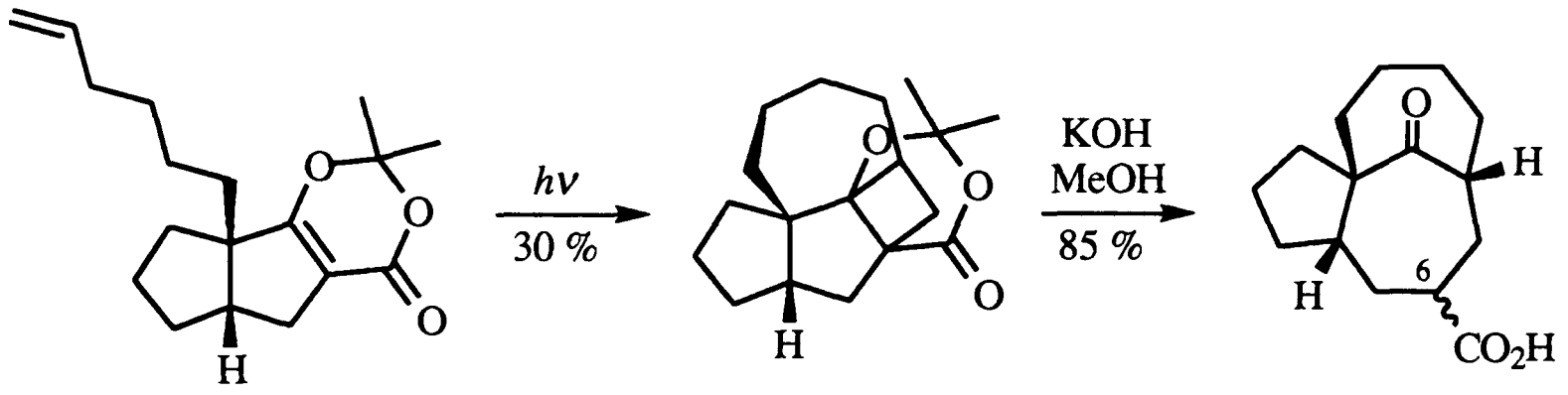
Ketene acetal (**157**) was generated by addition of tri*iso*propylsilyl triflate and triethylamine to a benzene solution of lactone (**156**) and subsequently rearranged through a boat-like transition state to furnish the desired multisubstituted *in-out* ingenane analogue (**158**) stereoselectively (**Scheme 30**).



(157) R = ^{i}Pr **(158)**

Scheme 30

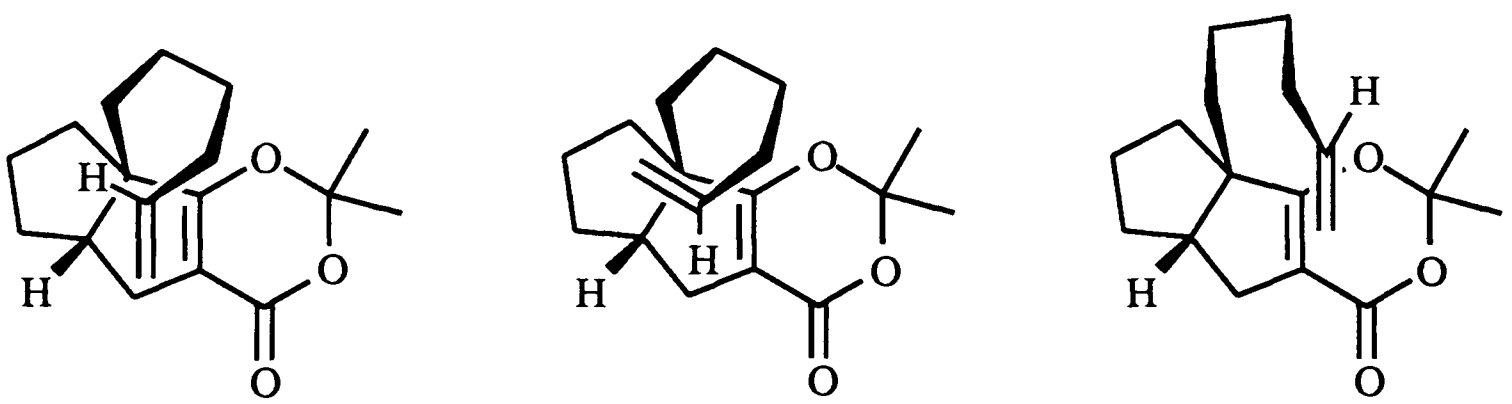
In an alternative approach, Winkler has utilised an intramolecular photocycloaddition to establish the inside-outside intrabridgehead stereochemistry.[67,76] The dioxolenone substrate (**159**) was irradiated for 90 minutes to provide a single photoadduct (**160**), in 83 % yield, that could be fragmented in base to the C-6 (ingenane numbering) epimeric keto acids (**161**) (**Scheme 31**).



(159) **(160)** **(161)**

Scheme 31

The formation of the correct *trans* stereochemistry across the bicyclo[4.4.1]undecane BC-nucleus was explained by analysis of possible transition state conformations. A *pseudo*-boat arrangement (**159c**) would be disfavoured by the presence of transannular eclipsing interactions. In *pseudo*-chair conformations, the alkene could adopt a perpendicular (**159b**) or parallel (**159a**) approach to the enone olefin function. Orthogonal double bond disposition would introduce unfavourable non-bonded interactions that would be absent in a parallel approach. Hence, consideration of the transition state conformations (**Figure 2**) could successfully account for the establishment of the correct inside-outside intrabridgehead stereochemistry in the defunctionalised ingenane analogue (**161**) by photochemical cyclisation.

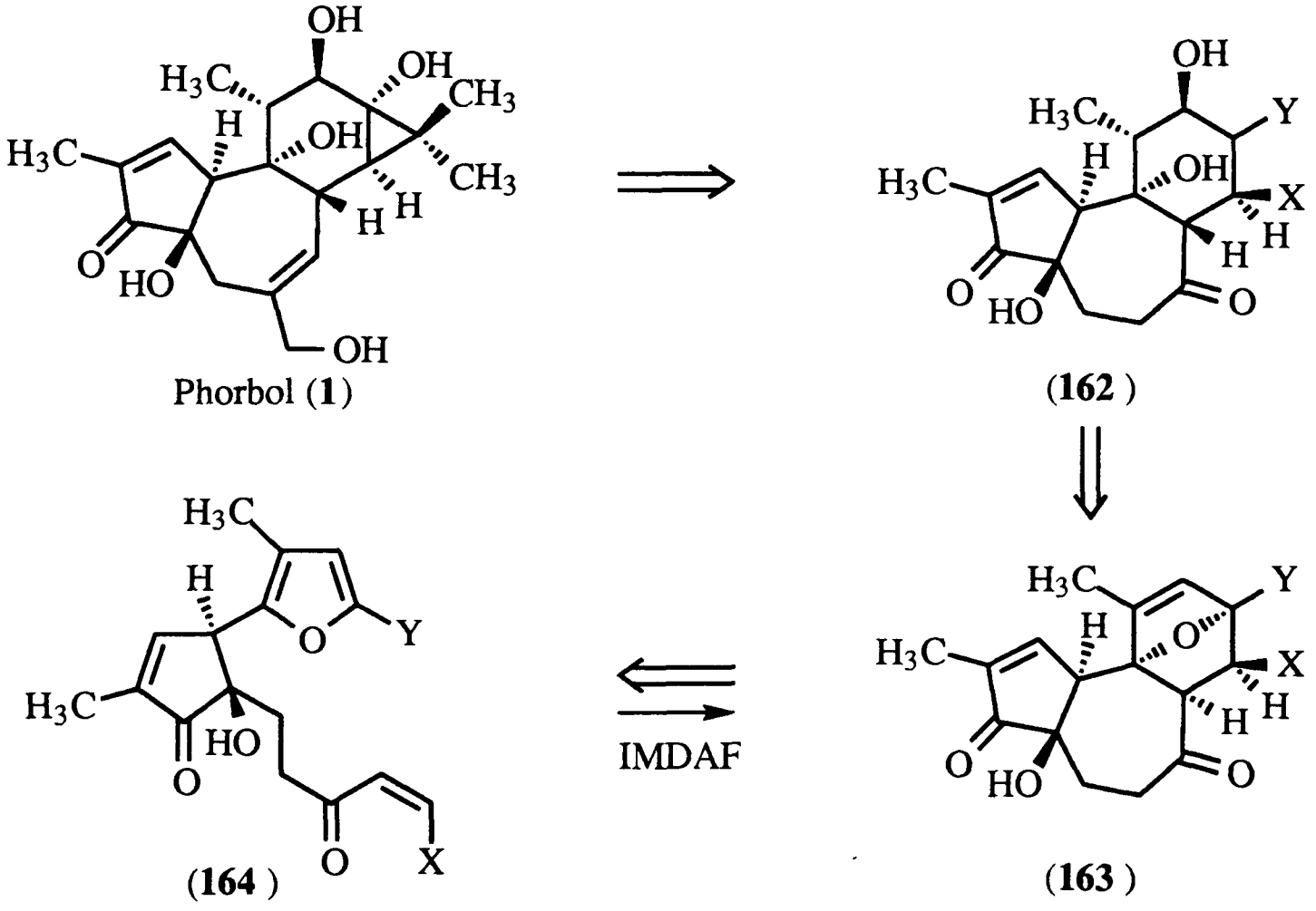


(159 a) **(159b)** **(159 c)**

Figure 2

1.4. A Retrosynthetic Approach.

In a retrosynthetic approach to the phorbols and structurally related daphnanes, it was envisaged that an intramolecular Diels-Alder reaction (IMDAF) of a suitably functionalised furan precursor (**164**) could establish the A-, B-, and C-rings of the tigliane skeleton and simultaneously specify cycloadduct (**163**) relative stereochemistry at four of the eight stereogenic centres present in the target natural product (**1**) (**Scheme 32**). Selection of a suitable diene activating moiety, -Y, could activate the IMDAF and facilitate the cleavage of the oxygen bridge in the product (**163**). Formation of an *endo*-cycloadduct (**163**) would enable the dienophilic activating group, -X, to be ideally positioned in (**162**) for closure of the cyclopropane D-ring. Even though an *endo* cycloaddition would incorrectly specify the stereochemistry at the C-8 stereogenic centre, it was hoped that this bridgehead position could be epimerised without disrupting the integrity of the C-4 hydroxyl[77] and destroying the substrates biological activity.[1]



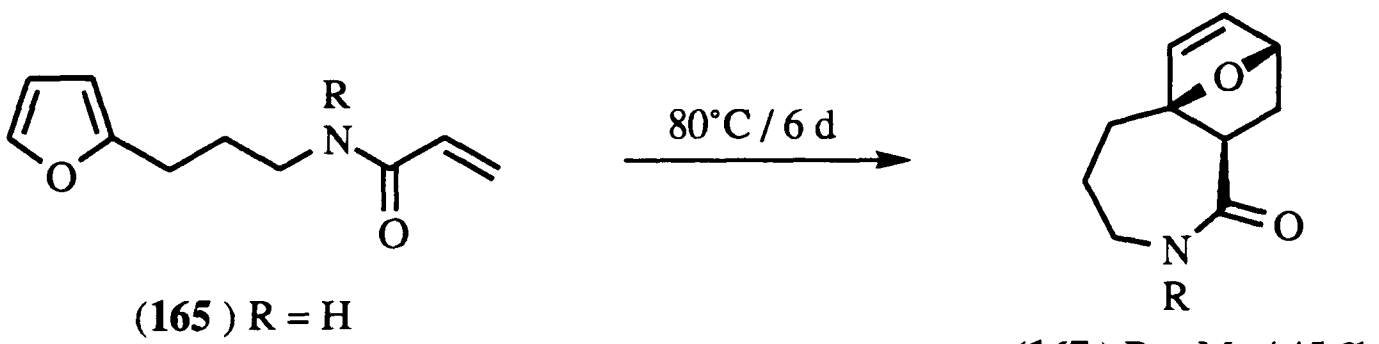
Scheme 32

1.5. Previous Work within the Group.

1.5.1. Prelude.

The intramolecular Diels-Alder addition of furan (**164**) is critical to the success of this strategy. Upon initiation of the project there was good literature precedent to validate the approach[78,79] as well as a wealth of information on furyl Diels-Alder reactions to draw upon.[80,81]

Prior to work in this field, Parker and Adamchuk reported that the tertiary methyl amide (**166**) underwent cycloaddition to form the 6, 7-fused *exo*-carbocycle (**167**) in 45 % yield (**Scheme 33**).[78] This cycloadduct was a grossly simplified nitrogen containing analogue of the required furyl tigliane precursor (**163**) and so the successful cyclisation provided encouragement. Interestingly, the secondary amide (**165**) displayed no evidence of ring closure; whereas subjecting tertiary benzyl amide (**168**) to the same reaction conditions improved the yield of cycloadduct (**169**) formation to 75 %. The observed increase in reactivity was attributed to the nitrogen substitution encouraging the adoption of reactive substrate conformations. It was hoped that the conformational constraint imposed by A-ring structural rigidity would promote the IMDAF in an analogous fashion.

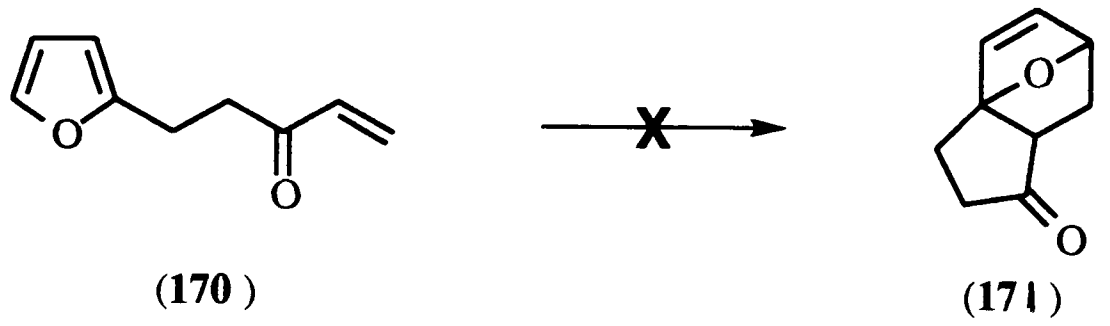


(**165**) R = H
(**166**) R = Me
(**168**) R = Bn

(**167**) R = Me / 45 %
(**169**) R = Bn / 75 %

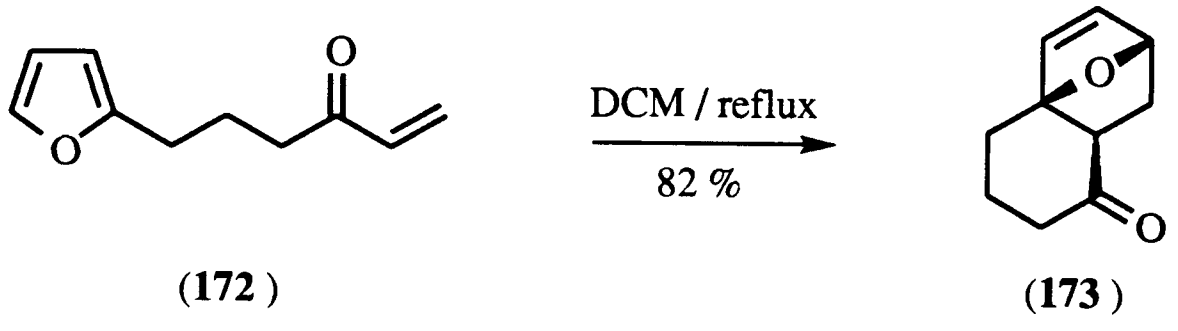
Scheme 33

The successful synthesis of a 6, 6-fused carbocycle (**173**) by DeClercq gave substance to the retrosynthetic proposal.[79] Although the closure of the furyl substrate (**170**) to the 5, 6-cycloadduct (**171**) was reported to be unsuccessful as a consequence of the "carbonyl co-planarity effect" (**Scheme 34**), the IMDAF of a precursor containing a longer dienophilic tether cyclised to form the *exo*-adduct (**173**) in 82 % yield (**Scheme 35**).



(**170**) (**171**)

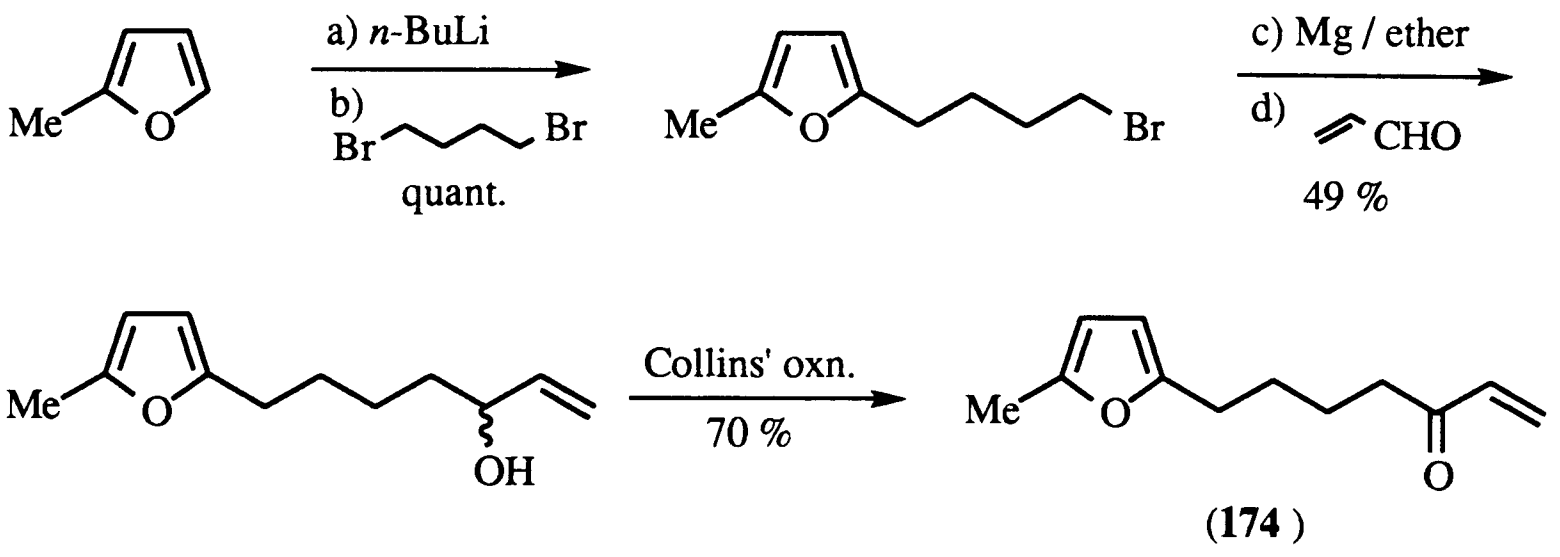
Scheme 34



(**172**) (**173**)

Scheme 35

Encouraged by these reports, the analogous furylheptenone (**174**) was synthesised within the Oxford group (**Scheme 36**) and submitted to conditions known to promote the IMDAF.[82] However attempts to effect the cycloaddition of (**174**), under thermal and Lewis acid catalysed conditions,[83] failed to afford any isolable products.



(**174**)

Scheme 36

1.5.2. High Pressure Cycloaddition Reactions.

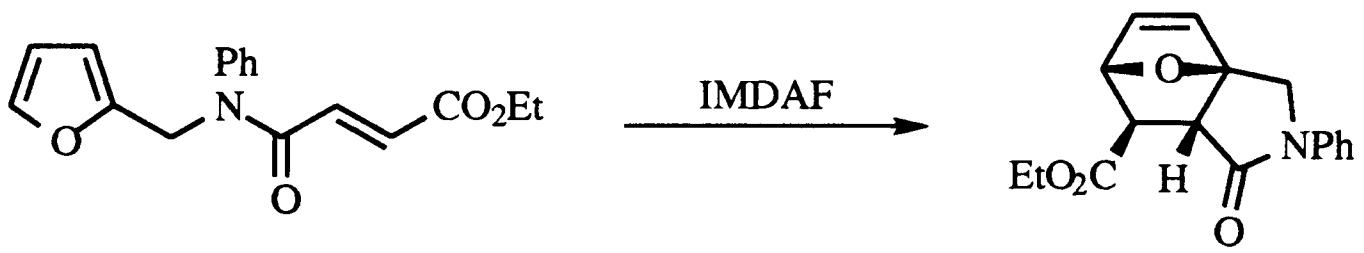
It was apparent that increasing the tether length of the furyl cycloaddition precursor (**174**) had reduced the reactivity advantage of the intramolecular process as a consequence of unfavourable entropic considerations. Work by Parker had illustrated the inefficiency of seven membered IMDAF ring closure.[78] However, reactions that have both a negative

activation volume ($-\Delta V^{\ddagger}$) (**Scheme 37**) and a negative reaction volume ($-\Delta V^{\theta}$) (**Scheme 38**) are favoured kinetically and thermodynamically by the application of a higher pressure.[81] This technique is particularly applicable to furan Diels-Alder cycloadditions[84] which, due to problems of reversibility, often fail to be promoted thermally.

$$\frac{\delta \ln k}{\delta P} = -\frac{\Delta V^{\ddagger}}{RT} \qquad \textbf{Scheme 37}$$

$$\frac{\delta \ln K}{\delta P} = -\frac{\Delta V^{\theta}}{RT} \qquad \textbf{Scheme 38}$$

The activation volume of the intramolecular Diels-Alder addition of furan (**175**) (**Scheme 39**) has been measured by Isaacs.[85] Predictably, although the activation volume of conversion to cycloadduct (**176**), measured at -25 (±2) cm^3mol^{-1}, was significantly lower in magnitude than typical intermolecular measurements (-30 to -40 cm^3mol^{-1}),[86] the contraction observed in the activation process indicated that application of high pressures should promote the IMDAF.

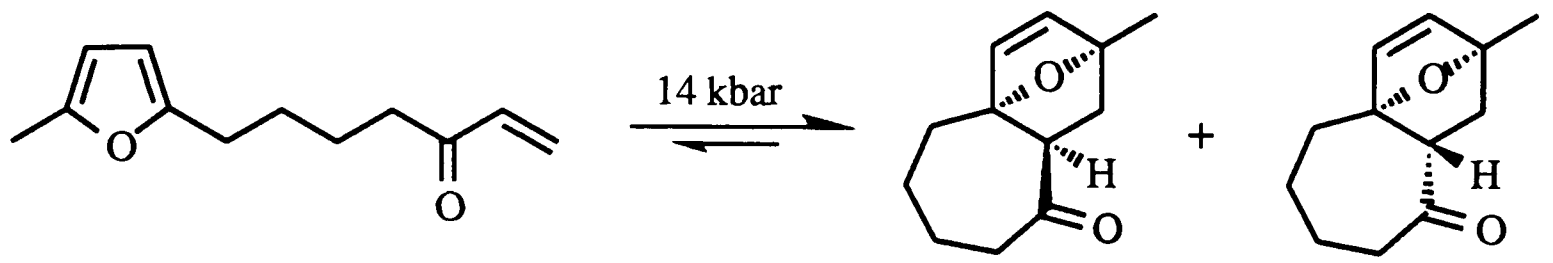


(**175**) (**176**)

Scheme 39

1.5.3. Previous Approaches towards Phorbols.

Subjecting a solution of the furylheptenone (**174**) in dichloromethane to pressures up to 19 kbar furnished *endo*- and *exo*-cycloadducts, (**177**) and (**178**) respectively.[87] The reaction was found to be reversible at high pressures (**Scheme 40**),[82] leading to the conclusion that retroaddition of an intramolecular reaction was more facile than the intermolecular process as a consequence of the smaller (in magnitude) negative activation volume of addition. Kotsuki has demonstrated the irreversibility of intermolecular furan Diels-Alder reactions under conditions of high pressure.[127]

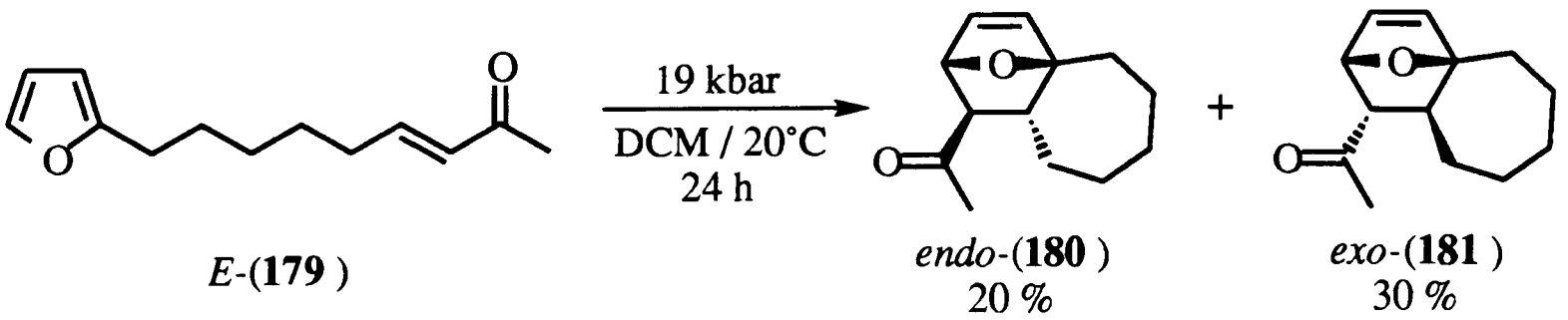


(**174**) *endo*-(**177**) *exo*-(**178**)

Scheme 40

Under high pressure conditions it was found that the *exo*-adduct (**178**) was the kinetically favoured product whilst the *endo*-adduct (**177**) was formed preferentially with time, a result contrary to the usual stereochemical outcome of Diels-Alder additions. With reversibility of reaction, a stereochemical bias could be imposed upon the cycloaddition by application of higher pressures (19 kbar) and longer reaction times (up to 48 hours) in order to optimise formation of the thermodynamic *endo*-product, (**177**).

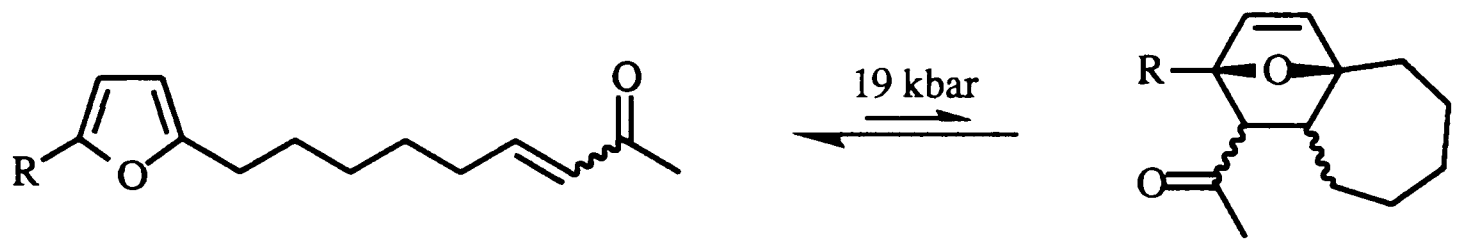
With the high pressure cycloaddition technology established, a comparative study was drawn on the propensity of internally and externally activated substrates to cyclise.[89] It was demonstrated that *E*-furyldecenone (**179**), possessing an externally activated dienophile, underwent addition to afford a mixture of *endo*-(**180**) and *exo*-(**181**) cycloadducts less efficiently than the internally activated furylheptenone (**174**) (**Scheme 41**). Subjecting the corresponding *Z*-furyldecenone (**182**) to the reaction conditions resulted in no isolation of cycloadducts (**183**) (**Scheme 42**). This observation indicated that activation of the IMDAF was maximised by an *endo*-orientation of external electron withdrawing dienophilic substituents.



E-(**179**) *endo*-(**180**) 20 % *exo*-(**181**) 30 %

Scheme 41

Z- and *E*-methylfurans (**184**), in comparison, afforded only unreacted starting material on submission to the high pressure conditions (**Scheme 42**), illustrating the adverse effect of increased steric crowding on transition state and cycloadduct (**185**) stability.

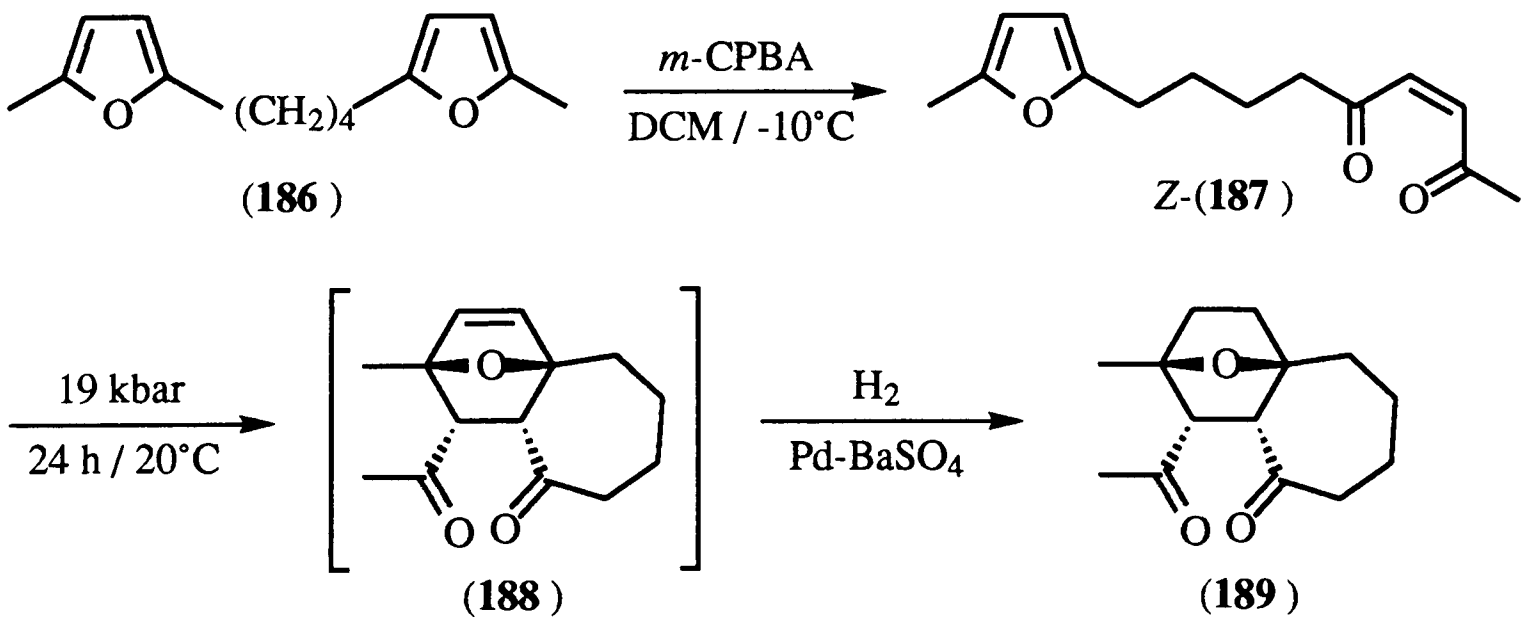


Z-(**182**) R = H,
E/*Z*-(**184**) R = Me

cis-(**183**), R = H
cis/*trans*-(**185**), R = Me

Scheme 42

In an effort to enhance the stereocontrol and cycloaddition efficiency of the IMDAF, recourse was made to furans containing doubly activated dienophiles.[90] Subjecting *Z*-enedione (**187**), generated by the oxidative cleavage of difuran (**186**), to 19 kbar pressure at 20°C for 24 hours led to the formation of a single reaction species identified as the *endo*-cycloadduct (**188**). Hydrogenation of the 7-oxabicyclo[2.2.1]heptene olefinic bond prevented cycloreversion and permitted isolation of the reduced product (**189**) in 35 % yield (**Scheme 43**).



(**186**)

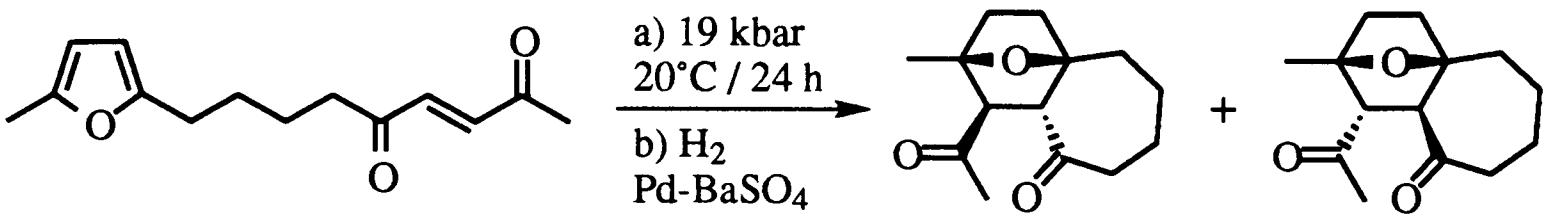
Z-(**187**)

(**188**)

(**189**)

Scheme 43

Conversely, submitting the *E*-enedione (**190**) to the same high pressure conditions resulted in the formation of a mixture of hydrogenated cycloadducts, (**191**) and (**192**), in which the *endo*-stereoisomer (**191**) predominated (**Scheme 44**).

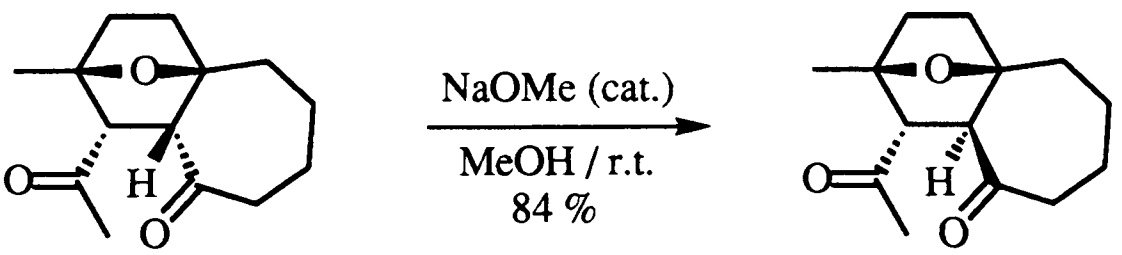


E-(**190**) (**191**) 25 % (**192**) 5 %

Scheme 44

It was apparent that in the case of the *E*-enedione (**190**) the stereochemical requirements of internal and external activating substituents were working in opposition, leading to the formation of a mixture. In this instance, the stereochemical demand of the more powerfully activating internal carbonyl moiety took precedence, encouraging the bridging chain to adopt an *endo*-orientation and furnishing (**191**) predominantly. In the case of the alternative *Z*-enedione substrate (**187**), the demands of the activating substituents were in accordance and generated the *endo*-stereoisomer (**189**) as the only reaction product.

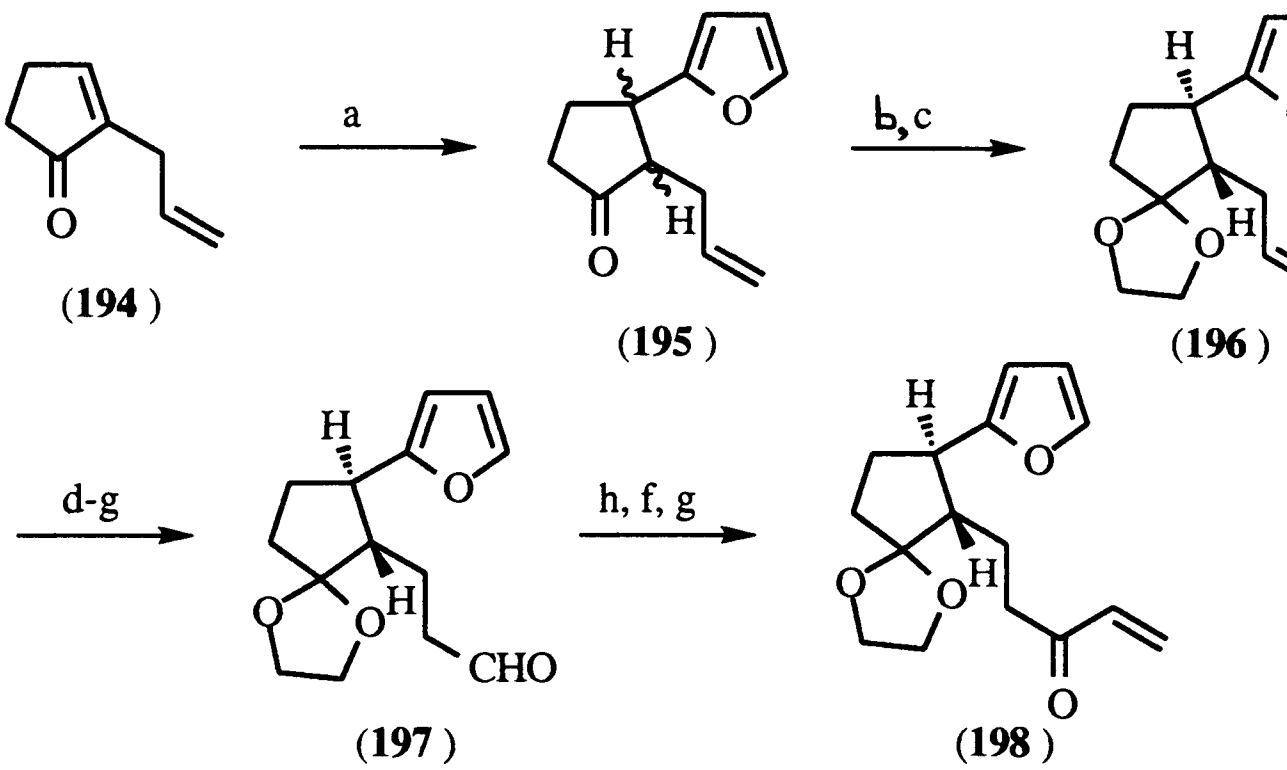
Although high pressure mediated IMDAF had facilitated stereospecific construction of tricyclic dione (**189**), the stereochemistry at the C-8 stereogenic centre (tigliane numbering) with respect to the oxygen bridge was incorrect. However, treatment of (**189**) with sodium methoxide in methanol at room temperature succeeded in epimerising the bridgehead position regioselectively to furnish (**193**) as a simplified BC phorbol analogue (**Scheme 45**).[90] This illustrated the different thermodynamic stability of *endo*- and *exo*-cycloadduct structures at ambient pressure.



(**189**) (**193**)

Scheme 45

With model studies for effecting the IMDAF with a high degree of stereocontrol complete, it was necessary to develop the protocol to introduce the phorbol cyclopentyl A-ring with specification of stereochemistry at the A-B ring junction stereogenic centres. According to the procedure of Lipschutz,[91] the 1, 4-addition of lithium di(2-furyl) cyanocuprate with 3-allylcyclopent-2-enone (**194**) in the presence of boron trifluoride furnished a 3 : 1 mixture of *trans*- and *cis*-dialkylcyclopentanes (**195**). Epimerisation with sodium methoxide in methanol established predominantly *trans* stereochemistry across the A-B ring junction and the product was then protected as the ethylene ketal (**196**). Grignard addition to aldehyde (**197**) and subsequent oxidation generated the monoactivated IMDAF substrate (**198**) (**Scheme 46**).[92]



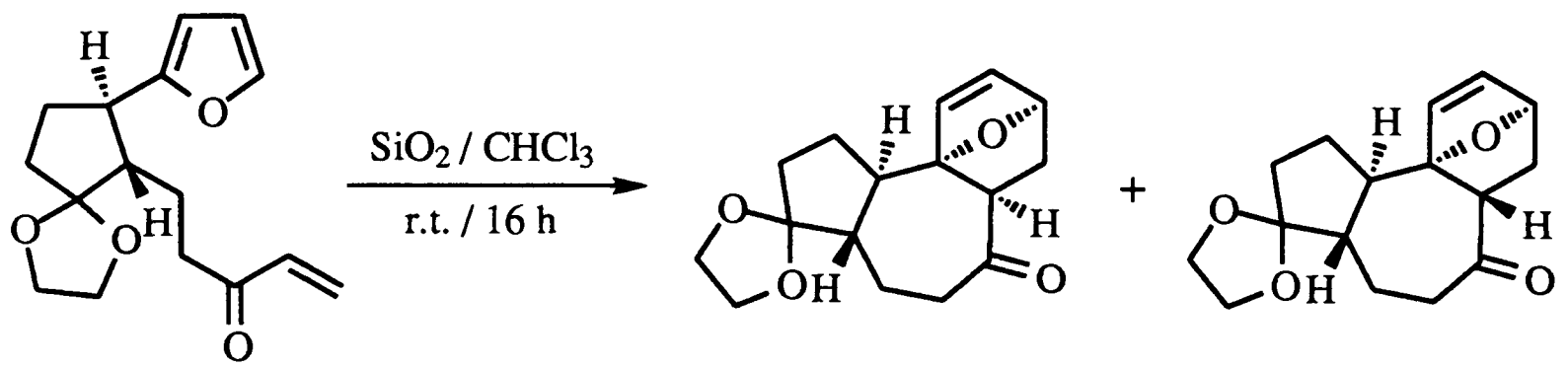
(**194**) (**195**) (**196**) (**197**) (**198**)

(a) lithium di(2-furyl)cyanocuprate / $BF_3.Et_2O$ / THF / -78°C; (b) NaOMe / MeOH / r.t.; (c) $HOCH_2CH_2OH$ / H^+ / toluene / reflux; (d) B_2H_6 / THF; (e) H_2O_2 / aq. NaOH; (f) $(COCl)_2$ / DMSO / DCM / -50°C; (g) Et_3N; (h)CH_2=CHMgBr / THF.

Scheme 46

The exposure of enone (**198**) to silica induced a spontaneous intramolecular cyclisation to afford *endo*-(**199**) and *exo*-(**200**) cycloadducts in a 2 : 1 ratio (**Scheme 47**). The success of the IMDAF without recourse to high pressure conditions presumably reflects the increased substrate reactivity that accompanies branching in the tethering chain.[93] Conformational constraints imposed by the structural rigidity of the A-ring had evidently negated the entropic disadvantage of a longer dienophilic tether, increasing the population of

reactive substrate rotamers. Additionally, total stereocontrol had been achieved across the A-B ring junction, with cycloadducts (**199**) and (**200**) differing only in the specification of the C-8 stereogenic centre, a position shown to be easily epimerised in base.[90]

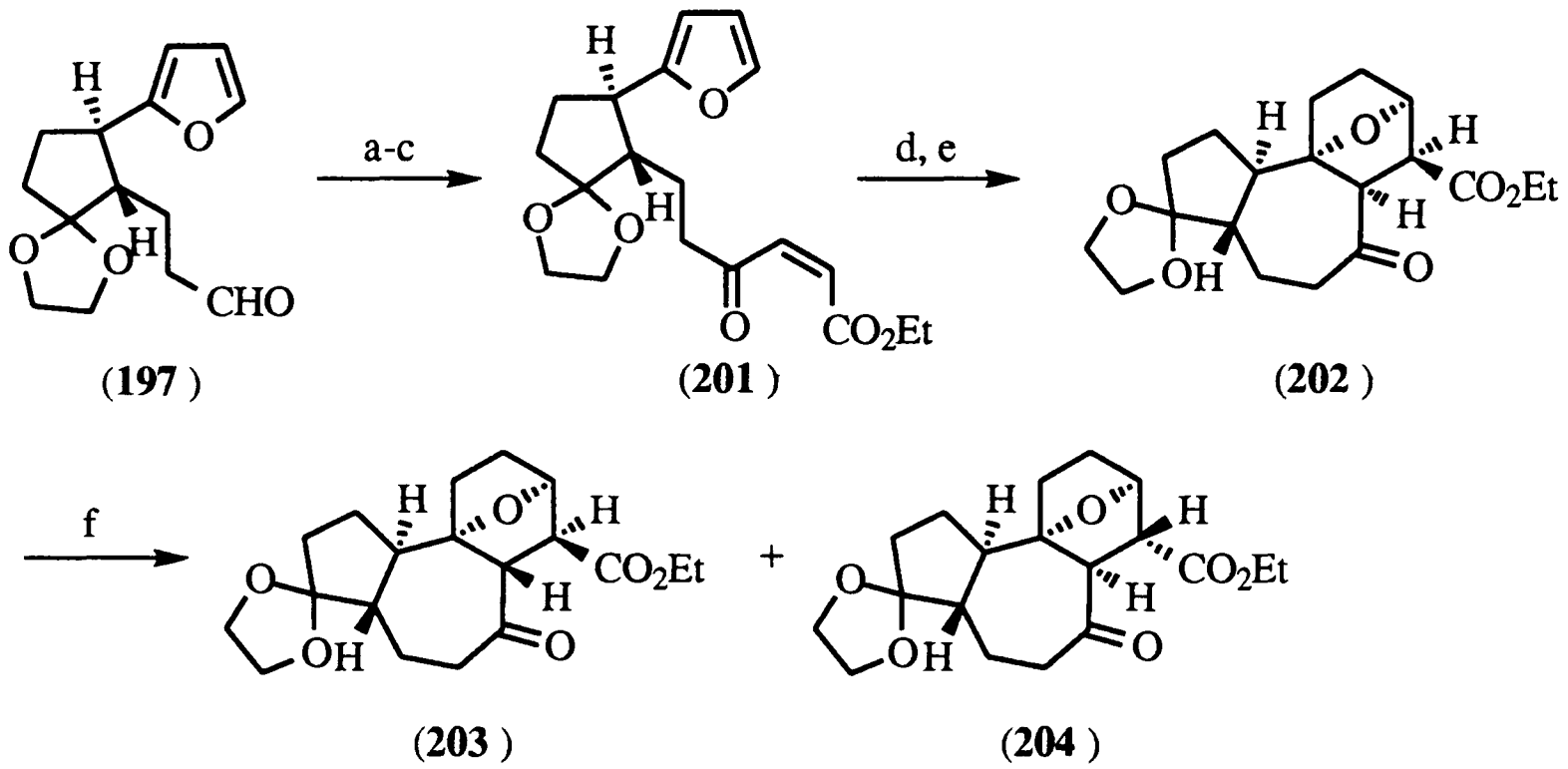


(**198**) (**199**) 2 : 1 (**200**)

Scheme 47

Interestingly, storage of the pure IMDAF precursor (**198**) at -12°C for 16 days resulted in preferential formation of the *exo*-cycloadduct (**200**) (*ca.* 2 : 1 ratio of (**200**) : (**199**)) as the kinetically preferred product, that crystallised out of the mixture and was thus prevented from equilibrating.[92,94]

In order to establish diactivated IMDAF substrates, the lithio derivative (**205**) of ethyl propynoate was added to aldehyde (**197**), according to the conditions of Midland.[95] Subsequent hydrogenation and alkynyl alcohol oxidation furnished the furan (**201**) that possessed a *Z*- configurated vinylogous ketoester dienophilic moiety. Subjecting a solution of (**201**) to high pressure conditions effected the IMDAF with some degree of stereocontrol, the *endo*-cycloadduct (**202**) being formed preferentially in 38 % yield following hydrogenation of the equilibrium mixture (**Scheme 48**).[96] Epimerisation of an ethanolic solution of (**202**) with sodium ethoxide generated (**203**) that possessed correct specification of stereochemistry at all six stereogenic centres in accordance with the natural product (**1**). The presence of a minor product (**204**) was detected in a ratio of 1 : 5 ((**204**) : (**203**)) as a consequence of the alternative epimerisation of the C-14 centre.



(197) **(201)** **(202)**

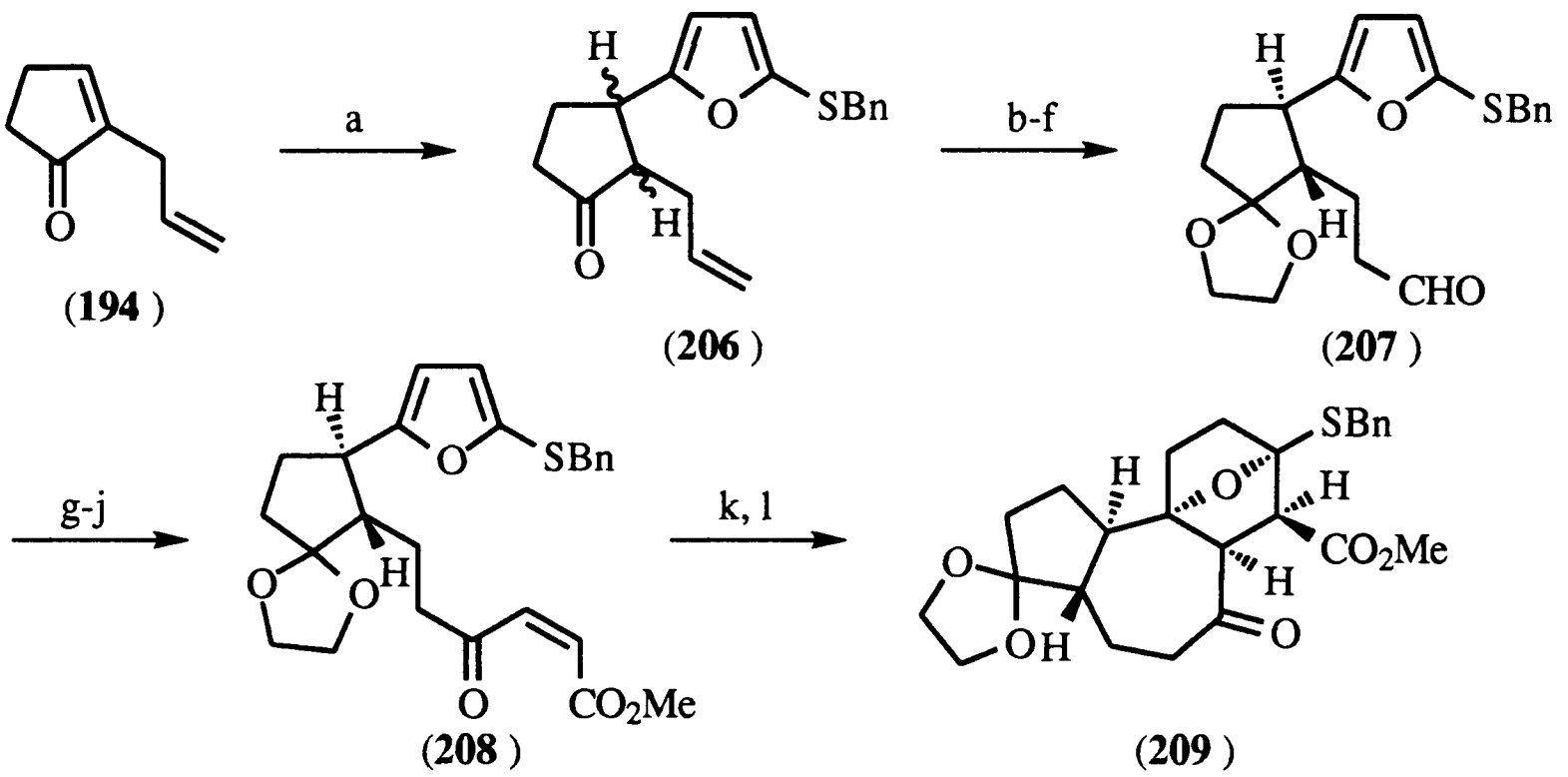
(203) **(204)**

(a) $LiC{\equiv}CCO_2Et$ (**205**) / THF / -70°C; (b) H_2 (1 atm) / Lindlar cat.; (c) activated MnO_2 (excess) / CCl_4 / r.t. / 15 min; (d) 19 kbar / DCM / 5 min; (e) H_2 (15 atm) / EtOAc / Pd-$BaSO_4$; (f) NaOEt (cat.) / EtOH / r.t.

Scheme 48

In order to improve on the stereocontrol of the IMDAF and direct cleavage of the cycloadduct oxygen bridge, the synthetic approach was modified to introduce an α'- benzylthio substituent onto the furan.[97] Utilising the trimethylsilyl iodide mediated coupling of Kraus,[98] a mixture of *trans*- and *cis*-3-benzylthiofuryl-2-allylcyclopentanones (**206**) were generated in a 12 : 1 ratio that could not be improved by treatment with sodium methoxide. Oxidation to aldehyde (**207**) and subsequent elaboration according to the established procedure led to the *Z*-vinylogous ketoester (**208**) containing a benzylthiofuryl diene component (**Scheme 49**).

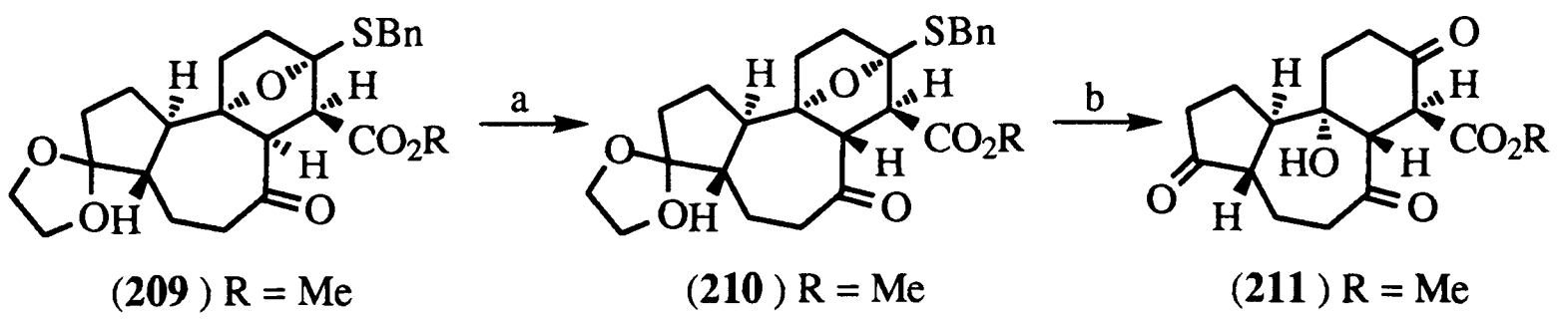
Subjecting a *ca.* 0.1 $moldm^{-3}$ solution of (**208**) to 19 kbar pressure for 13 hours successfully promoted the IMDAF and furnished a single cycloadduct. Hydrogenation of the oxabicyclo[2.2.1]heptene double bond prevented the cycloreversion and permitted isolation of the *endo*-stereoisomer (**209**), isolated in 68 % yield (**Scheme 49**). Evidently, the presence of the benzylthio diene activating substituent had dramatically improved the efficiency of the cyclisation and imposed total stereocontrol.



(a) 2-Benzylthiofuran / TMSI / $Me_2C{=}CHMe$ / DCM / -70°C; (b) $HOCH_2CH_2OH$ / H^+ / benzene / reflux; (c) B_2H_6 / THF; (d) H_2O_2 / aq. NaOH; (e) $(COCl)_2$ / DMSO / DCM / -60°C; (f) Et_3N; (g) $LiC{\equiv}CCO_2Me$ / THF / -80°C; (h) H_2 (1 bar) / 5 % Pd-$BaSO_4$ / EtOAc; (i) $(COCl)_2$ / DMSO / DCM / -60°C; (j) Et_3N; (k) 19 kbar / DCM / 13 h; (l) H_2 (17 bar) / 5 % Pd-$BaSO_4$ / EtOAc.

Scheme 49

Treatment of the *endo*-cycloadduct (**209**) with methanolic sodium methoxide at room temperature regioselectively epimerised the C-8 stereogenic centre to form (**210**) in 84 % yield. Subsequent hydrolytic fission of the oxygen bridge with mercuric chloride in aqueous acetonitrile was directed by the sulphide linkage to furnish the deketalised phorboid triketone (**211**) in 57 % yield (**Scheme 50**).



(**209**) R = Me (**210**) R = Me (**211**) R = Me

(a) NaOMe (cat.) / MeOH / r.t. / 84 %; (b) $HgCl_2$ / aq. MeCN / 50°C / 8 d / 57 %.

Scheme 50

It was concluded that introduction of the benzylthiofuryl substituent had not only optimised the efficiency of the IMDAF and cycloadduct epimerisation, but had facilitated

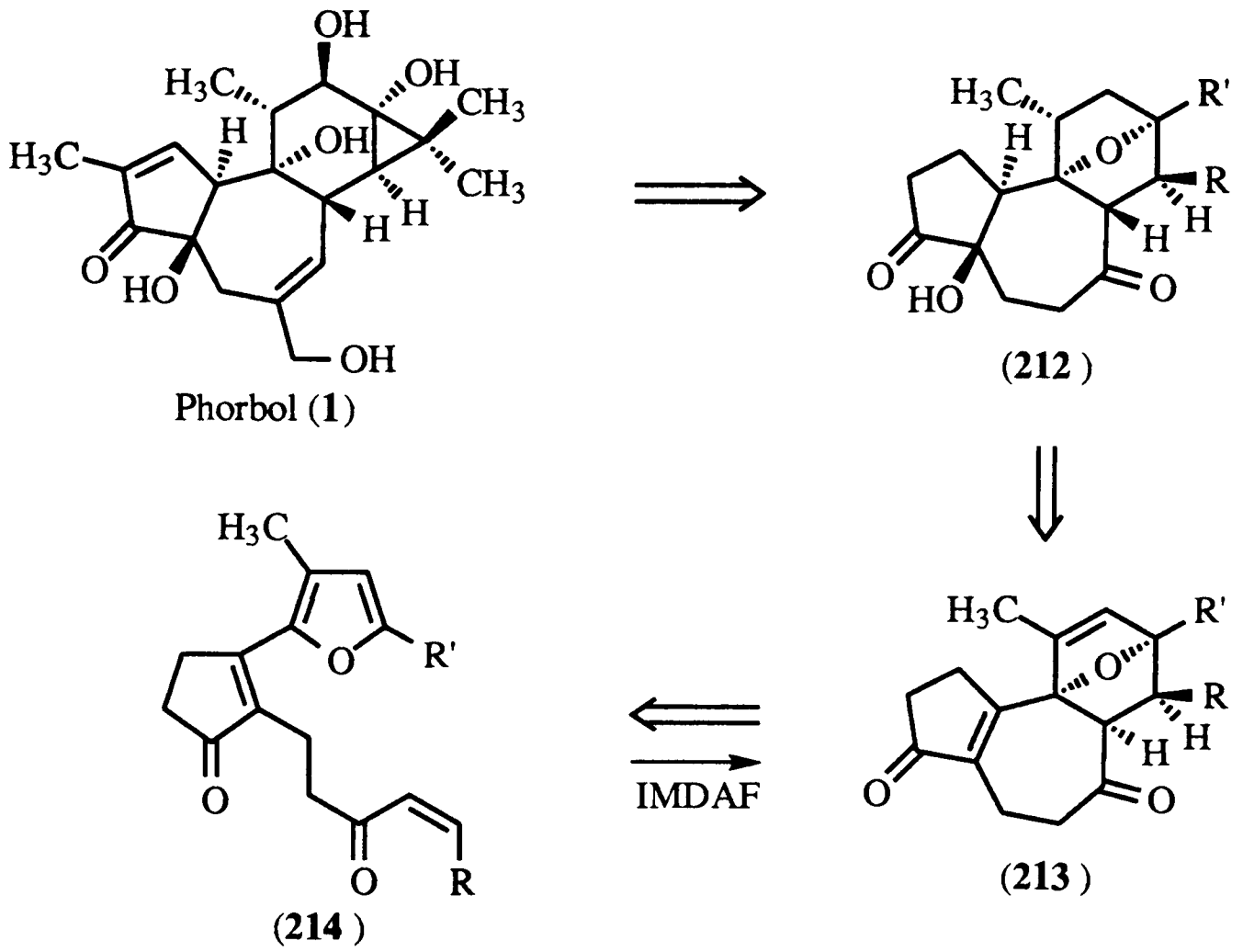
selective cleavage of the 7-oxabicyclo[2.2.1]heptyl bridge and imposed total stereocontrol in the cycloaddition, making it an invaluable aid in the IMDAF strategy of phorbol synthesis.

1.6. Aim of the Project.

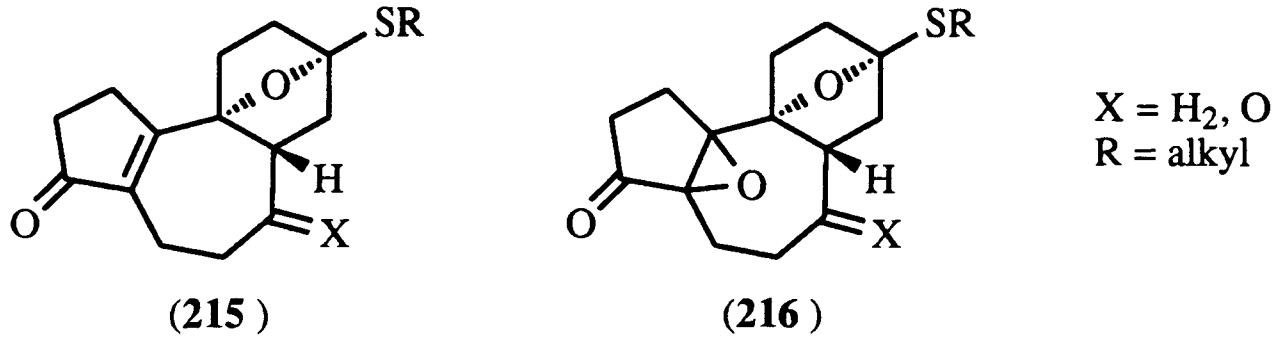
The successful cycloaddition of the suitably functionalised substrate (**208**) by Harwood *et al.*[97] has proven the validity of the IMDAF approach in construction of the A-, B-, and C-rings of the tigliane skeleton. In order for this strategy to achieve further success it was necessary to introduce correct functionality into the carbon framework and prepare cycloadducts that could be elaborated to produce the structure present in the target natural product (**1**).

It was thought that development of the approach first lay in the generation of cycloadducts bearing a suitably functionalised A-ring. Intramolecular Diels-Alder addition of a 2-substituted-3-furyl-2-cyclopentenone substrate (**214**) would form products, such as (**213**), that contained unsaturation at the crucial A-B ring junction and reflected the substitution pattern of the phorbol (**1**) C-ring. This would allow for later elaboration to the *trans*-stereochemical arrangement between C-4 and C-10 substituents and the required C-4 hydroxylation in (**212**) that has been thus far lacking from the synthetic strategy, without recourse to protection / deprotection technology (**Scheme 51**).

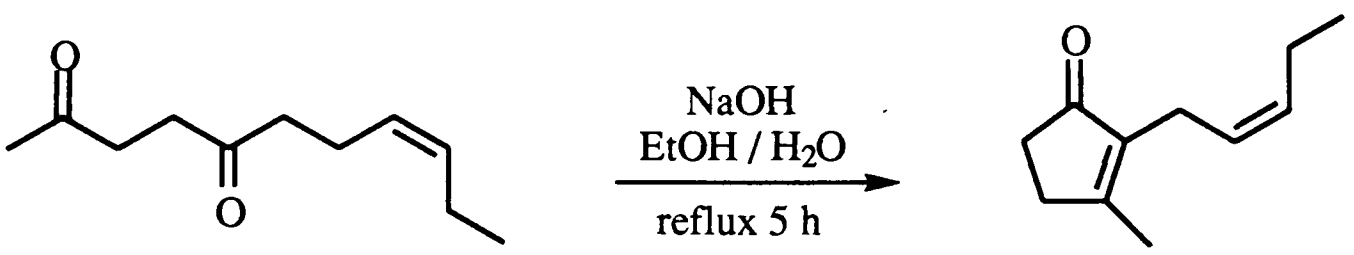
Not only would the cycloaddition of cyclopentenone (**214**) construct tigliane analogues (**212**) that more closely resembled the phorbol natural product (**1**), but it could facilitate a biomimetic approach to highly functionalised ingenane derivatives. The ring expansion of 7-oxabicyclo[2.2.1]heptanes, such as phorboid structures (**215**), and (**216**), by Wagner-Meerwein rearrangement would provide a useful means of synthetic access to this related class of natural products and would lend support to the biosynthetic hypothesis. The alkylthio substituent should serve to activate the IMDAF and facilitate the fission of the oxygen bridge, promoting the desired ring expansion.



Scheme 51

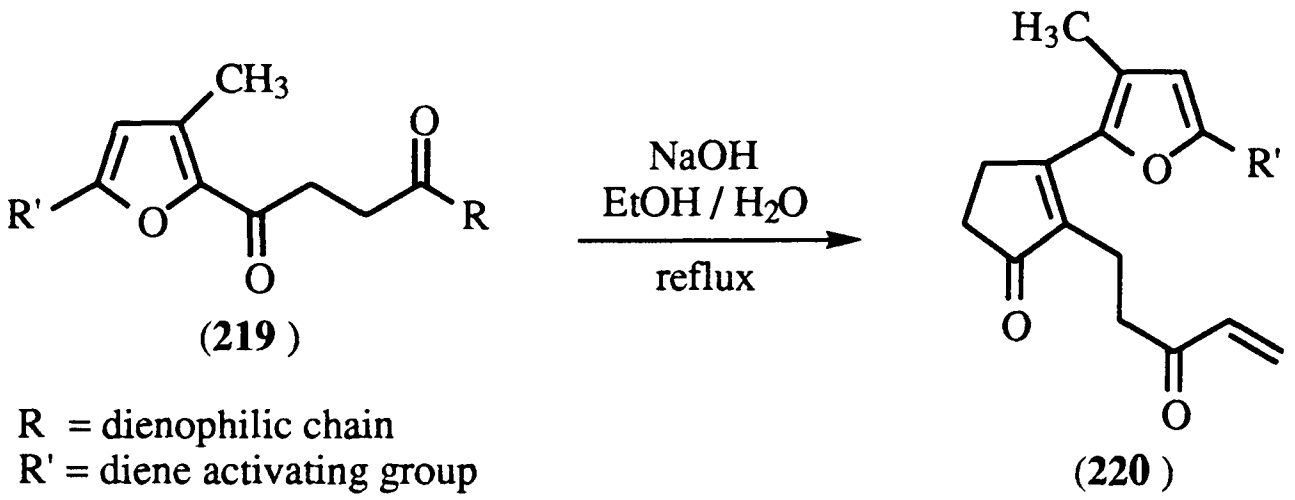


One method to construct functionalised cyclopent-2-enones is the intramolecular aldol cyclisation of 1, 4-diketones. Büchi and Wüest[99] and Rosini[100] have used this approach in the synthesis of 3-methylcyclopent-2-en-1-ones, including the natural product *Z*-jasmone (**218**), by the cyclisation in alkali of dione precursors such as *cis*-undec-8-ene-2, 5-dione (**217**) (**Scheme 52**).



Scheme 52

Adopting this strategy to the synthesis of furylcyclopent-2-enones, the aldol cyclisation of furyldiones such as (**219**) could generate a suitable IMDAF substrate (**220**), that contained the dienophilic moiety in a 2-alkyl chain, to approach functionalised analogues of phorbol or ingenane natural products (**Scheme 53**).



R = dienophilic chain
R' = diene activating group

Scheme 53

In previous studies within the Oxford group, the value of the benzylthio- activating group to the IMDAF strategy has been demonstrated.[97] It was the aim of this project to establish a method for incorporating this diene activating substituent into furylcyclopentenone synthesis. It was hoped that an aldol cyclisation approach to the A-ring, as suggested by preliminary studies within the group,[82] could introduce the correct A-ring substitution pattern into the cycloadducts and generate a route to C-11 substituted tiglianes by use of suitable methylfuran substrates.

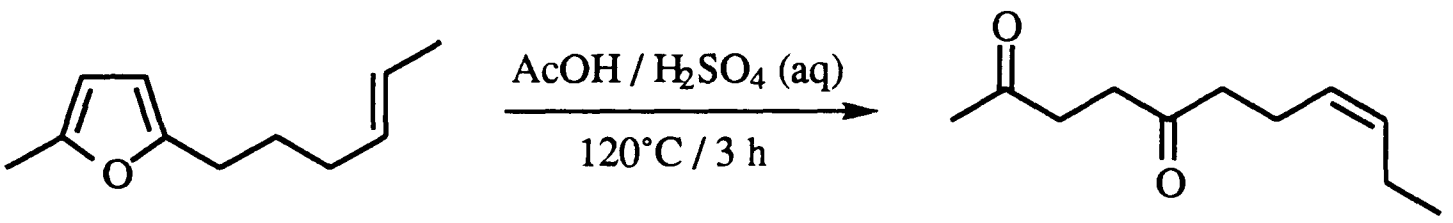
CHAPTER TWO

CHAPTER TWO - RESULTS AND DISCUSSION

IMDAF OF UNACTIVATED DIENOPHILIC SUBSTRATES

2.1. Introduction.

To test the validity of the intramolecular aldol cyclisation approach of Büchi and Wüest,[99] in the construction of 3-furylcyclopent-2-enones, a model IMDAF substrate, 3-(2-furyl)-2-(pent-4-enyl)cyclopent-2-enone (**221**), was chosen that contained an unactivated dienophilic moiety. Generation of the dione precursor (**217**) by acid catalysed hydrolysis of a 2-substituted-5-methylfuran (**222**), as detailed in the original synthesis (**Scheme 54**), was not applicable to the generation of 1-furyl-1, 4-diketones due to problems in effecting a chemoselective furyl cleavage and so an alternative strategy was sought.

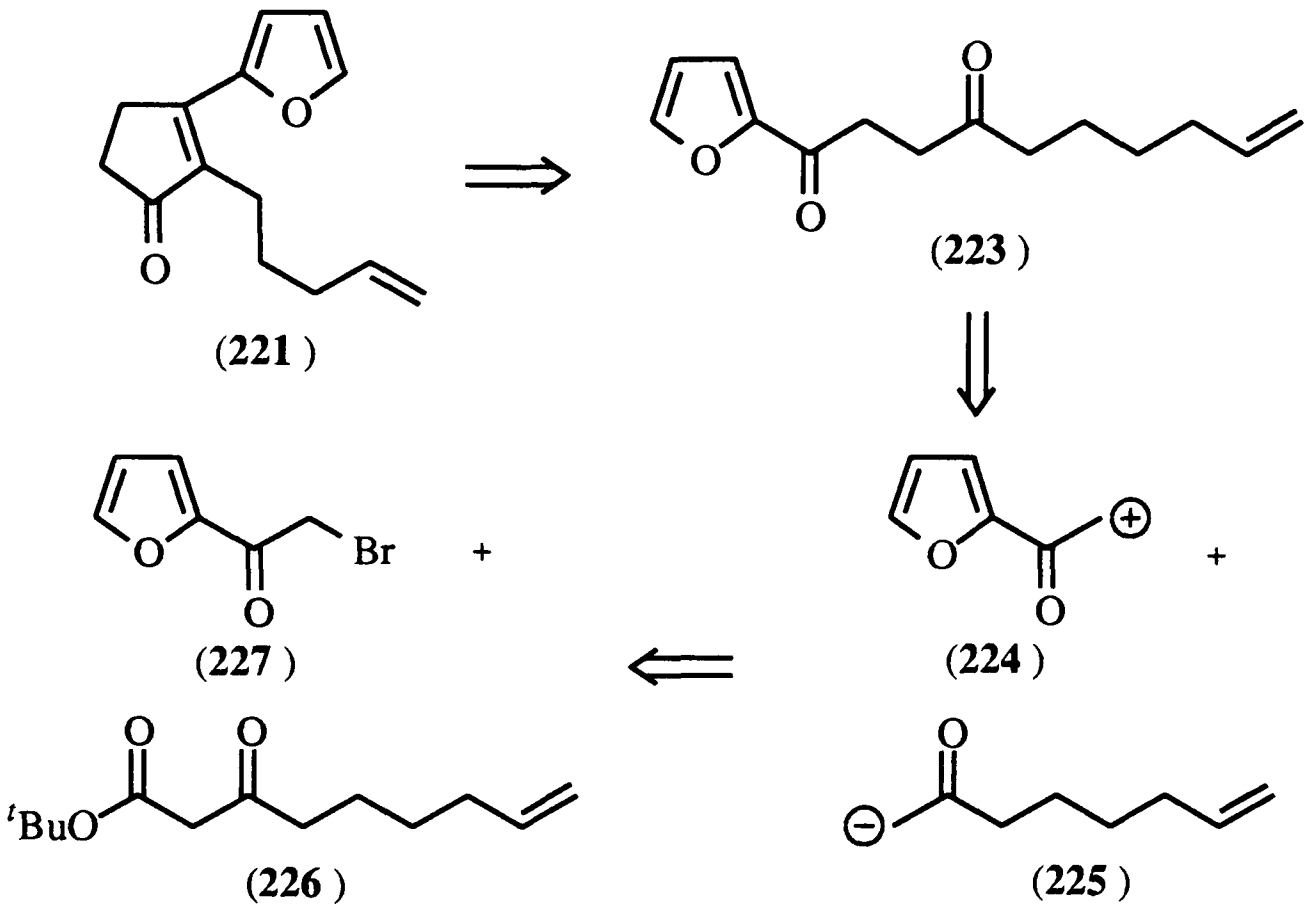


(**222**) (**217**)

Scheme 54

Retrosynthetic analysis suggested disconnecting 1-furyl-1, 4-dioxodecene (**223**) between C-2 and C-3 (**Scheme 55**). This implied introducing the acetylfuran component (**224**) by electrophilic addition to the acetoacetate derivative (**226**). Subsequent decarboxylation and intramolecular aldol cyclisation would furnish the desired IMDAF substrate (**221**) with potential for conducting both transformations in one synthetic step, as indicated by preliminary studies within the group.[82]

Not only does this strategy by-pass the problem of chemoselectivity that would be inherent in the Büchi and Wüest approach,[99] but it uses less steps than the alternative strategy of Rosini,[100] that disconnects dione between C-3 and C-4, and facilitates introduction of the phorbol C-2 methyl substituent by alkylating the acidic α-position of the *tert*-butyl acetoacetate (**226**).

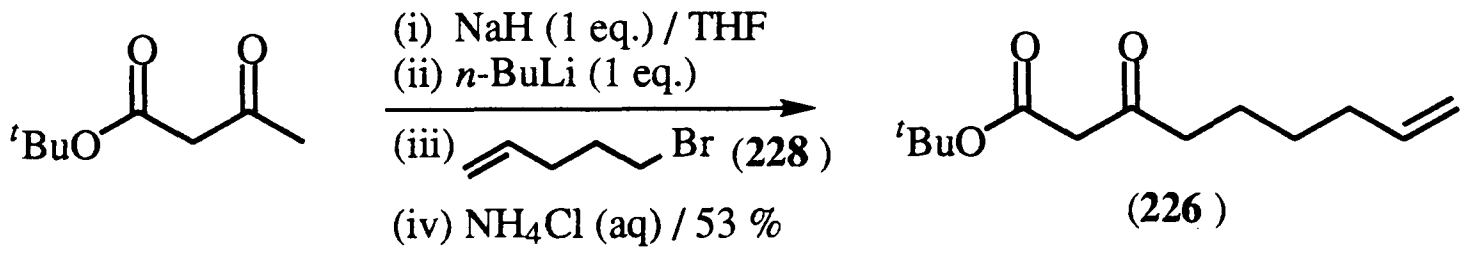


Scheme 55

2.2. Studies on 3-(2-Furyl)-2-(pent-4-enyl)cyclopent-2-enone (**221**).

2.2.1. Cyclopentenone synthesis by anionic alkylation / aldol cyclisation approach.

According to the procedure of Harwood and Leeming,[82] the functionalised acetoacetate (**226**) was prepared by addition of a pentenyl electrophile to the dianion of *tert*-butyl acetoacetate. The dianion was formed by addition of a non-nucleophilic base, sodium hydride, for the first deprotonation at 0°C in tetrahydrofuran. *n*-Butyllithium could then be employed for the second deprotonation and the more nucleophilic terminal anion quenched by the addition of 5-bromopent-1-ene (**228**) (**Scheme 56**).

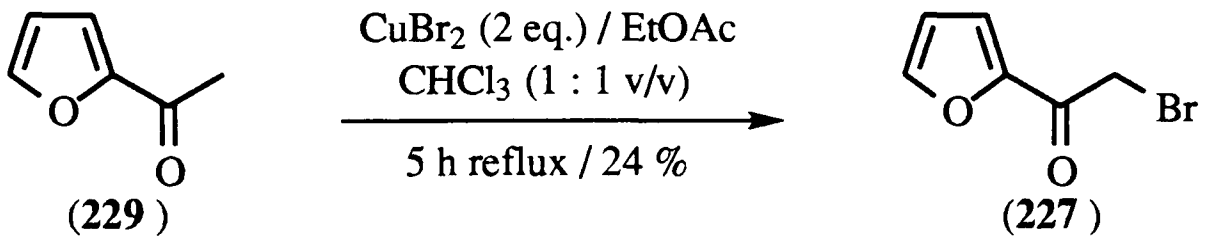


Scheme 56

The required *tert*-butyl acetoacetate derivative (**226**), furnished in 53 % yield, was identified by the presence of an olefinic absorption in the i.r. spectrum of the product at 1 642 cm^{-1}, the appearance of signals at δ5.83 - 4.95 p.p.m. in the ^1H n.m.r. spectrum, that

corresponded to 3 terminal alkene proton resonances, and the detection of the parent ions MNH_4^+ (244) and MH^+ (227) and the ion species M^+-^{t}BuO by mass spectrometry.

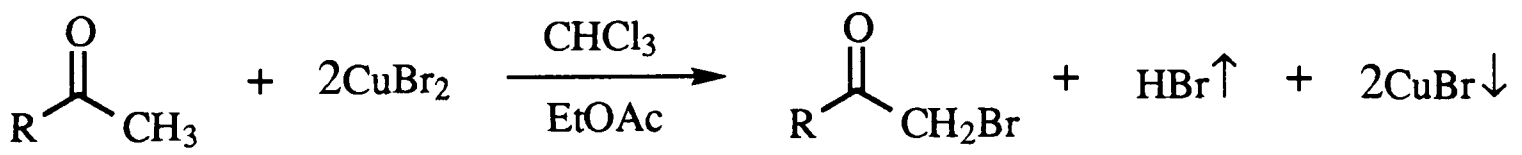
2-(Bromoacetyl)furan (**227**) was chosen as the synthetic equivalent of umpolung cation (**224**) and was derived by bromination of 2-acetylfuran (**229**) using the heterogeneous system of King and Ostrum.[101] Refluxing the furan with 2 equivalents of copper (II) bromide in 1 : 1 chloroform-ethyl acetate afforded the monobrominated product in only 24 % yield (**Scheme 57**) due to problems in separating the 2-(bromoacetyl)furan (**227**) from a trace of unreacted starting material.



(**229**) (**227**)

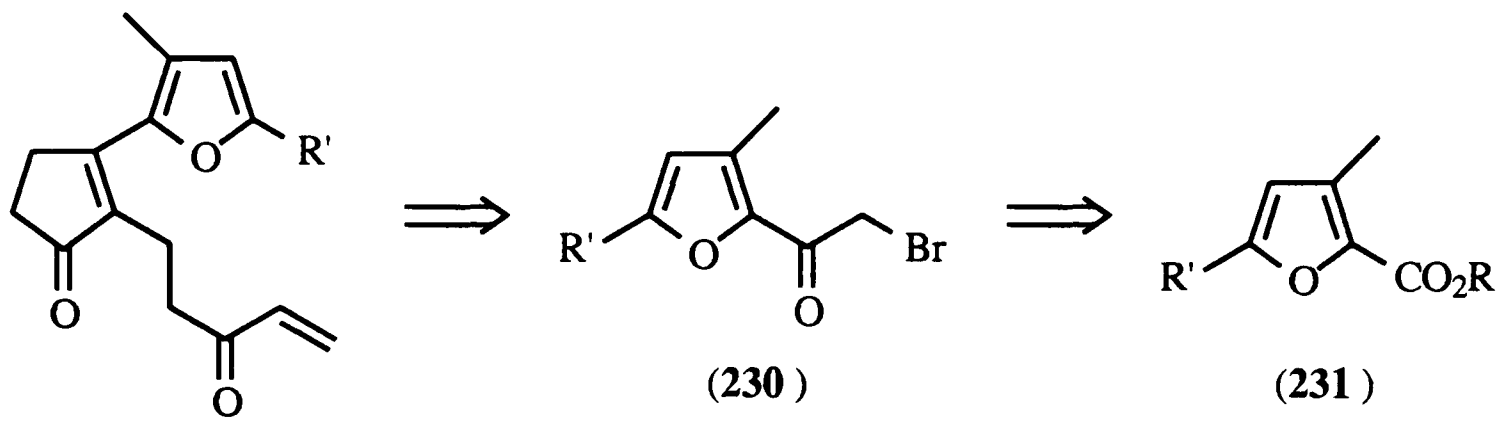
Scheme 57

The product was identified by the appearance of a singlet at δ4.33 p.p.m. in the ^{1}H n.m.r. spectrum, that corresponded to the deshielded bromomethylene protons, and this confirmed that only a single bromine had been incorporated. Two equivalents of bromide were required, facilitating the deposition of copper (I) bromide that was used to indicate the extent of reaction according to the following equation (**Scheme 58**).



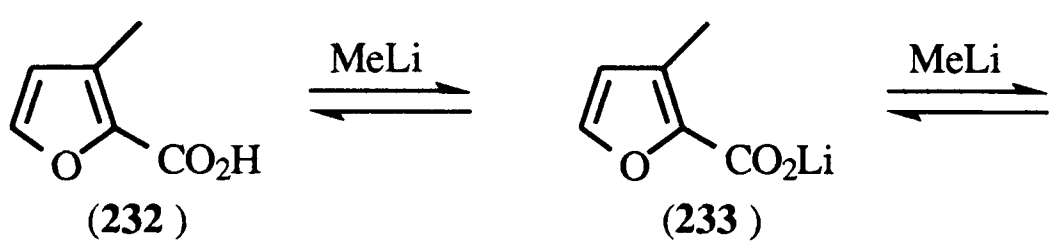
Scheme 58

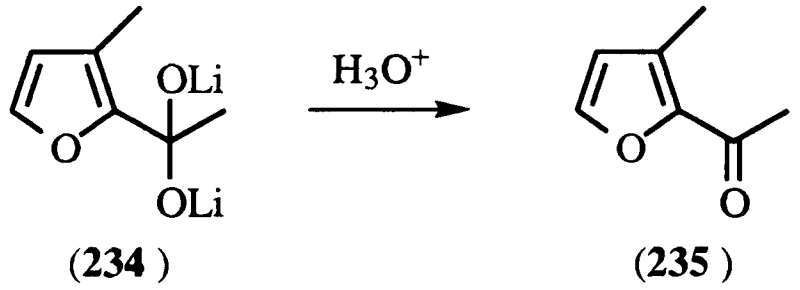
Although 2-(bromoacetyl)furan (**227**) was a suitable precursor for elaboration to model substrate (**221**), the target natural product, phorbol (**1**), contains a methyl substituent at C-11 that would be best introduced early in the synthetic sequence. Thus it was envisaged that the ideal cationic acetylfuran synthetic equivalent in synthesis of methylfuran IMDAF substrate (**220**), 3-methyl-2-(bromoacetyl)furan (**230**), could be derived by reduction of a readily available methyl furoate (**231**) (**Scheme 59**).



Scheme 59

It was considered that addition of 2 equivalents of methyllithium to 3-methyl-2-furoic acid (**232**), should form a tetrahedral dilithiated adduct (**234**) that, upon hydrolysis, would afford the acetylfuran precursor to the monobrominated product (**235**) (**Scheme 60**).

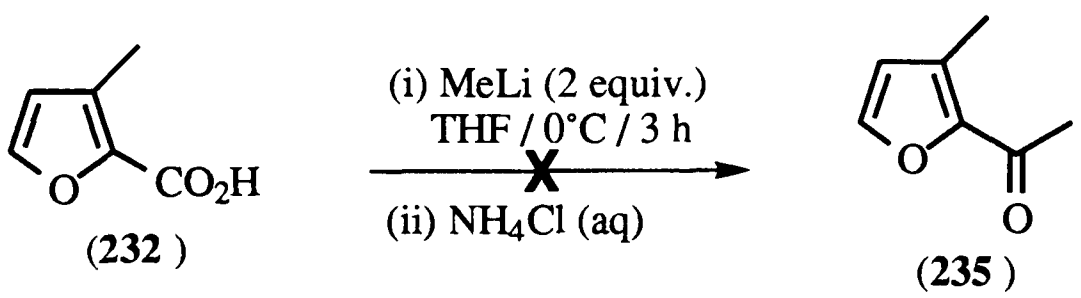




Scheme 60

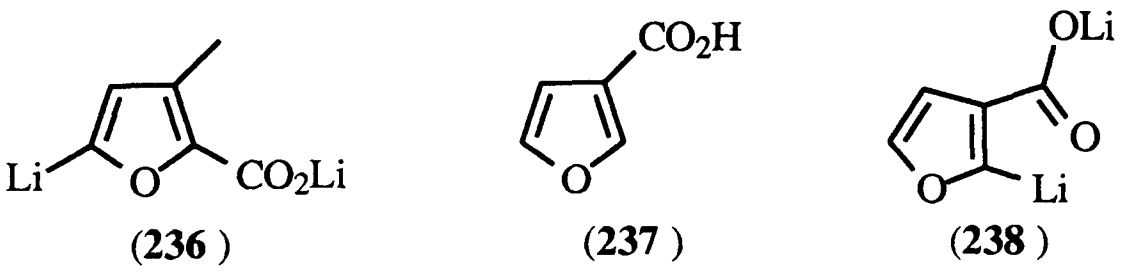
Hydrolysis of methyl 3-methyl-2-furoate, according to an adapted procedure of Burness,[102] by refluxing the ester with 3 equivalents of potassium hydroxide in 1 : 2 methanol-water (v/v) furnished 3-methyl-2-furoic acid (**232**) in 78 % yield. The product was identified by the appearance of a carbonyl absorption in the i.r. spectrum at 1 670 cm^{-1}, observation of only a single methyl resonance at δ2.41 p.p.m. in the ^1H n.m.r. spectrum, and detection of the parent ion species MNH_4^+ (144) and MH^+ (127) by mass spectrometry.

However, addition of 2 equivalents of methyllithium to the 2-furoic acid (**232**) in THF at 0°C did not lead to isolation of the required acetylfuran (**235**) but allowed only a 40 % recovery of starting material (**Scheme 61**).



Scheme 61

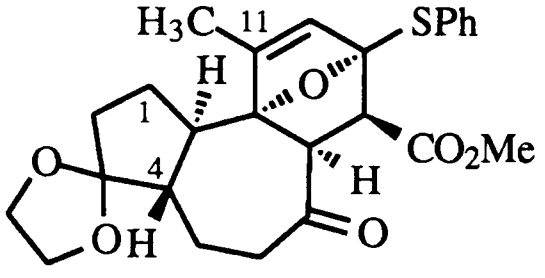
The failure in the addition of the lithium reagent was attributed to a combination of the high activation energy required to form the tetrahedral adduct (**234**), with corresponding loss in conjugation with the furan, and to a change in function of the methyllithium, instead behaving as a base and effecting a second deprotonation in preference to nucleophilic attack. The formation of dianions of aromatic carboxylic acid systems has been well established in the literature since the metallation of toluic acids was discovered by Creger in 1970.[103] The deprotonation of 3-methyl-2-furoic acid to the *bis*-anion (**236**) has been reported by Knight and is complete after only 3 minutes at -78°C using 2 equivalents of lithium diisopropylamide.[104,105] Similarly Keay has recently observed that 3-furoic acid (**237**) failed to afford addition products on treatment with *n*-butyllithium in tetrahydrofuran at -20°C and instead formed the *ortho*-lithiated *bis*-anion (**238**).[106]



On account of this evidence it seemed unlikely that 3-methyl-2-acetylfurans could be prepared by nucleophilic attack to lithio furoate (**233**) due to the basic function of the lithium reagent.

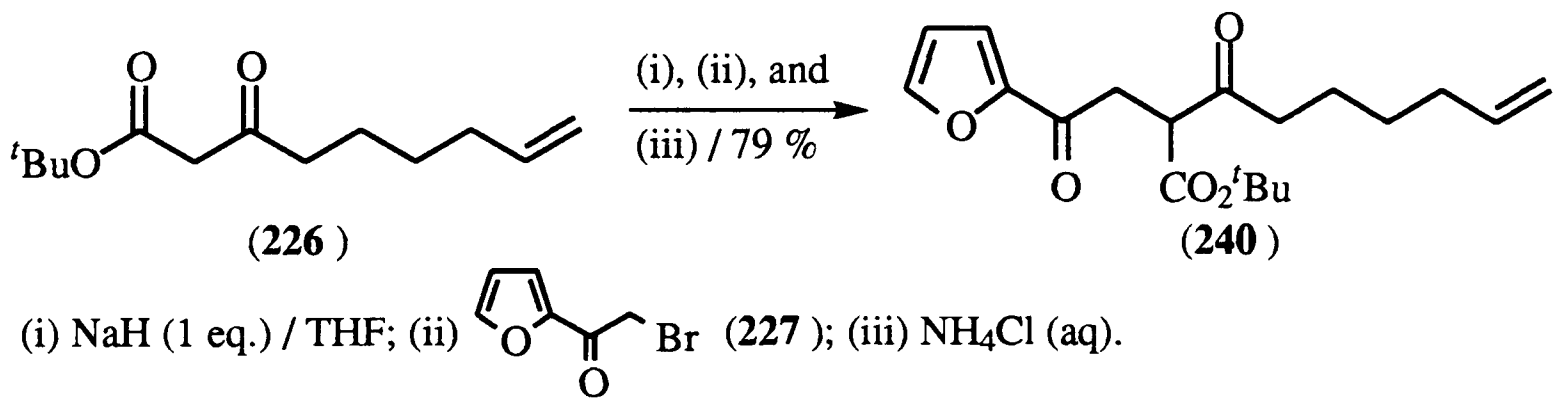
It has been suggested by previous molecular modelling experiments within the group that the IMDAF of 4-methyl furan precursors may be problematic.[107] Difficulty was anticipated based on the energy minimisation of the methylphenylthiofuran cycloadduct (**239**), using the MOPAC modelling package, that suggested that the close proximity of the

C-11 substituent (< 1.9 Å) to the hydrogen atoms on C-1 or C-4 could provide some steric constraints absent in the IMDAF precursor. Since the transition state structure must possess at least some product character it was apparent that unfavourable interactions would hinder successful intramolecular closure of Diels-Alder substrates by both kinetic and thermodynamic considerations. On account of this evidence and the difficulty experienced in methyl lithium addition, further studies were conducted on demethylated substrates.



(239)

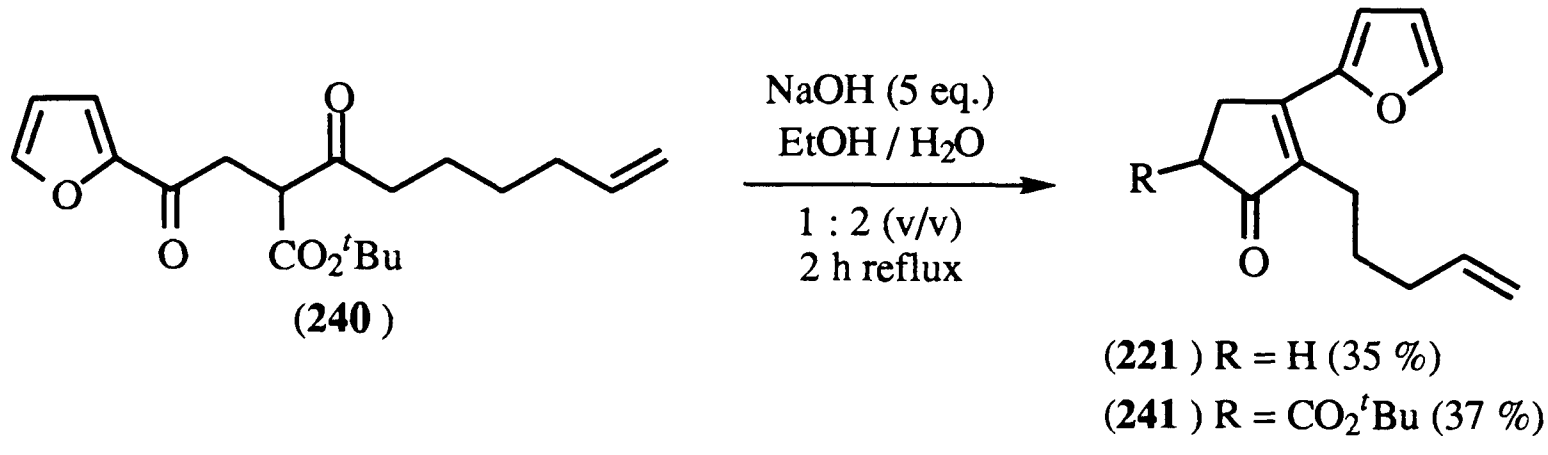
The coupling of furyl component (**227**) with the product of dianion addition (**226**) was achieved by deprotonating the acidic acetoacetate α-methylene position, with sodium hydride in tetrahydrofuran below 0°C, and then quenching the anion with one equivalent of 2-(bromoacetyl)furan (**227**) according to the reported procedure[82] to furnish the alkylated acetoacetate (**240**) in 79 % yield (**Scheme 62**).



Scheme 62

Identification of the product was possible by observation of carbonyl absorptions in the i.r. spectrum at 1 738, 1 715, and 1 679 cm^{-1}, the appearance of 3 sets of ABX resonances at δ4.11 - 3.32 p.p.m. in the ^1H n.m.r. spectrum that corresponded to the furoyl methylene and acetoacetate methine protons, and detection of the ion species MH^+ (335) by mass spectrometry.

However, hydrolysis of the *tert*-butyl ester function by refluxing acetocetate (**240**) for 2 hours in an ethanolic aqueous sodium hydroxide solution did not afford any of the 1, 4-diketone (**223**) and instead furnished the required model substrate (**221**) and the *tert*-butyl ester product of base catalysed aldol cyclisation (**241**), in approximately a 1 : 1 ratio and 72 % overall yield (**Scheme 63**).



(**240**)

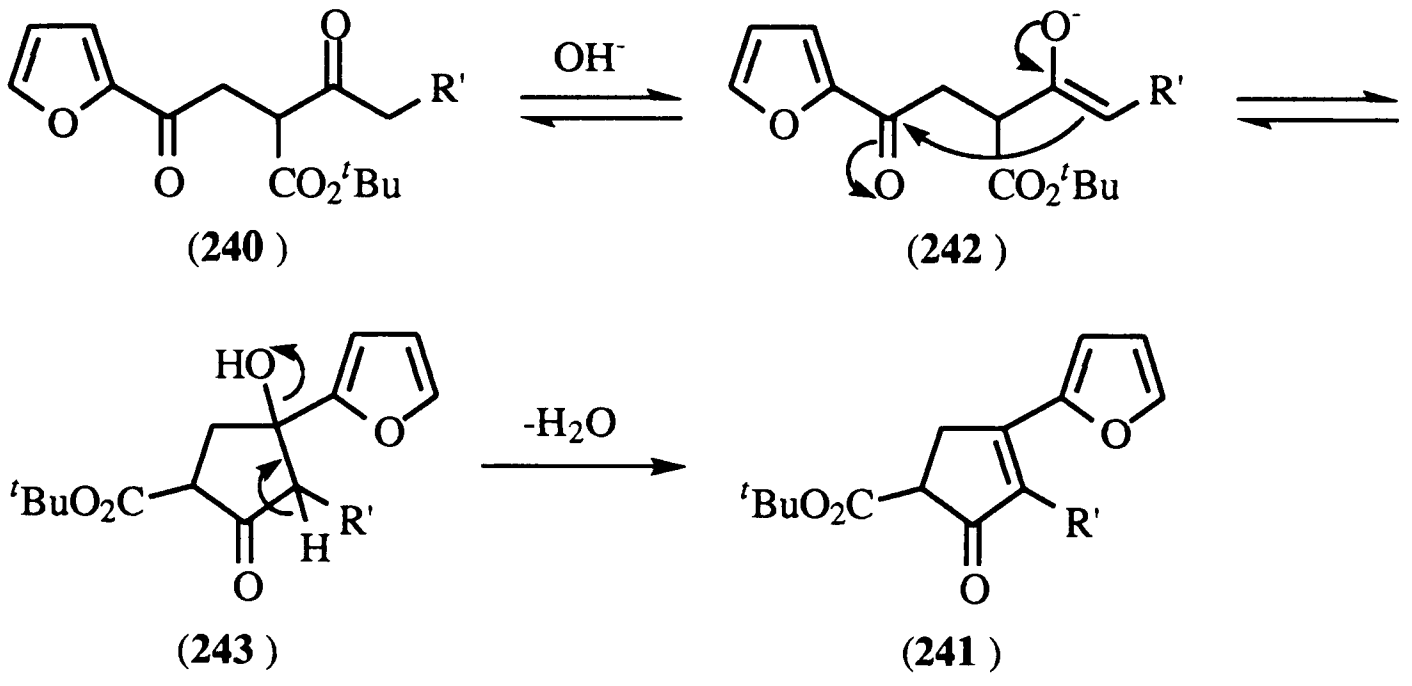
(**221**) R = H (35 %)
(**241**) R = $CO_2{}^tBu$ (37 %)

Scheme 63

The *tert*-butyl 2-oxocyclopent-3-enoate (**241**) was identified by carbonyl absorptions in the i.r. spectrum at 1 729 and 1 697 cm^{-1} and the appearance in the ^1H n.m.r. spectrum of 3 sets of ABX resonances at δ3.43 - 3.02 p.p.m., that corresponded to the cyclopentenone protons, and a 3-furyl proton signal that had shifted upfield by 0.4 p.p.m..

The furyl cyclopentenone (**221**) was identified by the presence of only a single carbonyl absorption in the i.r. spectrum at 1 693 cm^{-1}, the appearance of cyclopentenone methylene multiplet resonances at δ2.87 and 2.58 p.p.m. in the ^1H n.m.r. spectrum with an upfield shift in the 3-furyl proton signal by 0.4 p.p.m. and detection of the parent ion MH^+ (217) by mass spectrometry.

Increasing the reaction time to 18 hours permitted total hydrolysis and concomitant decarboxylation of the ester functionality and facilitated isolation of only a single reaction product, the 2-(pent-4-enyl)cyclopent-2-enone (**221**), in 87 % yield. The inability to detect the 1, 4-diketone (**223**) under these reaction conditions is indicative of a rapid intramolecular closure mechanism and facile dehydration relative to *tert*-butyl ester hydrolysis. Similarly, no regioisomeric products were observed, the required eliminative regiochemistry presumably being directed by formation of a conjugated product under thermodynamic conditions (**Scheme 64**).

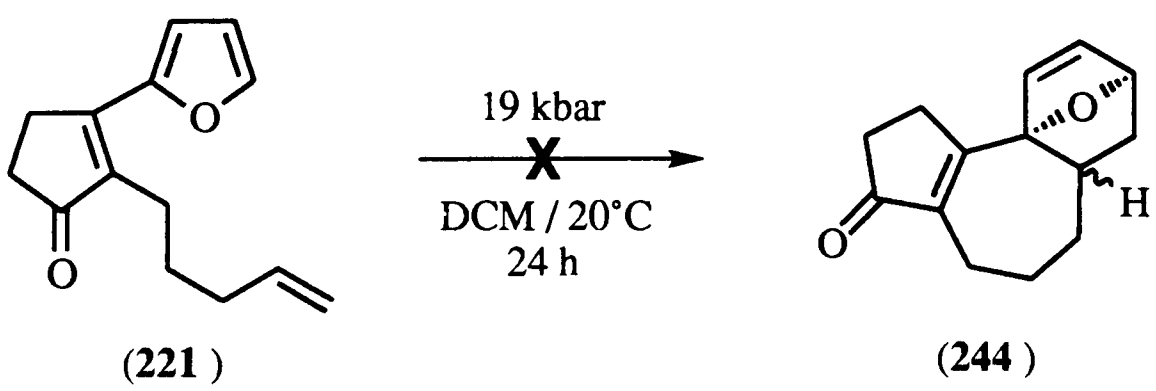


Scheme 64

This verified that furylcyclopentenones could be prepared by an anionic alkylation / aldol cyclisation approach, with potential for introduction of the C-4 hydroxyl and C-2 methyl substituents by a manipulation of existing functionality.

2.2.2. Diels-Alder addition of 3-(2-furyl)-2-(pent-4-enyl)cyclopent-2-enone (**221**).

Subjecting a solution of the model IMDAF substrate (**221**) in dichloromethane to 19 kbar pressure at 20°C for 24 h afforded only a quantitative recovery of unreacted starting material (**Scheme 65**).



Scheme 65

The failure of the cycloaddition was attributed to a combination of the following factors:-

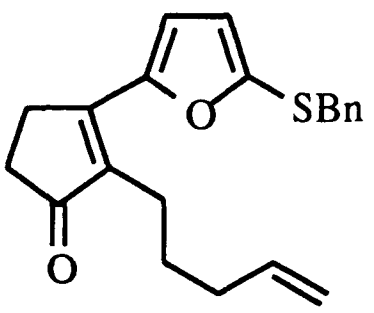
(i) An unactivated olefinic moiety results in a high energy dienophilic LUMO that reduces diene-dienophile interactions.

(ii) Deactivation of the furan by electron withdrawal into the cyclopentenyl moiety reduces the energy of the diene HOMO and reduces diene-dienophile interactions.

(iii) Introduction of α, β-unsaturation into the A-ring of the cycloaddition substrate (**221**), although it may cause restriction in bond rotation and so bring entropic advantage, may prevent diene and dienophile from being in close proximity and thus reduce interactions.

With successful construction of the model substrate (**221**) having now been achieved it was necessary to promote the crucial cycloaddition by modification of the precursor. It was proposed that the introduction of a diene activating substituent at the 5-position of the furan would be most easily implemented and could facilitate the reaction.

2.3. Studies on 3-[2-(5-benzylthio)furyl]-2-(pent-4-enyl)cyclopent-2-enone (**245**).



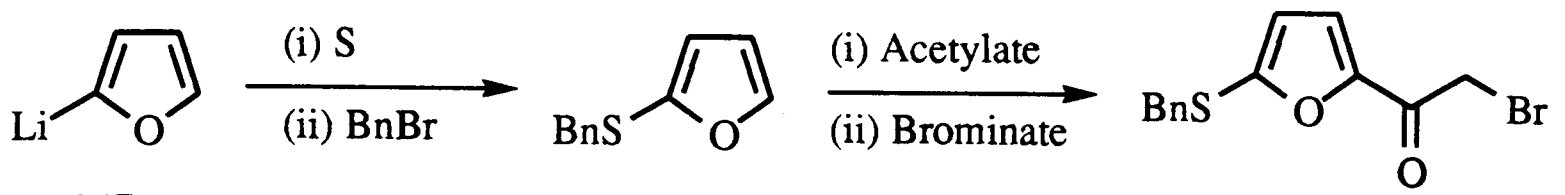
(245)

2.3.1. Introduction

Prompted by previous work within the group,[97] an alkylthio group was chosen as the activating substituent for the furan diene. Not only would this moiety favour successful cycloaddition, but it could facilitate cleavage of the oxygen bridge in the product by hydrolytic fission in an aqueous mercuric chloride system. In addition, mesomeric donation by sulphur lone electron pairs should promote the Wagner-Meerwein alkyl shift and permit study into the tigliane-ingenane rearrangement (see 1.6. Aim of Project).

Based on MOPAC molecular modelling calculations of diene HOMO coefficients and work by Marais, West, and Harwood,[207] a benzylthio moiety was selected to activate the diene. It has been reported in the literature by Niwa,[108] that furan (**246**) can be benzylthiolated by treating 2-lithiofuran (**247**) with sulphur and then quenching the lithiated thiol with benzyl bromide (**Scheme 66**). It was decided that it would be less problematic to introduce the substituent early in the synthetic sequence. 2-Benzylthiofuran (**248**) could

subsequently be acetylated and elaborated, using chemistry developed in the synthesis of furylcyclopentenone (**221**) (see section 2.2.1.), by generation of 2-benzylthio-5-(bromoacetyl)furan (**249**) (**Scheme 66**).



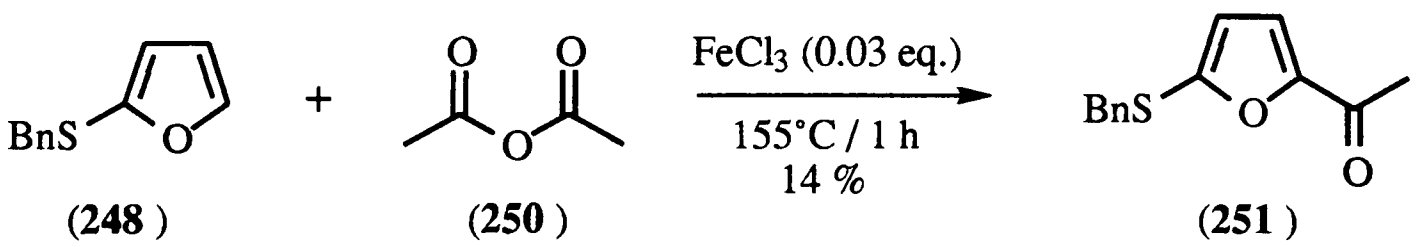
(**247**) (**248**) (**249**)

Scheme 66

2.3.2. Synthesis of 5-acetyl-2-thiofuran substrates.

The lithiofuran (**247**) was generated at -23°C, by the treatment of furan (**246**) with *n*-butyllithium in tetrahydrofuran, and was benzylthiolated according to the procedure of Niwa[108] to afford product (**248**) in 69 % yield. The presence of a singlet at δ3.97 p.p.m. in the ^{1}H n.m.r. spectrum indicated that the incorporation of the benzyl methylene protons had been successful. In addition, in the mass spectrum of the product, the parent ion MH^+ (191) as well as fragments corresponding to the formation of the tropylium ion were detected.

It was expected that acylation of the electron rich furan by a Lewis acid catalysed Friedel-Crafts reaction would cause few complications in the synthesis of the 5-acetylfuran (**251**). However, subjecting a solution of 2-benzylthiofuran (**248**) and a catalytic quantity of ferric chloride in acetic anhydride (**250**) to a temperature of 155°C for 1 h afforded the product (**251**) in only 14 % yield, after silica purification, and in insufficient purity to give a sample suitable for combustion analysis (**Scheme 67**).



(**248**) (**250**) (**251**)

Scheme 67

The i.r. spectrum of the product displayed a carbonyl absorption at 1 662 cm^{-1} and ^{1}H n.m.r. spectroscopy indicated a disappearance of the 5-furyl resonance and the appearance of a methyl singlet at δ2.44 p.p.m. corresponding to the acetyl proton signal. Detection of the

parent ion MH^+ (233) and the tropylium ion by mass spectrometric analysis completed the characterisation of the product.

Despite the success of these reaction conditions for acylating simple alkylfurans,[82] modifying the conditions did not improve on the poor reaction yield and so it was proposed that the activating effect of the sulphide substituent facilitated coordination of the furan to the Lewis acid. This would favour degradation of the heterocyclic system and formation of the intractable black polymeric tar, removed by silica purification, that predominated in the crude reaction mixture.

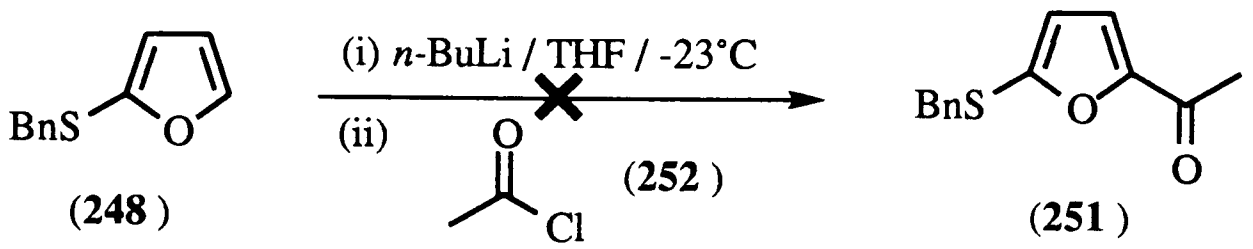
Although successful substitution of the furan had been achieved, the yield of reaction was low and needed to be optimised. Avoiding the use of silica in purification and attempting to distil the product at 160°C (bath temperature) / 1 mmHg resulted in degradation of the furan. Employing lower reaction temperatures or the use of organic solvents such as dichloromethane, in order to reduce the degree of polymerisation, failed to improve yields and below a temperature of 70°C, none of the desired product was isolated. Similarly, use of the alternative acylating agent, acetyl chloride (**252**), failed to change the extent of reaction and so a final effort to optimise the yield was made by changing the Lewis acid catalyst.

Employing aluminium trichloride or titanium tetrachloride, even at low temperatures, resulted in degradation of starting material and isolation of none of the desired product whereas the action of weaker Lewis acid catalysts such as magnesium bromide-etherate, zinc chloride, or zinc iodide failed to optimise the reaction. Omitting the catalyst from the system did afford a trace of 5-acetyl-2-benzylthiofuran (**251**) and succeeded in suppressing the degree of polymerisation, but predominantly afforded unreacted starting material.

As it appeared that it was the action of the Lewis acid that was causing the reduction in reaction yield, it was decided to adopt a route that avoided use of the problematic catalyst. Omission of Lewis acid should avoid difficulties with degradation of the thiofuran substrates and so an approach involving the acylation of 5-lithio-2-benzylthiofuran was investigated.

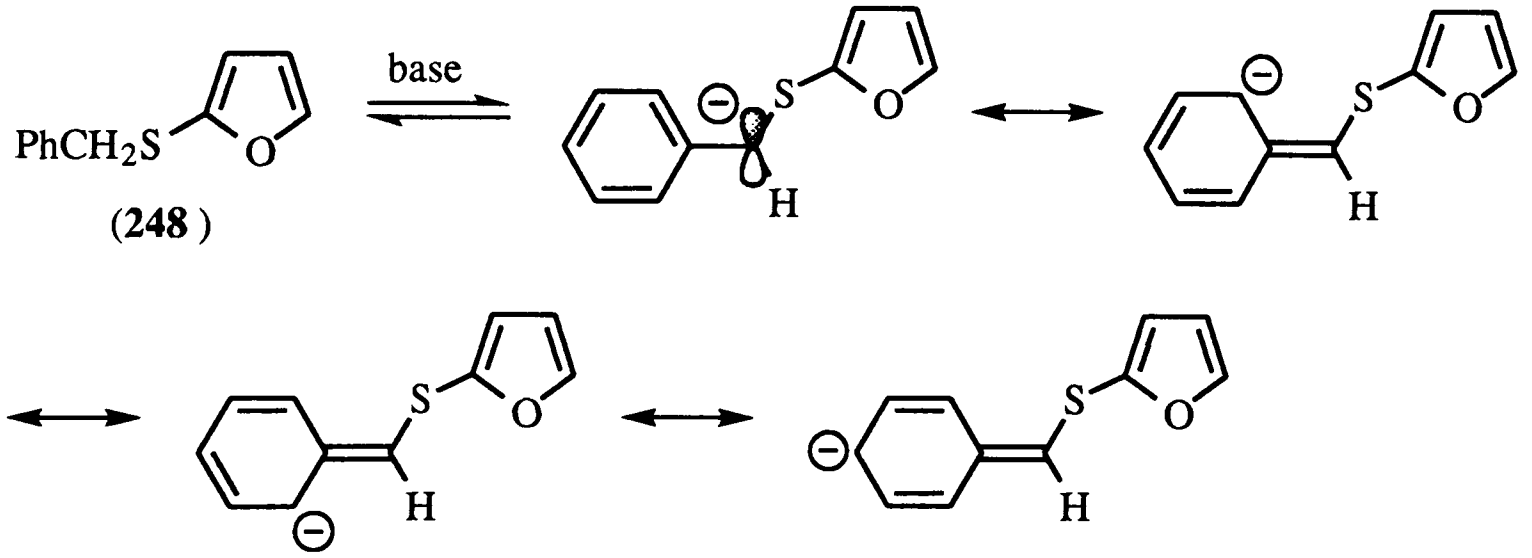
Deprotonating 2-benzylthiofuran (**248**), by the action of *n*-butyllithium in tetrahydrofuran, and quenching the lithiofuran with acetyl chloride (**252**) afforded a complex

mixture of products that contained none of the required 5-acetyl-2-benzylthiofuran (**251**) (**Scheme 68**).



Scheme 68

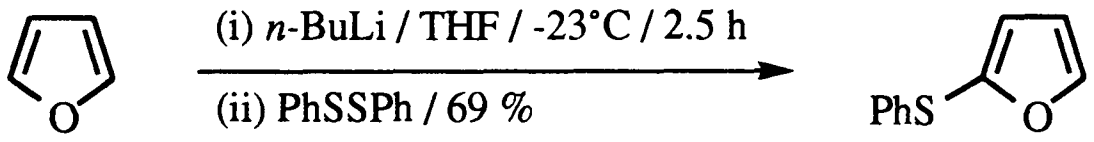
It was thought that failure to successfully acetylate the furan could be the result of competition for deprotonation between protons at the vinylic and benzylmethylene sites. The formation of a benzylic carbanion would allow the charge to be stabilised by delocalisation around the aromatic ring and so would be favoured under thermodynamic lithiation conditions (**Scheme 69**). The undesired preferential deprotonation of 2-benzylthiofuran (**248**) at the sp^3 carbon was in accord with previous observations within the group,[109] and could have been responsible for the failure in reaction.



Scheme 69

To remove the problem of chemoselectivity of lithiation, the acylation of an alkylthiofuran lacking the acidic benzyl methylene protons was investigated. The introduction of a phenylthio substituent in place of the benzylthio moiety would avoid any difficulties in directing lithiation, though delocalisation of sulphur lone electron pairs into the benzene aromatic system would reduce the mesomeric activation of the diene in the IMDAF.

2-Phenylthiofuran (**253**) was prepared in 69 % yield, according to a procedure adapted from Niwa,[108] quenching 2-lithiofuran (**247**), formed by the action of *n*-butyllithium on furan (**246**), with phenyl disulphide (**Scheme 70**).



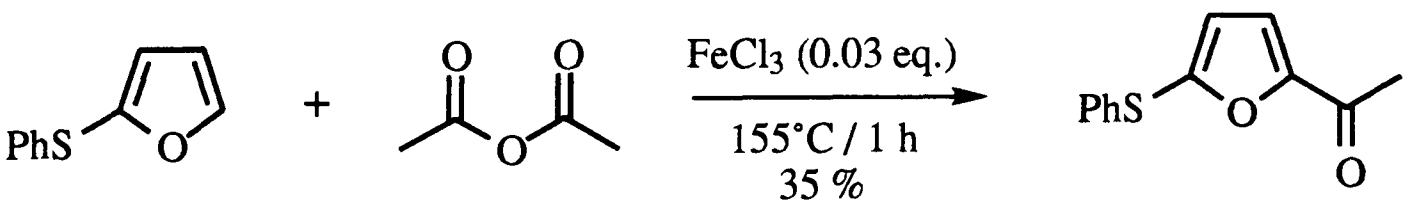
(**246**) (**253**)

Scheme 70

Identification was possible by the appearance of 3 furyl proton resonances in the ^1H n.m.r. spectrum of the unsymmetrical product between δ7.60 and 6.49 p.p.m. and detection of the parent ion MH^+ (177) by mass spectrometry.

Deprotonation of 2-phenylthiofuran (**253**) by the action of *n*-butyllithium and quenching the lithiofuran in acetyl chloride (**252**) at -23°C, as before, led to a complex mixture of products that this time contained the required product (**254**), albeit in very low yield. Hence although the problem of directing lithiation had been overcome, the approach was still considered invalid. This could be a consequence of deprotonation of the acetylfuran acidic protons in the product and subsequent condensation resulting in multiple addition.

However, Friedel-Crafts acylation of 2-phenylthiofuran (**253**), by refluxing a solution of the substrate and a catalytic quantity of ferric chloride in acetic anhydride (**250**) for 1 h, furnished 5-acetyl-2-phenylthiofuran (**254**) in a slightly more acceptable 35 % yield (**Scheme 71**).



(**253**) (**250**) (**254**)

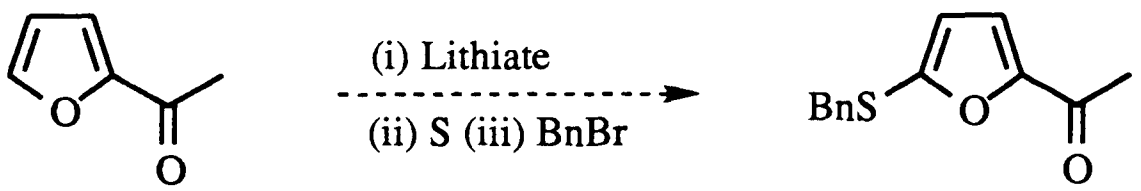
Scheme 71

The product was identified by a carbonyl absorption at 1 666 cm^{-1} in the i.r. spectrum, the disappearance of the 5-furyl resonance and the appearance of a methyl singlet at δ2.47 p.p.m. in the ^1H n.m.r. spectrum, that corresponded to the acetyl proton resonance,

and detection of the parent ions MNH_4^+ (236) and MH^+ (219) by mass spectrometric analysis.

The improved yield of acetylated product, with respect to the acylation of 2-benzylthiofuran (**248**), was attributed to delocalisation of sulphur lone electron pairs into the benzene aromatic system in the 2-phenylthio substrate (**253**) deactivating the furan to degradation by the Lewis acid catalyst.

Although the Friedel-Crafts acylation protocol had furnished both phenylthio and benzylthioacetylfurans, (**254**) and (**251**) respectively, yields were low and so it was decided to approach the products from 2-acetylfuran (**229**), thus avoiding the problematic acylation step. Deprotonation at the 5-furyl position and treatment of the lithiofuran to the conditions of Niwa[108] should produce the benzylthiolated acetylfuran (**251**) in only one synthetic step (**Scheme 72**).

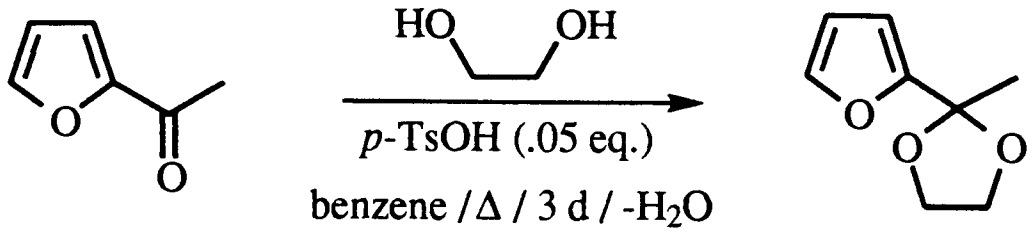


(**229**) (**251**)

Scheme 72

Standard conditions for the lithiation of the furan were employed, but instead of behaving as a base, *n*-butyllithium underwent nucleophilic addition to the acetyl carbonyl after 15 min at -23°C. Employing one or two equivalents of lithium di-*iso*propylamide, at 0 or -78°C and subjecting the lithiated substrate to the conditions of Niwa[108] resulted only in recovery of benzyl bromide starting material and the complete degradation of the furan.

Due to the failure in benzylthiolation of the mono and dianion of 2-acetylfuran (**229**), it was necesssary to protect the carbonyl moiety as an ethylene ketal in order to direct lithiation to the required site and reduce the electrophilicity of the ketone. Refluxing a solution of acetylfuran (**229**), ethane-1, 2-diol, and a catalytic quantity of *p*-toluenesulphonic acid for 3 days in benzene, with the azeotropic removal of water, furnished ethylene ketal (**255**) in 79 % yield (**Scheme 73**).



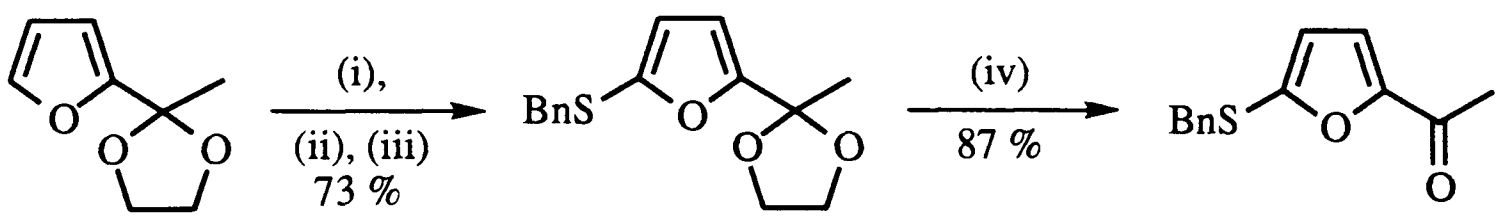
(**229**) (**255**)

Scheme 73

The ^{1}H n.m.r. spectrum of the product showed the methyl proton resonance had shifted upfield to δ1.75 p.p.m. and the appearance of a new multiplet signal at δ4.04 p.p.m., that corresponded to the ethylene ketal protons. Detection of the parent ion MH^+ (155) by mass spectrometric analysis completed characterisation of the product.

Benzylthiolation of the furyldioxolane (**255**), using the conditions of Niwa,[108] afforded the furylsulphide (**256**) in 73 % yield (**Scheme 74**). The product was identified by disappearance of the 5-furyl proton resonance at δ7.37 p.p.m. in the ^{1}H n.m.r. spectrum and the appearance of a methylene singlet at δ3.98 p.p.m., that indicated that incorporation of the benzyl substituent had been successful. The mass spectrum of the product showed the parent ion MH^+ (277) as well as fragments corresponding to the tropylium ion species.

Deprotection of the ethylene ketal moiety by refluxing (**255**) with 0.3 equivalents of *p*-toluenesulphonic acid in aqueous acetone afforded the unmasked 5-acetyl-2-benzylthiofuran (**251**) in 87 % yield (**Scheme 74**).



(**255**) (**256**) (**251**)

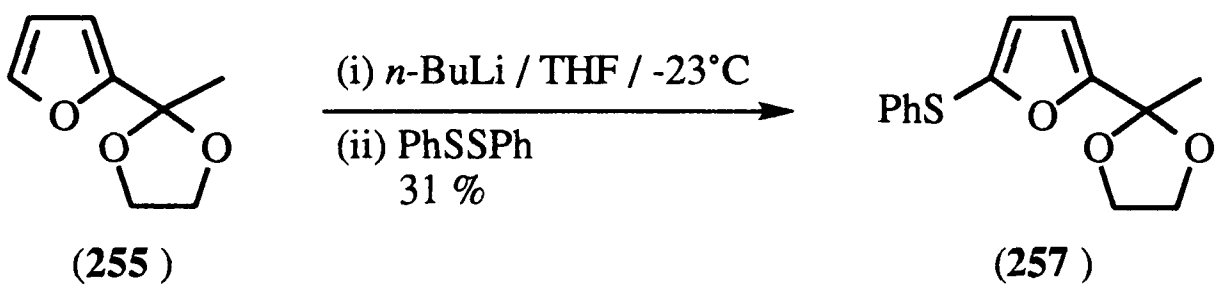
(i) *n*-BuLi / THF / -23°C / 2.5 h; (ii) S; (iii) BnBr; (iv) *p*-TsOH / H_2O-acetone (10 : 1 (v/v)) / 2 h reflux.

Scheme 74

The deprotected product (**251**) was found to be identical to the product of Friedel-Crafts acylation by i.r., ^{1}H n.m.r., and mass spectrometric analysis and was of sufficient purity to give correct combustion analysis. Hence, although this alternative approach had

increased the length of the synthetic sequence, the overall yield of 5-acetyl-2-benzylthiofuran (**251**) had improved from 10 % to 50 % over 3 steps and so became the adopted route.

Applying the protection / thiolation / deprotection strategy to the synthesis of 5-acetyl-2-phenylthiofuran (**254**), the lithiation of furyldioxolane (**255**) was achieved by the action of *n*-butyllithium in tetrahydrofuran at -23°C and subsequently quenched by addition of phenyl disulphide. Upon aqueous work up, the desired phenylthiofuran (**257**) was furnished in only 31 % yield with a 53 % recovery of phenyl disulphide starting material (**Scheme 75**).



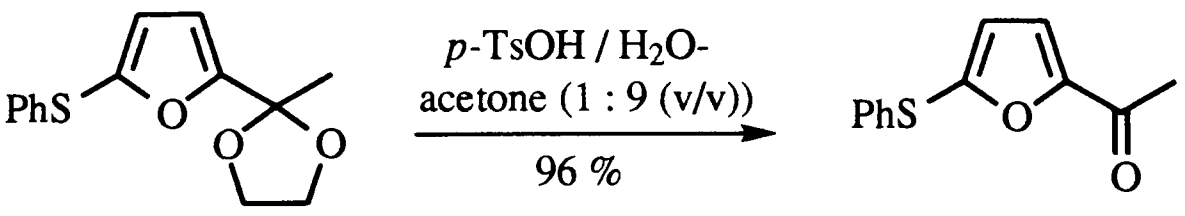
(**255**) (**257**)

Scheme 75

The product was identified by disappearance of the 5-furyl proton resonance at δ7.37 p.p.m. in the ^{1}H n.m.r. spectrum with the appearance of aromatic signals at δ7.30 - 7.15 p.p.m., that corresponded to 5 aromatic phenyl protons, and by detection of the parent ion MH^+ (263) by mass spectrometric analysis.

The lower yield of phenylthiolation, with respect to the benzylthiolation process, was attributed to the reduced electrophilicity of the sulphide reagent, stabilised to nucleophilic attack by conjugation of the sulphur lone electron pairs into the aromatic system.

Deprotection of the ethylene ketal moiety, by refluxing the dioxolane (**257**) with 0.3 equivalents of *p*-toluenesulphonic acid in aqueous acetone for 2 h, afforded the unmasked 5-acetyl-2-phenylthiofuran (**254**) in 96 % yield (**Scheme 76**).



(**257**) (**254**)

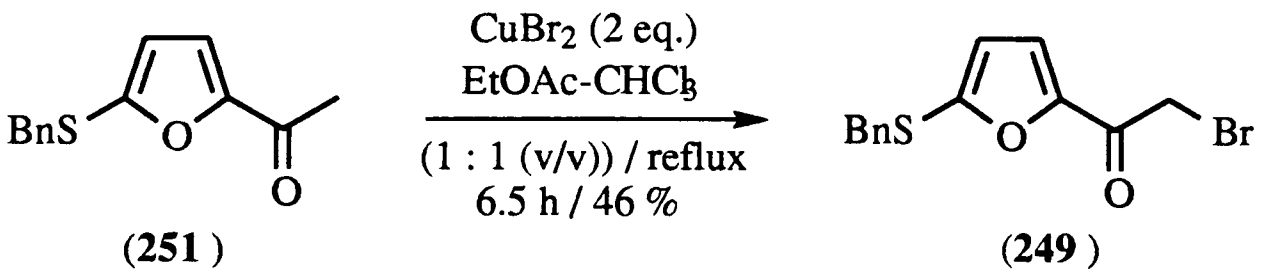
Scheme 76

Although the product was found to be identical spectroscopically to the product of Friedel-Crafts acylation, the overall yield of formation of the phenylthiofuran (**254**) was only 21 %. Comparing this with a 24 % overall yield obtained in only 2 synthetic steps by a Friedel-Crafts acylation approach and considering that no improvement in purity had been observed, it was decided that the acylation strategy would be adopted as the preferred method of generation of the phenylthio product (**254**).

2.3.3. Cyclopentenone synthesis by anionic alkylation / aldol cyclisation approach.

The successful syntheses of 2-phenyl and 2-benzylthio-5-acetylfuran, (**254**) and (**251**) respectively, has facilitated construction of thiofurylcyclopentenones by an anionic alkylation / aldol cyclisation approach (see section 2.2.1.). Transformation of the benzylthiolated species (**251**) into 2-benzylthio-5-(bromoacetyl)furan (**249**) and elaboration using the known protocol would not only optimise activation of the diene in the IMDAF (with respect to the phenylthiolated precursors), but would utilise the more efficient 5-acetyl-2-benzylthiofuran (**251**) synthesis.

Bromination of 5-acetyl-2-benzylthiofuran (**251**), by the method of King and Ostrum using 2 equivalents of copper (II) bromide,[101] furnished the monobrominated acetylfuran (**249**) in 46 % yield (**Scheme 77**).



(**251**) (**249**)

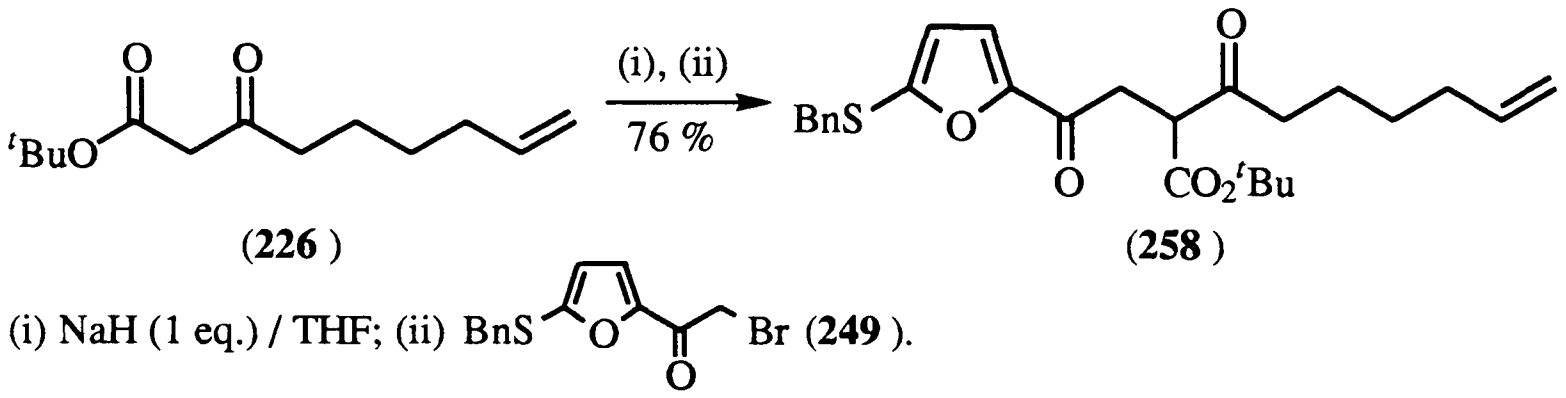
Scheme 77

Separation of the product from unreacted starting material and the trace of dibrominated product was less problematic and so afforded a higher reaction yield than the bromination of 2-acetylfuran (**229**).

The (bromoacetyl)furan (**249**) was stored at -12°C to inhibit polymerisation and was identified by the appearance of a singlet at δ4.24 p.p.m. in the ^{1}H n.m.r. spectrum, that corresponded to the deshielded bromomethylene protons, and by detection of the parent ion

MH^+ (313 and 311) of both isotopes of bromine, and the tropylium ion in the mass spectrum of the product.

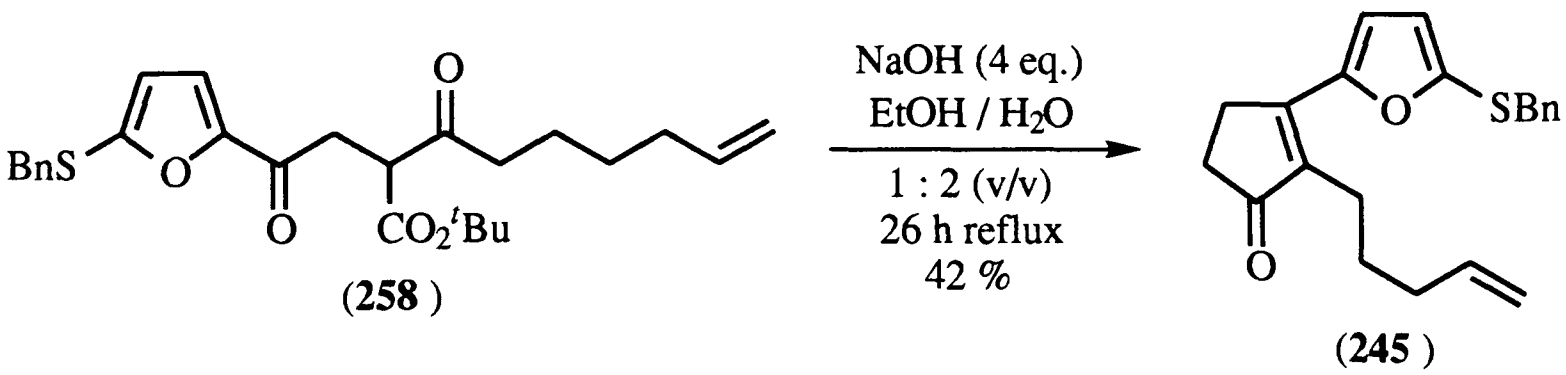
Coupling the (bromoacetyl)furan (**249**) with the product of dianion addition (**226**), by acetoacetate deprotonation with sodium hydride in tetrahydrofuran, furnished the alkylated acetoacetate (**258**) in 76 % yield (**Scheme 78**).



Scheme 78

The product was identified by carbonyl absorptions in the i.r. spectrum at 1 738, 1 714, and 1 675 cm^{-1}, ABX resonances in the ^1H n.m.r. spectrum at δ4.09 - 3.27 p.p.m., corresponding to the furoylmethylene and acetoacetate methine protons, and detection of the tropylium ion in the mass spectrum.

Gratifyingly, submitting the *tert*-butyl ester (**258**) to the Büchi and Wüest aldol cyclisation conditions[99] for 26 hours resulted in hydrolysis of the ester, conco mitant decarboxylation, and subsequent intramolecular cyclisation to afford the single product, furylcyclopentenone (**245**), in 42 % yield (**Scheme 79**).



Scheme 79

The product was identified by the appearance of only a single carbonyl absorption in the i.r. spectrum at 1 693 cm^{-1}. In the ^1H n.m.r. spectrum resonances at δ2.81 and 2.55 p.p.m.

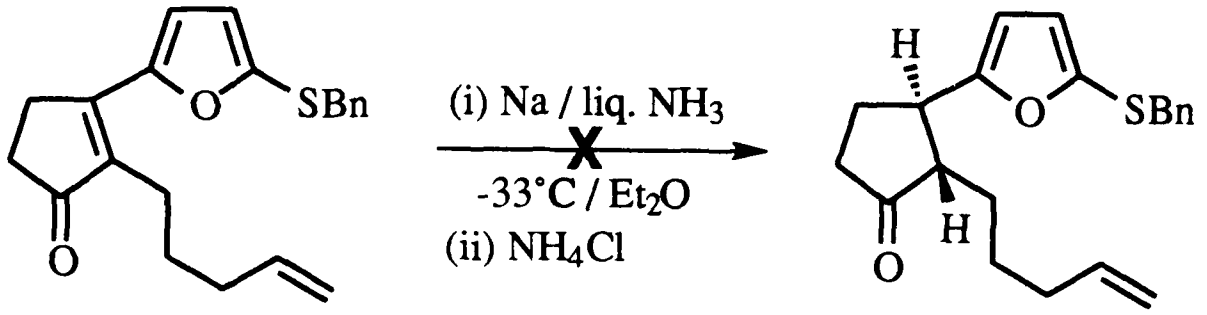
corresponded to the cyclopentenone methylene protons and the 3-furyl proton signal at δ6.71 p.p.m. had been shifted upfield by 0.4 p.p.m.. Detection of the parent ion MH^+ (339) and the tropylium ion by mass spectrometric analysis generated confidence in the characterisation of the product.

Ironically, it was noted that the intramolecular condensation had proceeded without complication and yet synthesis of the acetylbenzylthiofuran precursor (**251**), that was assumed at the outset to be relatively straightforward, had proved far from trivial to complete. However with the methodology established, benzylthiofurylcyclopentenone (**245**) had been derived from 2-benzylthio-5-(bromoacetyl)furan (**249**) by the aldol cyclisation approach.

2.3.4. Diels-Alder addition of 3-[2-(5-benzylthio)furyl]-2-(pent-4-enyl)cyclopent-2-enone (**245**).

Subjecting a solution of the benzylthiofurylcyclopentenone (**245**) in dichloromethane to 19 kbar pressure at 20°C for 24 h afforded predominantly unreacted starting material. After 4 days at 19 kbar pressure, the quantity of recovered starting material decreased and a complex mixture of products was obtained, that could not be separated. Thus, it was apparent that activation of the diene altered the outcome of the cycloaddition but did not lead to the formation of the intramolecular cyclisation product. It seemed likely that, in addition to electronic effects, sp^2 hybridisation in the olefinic cyclopentenone moiety had altered the spatial arrangement between the C-2 and C-3 substituents, expanding the bond angles from 109 to 120° and thus preventing diene and dienophile from being in close enough proximity for intramolecular addition. Based on this premise, it was decided to transform the cyclopentenone into the sp^3 hybridised cyclopentanone in order to observe the effect upon the IMDAF. The removal of the electron withdrawing influence and subsequent deactivation of the diene by the enone would favour cycloaddition.

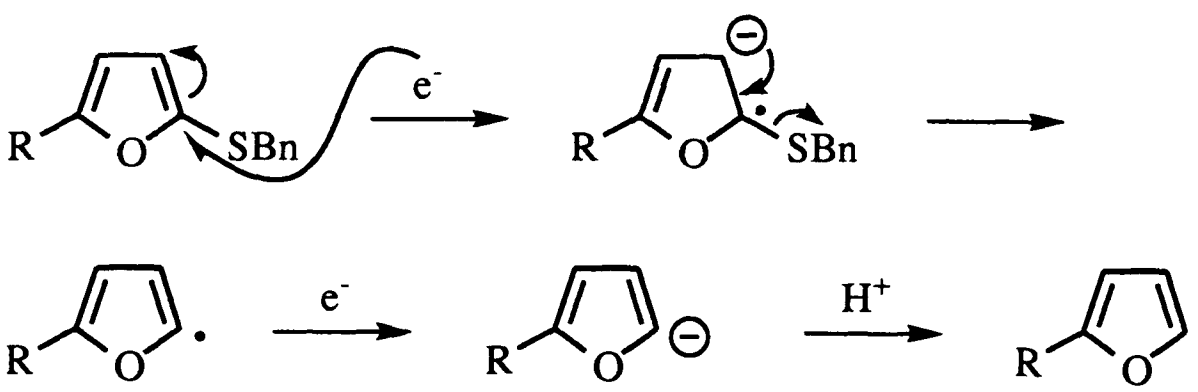
It was considered that the dissolving metal reduction of cyclopentenone (**245**) should derive cyclopentanone (**259**) with the required *trans*- stereochemistry present at the A-B ring junction in the target natural product (**Scheme 80**).



(**245**) (**259**)

Scheme 80

Treatment of an ethereal solution of substrate (**245**) with sodium in liquid ammonia for 20 min at -33°C resulted in the consumption of all starting material and furnished a complex mix of products that contained no signals in the ^1H n.m.r. spectrum between δ4.80 and 3.50 p.p.m.. The absence of the benzylmethylene proton resonance indicated preferential single electron thioether cleavage by delivery of electrons to the furan aromatic ring (**Scheme 81**). It had been demonstrated by previous studies within the group that simple furylcyclopentenones were compatible with these reaction conditions and formed *trans*-3-furyl-2-alkylcyclopentenones.[82] Thus the reduction of benzylthiofurans by the action of a dissolving metal electron transfer has been prevented by a problem in chemoselectivity.

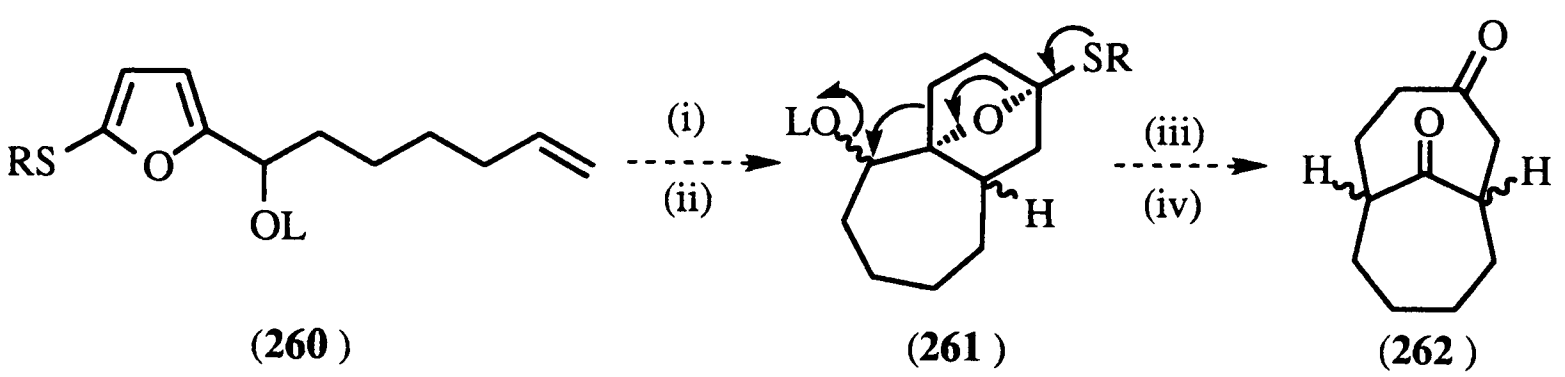


Scheme 81

Based on the failure of this approach to furnish IMDAF cycloadducts it was thought necessary to construct a model system that would test whether cycloaddition with an unactivated dienophile was possible in the synthesis of 6, 7-fused cycles and to investigate the ring expansion derivation of a model 7, 7-ingenane type system.

2.4. Model Study.

Although the literature contains many examples of successful IMDAF's with unactivated dienophiles in the formation of 6, 5- and 6, 6-fused cycles,[80] the synthesis of 6, 7-systems by this approach has not been reported. Thus, it was decided to investigate a model system in order to discover whether activation of the dienophile is necessary to facilitate successful cycloaddition. The incorporation of oxygenated functionality α- to furan (**260**) lends potential for rearrangement to an electron deficient centre in the hydrogenated adducts (**261**) by expulsion of a suitable oxygen containing leaving group. Hydrolysis of the alkylthio functionality would then furnish the model ingenane analogue (**262**) (**Scheme 82**).

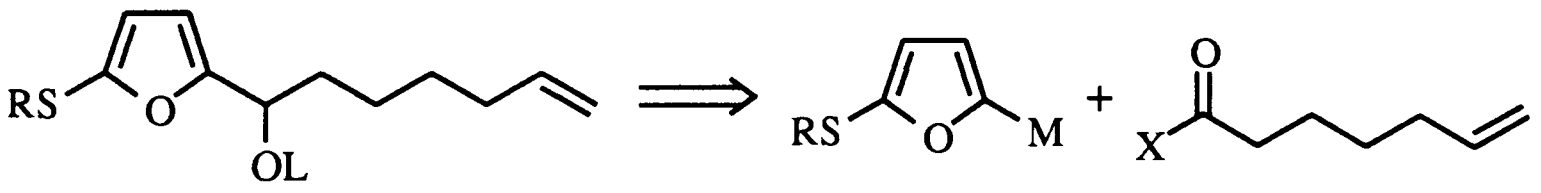


(**260**) (**261**) (**262**)

(i) IMDAF; (ii) H_2; (iii) Rearrangement; (iv) Hydrolysis.

Scheme 82

In the retrosynthetic analysis of IMDAF precursor (**260**) disconnection between furyl and alkoxy substituents suggested synthesis from metallo furan (**263**) and an oxaheptene (**264**) (**Scheme 83**).

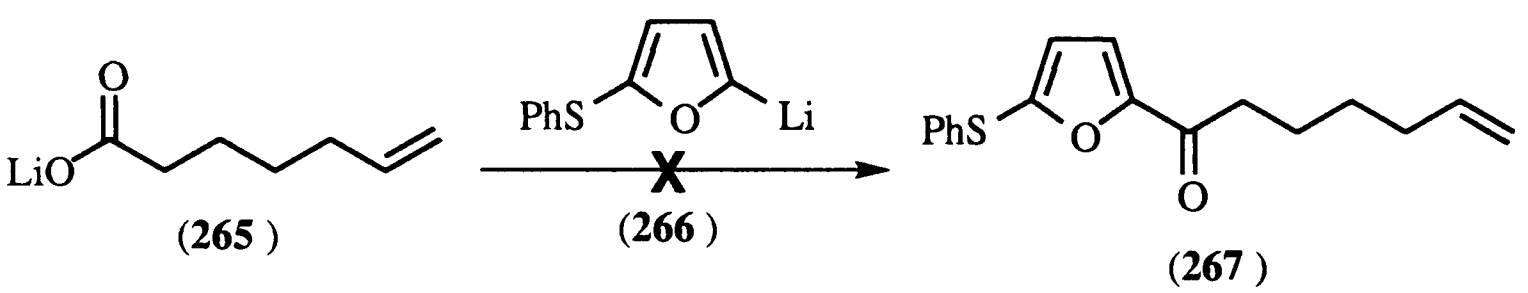


(**260**) (**263**) (**264**)

Scheme 83

Due to problems of chemoselectivity in deprotonating 2-benzylthiofuran (**248**),[109] with preferential lithiation occuring at the benzyl position, studies were conducted on 5-lithio-2-phenylthiofuran (**266**). Two equivalents of 2-phenylthiofuran (**253**) were deprotonated, by the action of *n*-butyllithium in tetrahydrofuran at -23°C, and the lithiofuran

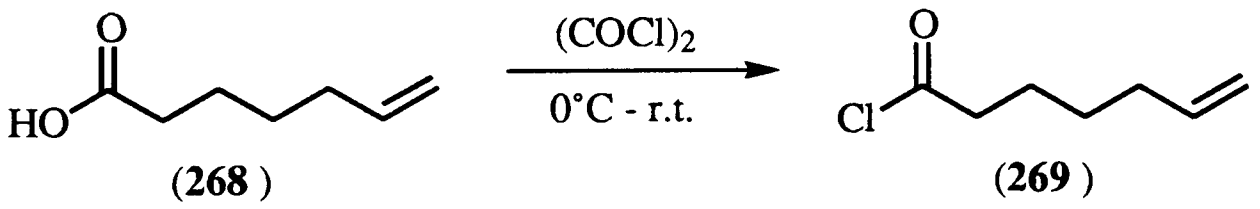
(**266**) was added to a solution of 6-heptenoic acid (**268**) in tetrahydrofuran at 0°C. It was assumed that the first equivalent of the lithium reagent would serve as a base to deprotonate the carboxylic acid, facilitating the addition by a second equivalent of lithiofuran (**266**). However following aqueous work up an 89 % recovery of unreacted starting material (**253**) was obtained. This indicated that the lithiofuran (**266**) was not nucleophilic enough to attack lithium hept-6-enoate (**265**) (**Scheme 84**) and form precursor (**267**).



(**265**) (**266**) (**267**)

Scheme 84

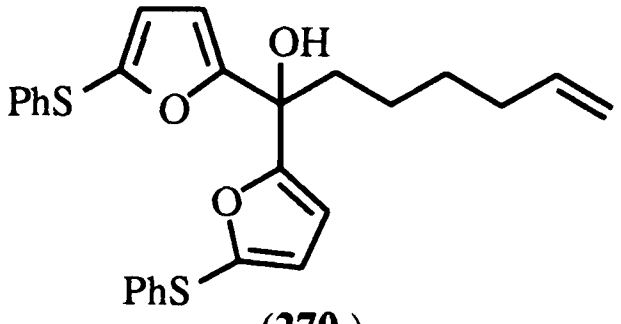
It was thought that the transformation of 6-heptenoic acid (**268**) into the corresponding acid chloride (**269**) would increase the reactivity of the electrophile and so could facilitate addition. This routine conversion was achieved by the use of oxalyl chloride in the absence of solvent (**Scheme 85**). The course of reaction was followed by i.r. spectroscopy, observing the disappearance in the acid carbonyl vibration at 1 719 cm^{-1} and an appearance of an acid chloride vibration at 1 801 cm^{-1}, and conversion was assumed to be quantitative.



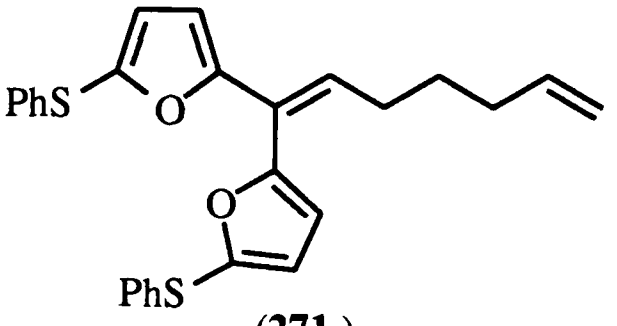
(**268**) (**269**)

Scheme 85

Addition of the acid chloride (**269**) to a solution of 5-lithio-2-phenylthiofuran (**266**) in tetrahydrofuran, prepared by the action of *n*-butyllithium on 2-phenylthiofuran (**253**) at -78°C, did not afford any of the desired product (**267**) after warming the reaction to ambient temperature, but furnished a mixture of unreacted starting material (**253**), the diaddition product (**270**), and subsequent dehydration product (**271**).



(270)

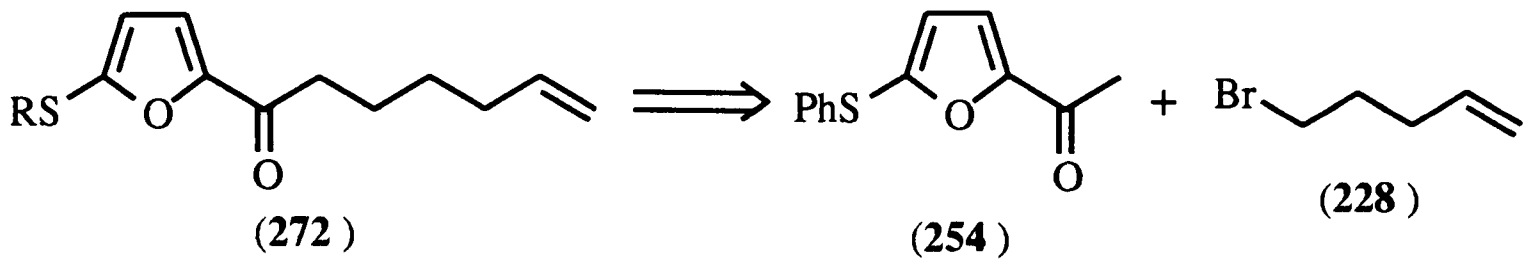


(271)

Adjusting the reaction conditions in order to favour monoaddition, the 5-lithiofuran (**266**) was added to a solution of the acid chloride (**269**) at -78°C in tetrahydrofuran and the reaction quenched at this temperature. However only unreacted starting materials and the diaddition product (**270**) were isolated from the mixture.

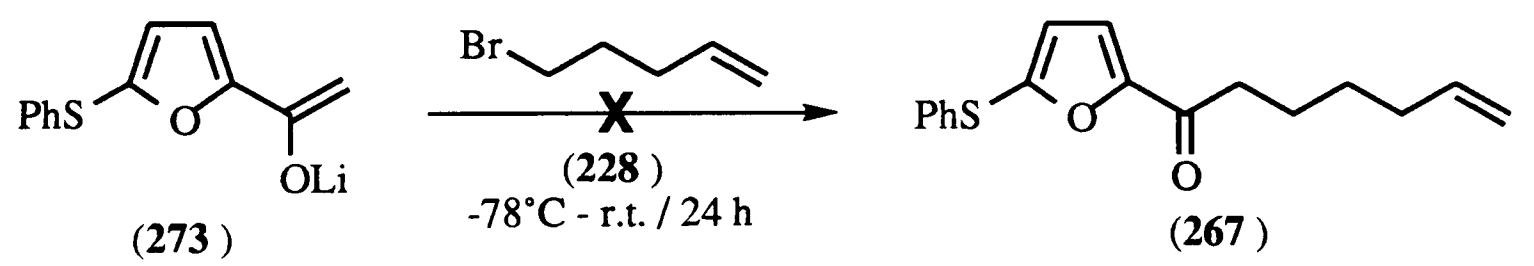
The absence of product from the reaction, even when quenched at -78°C before completion, indicated a problem in chemoselectivity. In order to prevent attack of a second molecule of 5-lithio-2-phenylthiofuran (**266**), the lithium reagent was replaced by the high order furyl cyanocuprate of Lipshutz.[91] Formation of the difuranyl higher order cuprate, by action of 2 equivalents of the lithiofuran (**266**) on a suspension of copper (I) cyanide in tetrahydrofuran at room temperature, and subsequent addition of the homogeneous solution to hept-6-enoyl chloride (**269**) only afforded a recovery of unreacted 2-phenylthiofuran starting material (**253**) in 75 % yield after 2 days. The absence of any reaction products was attributed to stabilisation of the thiofurylcuprate by delocalisation of charge into the furan and subsequent reduction in reactivity.

Based on the failure of this strategy to derive furylketone (**267**), an alternative approach was sought. Disconnecting the IMDAF substrate (**260**) adjacent to the alkoxy linkage (between C-2 and C-3 of the heptenyl chain) indicated a synthesis of the oxidised precursor (**272**) by addition of an acetylfuran component (**254**) to a pentenyl electrophile. Thus, lithiation of acetylfuran (**254**) and quenching the anion (**273**) with 5-bromopent-1-ene (**228**) should furnish the desired adduct (**272**) (**Scheme 86**).



Scheme 86

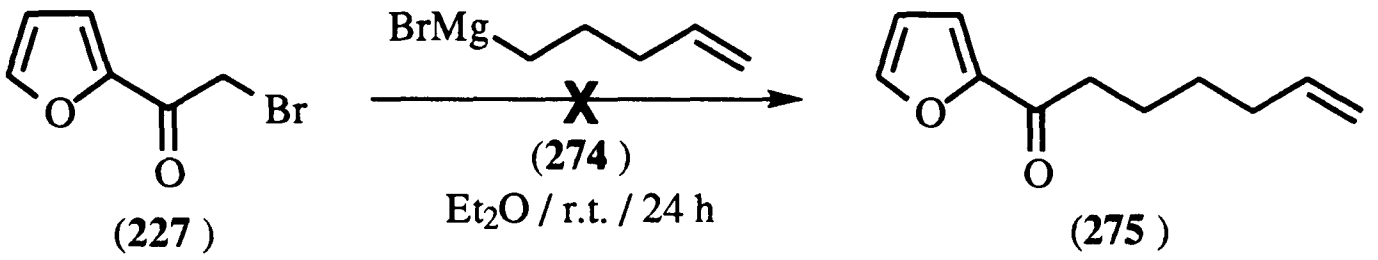
2-Phenylthio-5-acetylfuran (**254**), formed by a Friedel-Crafts acylation approach (section 2.3.2.), was lithiated by addition of the non-nucleophilic base, lithium diisopropylamine, at -78°C over 2 hours and quenched with 5-bromopent-1-ene (**228**). After overnight stir at room temperature, only unreacted starting material (**254**) was recovered from the reaction in 97 % yield (**Scheme 87**). The absence of reaction reflected the stability of the lithium enolate (**273**) and implied that the synthesis of furylketone (**267**) by this strategy was not possible. Based on this failure it was decided to neglect the phenylthio- activating substituent in order to concentrate on the successful introduction of the dienophilic tether.



Scheme 87

Maintaining the C-2 / C-3 disconnection, the replacement of the nucleophilic lithium enolate (**273**) with 2-(bromoacetyl)furan (**227**), and attack of this umpolung substrate with the Grignard reagent (**274**) derived from 5-bromopent-1-ene (**227**), provided a potential alternative approach to furylketone (**275**). The Grignard reagent was formed by vigorously stirring magnesium turnings in diethyl ether under an inert atmosphere for 24 h, followed by the addition of 5-bromopent-1-ene (**228**) to the activated metal at such a rate so as to maintain a gentle reflux. However, stirring the heptenylmagnesium bromide (**274**) with (bromoacetyl)furan (**227**) for 24 hours did not afford any of the required product (**275**) (**Scheme 88**), but furnished an oil that spontaneously polymerised upon isolation and evaporation *in vacuo*. Repeating the procedure with commercially available allyl magnesium

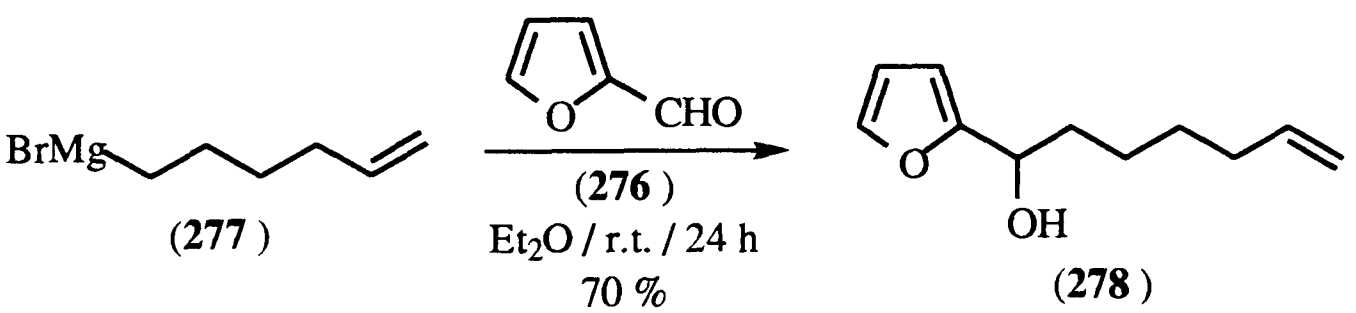
chloride as the Grignard reagent gave no improvement in the outcome of the reaction and so the approach was abandoned.



Scheme 88

Adjusting the synthetic strategy and omitting the reduction step, suggested an alternative disconnection between C-1 and C-2 in the retrosynthetic analysis. The IMDAF precursor (**275**) could thus be derived by nucleophilic attack on furaldehyde (**276**), to establish the α-hydroxyl group necessary to investigate the tigliane-ingenane rearrangement process.

The Grignard reagent (**277**) was formed by refluxing 6-bromohex-1-ene with 6 equivalents of magnesium turnings, activated by vigorously stirring in diethyl ether for 24 hours under an inert atmosphere prior to reaction. Addition of 2-furaldehyde (**276**) to the decanted supernatant from the Grignard preparation (**277**) afforded furyl alcohol (**278**) in 70 % yield (**Scheme 89**).

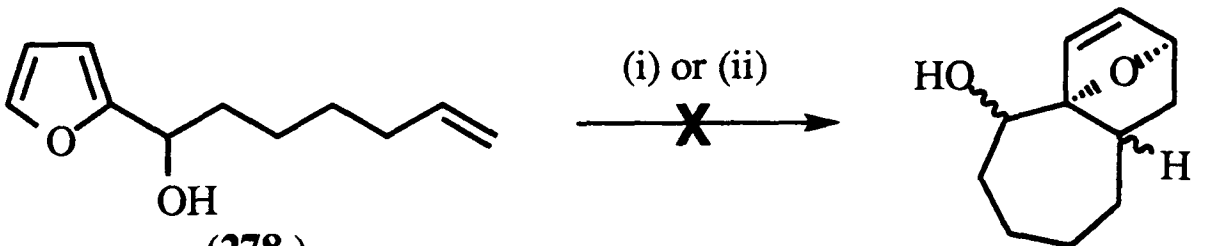


Scheme 89

The product was identified by an O-H absorption at 3 368 cm^{-1} and an alkene absorption at 1 641 cm^{-1} in the i.r. spectrum, a resonance at 4.68 p.p.m. in the ^1H n.m.r. spectrum that corresponded to the aliphatic methine proton, and by detection of the parent ion MH^+ (181) and dehydrated ion species $(MNH_4\text{-}H_2O)^+$ and $(MH\text{-}H_2O)^+$ in the mass spectrum.

Subjecting a solution of the furyl alcohol (**278**) in dichloromethane to 19 kbar pressure at 20°C for 24 h only afforded unreacted starting material in 96 % yield (**Scheme 90**). Considering the failure of the high pressure Diels-Alder reaction it was decided to investigate alternative conditions for the promotion of the cycloaddition.

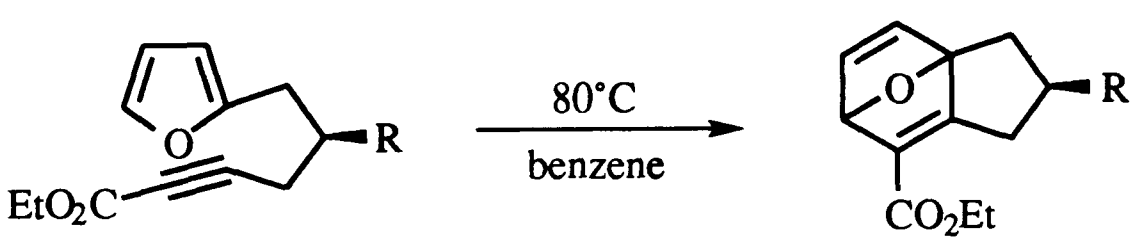
It has been reported in the literature that chromatography adsorbents such as silica cause a dramatic increase in the rate of cycloaddition reactions.[110] Based upon this premise and the success of this approach in promoting the IMDAF in previous studies within the group,[94] an attempt was made to effect cycloaddition by matrix adsorption. Vigorously stirring a solution of the furyl alcohol (**278**) in chloroform over silica for 20 days furnished only unreacted starting material, with no isolation of cycloadducts or degradation products (**Scheme 90**).



(i) 19 kbar / DCM / 20°C / 24 h;
(ii) Silica (20 times mass) / chloroform/ 20 d.

Scheme 90

It has been recognised for many years that, in general, alkyl substitution in the tethering chain of an IMDA precursor promotes the rate of ring formation and increases the concentration of cyclic material at equilibrium.[111] It has been shown by DeClercq, that the introduction of a bulky *tert*-butyl anchoring substituent in the dienophilic tether of substrate (**280**) causes a significant rate increase, k(**280b**)/(**280a**) = 240 (**Scheme 91**),[112] a rate acceleration known as the "*tert*-butyl effect".

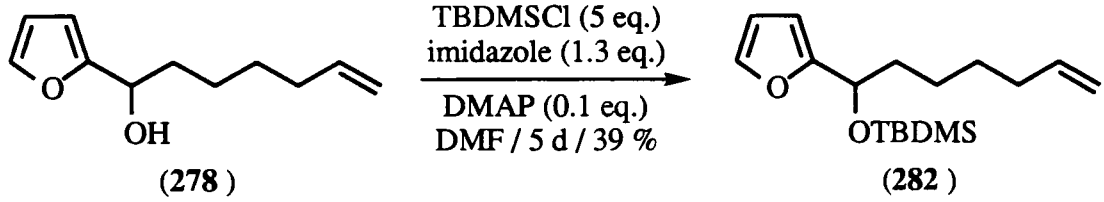


(**280**) (**281**)

(**a**) R = H; (**b**) R = ^{t}Bu

Scheme 91

It was proposed, based on observations by various groups,[113,114,115] that increasing the size and anchoring effect of the α-substituent would favour cycloaddition, and so transformation of hydroxyl to the corresponding silyl ether functionality in the model IMDAF substrates was investigated. Reaction of furyl alcohol (**278**) with a large excess of *tert*-butyldimethylchlorosilane in *N, N*-dimethylformamide in the presence of imidazole base and 4-dimethylaminopyridine as a silylation catalyst afforded only a 39 % yield of silyl ether (**282**), with 30 % recovery of starting material (**278**), after 5 days at room temperature (**Scheme 92**).

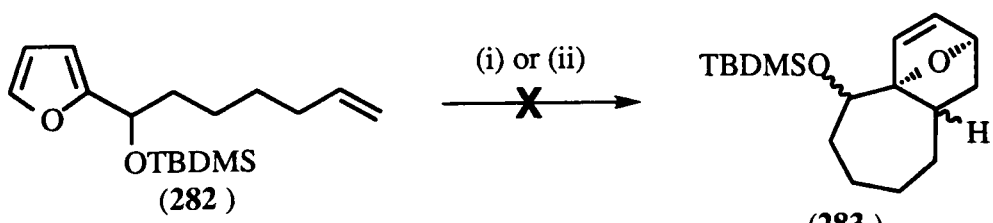


(**278**) (**282**)

Scheme 92

The silyl ether (**282**) was identified by the disappearance of the hydroxyl absorption at 3 368 cm^{-1} in the i.r. spectrum of the product and the appearance of three heavily shielded singlets in the ^1H n.m.r. spectrum that corresponded to resonance of silylated *tert*-butyl and dimethyl protons. Characterisation was complete by detection of a trace of the parent ion MH^+ (295) and the ion species $(M\text{-TBDMSO})^+$ (163) by mass spectrometric analysis.

Submitting a solution of the silyl protected substrate (**282**) in dichloromethane to 18 kbar pressure at 20°C for 24 h afforded a 91 % yield of unreacted starting material (**Scheme 93**). Chromatographic adsorbents also failed to promote the cycloaddition after stirring a solution of the silyl ether (**282**) in chloroform for 10 days over silica (**Scheme 93**).



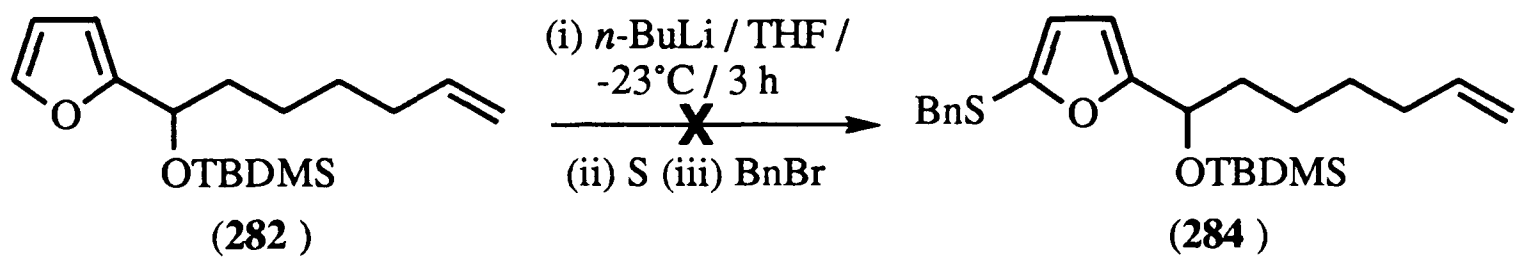
(**282**) (**283**)

(i) 18 kbar / DCM / 20°C / 24 h;
(ii) Silica(20 times mass) / chloroform/ 10 d.

Scheme 93

The failure of the IMDAF was attributed to the combined effect of poor diene-dienophile interactions with an unactivated olefin and the formation of seven membered carbocycles being entropically disfavoured with respect to closure to form a five membered ring. The production of an unfavourable equilibrium in the cycloaddition thus prevents isolation of the desired adducts (**283**).

In order to try to promote the IMDAF further, an attempt was made to introduce a benzylthio activating moiety into the furan diene according to the procedure of Niwa.[108] Deprotonation with *n*-butyllithium in tetrahydrofuran at -23°C and quenching the lithiofuran sequentially with sulphur and benzyl bromide afforded none of the desired benzylthiolated product (**284**) but furnished only a quantitative recovery of unreacted starting material (**282**) (**Scheme 94**).

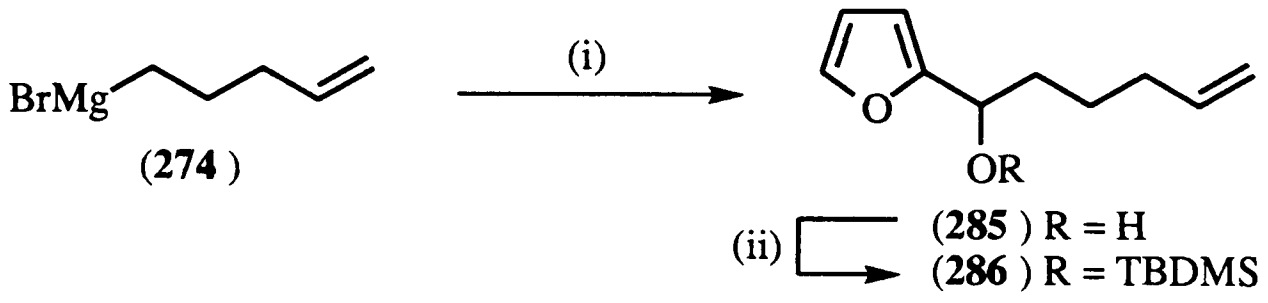


(**282**) (**284**)

Scheme 94

In order to determine which factor was responsible for the absence of cycloaddition, an IMDAF substrate that possessed a shorter dienophilic tether was synthesised by the established procedure. 2-Furaldehyde (**276**) was added to the Grignard reagent (**274**), formed by treatment of 5-bromopent-1-ene (**228**) with activated magnesium, to afford furylhexenol (**285**) in 69 % yield (**Scheme 95**). Reaction with *tert*-butyldimethylchlorosilane and imidazole in *N, N*-dimethylformamide furnished the hexenylsilyl ether (**286**) in 49 % yield indicating improvement in silylation efficiency with only an 11 % recovery of unreacted starting material (**Scheme 95**).

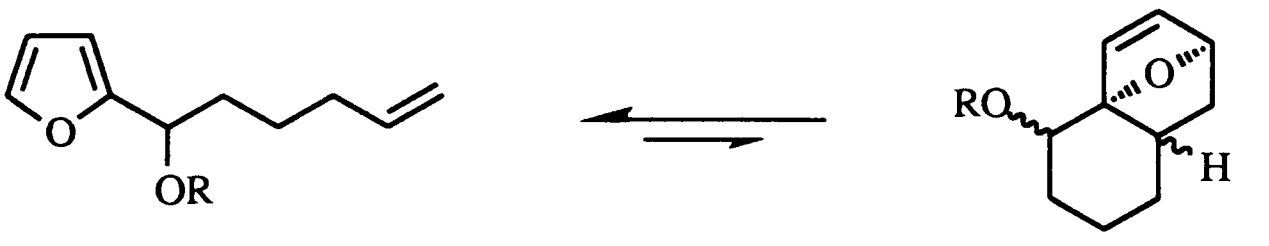
The product (**286**) was identified by comparison of spectroscopic data with the fully characterised furylheptenylsilyl ether (**282**) and by detection of the parent ion MH^+ (281) by mass spectrometric analysis.



(i) 2-Furaldehyde (**276**) / Et_2O / overnight / 69 %; (ii) TBDMSCl (5 eq.) / imidazole (1.1 eq.) / DMAP (0.1 eq.) / DMF / 4 d / 49 %.

Scheme 95

Submitting a solution of furylhexenol (**285**) to 19 kbar pressure at 20°C for 24 h afforded no cyclised material (**287**) and allowed only a recovery of unreacted starting material in 89 % yield. However, when the silyl protected species (**286**) was subjected to the same high pressure conditions a trace of cyclic product (**288**) could be detected, although unreacted starting material predominated in the equilibrium mixture. New alkene doublet resonances were observed at δ6.34 and 6.24 p.p.m. in the ^1H n.m.r. spectrum, however increasing the pressurisation time to 4 days at 19 kbar did not appreciably increase the proportion of product (**Scheme 96**). It was concluded that the failure in the IMDAF of the model substrates was due to poor interactions with the diene component when the dienophilic moiety is unactivated.



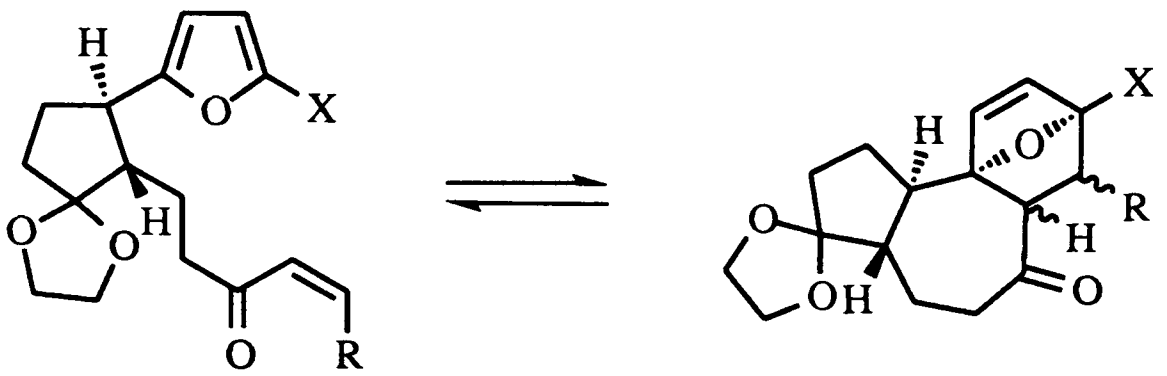
(**285**) R = H
(**286**) R = TBDMS

(**287**) R = H
(**288**) R = TBDMS

Scheme 96

Although the model systems have indicated a need for dienophilic activation to successfully access a simplified phorboid tricyclic framework, such as (**261**), they are not representative of the structural arrangement present in ideal cycloaddition precursors. The rigidity imposed on IMDAF substrates, such as (**289**) (**Scheme 97**) (section 1.5.),[94] by fusion

of the A-ring increases population of reactive conformers and so produces a favourable reaction equilibrium. Thus, to elaborate the model it is necessary to enforce a greater degree of structural rigidity, comparable to the introduction of a cyclopentane ring, upon the dienophilic tether.

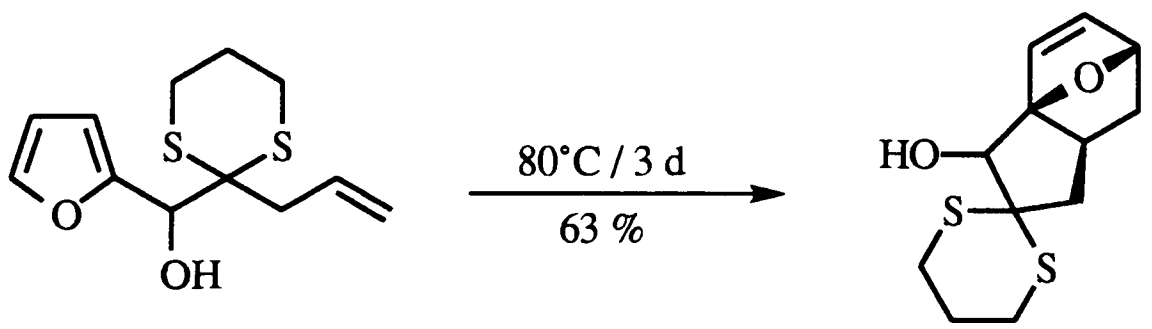


(**289**) X = H, SBn
R = H, CO_2Me

(**290**) X = H, SBn
R = H, CO_2Me

Scheme 97

The increase in the population of reactive rotamers has been utilised to good effect by Sternbach in the synthesis of fused 6, 5-carbocycles such as 7-oxabicyclo[2.2.1]heptene (**292**).[116] As a consequence of the "carbonyl coplanarity effect", that hinders closure of small rings with enone dienophilic tethers, these systems are often constructed using unactivated dienophiles.[80] The introduction of dialkyl substituents, such as the dithiane ring of (**291**), into a dienophilic tether disfavoured the ground state population of unreactive rotamers (**Scheme 98**) and so promoted cyclisation to 5, 6-adduct (**292**).



(**291**)

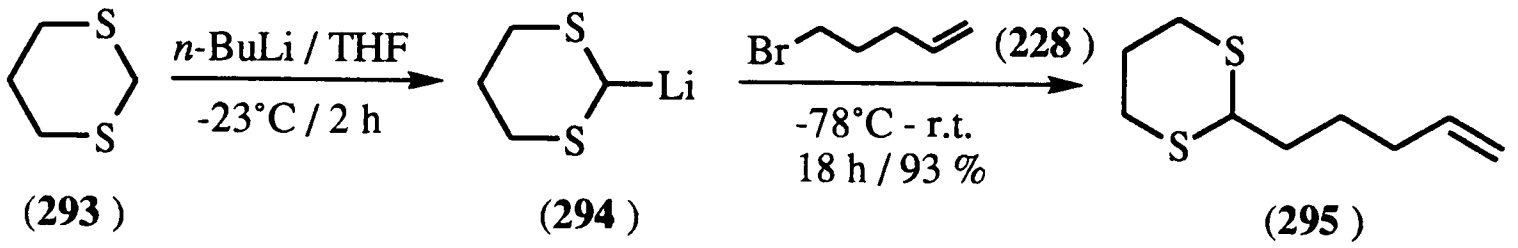
(**292**)

Scheme 98

Further studies by Sternbach[117] and Jung[118] indicated that *geminal* dialkyl substitution in the dienophilic tether favoured the IMDAF by increasing the population of reactive substrate rotamers. By utilising this "*gem* dialkyl effect", the model system could be

made more representative of a phorbol IMDAF substrate where rigidity in the A-ring enforces population of reactive conformations. Hence, the analogous Sternbach cycloaddition precursor for a 6, 7-fused carbocycle was generated.

1, 3-Dithiane (**293**) was lithiated at the acidic 2-position by treatment with *n*-butyllithium in tetrahydrofuran at -23°C according to the procedure of Seebach and Corey.[119] The 2-lithio-1, 3-dithiane (**294**) was alkylated by addition of 5-bromopent-1-ene (**228**) at -78°C, slowly warming the reaction mixture to room temperature in order to suppress eliminative side reactions.[119] This afforded the pentenyldithiane (**295**) of Chung and Dunn in 93 % yield after chromatographic purification on silica (**Scheme 99**).[120]

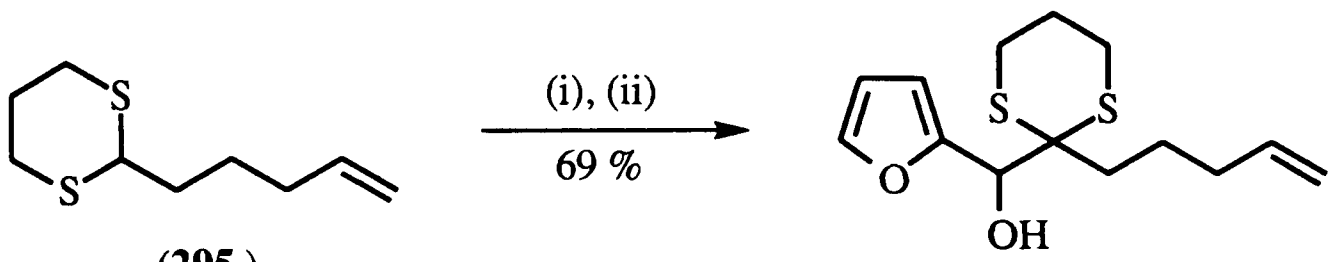


Scheme 99

The product was identified by an alkene absorption at 1 640 cm^{-1} in the i.r. spectrum and the appearance of a triplet at δ4.06 p.p.m., corresponding to the tertiary dithiolated methine, and vinylic resonances at δ5.81 - 4.98 p.p.m. in the ^1H n.m.r. spectrum. Detection of the parent ion MH^+ (189) by mass spectrometric analysis and comparison of the spectroscopic data with literature information[120] completed characterisation of the product.

Lithiation of dithiane derivative (**295**) with *n*-butyllithium using the established protocol,[119] and quenching the lithiodithiane (**296**) with 2-furaldehyde (**276**) furnished the (furylhydroxymethyl)dithiane (**297**) of Kanematsu[121] in 69 % yield (**Scheme 100**). The lower efficiency of alkylation was attributed to increased steric hindrance in addition of the electrophile to the dithiane anionic site.

The product was identified by a hydroxyl absorption at 3 451 cm^{-1} in the i.r. spectrum, the presence of a methine doublet resonance at δ5.13 p.p.m. in the ^1H n.m.r. spectrum and detection of the dehydrated ion species $(MH-H_2O)^+$ by mass spectrometric analysis.

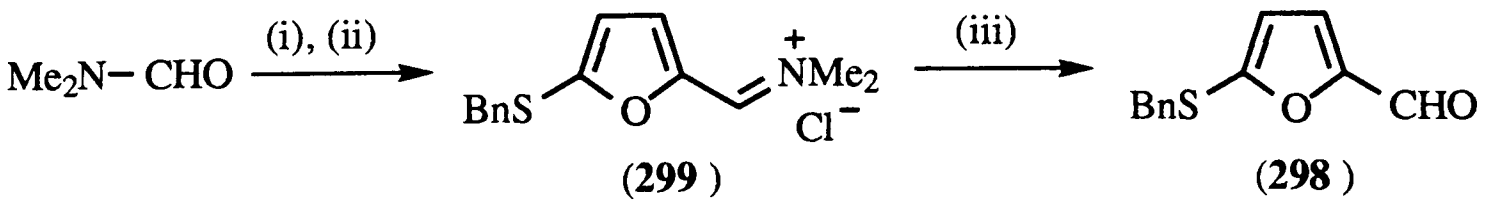


(**295**) (**297**)

(i) *n*-BuLi / THF / -23°C / 2 h; (ii) 2-Furaldehyde (**276**) / -78°C to r.t. overnight.

Scheme 100

With successful addition of lithiodithiane (**296**) to 2-furaldehyde (**276**) it was now proposed to attempt the introduction of a benzylthio- activating substituent necessary for rearrangement studies. It was thought that early incorporation, by addition to 2-benzylthio-5-furaldehyde (**298**), should not introduce complications to the established protocol and the subsequent activation of the diene could facilitate the IMDAF. It was decided to obtain the aldehyde (**298**) by the Vilsmeier formylation[122] of 2-benzylthiofuran (**248**) based on the high reactivity observed in these systems in acylation (section 2.3.2.) and the success of the Vilsmeier approach in formylating pyrrole and other heterocyclic substrates.[123,124,125] Following the procedure of James and Snyder[124] *N, N*-dimethylformamide was treated with phosphorus oxychloride at 0°C to form the chloroiminium electrophile which was added to 2-benzylthiofuran (**248**) at 35°C in DMF solution. The resultant furyliminium species (**299**) was hydrolysed by refluxing in aqueous sodium hydroxide to afford the furan carboxaldehyde (**298**) in 47 % yield (**Scheme 101**).



(**299**) (**298**)

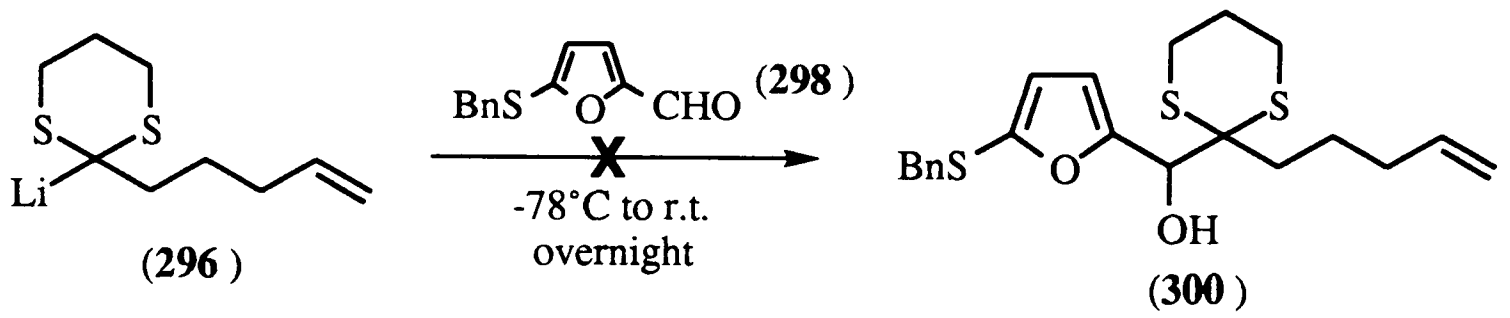
(i) $POCl_3$ / r.t.; (ii) 2-Benzylthiofuran (**248**) / Δ; (iii) NaOH (aq) / reflux / 1.5 h.

Scheme 101

The product was identified by a carbonyl absorption at 1 675 cm^{-1} in the i.r. spectrum, the disappearance of the 5-furyl proton resonance at δ7.51 p.p.m. and the appearance of a signal at δ9.56 p.p.m. in the ^1H n.m.r. spectrum that corresponded to the

heavily deshielded aldehyde proton, and detection by mass spectrometry of the parent ion MH^+ (219).

However when attempts were made to quench the lithiodithiane (**296**), formed by the action of *n*-butyllithium using Corey's procedure,[119] with 2-benzylthio-5-furaldehyde (**298**) none of the corresponding (benzylthiofuryl)hydroxymethyl product (**300**) was isolated (**Scheme 102**).

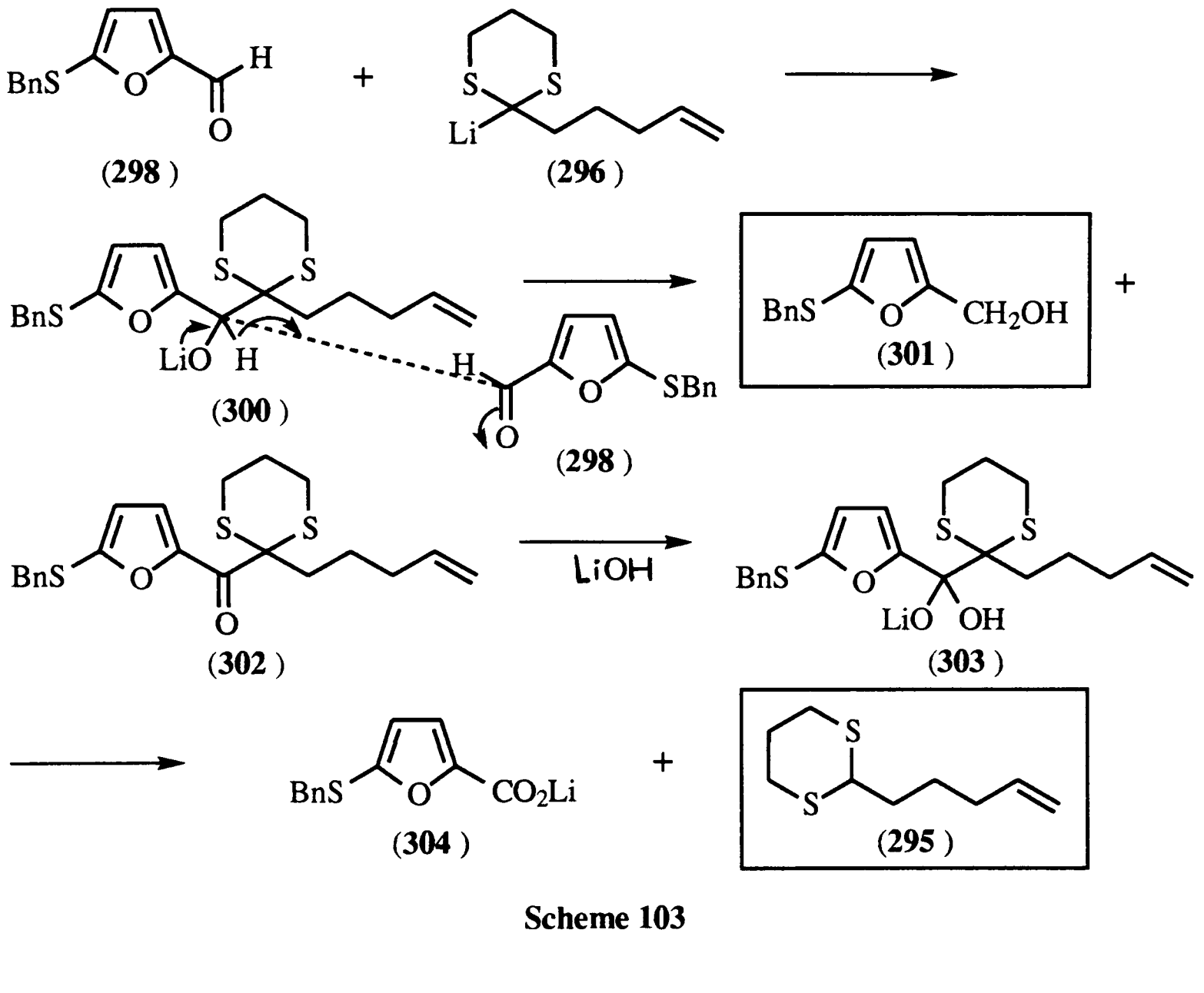


Scheme 102

From the reaction mixture an 87 % recovery of unreacted dithiane (**295**) was obtained as well as a new product, identified as 5-(2-benzylthio)furfuryl alcohol (**301**), isolated in 44 % yield. I.r. spectroscopy indicated disappearance of the carbonyl vibration at 1 675 cm^{-1} and an appearance of a hydroxyl absorption at 3 350 cm^{-1}. Similarly, from ^1H n.m.r. spectroscopy it was elucidated that the aldehyde substituent had been converted into a hydroxymethylene moiety by the presence of a doublet resonance at δ4.57 p.p.m. coupled with a triplet at δ1.70 p.p.m. that was exchangeable in D_2O. Characterisation of the product was complete by detection of the parent ion MH^+ (221) and the ion species $(M\text{-}OH)^+$ (203) by mass spectrometric analysis.

The high yield of recovered dithiane reactant (**295**) indicated that it had not directly participated in the reduction, but instead had functioned as a catalyst to facilitate a Cannizaro-type redox reaction. The change in function of lithiodithiane (**296**) was attributed to the drop in electrophilicity of furaldehyde (**298**) due to mesomeric donation from the sulphide substituent. The alternative redox reaction pathway could then operate to furnish furfuryl alcohol (**301**) in 44 % yield (**Scheme 103**). The oxidised product, presumably the corresponding lithiofuroate (**304**), was not isolated from the reaction as a consequence of the

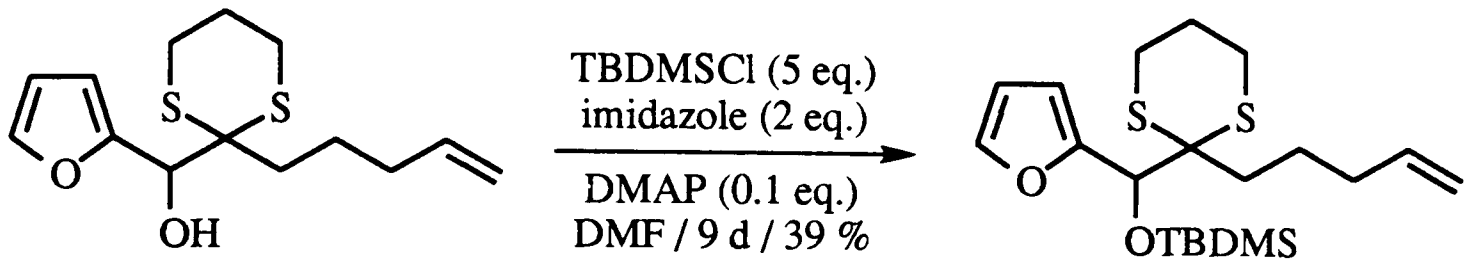
basic work up procedure but could have been generated by dithiane expulsion in (**303**) as a result of acetylfuran (**302**) hydrolysis.



Scheme 103

Proceeding with the unactivated furyl diene precursors, silylation with *tert*-butyldimethylchlorosilane and imidazole in *N, N*-dimethylformamide, catalysed by the action of 4-dimethylaminopyridine, led to formation of the silyl ether (**305**) in 32 % yield after 9 days at room temperature, with a 39 % recovery of unreacted starting material (**297**) (**Scheme 104**). The low efficiency of this conversion was comparable with the silylation yields of previous furylhydroxymethyl substrates (**278**) and (**285**). The product was identified by comparison of spectroscopic information with data for silyl ether (**282**).

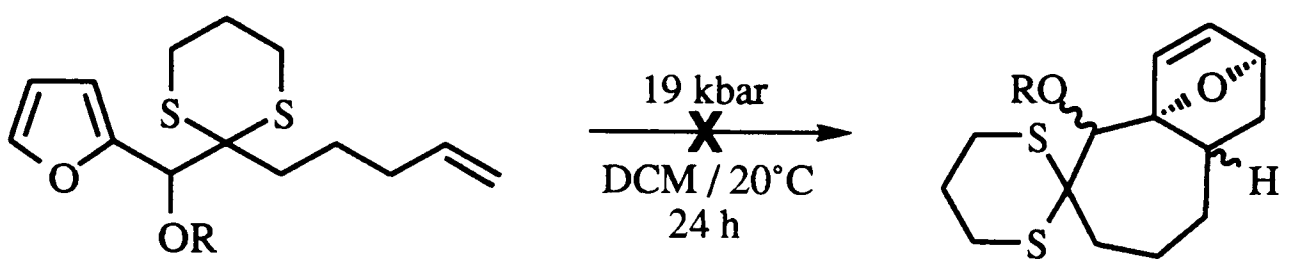
Submitting a solution of either (furylhydroxymethyl)dithiane (**297**) or the silyl protected substrate (**305**) to 19 kbar pressure at 20°C afforded no cyclised material (**306**), allowing only a quantitative recovery of unreacted starting material in both instances (**Scheme 105**).



(**297**) (**305**)

Scheme 104

Hence, even with conformationally more rigid dithiane precursors, (**297**) and (**305**), the IMDAF with an unactivated dienophile was unsuccessful in forming 6, 7-fused carbocycles.



(**297**) R = H
(**305**) R = TBDMS

(**306**) R = H
(**307**) R = TBDMS

Scheme 105

2.5. Summary.

It has been shown that IMDAF substrates containing an unactivated dienophilic moiety were incapable of undergoing cycloaddition. This was true both in the case of the model study (section 2.4.) and in the investigation into the cyclisation of tigliane precursors that contained a functionalised A-ring. The inertness of these substrates to high pressure conditions was considered to be a consequence of the increasing difficulty to affect an intramolecular cycloaddition with a longer tethering chain.

It was therefore considered necessary to either lower the energy of the dienophilic LUMO by electron withdrawal or raise the energy of the diene HOMO by electron donation in order to facilitate the cycloaddition. The failure in the IMDAF of 3-[2-(5-benzylthio)furyl]-2-(pent-4-enyl)cyclopent-2-enone (**245**) implied that it was necessary to activate the dienophilic moiety in order to achieve further success.

CHAPTER THREE

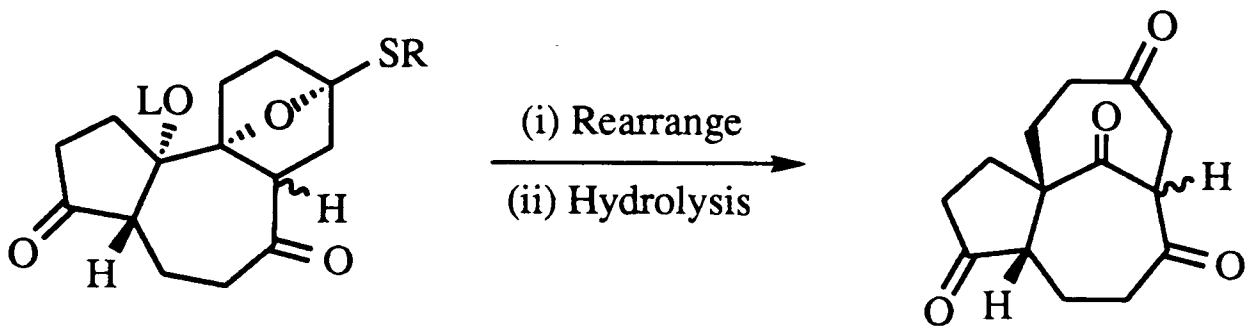
CHAPTER 3 - RESULTS AND DISCUSSION

MODEL STUDY : THE C-RING REARRANGEMENT

3.1. Introduction.

Due to the lack of success of the IMDAF strategy to probe the biomimetic expansion of the 7-oxabicyclo[2.2.1]heptyl framework (section 2.4.), it was decided to construct a second model system based on a known cycloaddition in order to investigate the rearrangement phenomenon.

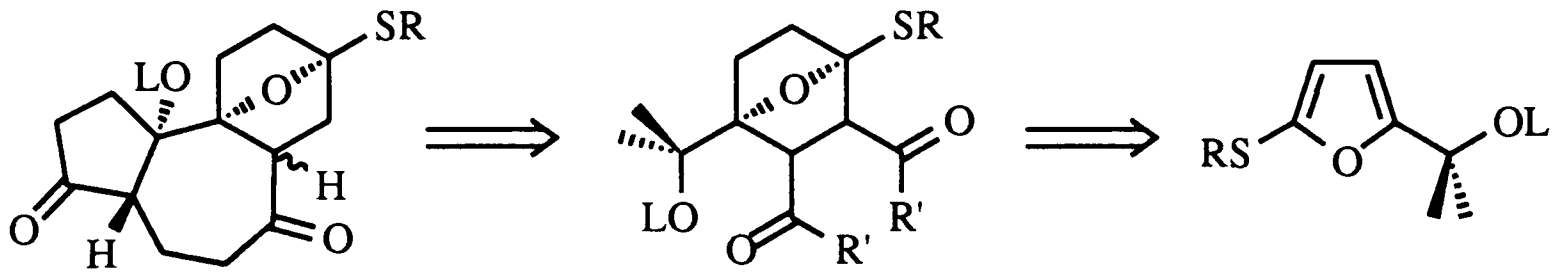
The expansion of the 7-oxabicyclo[2.2.1]heptyl C-ring of a cycloadduct (**308**) to the tertiary A-B α-ring junction carbon would facilitate a biomimetic route to the ingenane skeleton (**309**) (**Scheme 106**).



(308) **(309)**

Scheme 106

Based on the failure to generate the tricyclic system of study (**261**), and the inability to effect cycloaddition with unactivated dienophiles (section 2.4.), it was proposed to simplify the model substrate further. Omitting the A- and B-rings from the model substrate (**308**) and investigating a furyl cycloadduct (**310**) possessing an exocyclic leaving group α- to the bridgehead carbon, would test the biomimetic expansion of these systems. Based on previous studies within the group,[109] it was known that the bicyclic system (**310**) could be constructed by addition of a 5-alkylated 2-phenylthiofuran (**311**) to an activated dienophile (**Scheme 107**).

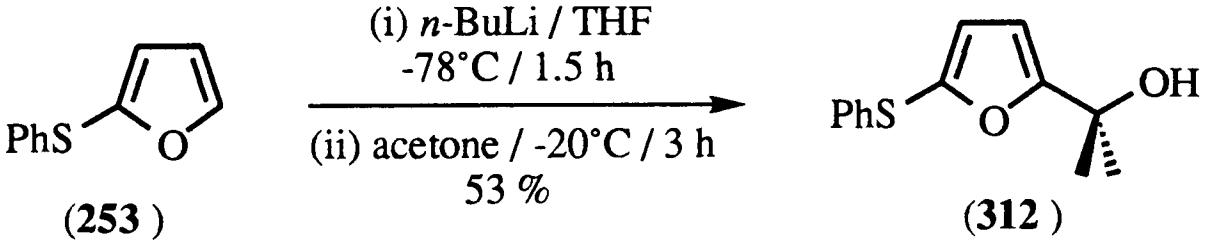


(308) **(310)** **(311)**

Scheme 107

3.2. Generation of Diels-Alder Adducts.

Deprotonating 2-phenylthiofuran (**253**) under standard conditions and quenching the 5-lithiofuran (**266**) with acetone afforded a 53 % yield of (phenylthio)furyl *iso*-propyl alcohol (**312**) (**Scheme 108**). This product not only possessed the oxygenation necessary for introduction of the exocyclic leaving group, but also contained a tertiary centre that was representative of the A-B ring junction present in the cycloaddition rearrangement substrate (**308**).



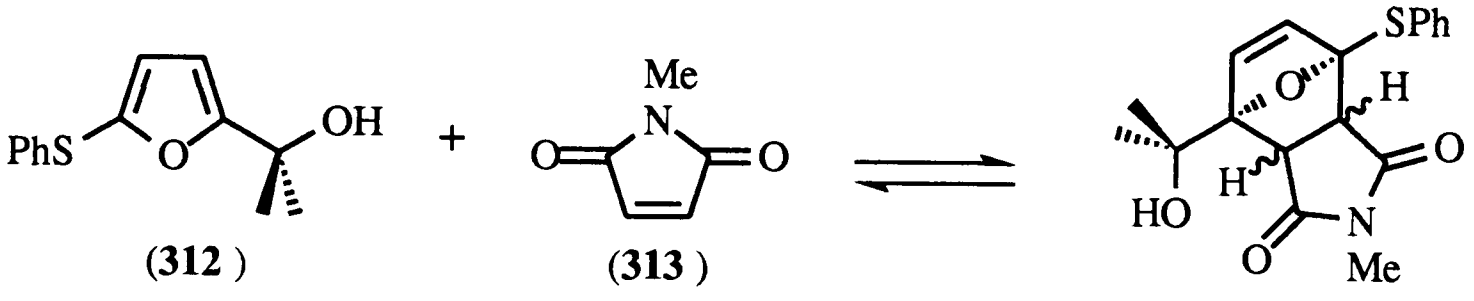
(253) **(312)**

Scheme 108

The product was identified by the presence of a hydroxyl absorption in the i.r. spectrum at 3 246 cm^{-1} and by the disappearance of the 5-furyl proton signal at δ7.60 p.p.m. in the ^1H n.m.r. spectrum. Resonances were observed at δ2.14 and 1.60 p.p.m., that corresponded to the hydroxyl proton, which was exchangeable in D_2O, and the dimethyl functionality respectively. Detection of the demethylated ion $(M-CH_3)^+$ (219) and the deoxygenated species $(M-OH)^+$ (217) by mass spectrometric analysis supported characterisation of the product.

The intermolecular Diels-Alder addition of furyl-*iso*-propyl alcohol (**312**) should furnish cycloadducts suitable for rearrangement studies. *N*-Methylmaleimide (**313**) was chosen as the dienophilic component as a diactivated olefinic bond would produce a favourable cycloaddition equilibrium. Stirring a solution of the phenylthiofuran (**312**) and

N-methylmaleimide (**313**) in dichloromethane in the dark for 6 days led to the appearance of two new sets of doublet resonances at δ3.4 - 3.8 p.p.m. in the ^{1}H n.m.r. spectrum. This corresponded to formation of a cycloadduct (**314**) in the reaction equilibrium in approximately a ratio of 1 : 2 (adduct : starting material) (**Scheme 109**). Increasing the reaction time to 13 days optimised the ratio of cycloadduct : starting material to 3 : 1, after which no further improvement was observed even after 21 days at room temperature.

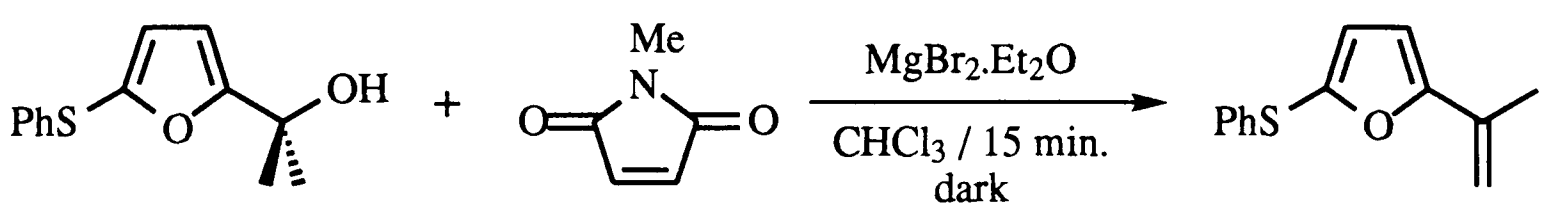


(**312**) (**313**) (**314**)

Scheme 109

In an effort to optimise the isolation of cycloadduct (**314**) a solution of furan (**312**) and *N*-methylmaleimide (**313**) was heated to reflux overnight, but this led to no improvement in the reaction yield.

Promoting the cycloaddition by the use of Lewis acids was similarly unsuccessful. The use of even the mild catalyst zinc iodide resulted in appreciable degradation and the formation of a complex mixture of inseparable products that appeared to contain only a trace of the desired adduct (**314**). Stirring a solution of the Diels-Alder substrates (**312**) and (**313**) in chloroform in the dark in the presence magnesium bromide etherate resulted in the total consumption of starting material after only 15 minutes, and the exclusive formation of the dehydrated furylmethylpropene (**315**) (**Scheme 110**). This product was subsequently found to have been present in the zinc iodide catalysed addition and may explain the lack of success of the Lewis acid mediated approach.

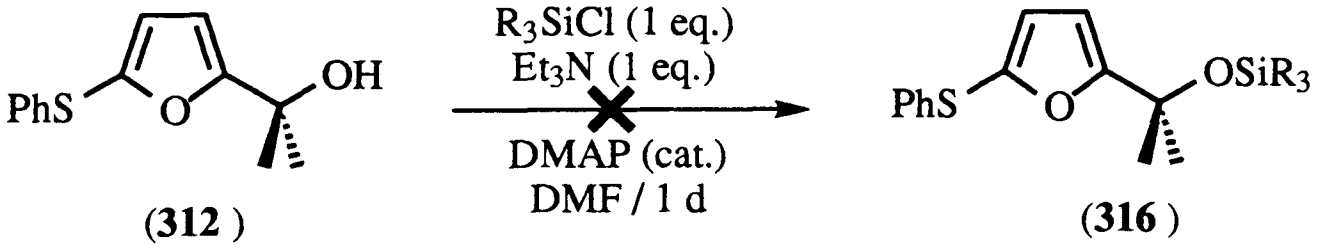


(**312**) (**313**) (**315**)

Scheme 110

The product (**315**) was identified by the presence of only a single methyl singlet resonance at δ2.04 p.p.m. in the ^{1}H n.m.r. spectrum and the appearance of 2 vinylic singlets at δ5.58 and 5.03 p.p.m., that displayed no geminal coupling and corresponded to two vinylic methylene protons. Detection of the parent ion MH^+ (217) by mass spectrometric analysis completed the recognition of the alkene product (**315**).

In order to investigate the Lewis acid mediated cycloaddition it was necessary to protect the labile hydroxyl functionality. Stirring a solution of the alcohol (**312**) in *N, N*-dimethylformamide with 1 equivalent of *tert*-butyldimethylchlorosilane and triethylamine and a catalytic quantity of 4-dimethylaminopyridine resulted only in the recovery of unreacted starting material (**312**) in 95 % yield (**Scheme 111**). Increasing the quantity of base or catalyst or employing trimethylchlorosilane as the silylating agent afforded none of the silyl protected species (**316**) and was indicative of the difficulty to silylate the tertiary furfuryl alcohol (**312**).

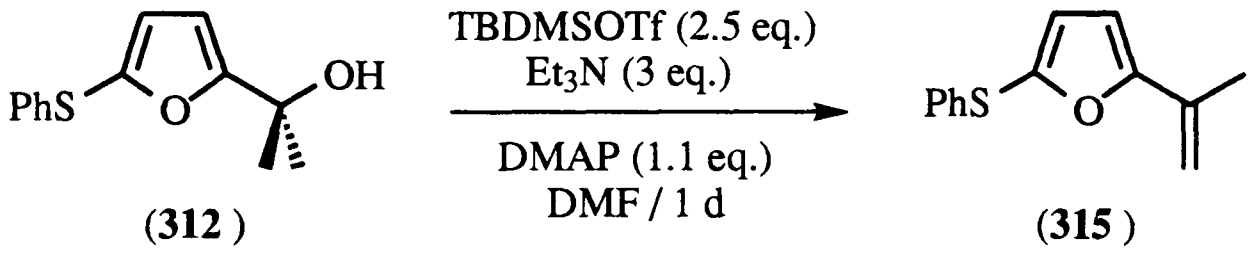


(**312**) (**316**)

Scheme 111

Use of the more reactive silylating agent *tert*-butyldimethylsilyl triflate and stirring with a solution of the alcohol (**312**) in chloroform for 30 minutes at room temperature furnished a complex mixture of products that contained a number of olefinic substituents by ^{1}H n.m.r. spectroscopy. This was indicative of the dehydration or degradation of the furan. Submission of the alcohol (**312**) and *tert*-butyldimethylsilyl triflate to the silylation conditions shown in **Scheme 112** afforded the dehydrated furylpropene (**315**) as the exclusive product in a crude yield of 96 %. The change in course of the reaction was thought to have been a consequence of the increased Lewis acidity of the silylating agent.

Based on the failure to silylate the tertiary hydroxyl (**312**), the Lewis acid-mediated cycloaddition was abandoned and alternative reaction conditions were investigated.



(**312**) (**315**)

Scheme 112

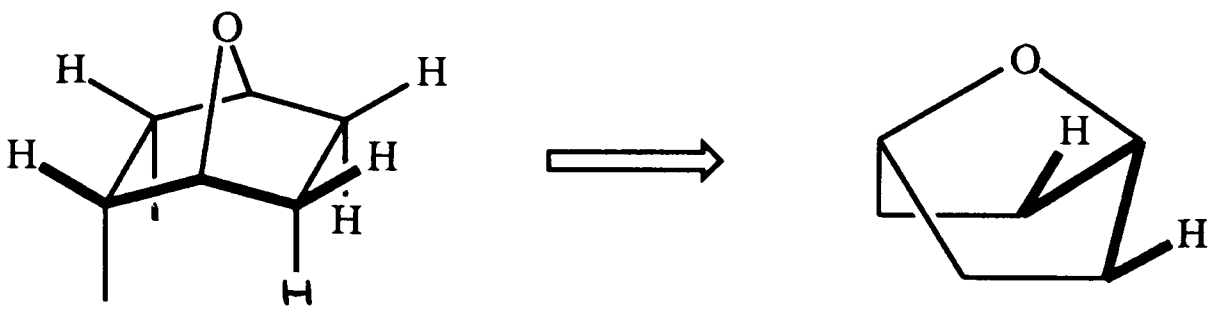
Submitting a solution of the Diels-Alder substrates (**312**) and (**313**) in dichloromethane to 19 kbar pressure for 24 hours at 20°C afforded cycloadduct (**314**) in essentially quantitative crude yield. Due to the reversible nature of the Diels-Alder reaction, the return of the solution of 7-oxatricyclodecene (**314**) to ambient pressure rendered the product unstable with respect to cycloreversion (**Scheme 109**). For this reason no attempt to purify adduct (**314**) was made as exposure to silica appeared to catalyse reversion to starting materials and standing at room temperature resulted in the disappearance of adduct (**314**) within 24 hours.[109]

The product was identified by ^{1}H n.m.r. spectroscopy. Doublet resonances with coupling constants of 5.6 Hz were observed at δ6.42 and 6.16 p.p.m., corresponding to the two mutually coupled bridgehead protons. Finally the presence of two methyl group signals, at δ1.48 and 1.44 p.p.m., was indicative of diastereotopy and completed characterisation of the product and the conclusion that the cycloaddition had been successful.

In order to prevent the cycloreversion of adduct (**314**), and to permit further characterisation and study, the olefinic bond was hydrogenated in ethyl acetate at 1 atmosphere pressure over palladium on carbon (10 %) to afford an 87 % yield of the reduced cycloadduct (**317**) over two steps (**Scheme 113**).

The product was identified by observation of hydroxyl and imide absorptions, at 3 501 and 1 775 cm^{-1} respectively, in the i.r. spectrum, by the disappearance of vinylic proton resonances at δ3.76 and 3.48 p.p.m. in the ^{1}H n.m.r. spectrum and appearance of four saturated methylene signals between δ2.0 and 1.6 p.p.m., corresponding to C-8 and C-9 *exo* and *endo* protons, and by the detection of the parent ion MH$^+$ (348) and the dehydrated ion species (M-OH)$^+$ (330) in the mass spectrum. The stereochemistry of cycloaddition was inferred by examination of the 500 MHz ^{1}H n.m.r. spectrum that showed four-bond

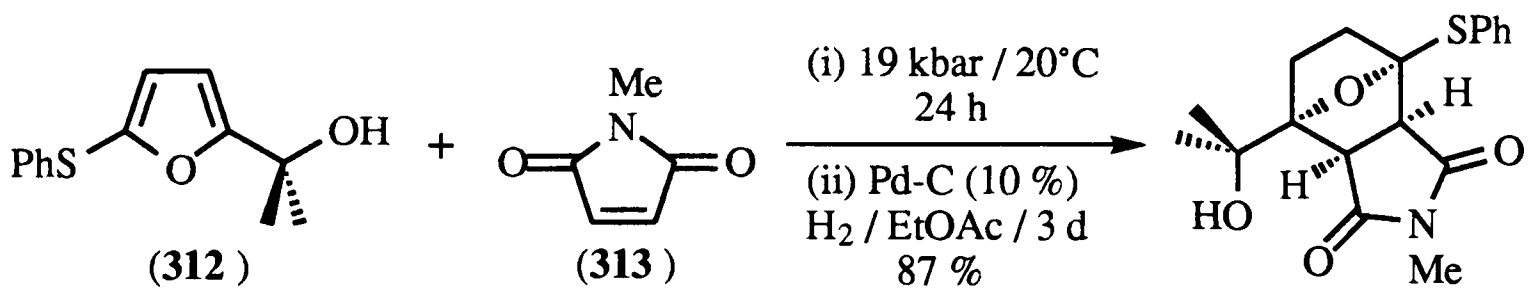
couplings, ^4J 2 Hz, across the oxabicycloheptane ring (**317a**). In this conformationally locked system, only *exo* orientated protons possess the stereochemical coplanarity necessary for W-coupling to be observed (**Figure 3**).[126]



(**317a**) (**317a**)

Figure 3

Thus, the observation of four-bond couplings, of magnitude 2.3 and 2.1 Hz, between protons α- to the imide function and the 8- and 9-*exo* protons of the oxabicyclic system indicated an *endo* stereochemistry of cycloaddition (**Scheme 113**), that was in accordance with the high pressure *endo* selectivity observed by Kotsuki in intermolecular furan additions[127] and against the usual *exo* stereoselectivity observed under thermodynamic control at ambient pressure.

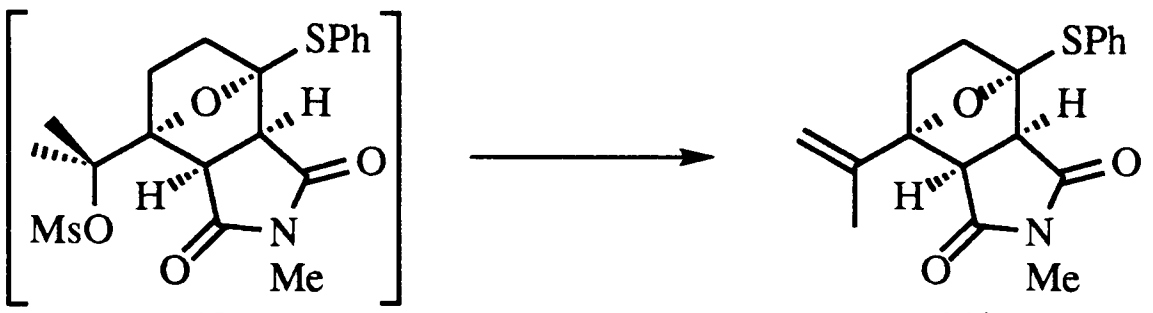


Scheme 113

3.3. C-Ring Rearrangement Studies.

With the technology in hand to stereospecifically generate the cycloadduct (**317**), and prevent cycloreversion by hydrogenation of the oxabicyclo[2.2.1]heptene double bond, it was now possible to investigate the biomimetic migration. It was hoped that generation of a carbonium ion α- to the ether bridgehead position would facilitate a skeletal rearrangement, permitting the isolation of simplified ingenane analogues.

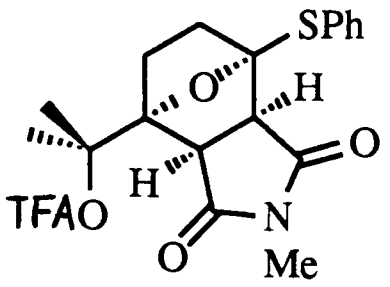
The introduction of a leaving group was attempted by formation of mesylate (**318**). Stirring a solution of alcohol (**317**) and two equivalents of methanesulphonyl chloride in pyridine in the presence of 0.2 equivalents of 4-dimethylaminopyridine for 24 hours at room temperature led to the isolation of a new product (**319**) that contained a vinylic methylene function by interpretation of the ^1H n.m.r. spectrum. It appeared that generation of the methanesulphonate (**318**) had been successful and that under the basic reaction conditions loss of the labile function was spontaneous. However no rearrangement was observed and only the product of the eliminative process (**319**) isolated (**Scheme 114**). Based on the failure to isolate the sulphonate intermediate (**318**), an attempt was made to introduce a less labile leaving group.



(**318**) (**319**)

Scheme 114

The trifluoroacetate ester (**320**) of *endo*-oxatricyclodecyl alcohol (**317**) was prepared in 85 % yield by refluxing with 10 equivalents of trifluoroacetic anhydride in dichloroethane for 7 hours. The crude reaction mixture indicated almost exclusive formation of a single product and a trace of a side product, shown by ^1H n.m.r. spectroscopy to contain a vinylic methylene function, indicative of elimination to propene (**319**).



(**320**)

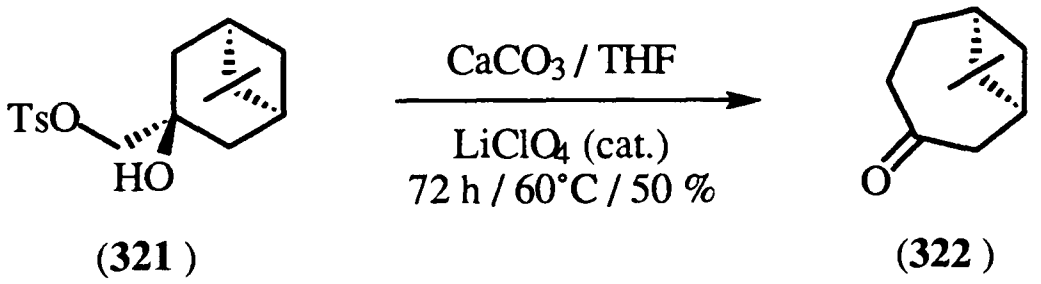
The esterified product (**320**) was identified by the disappearance of the hydroxyl absorption in the i.r. spectrum, by a downfield shift of 0.4 p.p.m. of the dimethyl resonances

in the ^1H n.m.r. spectrum, indicative of deshielding by the esterified hydroxyl, and by mass spectroscopic detection of the parent ions MNH_4^+ (461) and MH^+ (444) and the eliminated species $(MH\text{-}CF_3CO_2H)^+$.

The trace of propene (**319**) in the crude reaction mixture indicated that elimination of the leaving group was able to occur under the reaction conditions. However, increasing the reaction time led to no isolation of rearranged products and only increased the proportion of elimination to alkene (**319**) that was occuring.

Considering the failure in expanding the 7-oxabicycloheptene framework, by migration to the α-carbonium ion generated from mesylate (**318**) or triflate (**320**), it was decided to investigate alternative rearrangement conditions.

Tubiana and Waegell accessed bicyclo[4.1.1]octanone (**322**) by pinacolic rearrangement of bicycloheptane (**321**) (**Scheme 115**).[128] Based on the structural similarities between this system and the model substrates (**317**) and (**320**), the lithium perchlorate catalysed pinacolic ring expansion method of Corey was investigated.[129]

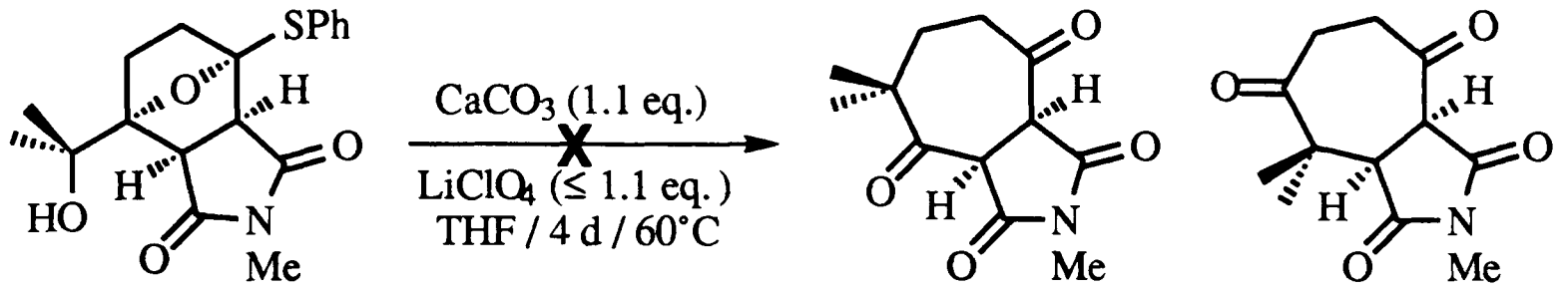


(**321**) (**322**)

Scheme 115

Heating a solution of the alcohol (**317**) in tetrahydrofuran to 60°C over calcium carbonate with 0.1 equivalents of lithium perchlorate afforded a quantitative recovery of unreacted starting material after 1 day. This result remained unchanged by employing one equivalent of the catalyst and increasing the reaction time to 4 days and resulted in a reduction in the (**317**) recovery and isolation of the dehydrated product (**319**) (**Scheme 116**).

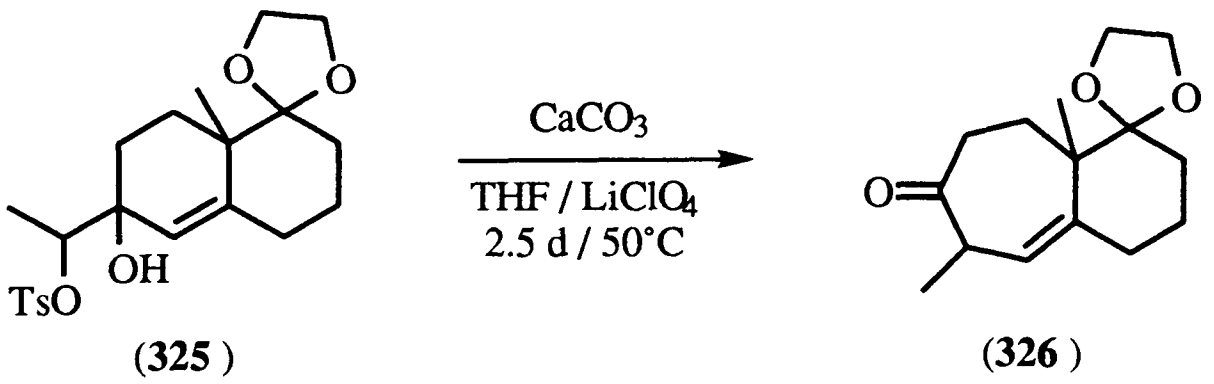
Submitting the trifluoroacetate (**320**) to the pinacolic rearrangement conditions of Corey,[129] reaction with calcium carbonate (1.2 equivalents) and a catalytic quantity of lithium perchlorate in tetrahydrofuran at 60°C for 5 days, furnished unreacted starting material in 59 % yield that was contaminated with the dehydration product (**319**).



(**317**) (**323**) or (**324**)

Scheme 116

The failure to effect rearrangement was attributed to enhanced stability of the tertiary carbonium ion formed by leaving group expulsion in the systems of study, relative to the primary tosylate (**321**) of Tubiani and Waegell (**Scheme 115**)[128] and secondary system (**325**) of Corey employed in the synthesis of longifolene (**Scheme 117**).[129] It was also postulated that the increased structural rigidity of the tricyclic rearrangement substrates, (**317**) and (**320**), would inhibit the migration.

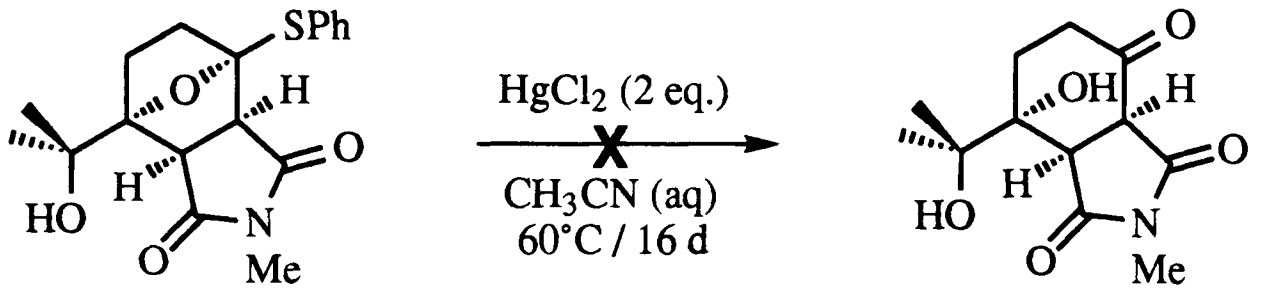


(**325**) (**326**)

Scheme 117

Preference for the more rapid elimination to propene (**319**) to occur rather than cleavage of the oxabicyclic skeleton prevented isolation of the desired products, (**323**) or (**324**). Hence it was decided to cleave the oxygen bridge of substrate (**317**) prior to submission to rearrangement conditions in order to form a system more representative of Corey's pinacolic precursor (**325**) (**Scheme 117**) and to enable the ring expansion.

Treatment of the oxatricyclodecyl alcohol (**317**) with mercuric chloride in aqueous acetonitrile at 60°C for 16 days failed to mediate cleavage of the oxygen bridge to diol (**327**) and only led to recovery of unreacted starting material in 86 % yield (**Scheme 118**).



(**317**) (**327**)

Scheme 118

The failure of the ring opening reaction, known to be successful in oxygen bridge cleavage of benzylthio- cycloadducts,[97] was attributed to the reduced availability of the sulphide lone pairs, due to delocalisation into the phenyl ring, that prevented formation of the sulphonium ion necessary for hydrolysis. It was thought that this phenomenon, coupled with the propensity for the tertiary carbocation to eliminate, was responsible for the inability of model substrates (**317**) and (**320**) to mimic the tigliane-ingenane C-ring expansion to afford rearranged products (**323**) or (**324**). Based on this conclusion, it seemed unlikely that the model study would yield success without structural modification and so further investigation was abandoned in favour of formation of phorboid analogues that poss essed the tigliane skeleton.

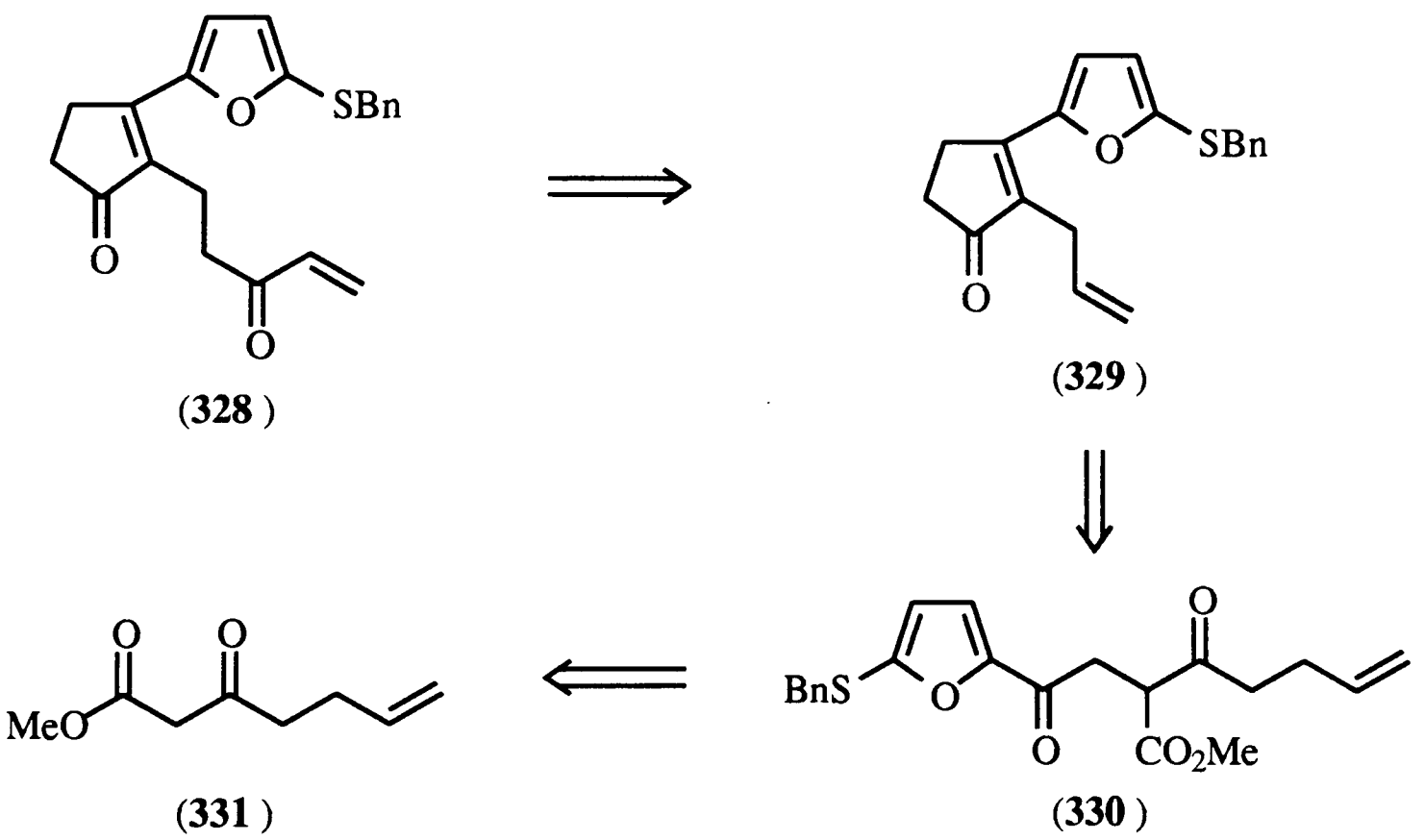
CHAPTER FOUR

CHAPTER 4 - RESULTS AND DISCUSSION

IMDAF OF ACTIVATED DIENOPHILIC SUBSTRATES

4.1. Elaboration of an Allyl Cyclopentenone.

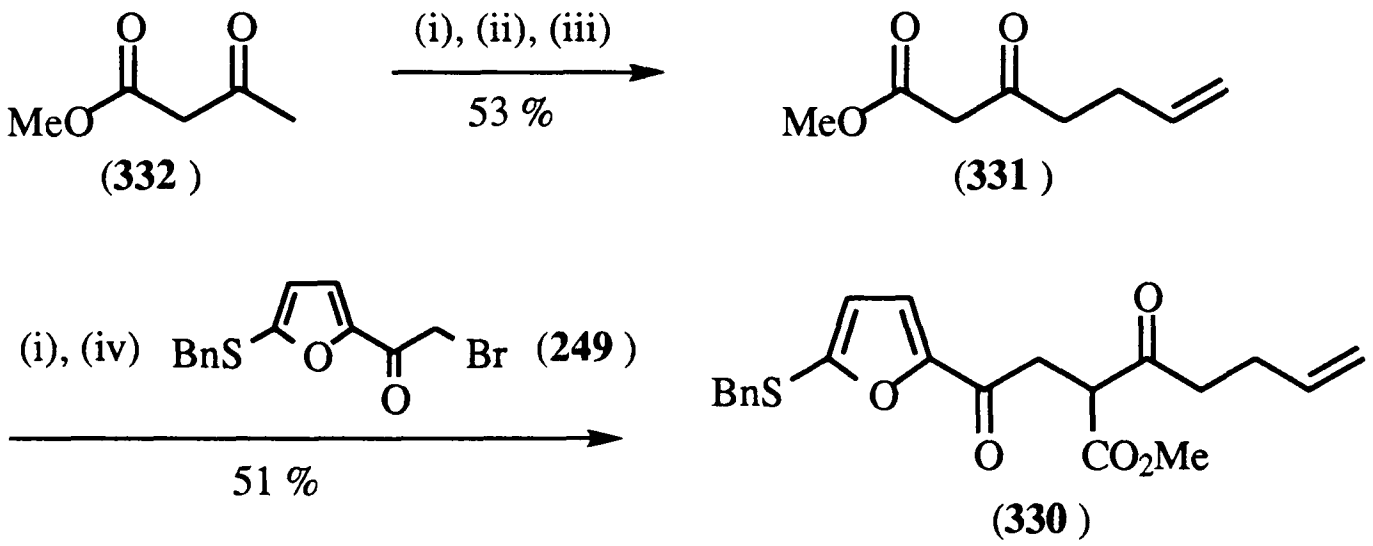
Based on the model studies (section 2.4. and chapter 3), it was apparent that the dienophilic component needed to be activated in order to generate a favourable equilibrium in the IMDAF. Previous studies within the group have shown that an α, β-unsaturated ketone, as an activated dienophile, was capable of promoting cycloaddition and facilitating isolation of phorboid adducts.[92] Adopting a similar approach to introduce the dienophile, it was envisaged that furylcyclopentenone (**328**) could be constructed from the allyl substituted precursor (**329**) formed by the aldol cyclisation protocol (**Scheme 119**), successful in the synthesis of pentenyl systems (section 2.3.3.).



Scheme 119

The functionalised acetoacetate (**331**) was prepared using the established procedure[82] by alkylating the dianion of methyl acetoacetate (**332**), formed by the successive action of sodium hydride and *n*-butyllithium in tetrahydrofuran, with allyl bromide (**Scheme 120**). The methyl heptenoate (**331**) was furnished in 53 % yield and identified by comparison of

spectroscopic data with recorded information[82] and those of the previously characterised alkenyl acetoacetate derivative (**226**). Deprotonating the product with sodium hydride in tetrahydrofuran and alkylating with benzylthio(bromoacetyl)furan (**249**) afforded a 51 % yield of the (furoylmethyl)heptenoate (**330**) after 2 hours at 0°C (**Scheme 120**).

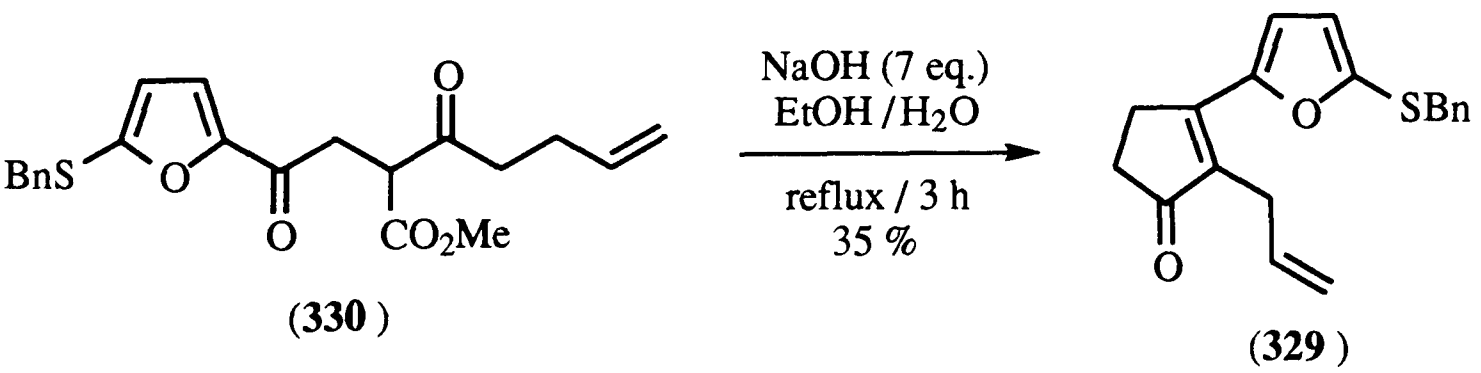


(i) NaH (1 equiv.) / THF / 0°C; (ii) *n*-BuLi (1 equiv.); (iii) Allyl bromide; (iv) 0°C / 2 h.

Scheme 120

The product was identified by observation of three carbonyl vibrations in the i.r. spectrum at 1 746, 1 721, and 1 674 cm^{-1}, the appearance of three sets of ABX resonances in the ^1H n.m.r. spectrum at δ4.20, 3.55, and 3.34 p.p.m., and detection of the parent ion MH^+ (387) and the tropylium ion by mass spectrometry.

The intramolecular aldol cyclisation was effected by refluxing an aqueous ethanolic solution of substrate (**330**) with 7 equivalents of sodium hydroxide for 3 hours to afford furylcyclopentenone (**329**) in 35 % yield (**Scheme 121**).



Scheme 121

The product was identified by the presence of only a single carbonyl absorption in the i.r. spectrum at 1 684 cm^{-1}. In the ^1H n.m.r. spectrum the 3-furyl proton signal had been shifted upfield by 0.4 p.p.m. and resonances were observed at δ2.87 and 2.53 p.p.m., data indicating successful formation of the 3-furylcyclopentenone ring. In addition, the allyl methylene proton signal had changed from a doublet of triplets at δ2.40 to a doublet at δ3.31p.p.m. as a consequence of the intramolecular cyclisation. Characterisation was completed by detection of the parent ion MH^+ (311) and the tropylium ion by mass spectrometric analysis.

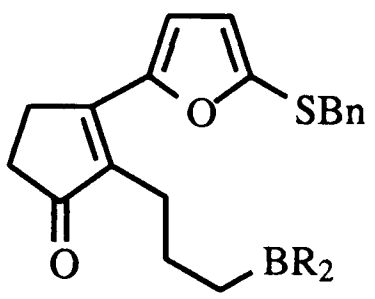
Although intramolecular cyclisation had been effective in forming only a single product (**329**), the reaction yield was low. Increasing the quantity of sodium hydroxide and reaction time appeared to reduce the yield of product. Conducting the reaction at room temperature slowed down the rate of product formation and reduced the yield to only 14 % and so the use of alternative conditions was investigated.

Submitting an aqueous ethereal solution of the cyclisation precursor (**330**) and sodium hydroxide to the reaction conditions failed to furnish the product and only afforded unreacted starting material at room temperature. The action of sodium *tert*-butoxide in *tert*-butanol at 50°C was also unsuccessful, although the conditions resulted in hydrolysis of the methyl ester function. Finally, in an attempt to isolate the 1, 4-diketone intermediate, a solution of substrate (**330**) in wet dimethyl sulphoxide was heated to 140°C for 2 hours in the presence of sodium chloride according to the decarbomethoxylation conditions of Krapcho.[130] However, only an incomplete recovery of starting material was obtained from the reaction mixture, accompanied with appreciable degradation, and so attempts to improve on the disappointing cyclisation yield were abandoned.

In an effort to elaborate the allyl chain to the activated dienophile, cyclopentenone (**329**) was subjected to conditions for hydroboration. It was proposed that chemoselective attack of the less hindered terminal olefin over the tetrasubstituted double bond, conjugated with furan and carbonyl functionality, should be possible with even less sterically sensitive hydroborating agents. Treatment of a solution of allylcyclopentenone (**329**) in tetrahydrofuran with one equivalent of borane-tetrahydrofuran complex, followed by an

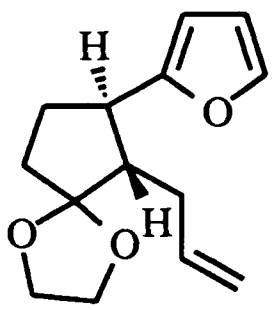
oxidative work up procedure, afforded after 3 hours at room temperature unreacted starting material in 69 % yield. The presence of an unidentified contaminant was noted, and it appeared to correspond to formation of *n*-butanol by the presence of two triplet signals in the ^{1}H n.m.r. spectrum, at δ3.66 and 0.94 p.p.m., corresponding to the terminal carbon proton resonances. Increasing the reaction time to 24 hours still failed to hydroborate the olefin.

To find whether it was the formation of the alkylborane (**333**) that was the problematic step, the oxidative work-up procedure was omitted and an aqueous treatment employed. In this instance, only unreacted starting material and the contaminant were isolated from the reaction and no evidence for alkylborane formation was observed.

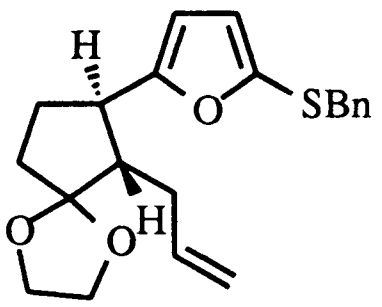


(**333**)

Failure of the reaction was attributed to the presence of the α, β-unsaturated ketone moiety, based on the report that furylcyclopentanone ethylene ketal (**196**)[92] and the corresponding benzylthiofuryl substrate (**334**)[97] have been hydroborated in previous studies within the group.



(**196**)

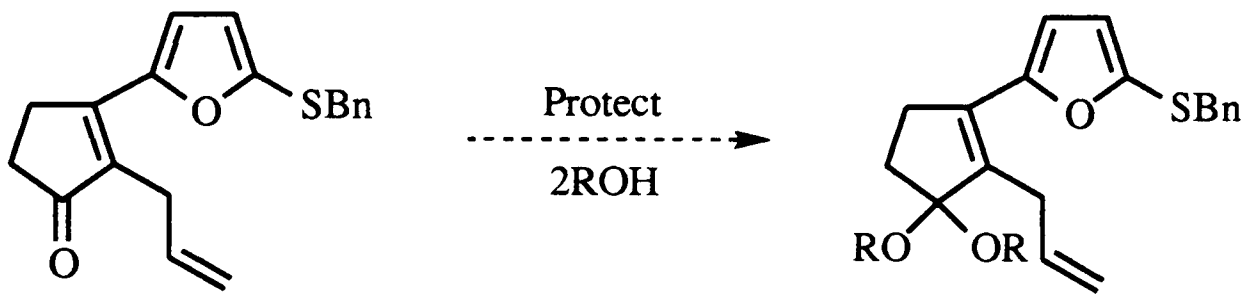


(**334**)

Since it seemed unlikely that the tetrasubstituted double bond was interfering with the reaction course and reacting in preference to the terminal olefin, it was assumed that it was the presence of the carbonyl group that was preventing the reaction. Coordination of the Lewis basic carbonyl oxygen to the borane complex would reduce the electrophilicity of the

reagent. Since the terminal olefin was removed from this site of coordination, it was postulated that the addition of more than one equivalent of the hydroborating agent could facilitate reaction. Employing a large excess of the borane-tetrahydrofuran complex (10 equivalents) resulted in the total consumption of starting material by t.l.c. analysis after two hours at room temperature. However, oxidative work up with sodium hydroxide and hydrogen peroxide resulted only in isolation of the contaminant and degraded material.

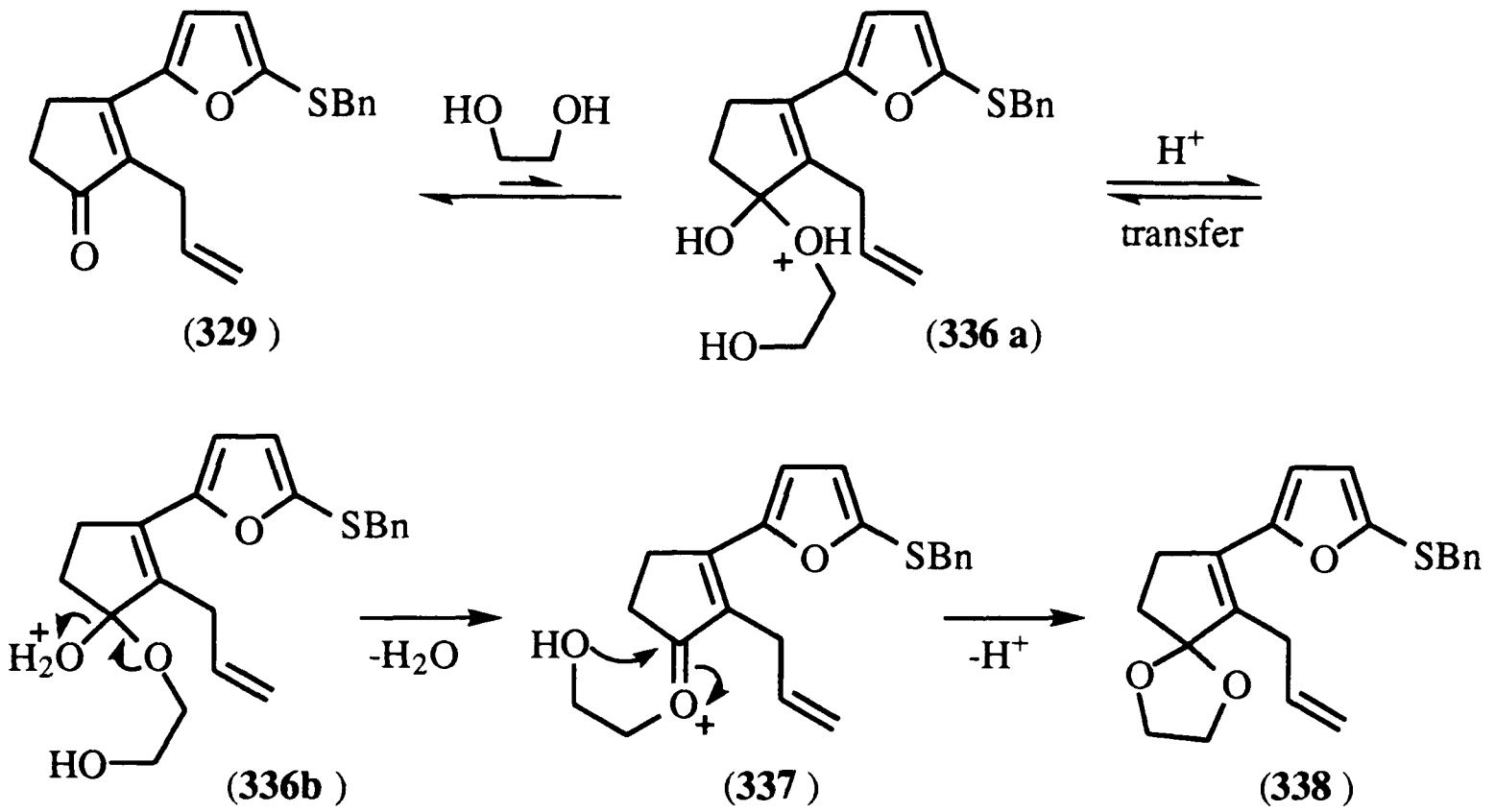
Based on these observations it was apparent that the cyclopentenone moiety was preventing hydroboration. It was therefore considered that ketal protection of the carbonyl in (**335**) should reduce the oxygen Lewis basicity (**Scheme 122**) and would generate a closer analogue of the successful hydroboration substrate studied previously within the group, the cyclopentanone ethylene ketal (**334**).[97]



(**329**) (**335**)

Scheme 122

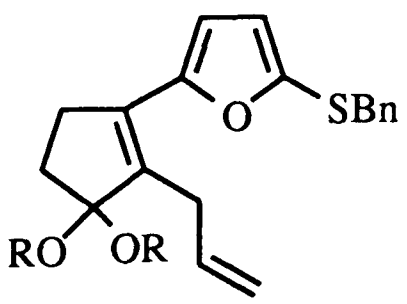
Refluxing a solution of the furylcyclopentenone (**329**), ethane-1, 2-diol, and a catalytic quantity of *p*-toluenesulphonic acid in benzene for 6 days, with the azeotropic removal of water, only resulted in the isolation of impure unreacted starting material. The resistance of the substrate to standard ketalisation conditions was attributed to the conjugation of the enone function with the 5-benzylthiofuran establishing an unfavourable equilibrium concentration of hemiacetal (**336a/b**). This would inhibit dehydration to oxonium species (**337**) and thus hinder ketal (**338**) formation (**Scheme 123**).



Scheme 123

In an effort to drive the equilibrium to the desired product (**338**) the ketalisation was repeated and the solvent evaporated from the reaction overnight at 120°C (bath temperature). However, under these conditions only polymeric material was observed.

Formation of the alternative dimethyl ketal (**339**) was similarly unsuccessful. Stirring a solution of cyclopentenone (**329**) and trimethylorthoformate in methanol over ammonium chloride[131] for 4 days or refluxing the mixture for 2 days only furnished a quantitative recovery of starting material. Employing a sulphonic acid resin, Amberlyst-15®, to catalyse the ketalisation according to the conditions of Patwardhan and Dev[132] similarly afforded no return of product (**339**) and *p*-toluenesulphonic acid induced the complete degradation of the substrate. This may reflect the thermodynamic stability of a furyl enone function.

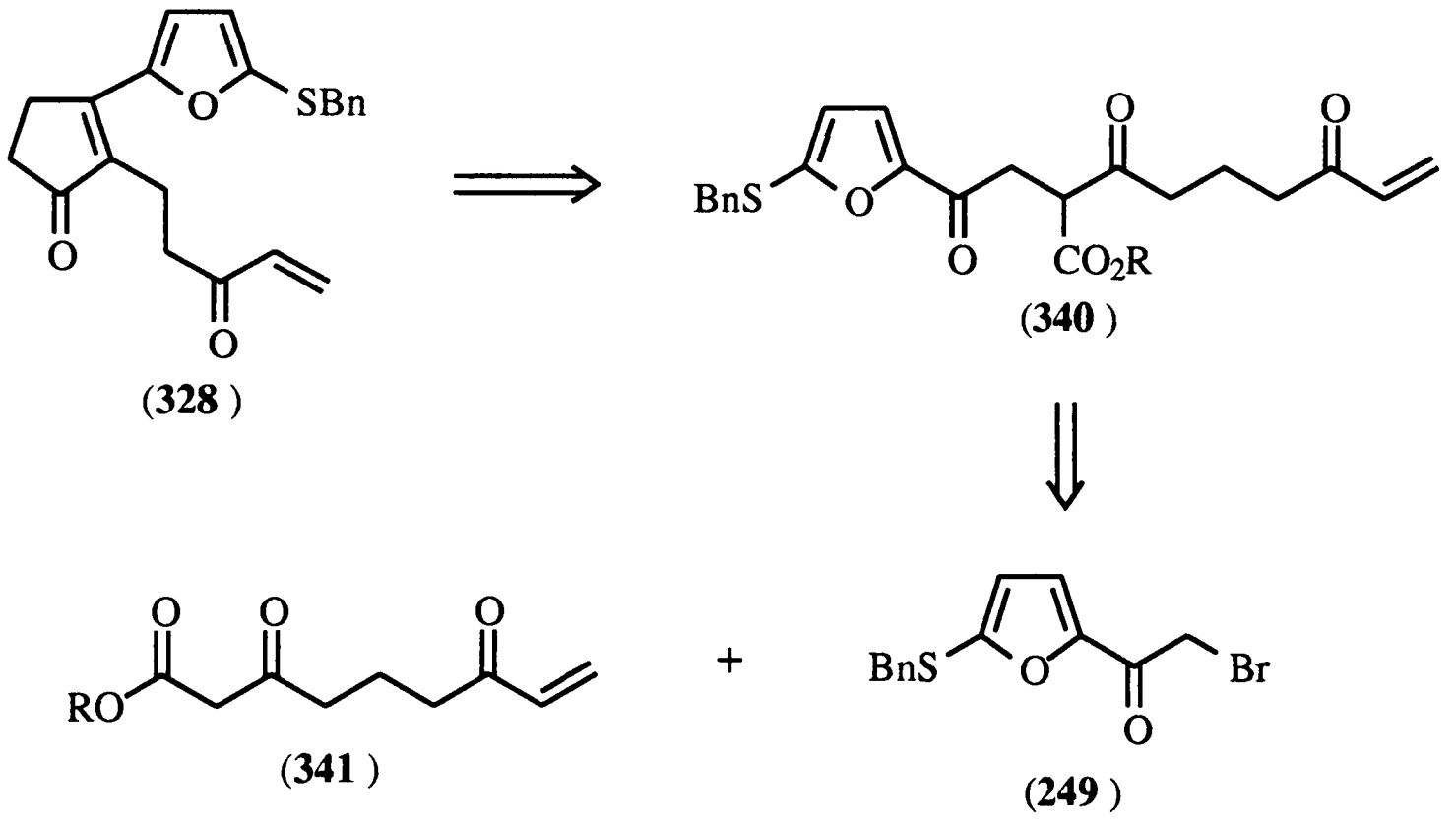


(**339**) R = Me

Due to the resistance of these systems to acid catalysed ketalisation procedures and their propensity to polymerise under the action of stronger catalysts it was concluded that carbonyl protection was not possible under these conditions. Thus it was proposed to circumvent the problem of dienophile elaboration by constructing the tether before coupling to a furyl component.

4.2. Elaboration of an Acetoacetate Derivative.

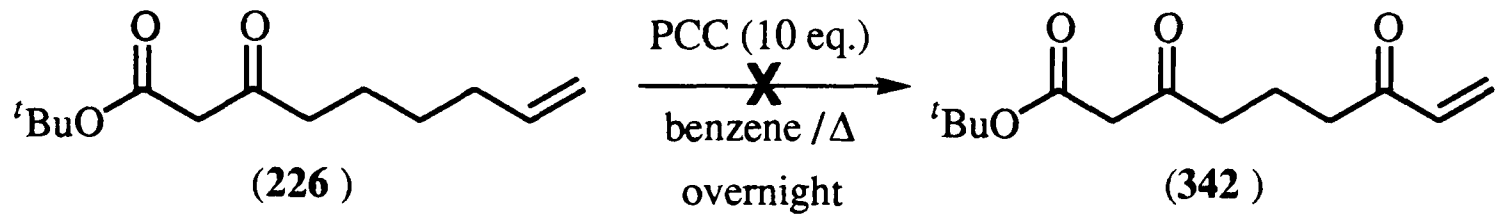
The introduction of the dienophile early in the synthetic sequence required generation of an acetoacetate (**341**) possessing an activated α, β-unsaturated alkyl keto chain. The coupling of this derivative with the (bromoacetyl)furan (**249**) would furnish the desired activated IMDAF precursor (**328**) and could facilitate cycloaddition (**Scheme 124**).



Scheme 124

An attempt was made to access the enone (**342**) directly by the allylic oxidation of *tert*-butylnonenoate (**226**) generated in the synthesis of alkenylcyclopentenones (**221**) and (**245**) (section 2.2.1. and 2.3.3.). Pyridinium chlorochromate had been employed as an effective reagent for allylic oxidation in steroid systems, forming α, β-unsaturated ketones in high yields.[133] Subjecting the acetoacetate derivative (**226**) to the conditions of Parish,[133] refluxing overnight in a benzene solution with 10 equivalents of pyridinium chlorochromate,

led to the complete degradation of starting material and no isolation of the required product (**342**) (**Scheme 125**). Failure was attributed to the presence of a secondary activated methylene position.



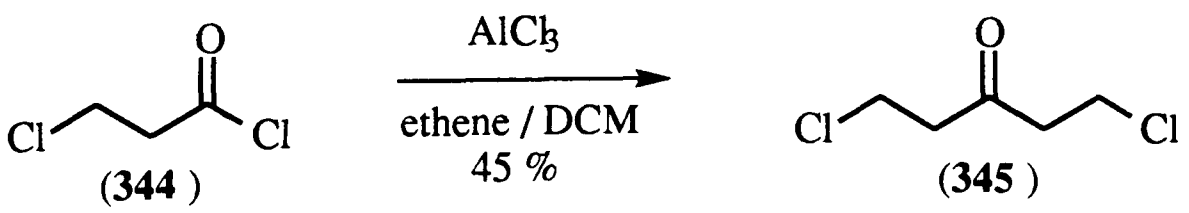
(**226**) (**342**)

Scheme 125

Applying the milder system of Chandrasekaran, also used in steroid oxidation, and stirring a solution of the substrate and *tert*-butylhydroperoxide in benzene over pyridinium dichromate and Celite® for 24 hours[134] furnished only a 91 % recovery of unreacted starting material.

Since it was clear that the oxidation of nonenoate (**226**) would bring little success in producing the enone (**342**) an alternative approach was investigated. Based upon a retrosynthetic C-4 / C-5 disconnection, it was considered that the required derivative (**342**) might be prepared by quenching an acetoacetate dianion with divinyl ketone (**343**). This alkylating agent was first synthesised by Jones and Taylor, invoking a base catalysed dehydrohalogenation of 1, 5-dichloro-3-pentanone (**344**).[135]

The precursor of Baddeley, Taylor, and Pickles, (**345**), was generated according to the literature procedure by a Lewis acid catalysed Friedel-Crafts type aliphatic alkylation of an alkene.[136] Dry ethene was passed through a solution of 3-chloropropanoyl chloride (**344**) and aluminium chloride in dichloromethane below -5°C (**Scheme 126**). Reaction was complete after 3 hours and was followed by i.r. spectroscopy, observing the disappearance of the acid chloride substrate absorption at 1 795 cm^{-1} and appearance of a ketone absorption at 1 719 cm^{-1}.

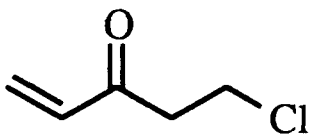


(**344**) (**345**)

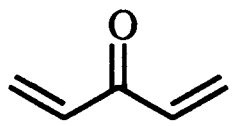
Scheme 126

The dichloropentanone (**345**) was obtained in 45 % yield and was identified by the appearance of two triplets in the ^1H n.m.r. spectrum, at δ3.75 and 2.95 p.p.m., that corresponded to resonances of methylene ketone and methylene chloride protons, and by detection of the parent ion MNH_4^+, containing mixed isotopes of chlorine, by mass spectrometric analysis.

Dehydrohalogenation according to the original procedure of Jones and Taylor, by distilling dichloropentanone (**345**) from an excess of anhydrous sodium carbonate,[135] resulted in incomplete elimination and the isolation of a mixture of unreacted starting material (**345**), the monodehydrohalogenated product (**346**), and divinyl ketone (**343**).



(**346**)



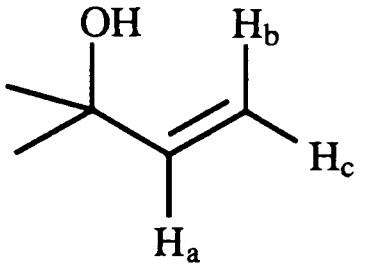
(**343**)

Applying the alternative conditions of Jung and distilling the product at 150°C under water aspirator pressure[137] afforded complete dehydrohalogenation to divinyl ketone (**343**). However, rather than achieving pure material from the reaction as indicated by the report, co-distillation of the quinoline base (b.p. 113-114°C / 17 mmHg) was found to occur under the reaction conditions. This was confirmed by ^1H n.m.r. spectroscopic analysis. Attempts to remove this distillate by washing with aqueous copper (II) sulphate solution led to the total destruction of divinyl ketone (**343**). Employing a slightly lower reaction temperature (110-140°C (bath temperature) / 30 mmHg) prevented co-distillation but resulted in incomplete conversion and the isolation of the monodehydrohalogenated vinyl ketone (**346**) as a minor bi-product. As the required product predominated in the reaction this became the adopted procedure, furnishing divinyl ketone (**343**) in 39 % yield.

Identification was possible by observation of a carbonyl absorption at 1 674 cm^{-1} and an olefinic vibration at 1 611 cm^{-1} in the i.r. spectrum and by double-doublet vinylic proton resonances, at δ6.65, 6.32, and 5.89 p.p.m., in the ^1H n.m.r. spectrum of the product.

Quenching the dianion of methyl acetoacetate (**332**), formed by the successive action of sodium hydride and *n*-butyllithium at 0°C in tetrahydrofuran, with divinyl ketone (**343**)

simply resulted in an 86 % recovery of unreacted acetoacetate starting material with complete degradation of alkylating agent and no evidence of addition. Conducting the reaction at -78°C and quenching at this temperature after only 40 minutes still did not lead to isolation of enone (**341**). ^{1}H n.m.r. spectroscopic analysis indicated a predominance of acetoacetate (**332**) and a trace of an alternative product with evidence of vinylic incorporation. Observation of a double-doublet at δ5.90 p.p.m. and doublets at δ5.30 and 5.15 p.p.m., mutually coupled but exhibiting no external couplings, indicated the presence of an α-quaternary centre (**Figure 4**).



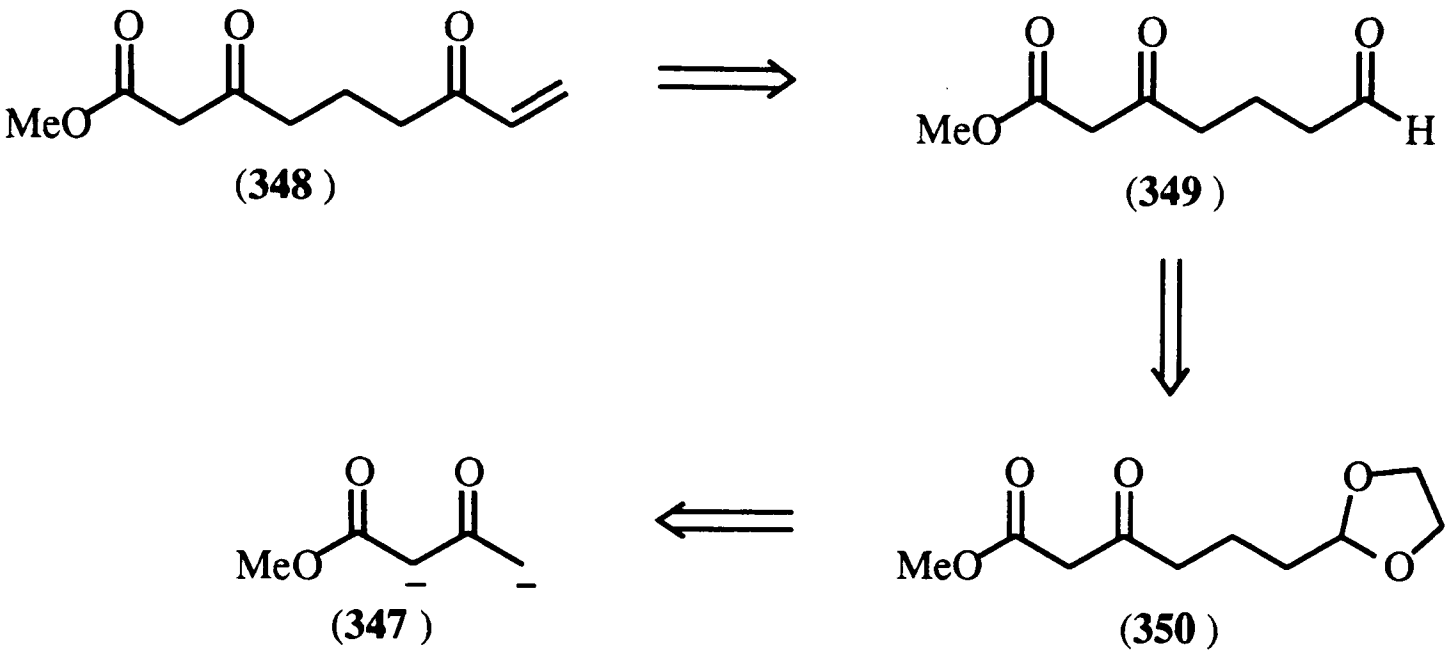
H_a : 5.90 (1H, dd, *J* 17.3, *J'* 10.6 Hz)
H_b : 5.30 (1H, d, *J* 17.3 Hz)
H_c : 5.15 (1H, d, *J* 10.6 Hz)

Figure 4

Thus the α, β-unsaturated ketone must have been attacked in the degradation pathway, either by secondary 1, 2-addition of the nucleophilic reagent or by an intramolecular cyclisation mechanism. The problem of chemoselectivity and instability of the product under the reaction conditions confirmed the invalidity of the approach.

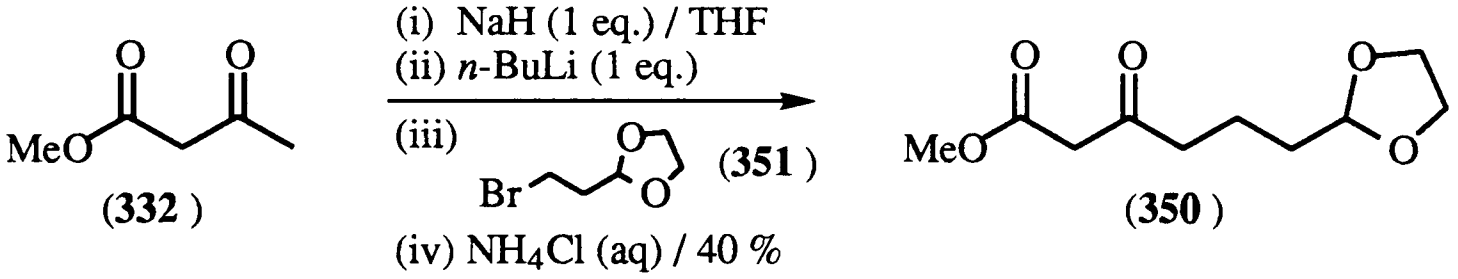
Addition of the dianion (**347**) to the dichloropentanone precursor (**345**) at 0°C was similarly unsuccesssful, resulting in an eliminative process over addition, furnishing predominantly the monodehydrohalogenated product (**346**).

Investigating an alternative C-7 / C-8 retrosynthetic disconnection of the target nonenoate (**348**) suggested synthesis by nucleophilic addition of an organometallic to aldehyde (**349**), a similar method of dienophilic elaboration to those studied previously within the group in derivation of cyclopentanyl substrates (see section 1.5.).[92] In addition, this approach possessed potential for the construction of both mono- and bis-activated dienophiles by variation of nucleophile, utilising both vinyl and alkynoate organometallic reagents.[95] It was envisaged that aldehyde (**349**) could be prepared by deprotection of dioxolane (**350**), the product of a terminal electrophilic addition to the methyl acetoacetate dianion (**347**) (**Scheme 127**).



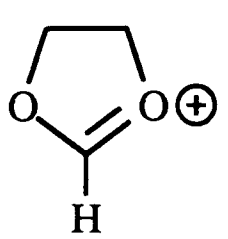
Scheme 127

The dianion (**347**) was generated by the successive action of sodium hydride and *n*-butyllithium on methyl acetoacetate (**332**) in tetrahydrofuran below 0°C. Quenching with 2-(2-bromoethyl)-1, 3-dioxolane (**351**) afforded the required dioxolane (**350**)[82] in 40 % yield (**Scheme 128**).



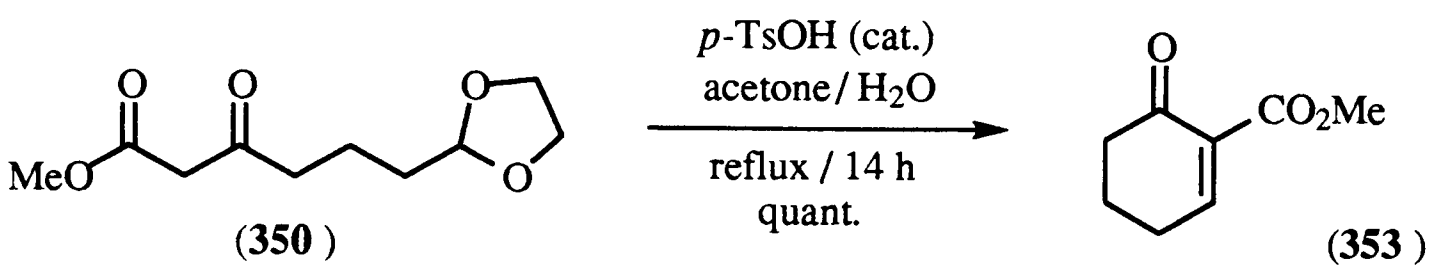
Scheme 128

The product was identified by the presence of a ketone absorption at 1 718 cm^{-1} and the higher wavenumber ester absorption at 1 747 cm^{-1}, by observation of a triplet signal at δ4.83 p.p.m. that corresponded to resonance of the C-2 acetal proton and the acidic acetoacetate methylene singlet at δ3.44 p.p.m. by ^1H n.m.r. spectroscopy and the detection of parent ions MNH_4^+ (234) and MH^+ (217) and the dioxonium ion species (**352**) (73) by mass spectrometric analysis.[82,138]



(**352**)

Deprotection of the acetal function under standard conditions by refluxing a solution of the substrate (**350**) in acetone-water (9 : 1 v/v) in the presence of a catalytic quantity of *p*-toluenesulphonic acid, afforded none of the unmasked aldehyde (**349**). The product was identified as oxocyclohexenyl carboxylate (**353**) (**Scheme 129**) by observation of carbonyl absorptions at 1 746 and 1 689 cm^{-1} and an olefinic vibration at 1 619 cm^{-1} in the i.r. spectrum, the presence of a triplet signal at δ7.73 p.p.m. in the ^1H n.m.r. spectrum corresponding to resonance of a single vinylic proton, and by comparison of spectroscopic data with literature information.[138]



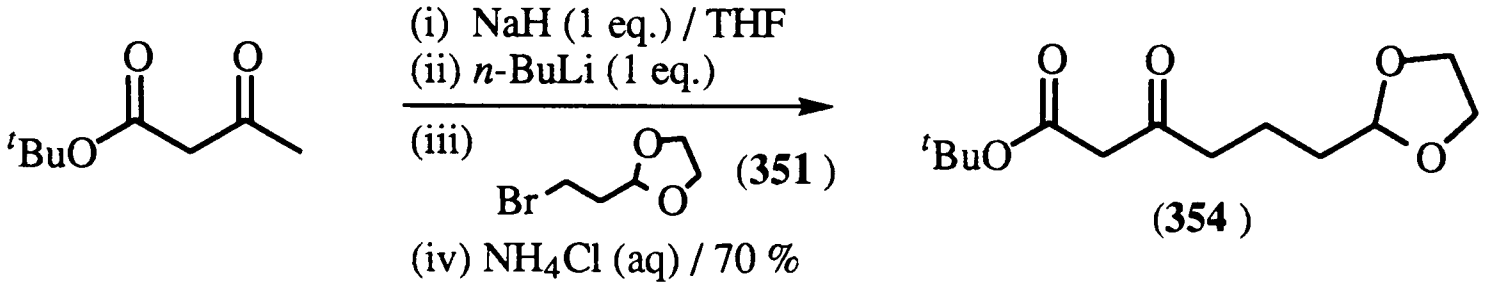
Scheme 129

Taking samples from the reaction at hourly intervals, and subjecting them to analysis by ^1H n.m.r. spectroscopy, indicated that the initial generation of cyclohexenone (**353**) was accompanied by formation of only a trace of the aldehyde (**349**), identified by the appearance of a proton resonance at δ9.8 p.p.m.. This concentration built up over the first three hours of reaction and then disappeared with the preferential formation of the elimination product. Based upon this observation, a deprotection under milder conditions was investigated. Stirring the substrate (**350**) in a solution of acetone-dilute aqueous hydrochloric acid (9 : 1 v/v) and halting the reaction before completion only furnished a trace of the aldehyde (**349**), as cyclohexenone (**353**) and unreacted starting material once again predominated.

In an effort to arrest the reaction at the intermediate (**349**), the mild deacetalisation conditions of Conia were employed.[139] However, stirring a solution of the dioxolane (**350**) in dichloromethane over wet silica gel for 24 hours only led to incomplete recovery of starting material in 49 % yield.

It was thought that the introduction of a more bulky ester group in the dioxolane precursor (**354**) would inhibit the intramolecular cyclisation under the mild deacetalisation and so could allow aldehyde isolation. Repeating the dianion addition with *tert*-butyl

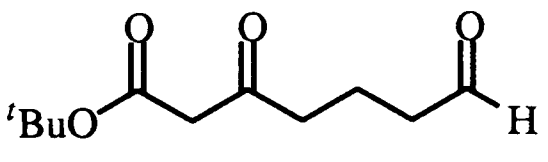
acetoacetate furnished the *tert*-butyl substituted dioxolane of Yoshikoshi[138] (**354**) in 70 % yield (**Scheme 130**).



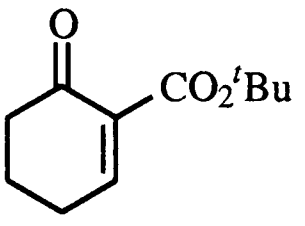
Scheme 130

The product was identified by the presence of carbonyl absorptions at 1 737 and 1 714 cm^{-1} in the i.r. spectrum and observation of the C-2 acetal and acidic acetoacetate methylene proton resonances, at δ4.85 and 3.34 p.p.m. respectively, by ^1H n.m.r. spectroscopy. Characterisation was complete by comparison of spectroscopic information with literature information[138] and data for methyl hexanoate (**350**) and the detection of a trace of the parent ion MNH_4^+ (276) and the dioxonium ion species (**352**) by mass spectrometric analysis.

However the unmasking of the aldehyde functionality under mild deactalisation conditions, stirring dioxolane (**354**) in a solution of acetone-dilute aqueous hydrochloric acid (9 : 1 v/v), afforded only a trace of the deprotected aldehyde (**355**) and preferentially formed the intramolecularly cyclised cyclohexenyl ester (**356**) of Yoshikoshi.[138]



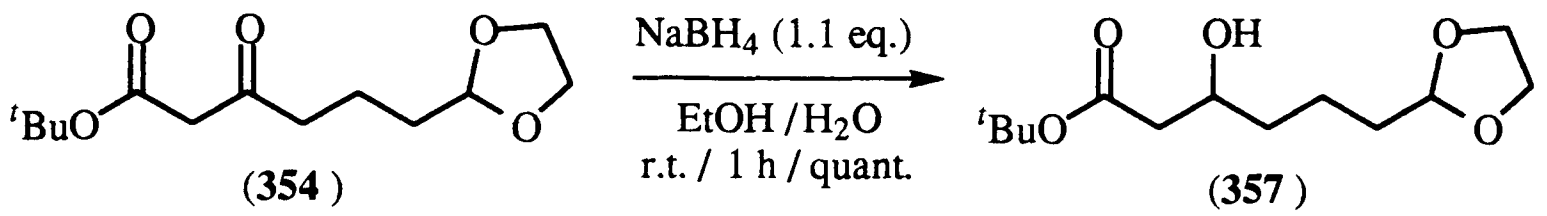
(**355**)



(**356**)

Although increasing the bulk of the ester group did not inhibit the internal condensation which spontaneously occured under the acidic reaction conditions, it was postulated that reducing the acidity of the α-methylene acetoacetate position would disfavour the unwanted closure. Reduction of the *tert*-butyl hexanoate β-ketone would remove the electron withdrawing effect of this function and so should prevent intramolecular attack of the unmasked aldehyde moiety.

The selective reduction of dioxolane (**354**) was achieved by the action of sodium borohydride in aqueous ethanol to afford the β-hydroxy ester (**357**) in a quantitative crude yield and in sufficient purity to give correct combustion analysis (**Scheme 131**).

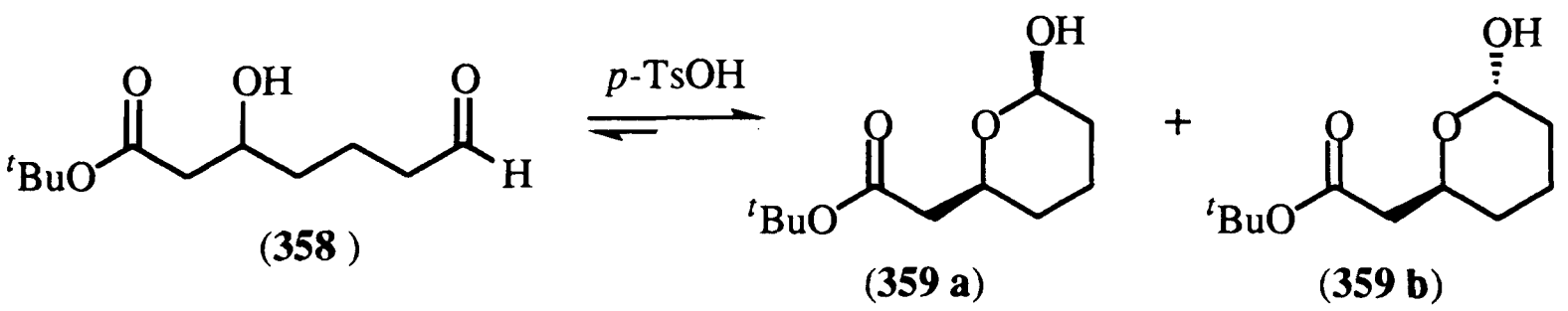


(**354**) (**357**)

Scheme 131

The product was identified by the presence of a sharp intramolecularly hydrogen-bonded hydroxyl absorption at 3 474 cm^{-1} in the i.r. spectrum, that had replaced the ketone vibration at 1 714 cm^{-1}, and a shift to lower frequency by 10 cm^{-1} of the ester carbonyl absorption. ^1H n.m.r. spectroscopy exhibited double-doublet resonances at δ2.45 and 2.32 p.p.m., indicating successful conversion of the acidic acetoacetate position to a diastereotopic methylene moiety in formation of the β-hydroxyl. Detection of the parent ion MH^+ (261) and the dioxonium ion species (**352**) completed characterisation of the product.

Deprotection of the dioxolane (**354**) by refluxing a solution of the substrate in acetone-water (10 : 1 v/v) in the presence of a catalytic quantity of *p*-toluenesulphonic acid resulted in total deacetalisation in only 2.5 hours. However, once more, none of the required aldehyde (**358**) was isolated as a consequence of product instability under acidic reaction conditions. In this instance, the *O*-alkylated product of an intramolecular aldol condensation was isolated in 63 % yield, as an inseparable mixture of *cis*-(**359a**) and *trans*-(**359b**) diastereomeric hemiacetals (**Scheme 132**).



(**358**) (**359 a**) (**359 b**)

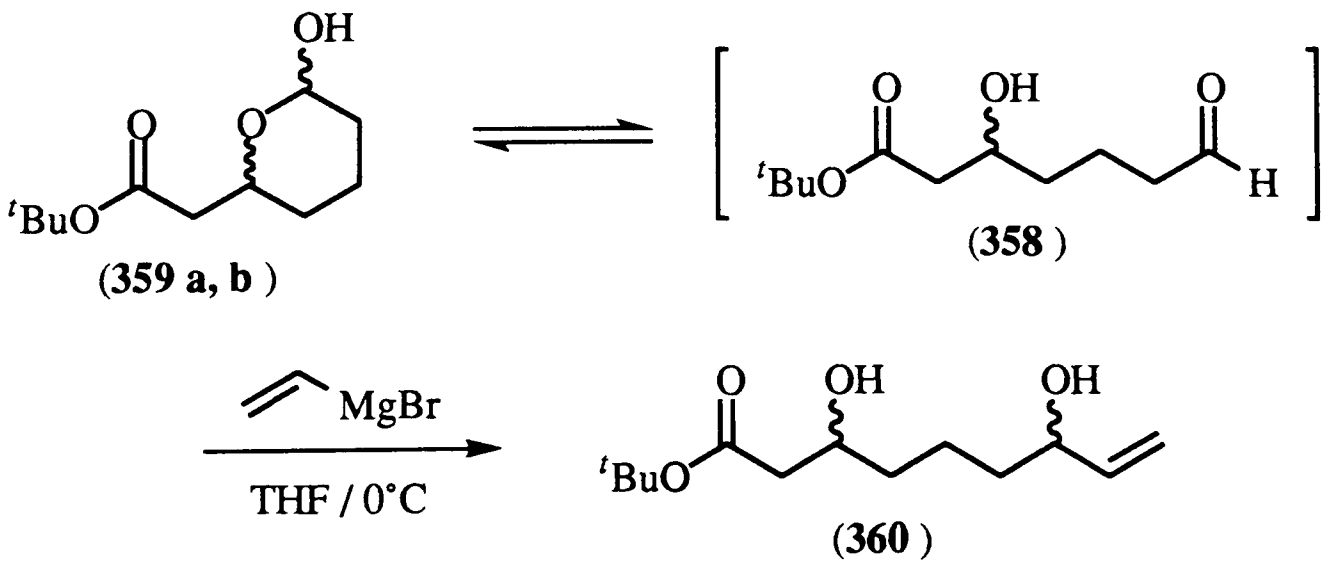
Scheme 132

The structural assignment was supported by observation of a hydroxyl absorption at 3 430 cm^{-1} and a single carbonyl vibration at 1 732 cm^{-1} in the i.r. spectrum. ^1H n.m.r.

spectroscopy indicated absence of the aldehyde signal and showed two different hemiacetal proton resonances at δ5.29 and 4.76 p.p.m., corresponding to axial and equatorial stereochemical environments. By signal integration it was elucidated that the epimers of (**359**) were present in approximately equal ratios, with preference for generation of the more thermodynamically stable *cis*- isomer (**359a**) in which hydroxyl and acetate substituents have both adopted equatorial positions.

It was noted that the derivation of the hemiacetal product was achieved in only 2.5 hours, and this very rapid deprotection was attributed to *O*-alkylation removing aldehyde (**358**) from the reaction mixture, thus driving the equilibrium through to the products. The preference for *O*- over *C*-alkylation was a consequence of a reduction in the acidity of the C-2 methylene and the preference of the hard electrophilic aldehyde function for the harder, more electronegative oxygen nucleophile.

Due to a lower propensity for hemiacetal (**359**) to dehydrate, with respect to elimination to the *C*-alkylated product (**356**), the reversible nature of the aldol cyclisation could be utilised to good effect. The reaction of an excess of vinyl magnesium bromide with a solution of the hemiacetals, (**359a**) and (**359b**), in tetrahydrofuran at 0°C furnished Grignard addition products in 99 % crude yield as a mixture of allylic alcohol stereoisomers (**360**) (**Scheme 133**). The reaction presumably proceeded by addition to a trace concentration of aldehyde (**358**), its consumption forcing the equilibrium over and encouraging irreversible product formation.

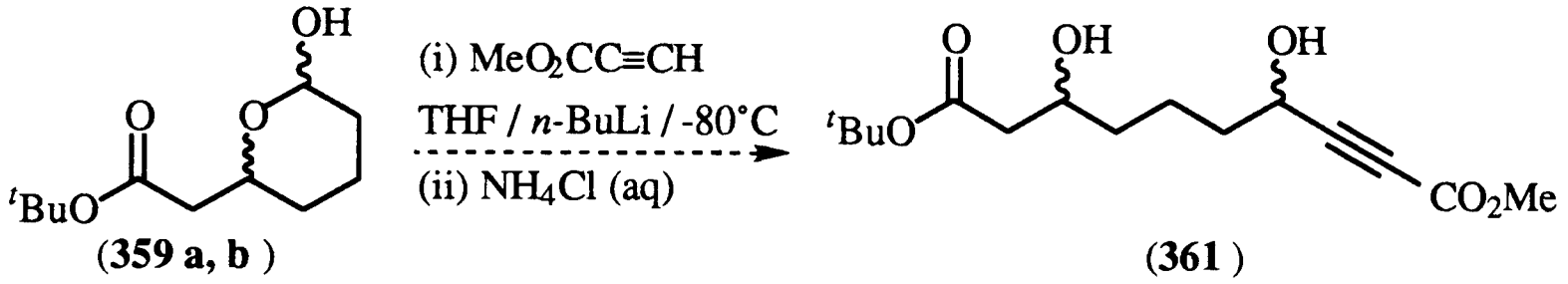


Scheme 133

Attempts to purify the allylic alcohols (**360**) by flash chromatography on silica resulted in appreciable degradation of material and the isolation of the pure product in only 39 % yield, but in sufficient purity to permit correct combustion analysis.

The product was identified by absorptions in the i.r. spectrum attributed to vibration of a hydroxyl at 3 398 cm^{-1}, an ester carbonyl at 1 728 cm^{-1}, and an alkene at 1 651 cm^{-1}. ^1H n.m.r. spectroscopy indicated that incorporation of the nucleophile had been successful with vinylic resonances at δ5.88, 5.23, and 5.12 p.p.m.. Multiplet signals at δ4.12 and 3.97 p.p.m. confirmed the presence of two hydroxymethine groups in the product and characterisation was completed by detection of the parent ion MH^+ (245) by mass spectrometric analysis.

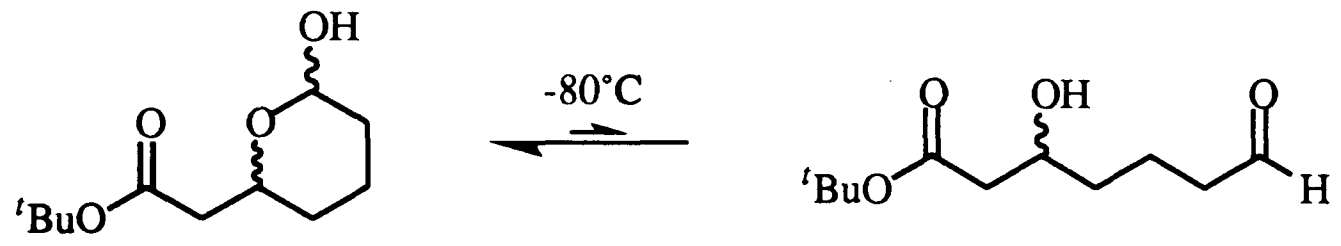
Thus, the approach had been successful in introducing an alkene moiety having potential for elaboration to a monoactivated dienophile. In order to investigate whether this would also be the case for diactivated substrates an attempt was made to form the hydroxy alkynoate (**361**) according to the procedure of Midland (**Scheme 134**).[95]



(**359 a, b**) (**361**)

Scheme 134

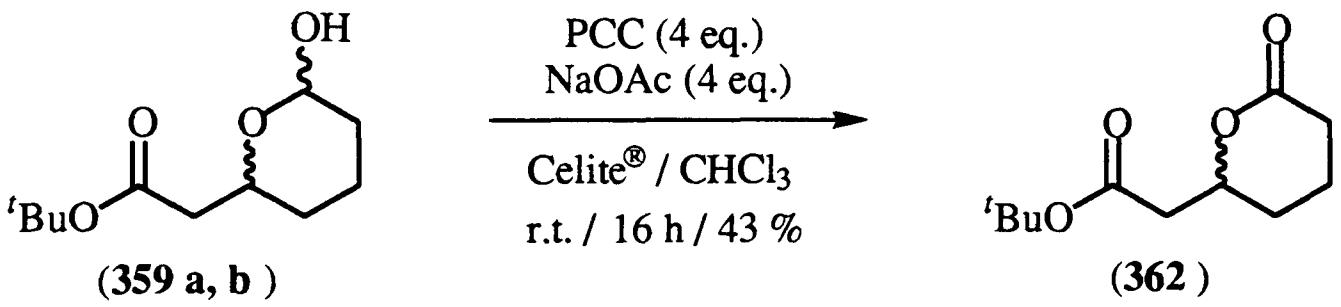
Generation of the lithium acetylide anion, according to the reported procedure,[95] was achieved by treating methyl propiolate with *n*-butyllithium at -80°C in tetrahydrofuran. Addition of the substrate (**359**) and maintaining the temperature below -80°C resulted only in the isolation of recovered hemiacetal (**359**). By repeating the addition and slowly raising the reaction temperature, the lithium reagent decomposed to form a black solution[95] from which predominantly starting material was isolated. Based upon these observations it was decided that at the low temperatures necessary for lithium alkynoate stability, the hemiacetal (**359**) was unable to equilibrate to acyclic aldehyde (**358**), a process entropically favoured by the application of higher temperatures (**Scheme 135**). Thus contrasting requirements of addition and acetal equilibration have prevented generation of a diactivated substrate.



(359 a, b) **(358)**

Scheme 135

In order to remove the interference of the unfavourable equilibrium from the addition process, hemiacetal (**359**) was oxidised to the corresponding lactone (**362**). Treatment with 4 equivalents of pyridinium chlorochromate and anhydrous sodium acetate buffer[140] in chloroform in the presence of Celite®, to absorb chromium reaction residues, furnished a 43 % yield of product (**362**) (**Scheme 136**).

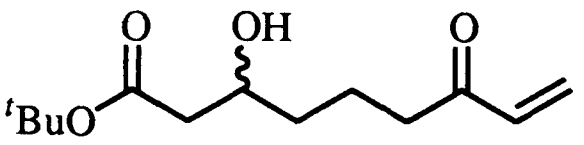


(359 a, b) **(362)**

Scheme 136

The product was identified by disappearance of the hydroxyl absorption at 3 398 cm^{-1} in the i.r. spectrum and observation of a broad carbonyl absorption at 1 746 cm^{-1} encompassing vibration of both lactone and ester functionalities. ^1H n.m.r. spectroscopy indicated the presence of only a single hydroxymethine multiplet resonance at δ4.71 p.p.m., deshielded by the electron withdrawing influence of the newly formed carbonyl moiety. Confirmation of oxidation was complete by detection of the parent ion MNH_4^+ (232) and the deesterified ion species $(MNH_4\text{-}^tBuO)^+$ (176) by mass spectrometric analysis.

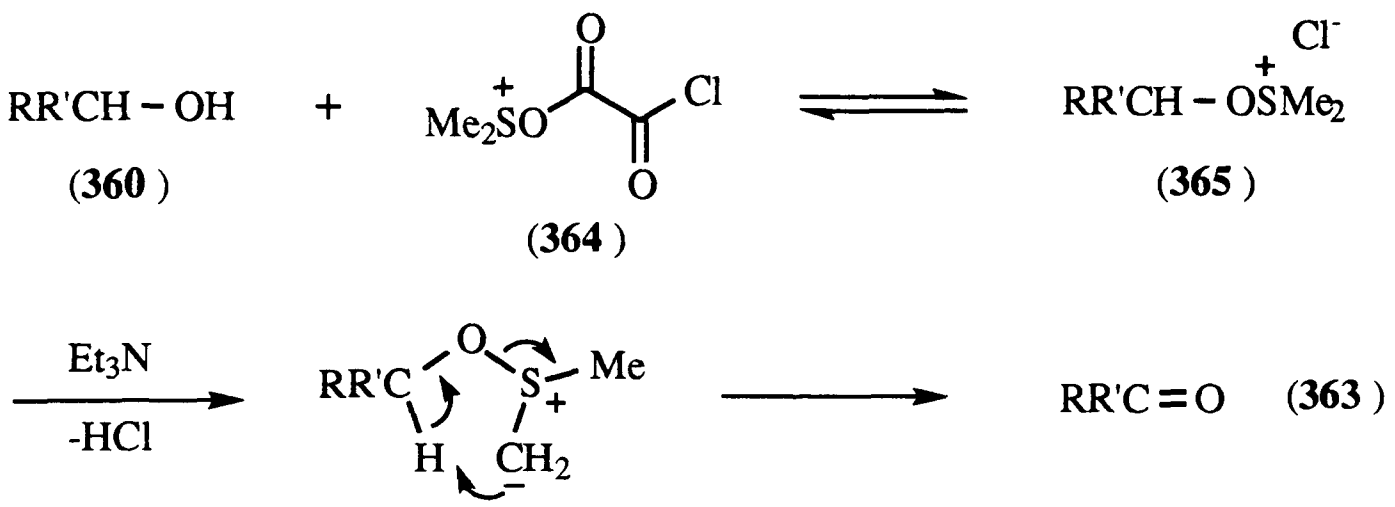
The Grignard addition of vinyl magnesium bromide to a solution of the lactone (**362**) in tetrahydrofuran at -78°C resulted in isolation of a mixture of unreacted starting material and the acyclic enone (**363**), in approximately a 2 : 1 ratio, after 2 hours. The product was recognised by ^1H n.m.r. spectroscopic analysis and observation of 3 double-doublet vinylic resonances, shifted downfield by the electron withdrawing influence of the carbonyl moiety to δ6.39, 6.24, and 5.85 p.p.m..



(363)

The application of a longer reaction time did not improve the proportion of product and allowed formation of a side product that appeared to correspond to enone reduction, possibly *via* an intramolecular condensation mechanism.

In order to establish an alternative route to enone (**363**) the Grignard addition product, diol (**360**), was subjected to Swern oxidation conditions.[141] The treatment of a solution of the substrate (**360**) in dichloromethane with the sulphonium electrophilic intermediate (**364**), formed by the action of oxalyl chloride on dimethyl sulphoxide at -50°C, followed by breakdown of the alkoxysulphonium salt (**365**) by addition of triethylamine should generate the oxidised (**363**) (**Scheme 137**).

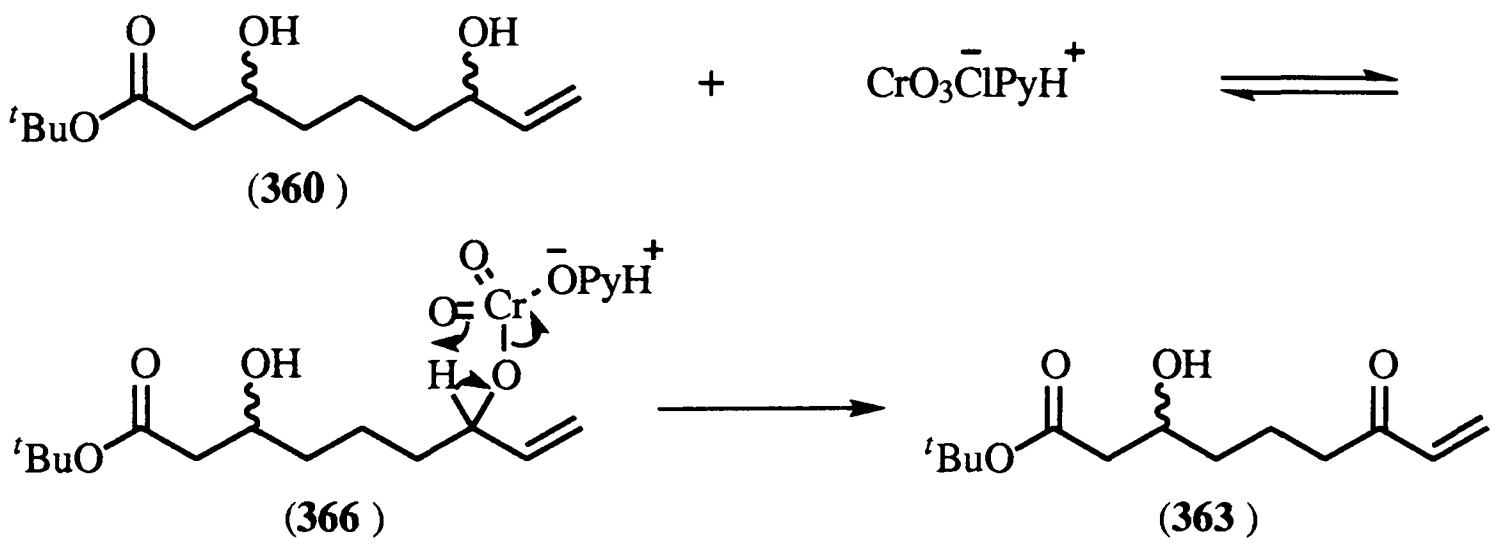


Scheme 137

Following the reported procedure and allowing the reaction to warm to room temperature, after addition of 6 equivalents of triethylamine to eliminate dimethyl sulphide, furnished only a quantitative recovery of unreacted starting material (**360**).

Employing an alternative reagent for the oxidation and subjecting a solution of the diol substrate (**360**) in chloroform to one equivalent of pyridinium chlorochromate for 3 days at room temperature in the presence of sodium acetate buffer furnished enone (**363**) in 54 % yield, identified by comparison of spectroscopic information with data from the product of Grignard addition to lactone (**362**).

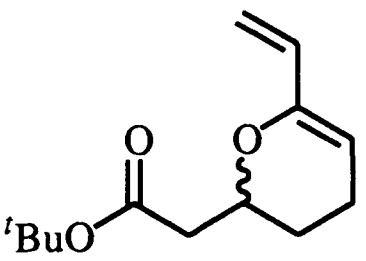
The observed regioselectivity indicated a greater propensity for oxidation at the allylic position over the secondary alcoholic function. Presumably this was a consequence of the increased acidity of the methine proton, due to conjugation with the double bond, that produced a more rapid breakdown of chromic ester intermediate (**366**) in oxidation of the allylic site (**Scheme 138**).



Scheme 138

Difficulties in separating the product from chromium residues, even by addition of Celite® to the reaction mixture, poor yields, and the presence of unwanted side products forced investigation of an alternative oxidative system.

Stirring a solution of diol (**360**) in chloroform over activated manganese dioxide on charcoal[142] at room temperature afforded a mixture of two products, elucidated by ^{1}H n.m.r. spectroscopy as the required enone (**363**) predominantly and the product of an intramolecular *O*-alkylative cyclisation and subsequent dehydration, (**367**).

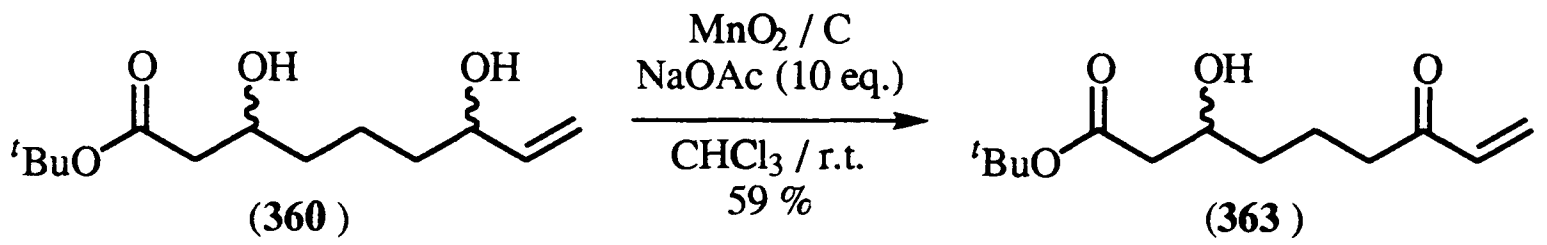


(**367**)

Cyclic enol (**367**) was identified by the appearance of four olefinic proton signals in the ^{1}H n.m.r. spectrum. Although three mutually coupled vinylic resonances displayed no

other vicinal couplings, the fourth olefinic signal appeared as a triplet and was heavily shielded at 4.81 p.p.m., indicating proximity to the mesomerically donating heteroatom.

It was assumed that formation of the intramolecularly cyclised product (**367**) was being catalysed by the mildly basic nature of the manganese dioxide reagent. Thus the reaction was repeated and the action of the oxidant buffered with 10 equivalents of anhydrous sodium acetate. After stirring overnight at room temperature this allowed exclusive formation of enone (**363**) and prevented the unwanted closure, furnishing the product in 59 % yield (**Scheme 139**).



Scheme 139

Enone (**363**) displayed carbonyl absorptions in the i.r. spectrum at 1 728 and 1 684 cm^{-1}, indicating successful oxidation of the allylic alcohol function, and an olefinic vibration at 1 616 cm^{-1}. Analysis of ^1H n.m.r. spectroscopic data (see earlier) and detection of a trace of the parent ion MH^+ (243) by mass spectrometry completed the characterisation of the product.

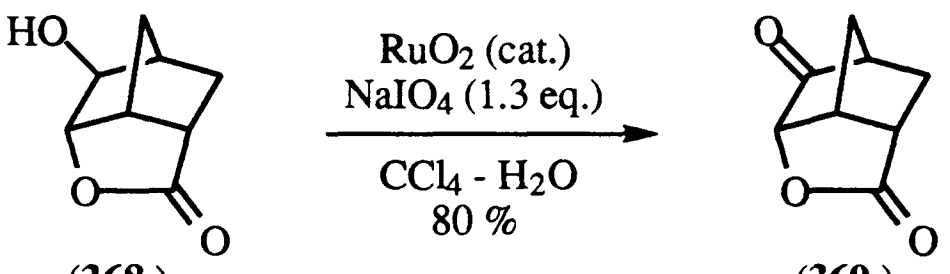
Oxidation of the secondary alcoholic function of (**363**) using pyridinium chlorochromate in chloroform in the presence of 4 equivalents of anhydrous sodium acetate buffer and Celite® furnished a complex mix of products containing what was thought to be a trace of the target compound (**342**). Unfortunately attempts to isolate the required acetoacetate derivative (**342**) from the mixture failed to afford any product. As it appeared that a chromate oxidation system was capable of generating the required target (**342**), the direct transformation of Grignard adduct (**360**) was attempted.

Oxidation of the diol (**360**) with a large excess of pyridinium chlorochromate, in the presence of anhydrous sodium acetate buffer, resulted in complete degradation of starting material with no isolation of product. Decreasing the quantity of oxidant led to the product of allylic oxidation (**363**) to be isolated. In a similar fashion, reducing the quantity of buffer did

not favour the second oxidation and only facilitated *O*-alkylation, by intramolecular attack of the enone carbonyl, that protected the secondary hydroxyl from the action of the oxidant.

The difficulty in deriving the target molecule (**342**) by the action of pyridinium chlorochromate on diol (**360**) or the manganese dioxide oxidation product (**363**) was attributed to a degradation of the acetoacetate (**342**), even under the buffered oxidative conditions, and this necessitated study into alternative oxidation systems.

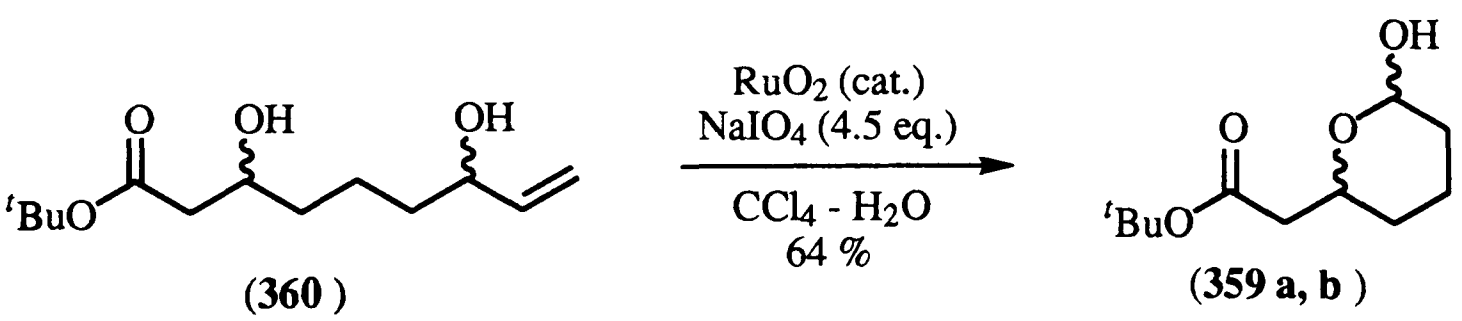
The oxidation of the secondary alcoholic function of (**368**) has been reported in the literature to be inordinately problematical, possibly as a consequence of the acid sensitivity of the product (**369**). Moriarty *et al.* have reported successful oxidation of this precursor using ruthenium tetroxide,[143] generated *in situ* by the action of sodium periodate on a catalytic quantity of ruthenium dioxide in a biphasic system (**Scheme 140**).



(**368**) (**369**)

Scheme 140

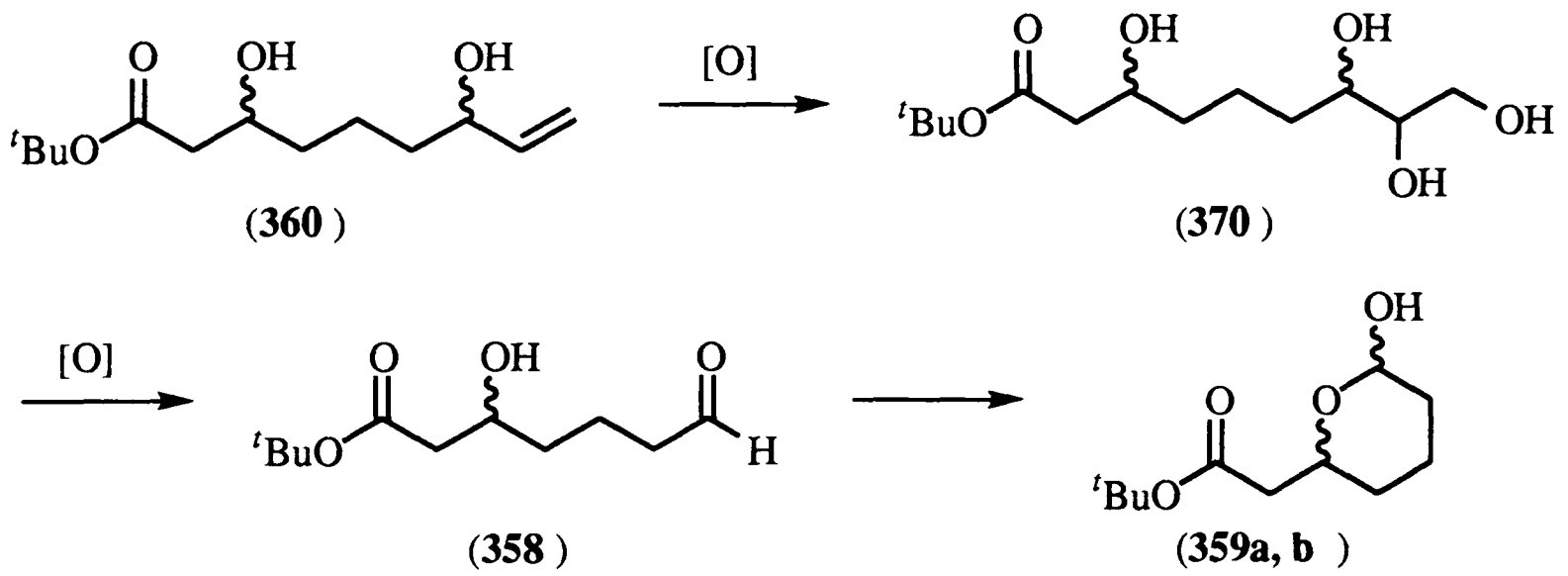
Sodium periodate was added to a suspension of ruthenium dioxide and diol (**360**) in a carbon tetrachloride-aqueous system, according to the literature procedure.[139] After the addition of 4.5 equivalents of the co-oxidant, t.l.c. analysis indicated that starting material had been consumed. At this stage, a yellow colouration persisted in the aqueous phase characteristic of formation of the ruthenium tetroxide in the absence of substrate. After quenching the reaction with *iso*-propyl alcohol and aqueous work up, the sole reaction product was identified as the diatereomeric hemiacetals (**359a, b**), isolated in 64 % crude yield (**Scheme 141**).



(**360**) (**359 a, b**)

Scheme 141

This curious reaction course was presumably the result of undesired chemoselectivity, the olefinic bond being oxidised preferentially. A glycol periodate cleavage of the tetraol (**370**), extremely soluble in the aqueous oxidation medium, would afford the aldehyde precursor (**358**) of hemiacetal (**359**) (**Scheme 142**).



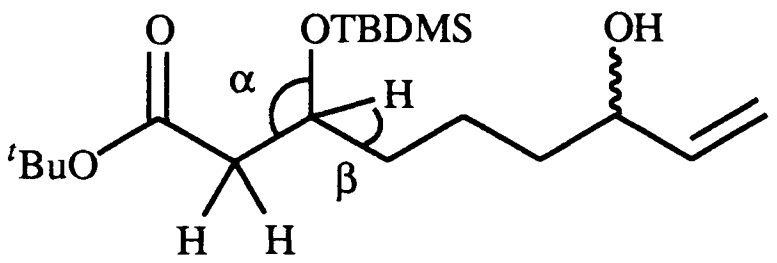
Scheme 142

This mechanism would explain the reaction's requirement for 4 equivalents of sodium periodate and has some literature precedence. Oxidants such as pyridinium chlorochromate, activated manganese dioxide, and periodic acid have been shown to effect the oxidative cleavage of glycols in good yields.[144] It also seemed reasonable to suggest that a similar oxidative cleavage could have been responsible for degradation of the product in other oxidation systems.

The double oxidation of diol (**360**) was investigated using pyridinium dichromate in the hope that the product (**342**) would now be stable under these alternative conditions. Stirring a solution of the substrate in chloroform with 2.5 equivalents of PDC in the presence of Celite® furnished only the singly oxidised enone (**363**) in 29 % crude yield. It appeared that the product was still not stable under the conditions of chromate oxidation and so it was proposed to protect one of the hydroxyl substituents in order to prevent over-oxidation and to inhibit the intramolecular condensation, either of which could have been responsible for product degradation.

Stirring a solution of the diol (**360**) in *N, N*-dimethylformamide in the presence of one equivalent of imidazole base and *tert*-butyldimethylchlorosilane for one day at room temperature furnished a 22 % recovery of unreacted starting material (**360**) and two new products, that were formed in approximately a 2 : 1 ratio (**Scheme 143**).

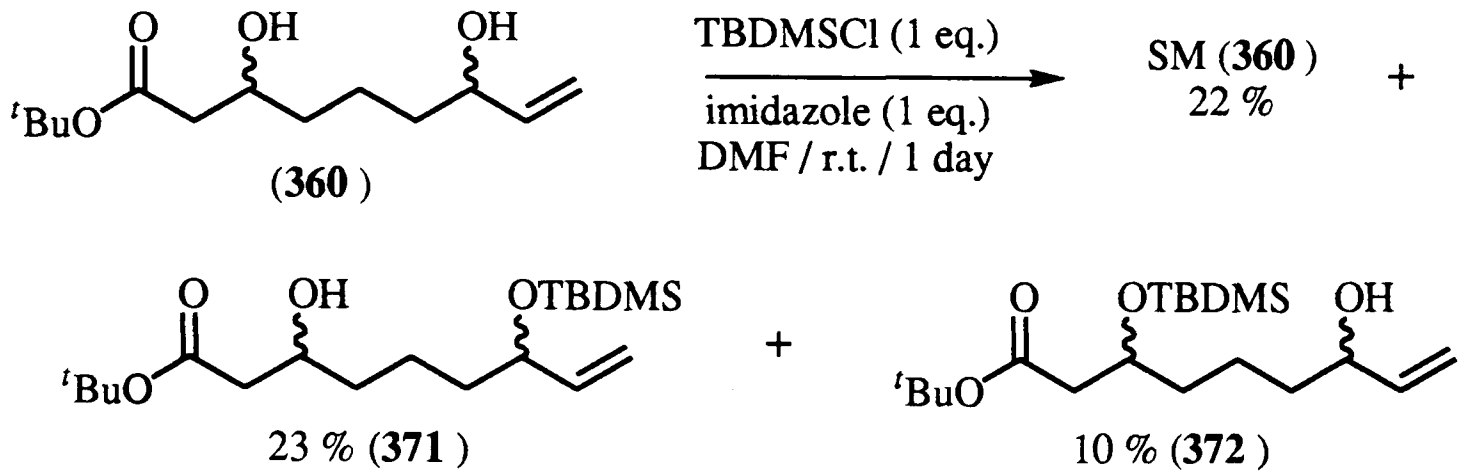
By i.r. spectroscopy both products displayed hydroxyl, ester carbonyl, and olefinic absorptions and mass spectrometric analysis confirmed that they corresponded to regioisomeric monoprotected silyl ethers, (**371**) and (**372**), by detection of the parent ion MH^+ (359) in both instances. An inference of the identity of the regioisomeric products was made by ^1H n.m.r. spectroscopy. Both compounds exhibited a singlet resonance at δ0.9 p.p.m. confirming successful introduction of shielded *tert*-butylsilane protons. However the minor isomer (**372**) displayed an interesting feature in the magnitude of the coupling constants of the diastereotopic α-ester methylene protons. The magnitude of the geminal coupling was reduced from ^2J 16.5 to ^2J 13 Hz, relative to the spectrum of diol (**360**), and the vicinal couplings were now both ^3J 4.3 Hz. The phenomenon was attributed to the Thorpe-Ingold effect, substitution of a bulky silyl protecting group at the C-3 hydroxyl would increase angle α, with increase in the mutual substituent repulsion, resulting in a change in angle β that would alter the magnitude of the C-2 methylene coupling constants (**Figure 5**).



(**372**)

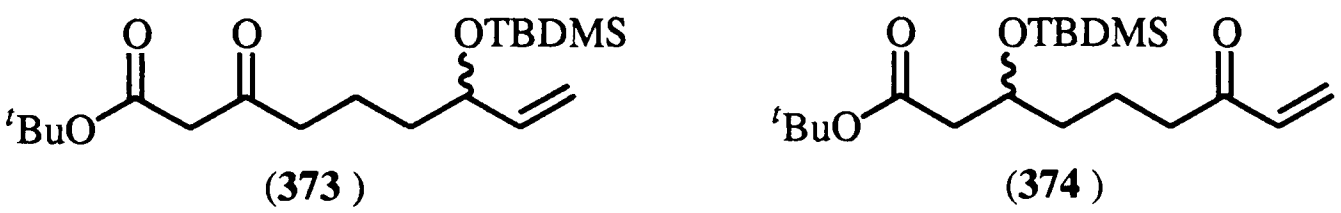
Figure 5

Thus it was inferred from the spectroscopic data that the major isomer was the allyl protected silyl ether (**371**) with minor formation of the protected secondary alcohol (**372**), in 23 and 10 % yields respectively (**Scheme 143**).

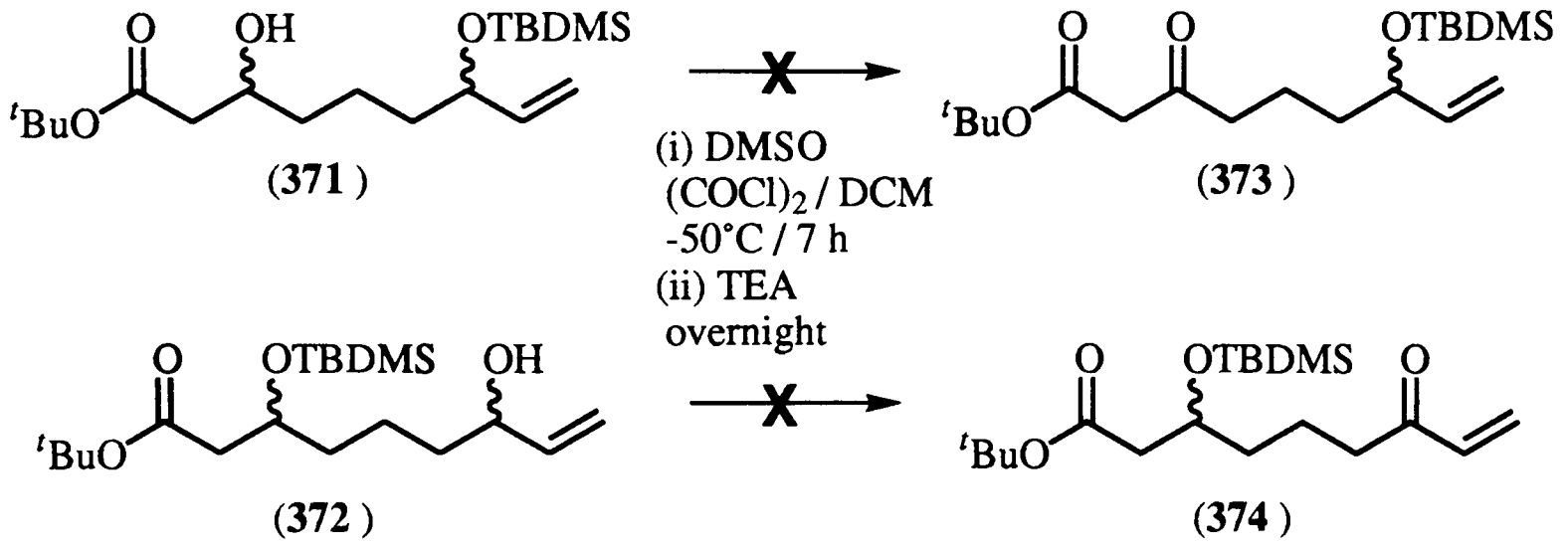


Scheme 143

In order to verify the ^1H n.m.r. spectroscopic assignment of the regioisomers, an attempt was made to oxidise (**371**) and (**372**). Structurally the oxidation products would be very different and so acetoacetate (**373**) and enone (**374**) should be easily distinguished spectroscopically. In addition, oxidation of an allylic hydroxyl to afford the α, β-unsaturated ketone (**374**) should be more facile as a consequence of the increased acidity of the C-2 proton and so this should aid in regioisomer assignment.

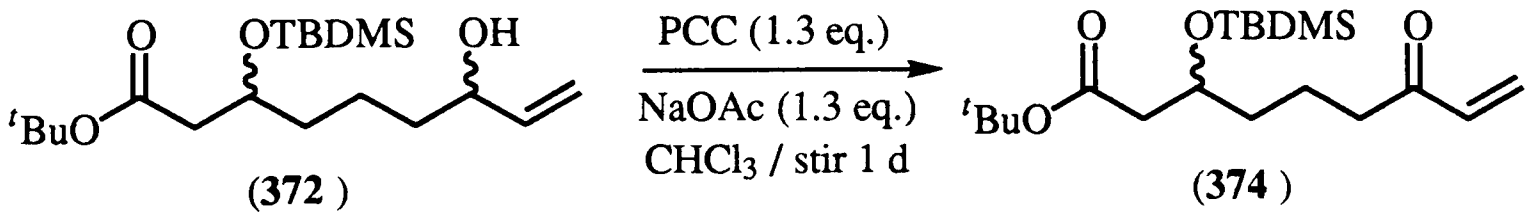


The isomeric products were both subjected to conditions for Swern oxidation,[141] a solution of (**371**) or (**372**) in dichloromethane treated with the sulphonium electrophilic species (**364**), formed by the action of oxalyl chloride on dimethyl sulphoxide, for 7 hours at -50°C. In both instances only a quantitative return of starting material was obtained after an overnight quench with triethylamine (**Scheme 144**).



Scheme 144

Employing an alternative reagent and submitting what was assumed to be the allylic alcohol (**372**) to pyridinium chlorochromate oxidation, with 1.3 equivalents of oxidant in the presence of anhydrous sodium acetate buffer and Celite®,[140] resulted in the rapid consumption of starting material by t.l.c. analysis. However, upon work up, appreciable degradation had occured and only a trace of product was obtained, a quantity insufficient to confirm isolation of enone (**374**). Resonances at δ6.35, 6.25, and 5.83 p.p.m. in the ^{1}H n.m.r. spectrum implied olefinic proton deshielding introduced by the oxidative conversion and this correlated well with data for the unprotected enone (**363**), further supporting the regioisomeric assignment (**Scheme 145**).



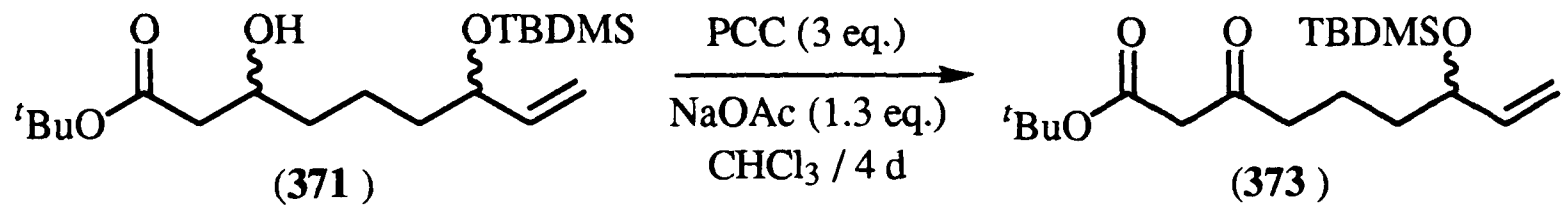
Scheme 145

The pyridinium chlorochromate oxidation of the alternative isomer (**371**) under identical conditions was found to be extremely sluggish, and this implied that the proton at the secondary oxidation site was less acidic. Stirring the substrate with 3 equivalents of oxidant speeded up the reaction and afforded acetoacetate (**373**) in 46 % yield.

The product (**373**) was identified by carbonyl absorptions in the i.r. specrum at 1 738 and 1 718 cm^{-1}, an olefinic absorption at 1 645 cm^{-1}, and absence of the hydroxyl vibration at 3 447 cm^{-1} present in the precursor (**371**). ^{1}H n.m.r. spectroscopy indicated that oxidation

had been successful as the *diastereotopic* C-2 methylene protons had been transformed into a deshielded singlet resonance at δ3.33 p.p.m., typical of an acetoacetate function. Detection of the parent ion MH^+ (357) by mass spectrometry completed characterisation of the product and confirmed that the ^1H n.m.r. spectroscopic assignment of regioisomers (**371**) and (**372**), formed in silyl protection, had been correct.

Oxidation was optimised by portionwise addition of the pyridinium chlorochromate oxidant, stirring for 4 days, and by following the course of reaction by t.l.c. analysis. It was thought that this would minimise any acidic build up and so would prevent degradation or deprotection of the acid sensitive product. Under these conditions a 92 % yield of acetoacetate (**373**) was obtained (**Scheme 146**).



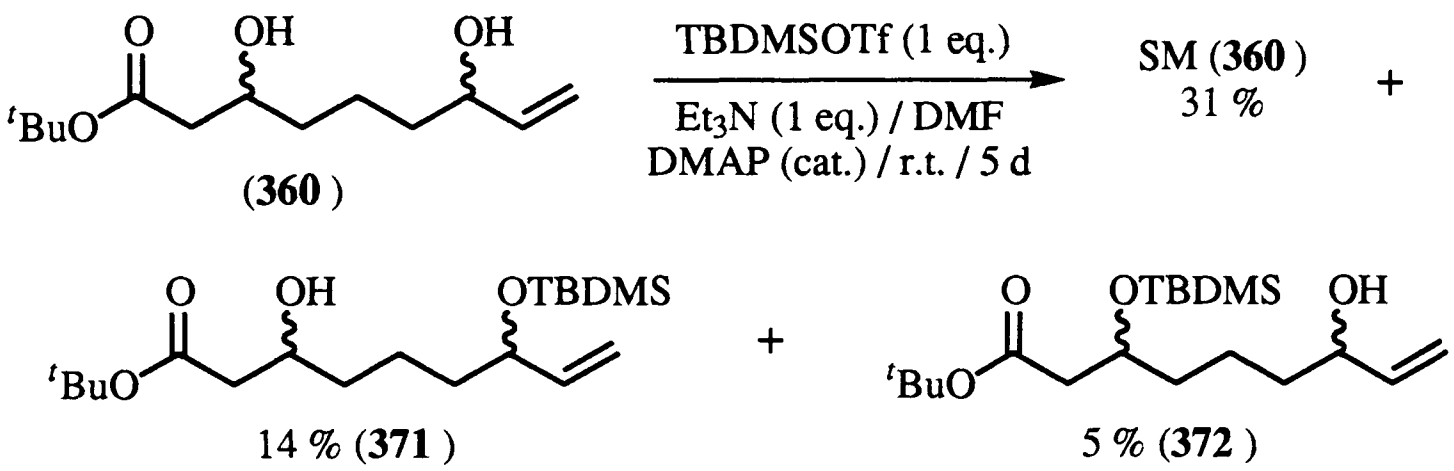
(**371**) (**373**)

Scheme 146

The failure in the oxidation of the allylic alcohol was indicative of system degradation under these mildly acidic oxidative conditions. Indeed it may have been this factor that was responsible for the inability to access the original target enone (**342**) directly by diol (**360**) oxidation and that has hampered the success of this approach. Despite this obstruction, an excellent oxidation efficiency should by-pass this problem if the silylation regioselectivity and yield could be improved upon.

Although a reasonable regioselectivity had been obtained in the protection of diol (**360**) (2.3 : 1) (**Scheme 143**), the efficiency of conversion was disappointing. Efforts to improve on this procedure by stirring for up to 14 days at room temperature, heating the reaction, employing triethylamine as the base, or by increasing the number of equivalents of base or silylating agent all failed to optimise the yield or regioselectivity of reaction. The addition of 4-dimethylaminopyridine to the mixture was similarly unsuccessful and appeared to favour formation of the diprotected product (**375**). Utilising a more reactive silylating agent and quenching the diol (**360**) with *tert*-butyldimethylsilyltriflate in the absence of base

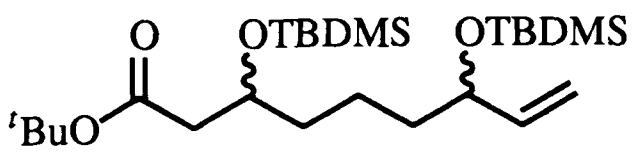
furnished only a trace of the desired product (**371**) and predominantly returned unreacted starting material (**360**). In the presence of triethylamine and a catalytic quantity of 4-dimethylaminopyridine regioselectivity of reaction was improved but the yield of product (**371**) was significantly reduced, invalidating the approach (**Scheme 147**).



Scheme 147

It was thought that formation of the disilylated product (**375**) could be responsible for reducing the reaction yields and so it was postulated that introducing a more bulky protecting group would disfavour disubstitution on steric grounds. However repeating the procedure with *tert*-butyldiphenylchlorosilane resulted in no yield improvement and only appeared to slow down the rate of substitution. This situation was not altered by raising the reaction temperature.

Assuming the propensity of the system to form disubstituted products, an effort was made to generate the disilylated species (**375**). A monodeprotection could then be employed to furnish the required silyl protected (**371**) with possibility for yield improvement and enhancement of regioselectivity. However an attempt to drive the diprotection by stirring diol (**360**) with 5 equivalents of *tert*-butyldimethylchlorosilane in *N, N*-dimethylformamide in the presence of triethylamine and 4-dimethylaminopyridine afforded (**375**) in only 27 % yield.



(**375**)

The product was identified by the disappearance of hydroxyl absorptions in the i.r. spectrum, the uniform vicinal couplings of the C-2 methylene in the ^{1}H n.m.r. spectrum as a consequence of successful incorporation of the C-3 silyl group, and observation of two silyl *tert*-butyl resonances at δ0.90 and 0.88 p.p.m.. Detection of the de-esterified ion species $(MH\text{-}C_4H_8)^+$ (417) by mass spectrometric analysis completed the characterisation and confirmed incorporation of two silyl protecting species.

Unfortunately deprotecting (**375**) by the addition of one equivalent of tetrabutylammonium fluoride in tetrahydrofuran appeared, by t.l.c. analysis, to favour the removal of both protecting groups and only a trace of the monosilylated (**371**) and (**372**) could be formed at any time. As a result, approach from the diprotected (**375**) was abandoned.

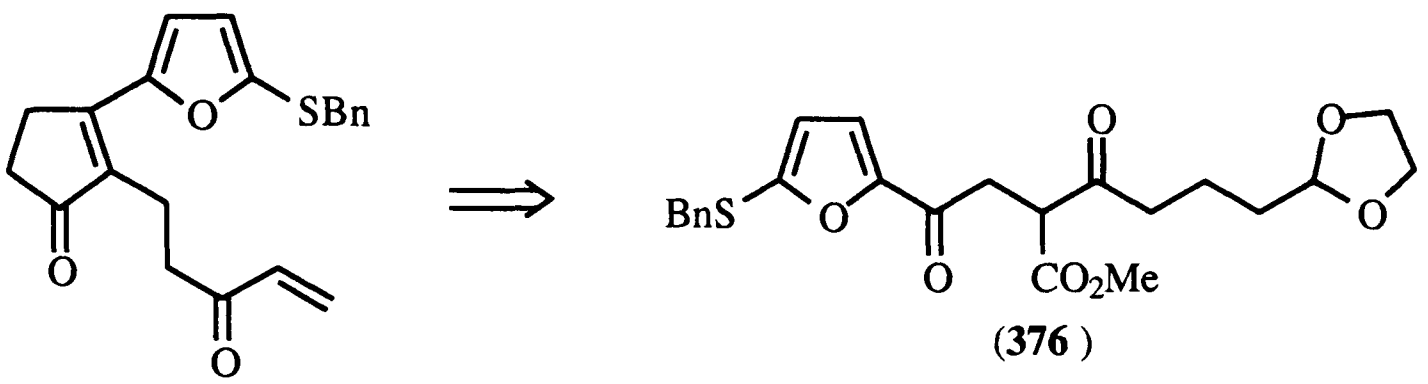
Although the efficiency of oxidation of the monosilylated (**371**) had been optimised to 92 % (**Scheme 146**), the low yield and poor reproducibility of the silyl protection forced this route to be abandoned. The failure of the approach was attributed to the presence of nucleophilic and electrophilic residues within the same molecule and the sensitivity of the target enone (**342**) to even mildly acidic oxidative media. Thus, it was proposed to now reserve elaboration of the dienophile until late in the synthetic sequence. Although this would transform the convergent strategy into a less efficient more linear approach, it should by-pass the functional group transformational problems encountered.

Despite the unexpected lack of results, the procedure demonstrated successful construction of the dienophile by addition to aldehyde (**358**), the product of dioxolane (**354**) deprotection, and this protocol could be put to good use to preserve the electrophilic carbonyl through acetoacetate alkylation.

4.3. Elaboration of a (Furoylmethyl)acetoacetate Derivative.

Delaying the oxidative elaboration of the activated dienophile until later in the synthetic sequence suggested maintaining the acetal protection of the aldehyde beyond the acetoacetate alkylation step. The methyl acetoacetate derivative (**350**), synthesised in approach to enone (**348**), should couple routinely with (bromoacetyl)furan (**249**). In the

absence of a C-7 carbonyl, the propensity for intramolecular cyclisation would be removed and this should facilitate generation of IMDAF precursor (**328**) by subsequent deprotection and alkylative elaboration (**Scheme 148**).



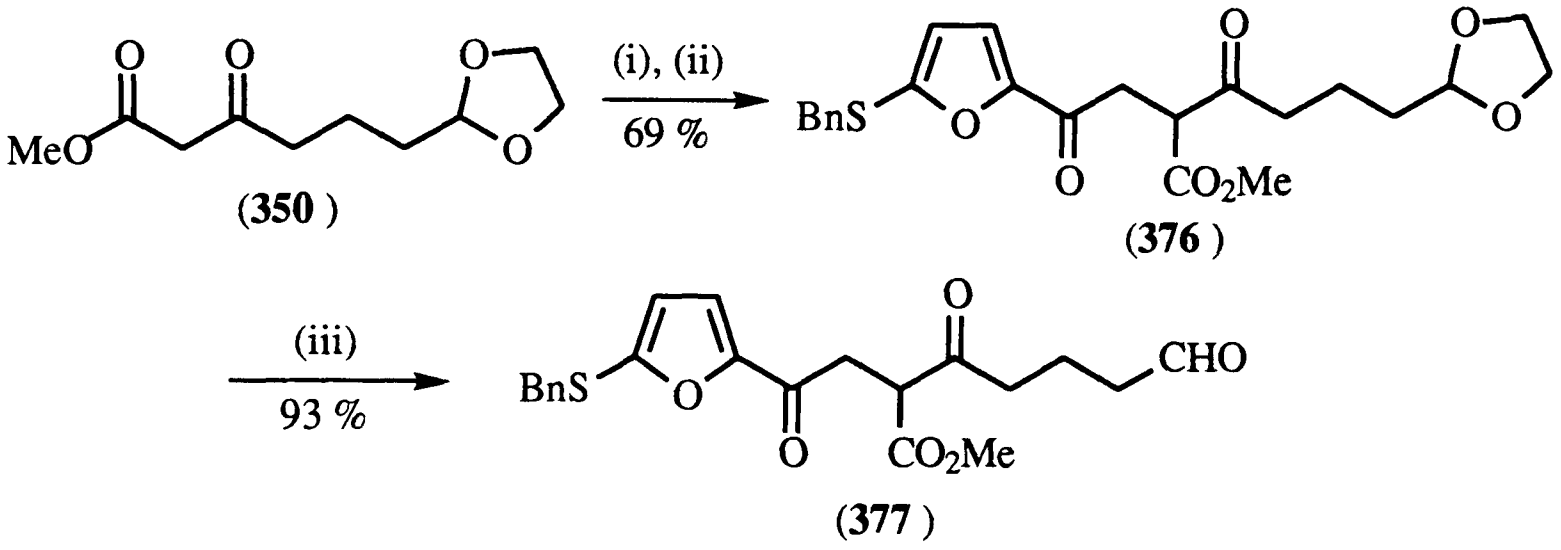
(**328**) (**376**)

Scheme 148

Methyl acetoacetate (**350**) was deprotonated by the action of sodium hydride in tetrahydrofuran at 0°C and the anion quenched by addition of (bromoacetyl)furan (**249**) to furnish the coupled derivative (**376**) in 69 % yield on warming to room temperature (**Scheme 149**).

The product was identified by carbonyl absorptions in the i.r. spectrum at 1 746, 1 720, and 1 675 cm^{-1}, the appearance of ABX signals at δ4.17, 3.51. and 3.32 p.p.m. in the ^1H n.m.r. spectrum that corresponded to resonance of the furoylmethylene and acetoacetate methine protons, detection of the parent ion MH^+ (217) by mass spectrometric analysis, and comparison of spectroscopic information with data for (furoylmethyl)nonenoate (**258**).

Deprotection of the dioxolane (**376**) using standard conditions, refluxing overnight in a solution of acetone-water (10 : 1 v/v) in the presence of a catalytic quantity of *p*-toluenesulphonic acid, predominantly furnished aldehyde (**377**) in 93 % crude yield (**Scheme 149**) with traces of an unknown side product.

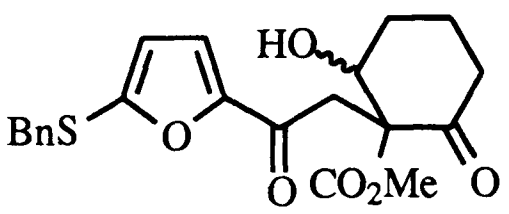


(i) NaH (1 eq.) / THF; (ii) BnS Br (**249**); (iii) *p*-TsOH (cat.) / acetone-H_2O (10 : 1 v/v) / Δ / overnight.

Scheme 149

The product was identified by disappearance of the cyclic ethylene acetal multiplet resonance at δ3.98 - 3.83 p.p.m. in the crude ^1H n.m.r. spectrum and appearance of a new signal at δ9.79 p.p.m. that corresponded to the deshielded aldehyde proton.

Attempts to purify the crude material by flash chromatography on silica or neutral alumina resulted in total and spontaneous conversion to the side product. This was suggested by ^1H n.m.r. spectroscopic analysis to be the product of an intramolecular aldol condensation, (**378**). Resonances due to the aldehyde and acetoacetate methine protons had disappeared and signals that corresponded to the furoylmethylene protons now displayed no vicinal couplings, implying successful alkylation at the acidic acetoacetate position. I.r. spectroscopic analysis supported the product assignment, showing carbonyl absorptions at 1 734, 1 713, and 1 672 cm^{-1} and an absorption at 3 811 cm^{-1} as a result of vibration of the newly formed hydroxyl moiety.

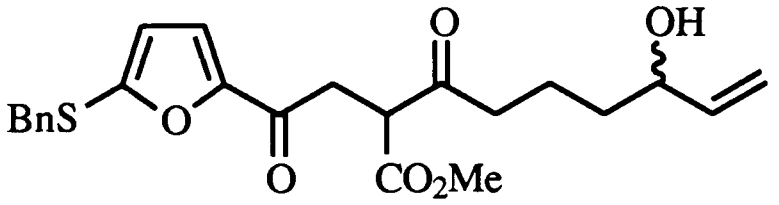


(**378**)

Comparing the propensity for aldehyde (**377**) to cyclise to that of the unsubstituted acetoacetate (**349**), under acid catalysed conditions, it was apparent that substitution at C-2 had drastically slowed down the rate of closure. This was evidently a consequence of a sluggish dehydration when the system was unable to form the more thermodynamically stable α, β-unsaturated ketone.

Based on the inability to purify aldehyde (**377**), an effort was made to explore an alternative deacetalisation that would exclude formation of the side product (**378**). Employing milder conditions and stirring a solution of dioxolane (**376**) in acetone-dilute aqueous hydrochloric acid (10 : 1 v/v) only afforded incomplete deprotection to the required aldehyde (**377**) and so failed to effect exclusive product formation.

Submitting a solution of aldehyde (**377**) in tetrahydrofuran, contaminated with the irremovable side product (**378**), to conditions for Grignard addition with vinyl magnesium bromide at -78°C resulted only in a trace of the desired adduct (**379**) and instead catalysed the intramolecular condensation to form (**378**) with no return of starting material.

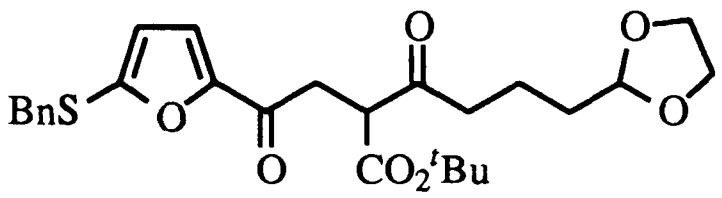


(**379**)

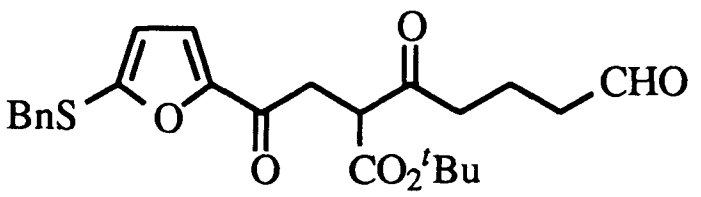
In order to inhibit the aldol closure, a more bulky ester group was introduced. Alkylating *tert*-butyl acetoacetate (**354**) at the acidic C-2 position by deprotonation with sodium hydride in tetrahydrofuran at 0°C followed by treatment with (bromoacetyl)furan (**249**) furnished the coupled furan adduct (**380**) in 49 % yield. Identification of the product was facilitated by the comparison of spectroscopic information with data for (**376**) and detection of the parent ion MH^+ (489) by mass spectrometric analysis.

Submitting dioxolane (**380**) to mild deprotection conditions and stirring in a solution of acetone-dilute hydrochloric acid (10 : 1 v/v) sluggishly formed the required aldehyde (**381**) in an equilibrium that resisted efforts to force to completion with increase in reaction time or quantity of catalyst. Utilising the harsher standard conditions and refluxing the

substrate (**380**) in a solution of acetone-water (10 : 1 v/v) in the presence of a catalytic quantity of *p*-toluenesulphonic acid for 24 hours allowed exclusive formation of aldehyde (**381**) in 91 % crude yield.



(**380**)



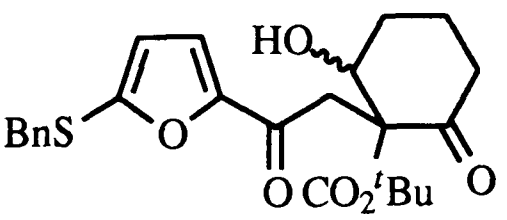
(**381**)

The aldehyde (**381**) was identified by disappearance of the cyclic ethylene acetal multiplet resonance at δ4.01 - 3.81 p.p.m. by ^{1}H n.m.r. spectroscopy and the appearance of a deshielded aldehyde proton signal at δ9.80 p.p.m.. Detection of the parent ion MH^+ (445) and the tropylium ion by mass spectrometry permitted further characterisation of the product.

Attempts to purify the product by flash chromatography on silica resulted in an albeit incomplete intramolecular cyclisation to occur and so the aldehyde (**381**) was submitted without purification to conditions for Grignard addition.

Evidently the introduction of a more bulky ester function had successfully inhibited the intramolecular aldol condensation. By utilising the stronger deacetalisation conditions complete deprotection had been achieved, negating the need for chromatographic purification that would inevitably cyclise the substrate. Thus, substitution at the acetoacetate position had prevented the facile dehydration to an α, β–unsaturated ketone and so stabilised aldehyde (**381**) in acidic media.

Addition of less than one equivalent of vinyl magnesium bromide to a solution of the crude aldehyde (**381**) in tetrahydrofuran at -78°C resulted in no isolation of allylic alcohol but induced the spontaneous intramolecular condensation to furnish alcoholic (**382**) in quantitative crude yield.



(**382**)

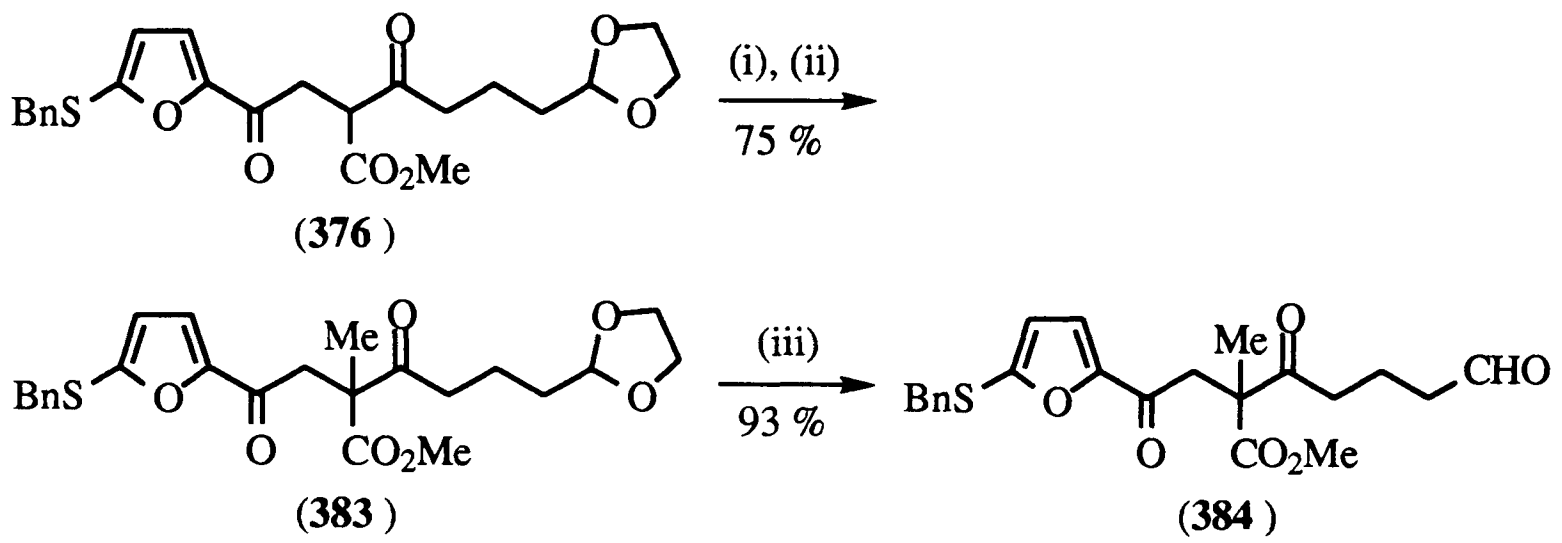
Formation of (**382**) was inferred by ^1H n.m.r. spectroscopy, observing disappearance of aldehyde and acetoacetate methine proton signals and an absence of vicinal couplings in the furoylmethylene proton resonance. Detection of the parent ion MH^+ (445) and dehydrated ion species $(MH\text{-}H_2O)^+$ (427) by mass spectrometric analysis further verified that the intramolecular cyclisation had been effected under the reaction conditions.

It was evident that vinyl magnesium bromide was behaving as a base rather than a nucleophile. This problem could have been solved by utilising a less basic organometallic nucleophile such as a cadmium, cerium, copper, or zinc reagent. However in the phorbol natural product (**1**) it was observed that a methyl substituent is in place at the C-2 tigliane position on the A-ring and this corresponded to alkylation at the acidic acetoacetate site. Hence it was suggested that the problem of aldol cyclisation and reagent basicity could be totally bypassed by C-2 methylation, thus preventing acetoacetate enolisation and intramolecular attack on aldehyde (**377**).

The coupled furan adduct (**376**) was deprotonated with sodium hydride in tetrahydrofuran at 0°C and the anion quenched by the addition of 2 equivalents of methyl iodide, warming the mixture to room temperature. The methylated product (**383**) was furnished in 24 % yield and identified by ^1H n.m.r. spectroscopy. Appearance of the furoylmethylene proton signal as a singlet at δ3.44 p.p.m., in the absence of vicinal couplings, disappearance of the acetoacetate methine resonance, and appearance of a new singlet at δ1.55 p.p.m. confirmed that methylation had occured. Observation of a new quartet signal at δ20.38 p.p.m. in the ^{13}C n.m.r. spectrum and detection of the parent ion MH^+ (461) by mass spectrometric analysis completed characterisation of the product.

Although the reaction had been successful, the yield of methylation was low and required improvement. Repeating the reaction with a large excess of the methylating agent resulted in an improvement in efficiency and facilitated acetoacetate (**383**) formation in 75 % yield (**Scheme 150**).

Deprotecting the methyl substituted dioxolane (**383**) by refluxing in a solution of acetone-water (9 : 1 v/v) in the presence of *p*-toluenesulphonic acid resulted in isolation of aldehyde (**384**) in 93 % yield (**Scheme 150**).



(i) NaH / THF / 0°C; (ii) MeI (10 equiv.) / 0°C to r.t.; (iii) *p*-TsOH (cat.) / acetone-H_2O (9 : 1 v/v) / 17 h reflux.

Scheme 150

The product was identified by appearance of a new absorption in the i.r. spectrum at 1 713 cm^{-1} that corresponded to the aldehyde carbonyl function. Additionally the resonance of the ethylene acetal methylene protons in the ^1H n.m.r. spectrum at δ3.93 p.p.m. had been replaced by a triplet signal at δ9.78 p.p.m., corresponding to formation of a deshielded aldehyde proton. Detection of the parent ion MH^+ (417) by mass spectrometric analysis completed characterisation of the product.

It was apparent that methyl substitution at the acetoacetate position had successfully blocked the intramolecular cyclisation and enabled isolation of product (**384**). It was now necessary to attempt to elaborate the dienophile by addition of a suitable nucleophile to the unmasked aldehyde moiety.

In order to minimise problems in chemoselectivity and encourage attack of the more reactive carbonyl function, vinylmagnesium bromide was added to a solution of the aldehyde (**384**) in tetrahydrofuran at -78°C and quenched after 30 minutes at this temperature by addition of saturated aqueous ammonium chloride solution. The allylic alcohol (**385**) was furnished as the sole reaction product in 32 % yield (**Scheme 151**) with 31 % return of unreacted starting material indicating that reaction had not yet reached reached its completion.

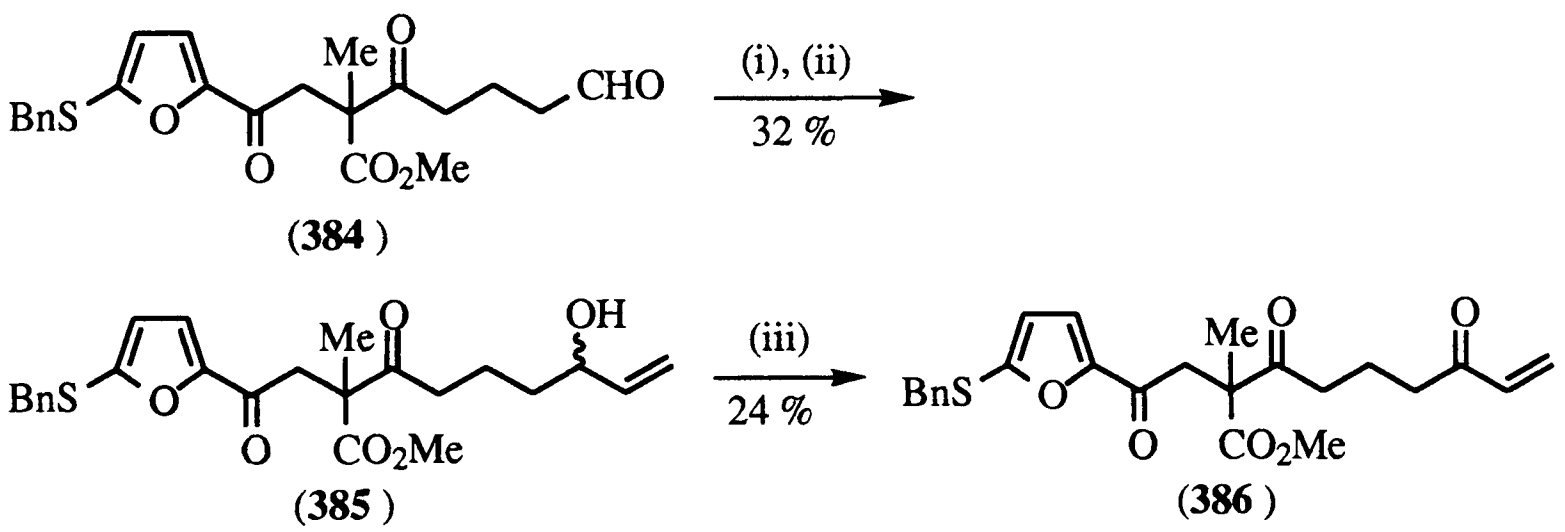
The product was identified by disappearance of the aldehyde carbonyl vibration at 1 715 cm^{-1} and appearance of a hydroxyl absorption at 3 500 cm-1 and an olefinic absorption

at 1 603 cm^{-1}. ^1H n.m.r. spectroscopy confirmed that introduction of the vinylic substituent had been successful with olefinic signals at δ5.88, 5.24, and 5.12 p.p.m., an allylic proton resonance at δ4.09 p.p.m., and hydroxyl resonance at δ1.88 p.p.m. that was exchangeable on addition of D_2O. Detection of a trace of the parent ion MH^+ (445) and the dehydrated ion species $(MH\text{-}H_2O)^+$ (427) completed the characterisation of the product.

An effort to optimise the conversion by application of a longer reaction time led to little improvement in yield. Repeating the procedure and quenching after stirring for 6 hours at -78°C resulted in the total consumption of starting material but the efficiency was limited by the instability of the product to silica or neutral alumina chromatographic purification.

Evidently the problem of the intramolecular aldol cyclisation had been bypassed by acetoacetate substitution and thus facilitated introduction of dienophilic and tigliane C-2 methyl substituents.

Oxidation of the allylic alcohol by stirring (**385**) in chloroform for 24 hours at room temperature in the presence of activated manganese dioxide on charcoal furnished a 24 % yield of enone (**386**) (**Scheme 151**) with a 40 % return of unreacted starting material.



(385) (386)

(i) Vinylmagnesium bromide / THF / -78°C / 30 min; (ii) NH_4Cl (aq); (iii) MnO_2 / C / $CHCl_3$ / r.t. / 24 h.

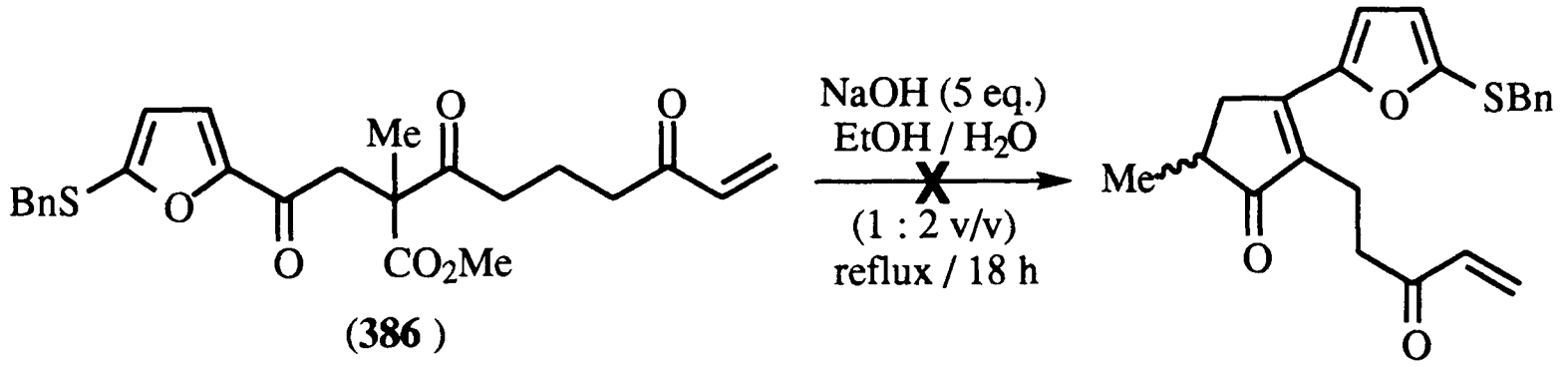
Scheme 151

The oxidised product (**386**) was identified by disappearance of the hydroxyl absorption at 3 500 cm^{-1} in the i.r. spectrum, and the observation of conjugated carbonyl vibrations at 1 681 and 1 673 cm^{-1} that corresponded to the furylketone and enone absorptions respectively, and an olefinic vibration at 1 616 cm^{-1}. ^1H n.m.r. spectroscopy

confirmed successful transformation of the allylic alcohol and inferred formation of the enone (**386**) by the deshielding of the vinylic protons and removal of allylic proton couplings, the olefinic resonances now being observed as three double-doublet signals at δ6.37, 6.23, and 5.84 p.p.m.. Detection of the parent ion MH^+ (443) completed the characterisation of the product and confirmed successful dienophilic elaboration.

Efforts to improve the yield by resubmitting a solution of the substrate (**385**) in chloroform to the reaction conditions and refluxing for 2 days resulted in complete degradation and isolation of only a trace of product (**386**).

Treating an aqueous ethanolic solution of enone (**386**) with 5 equivalents of sodium hydroxide and refluxing for 18 hours according to the procedure for intramolecular aldol cyclisation afforded none of the desired cyclopentenone (**387**) (**Scheme 152**) but appeared to induce substrate degradation with the formation of at least 9 different products by t.l.c. analysis.



(**386**) (**387**)

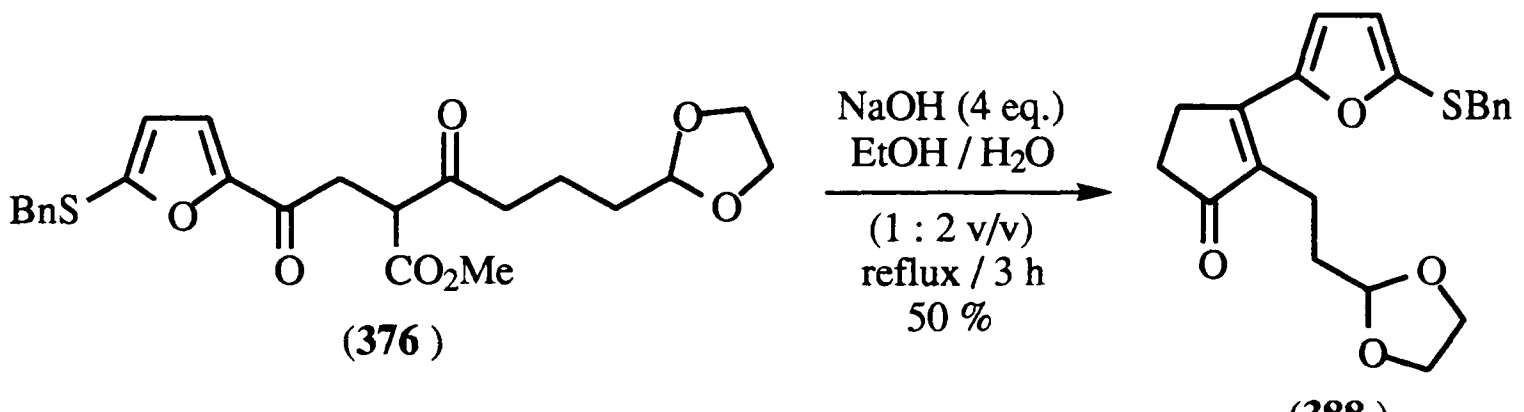
Scheme 152

It was postulated that the failure of reaction could be a result of the presence of an alter native enolisable carbonyl in the substrate (**386**). It was not known whether furylcyclopentenone (**387**), possessing activated diene and dienophilic components, would be stable under the reaction conditions and this could also account for the lack of success, although no evidence of cycloaddition was observed.

Considering the failure of this procedure, that is known to be successful for cyclising furyl-1, 4-diketones (section 2.2.1.),[82] it was suggested that the coupled furyl adduct (**376**) should be submitted to conditions for intramolecular aldol condensation, delaying elaboration of the dienophilic tether until the end of the synthesis. Not only would this remove the

alternative enolisable ketone but it would minimise the number of alternative electrophilic sites in the substrate and avoid the use of low yielding synthetic steps that have been problematical in dienophile elaboration.

Refluxing an ethanolic aqueous solution of (furoylmethyl)acetoacetate (**376**) for 5 hours in the presence of 4 equivalents of sodium hydroxide furnished a 90 % crude yield of cyclopentenone (**388**) polluted with a small amount of an unknown dioxolane side product. Purification of the crude reaction mixture by recrystallising from ethanol at -12°C isolated the product (**388**) in 50 % yield (**Scheme 153**) and concentrated the side product in the mother liquor to enable identification.



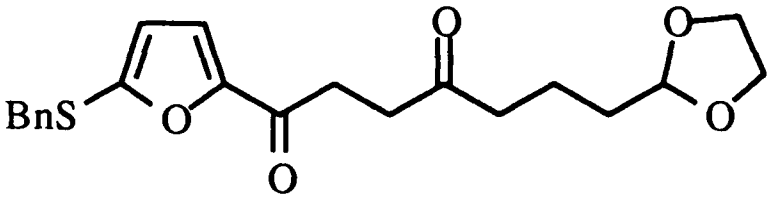
(**376**) (**388**)

Scheme 153

Cyclised product (**388**) was identified by absorptions in the i.r. spectrum at 1 692 and 1 620 cm^{-1}, corresponding to cyclopentenone vibrations. Observation of a 0.3 p.p.m. upfield shift in the 3-furyl proton signal by ^1H n.m.r. spectroscopy and the presence of cyclopentenone methylene multiplet resonances at δ2.83 and 2.50 p.p.m. confirmed the success of the intramolecular reaction. Detection of the parent ion MH^+ (371), the tropylium ion, and the ion species $C_3H_5O_2^+$ (**352**) (73) completed the characterisation of the product.

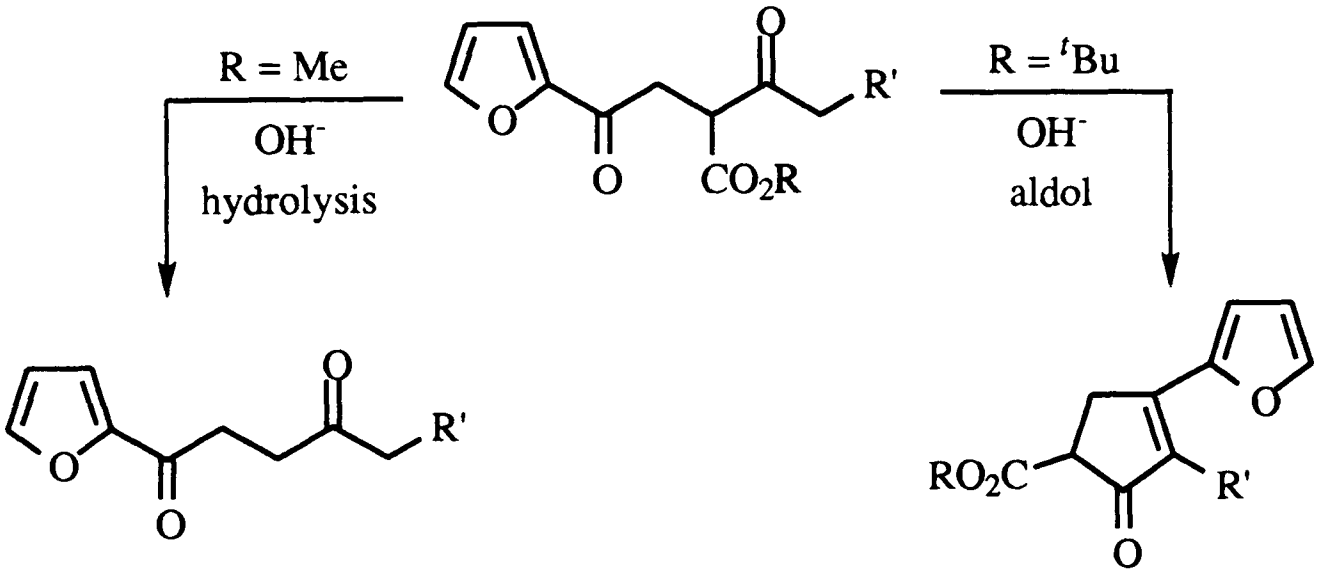
The side product was identified as the 1, 4-diketone cyclisation precursor (**389**) by ^1H n.m.r. spectroscopic analysis of the mother liquor. The resonance of the 3-furyl proton was observed at low field, δ7.13 p.p.m., indicating that successful transformation of the acetylfuran function into a cyclopentenone had not yet been achieved. A triplet signal at δ4.97 p.p.m. confirmed the integrity of the dioxolane substituent. In addition, the absence of the methyl ester and acetoacetate methine resonances, with the appearance of the

furoylmethylene signal as a simple triplet, indicated that the product had undergone de-esterification and concomitant decarboxylation to the 1, 4-diketone (**389**).



(**389**)

The isolation of the de-esterified species (**389**) from the reaction mixture is in contrast to the behaviour of the *tert*-butyl substrate (**240**) upon reflux in basic media. In that instance, intramolecular cyclisation was more facile with isolation of *tert*-butyl cyclopentenoate (**241**). However, in the absence of *tert*-butyl steric constraints, the ester hydrolysis would be more rapid (typically by a factor of 125)[145] resulting in a change in the mechanistic course with de-esterification and concomitant decarboxylation occuring in preference to the intramolecular condensation (**Scheme 154**).



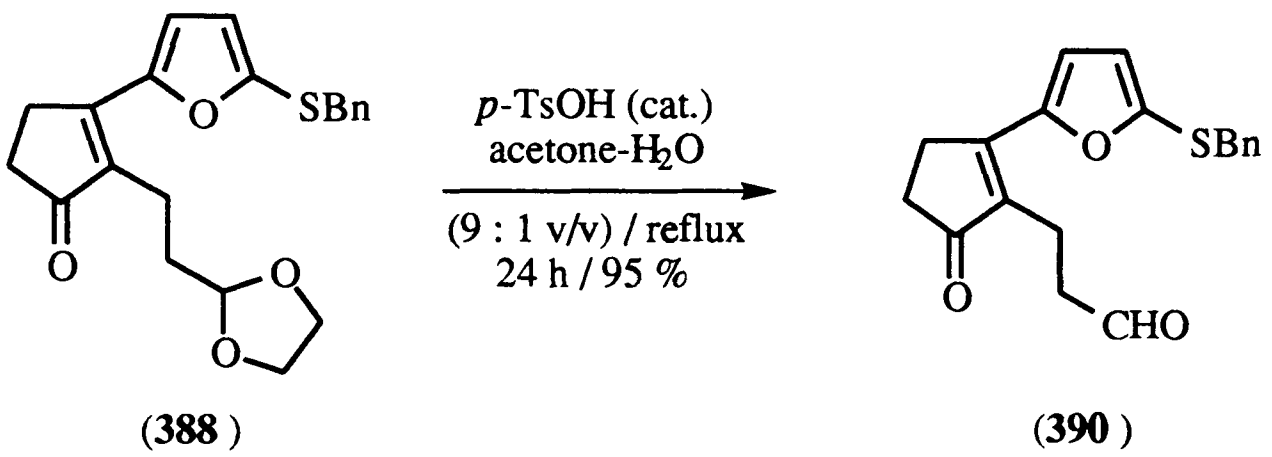
Scheme 154

Resubmitting the mother liquor to the reaction conditions and refluxing overnight successfully cyclised the 1, 4-diketone intermediate (**389**) to furnish pure cyclopentenone (**388**) in an additional yield of 20 %, taking the total reaction efficiency to 70 %.

Interestingly if the substrate (**376**) was resubmitted to the reaction conditions and refluxed for 5 hours in high dilution in the basic medium then none of the 1, 4-diketone intermediate (**389**) was isolated and the product (**388**) was obtained in 89 % yield. From

this observation it was understood that diluting the reaction was speeding up the rate determining step, perhaps by favouring the intramolecular process over intermolecular condensations that, although reversible under the reaction conditions, would serve to reduce the concentration of substrate and so hinder cyclisation.

Deprotection of the acetal (**388**) by refluxing the substrate for 24 hours in acetone-water (9 : 1 v/v) in the presence of a catalytic quantity of *p*-toluenesulphonic acid afforded the unmasked aldehyde (**390**) in 95 % yield with a trace of unreacted starting material that could not be removed by chromatographic purification on silica (**Scheme 155**).



(**388**) (**390**)

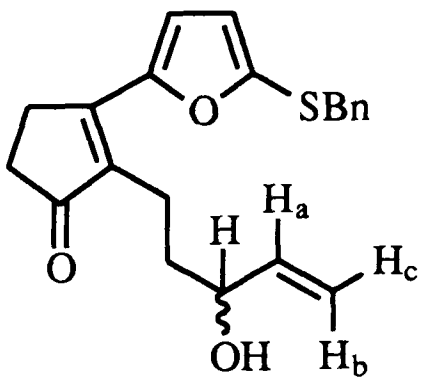
Scheme 155

The product was identified by the observation of a new carbonyl absorption at 1 720 cm^{-1} in the i.r. spectrum and disappearance of the acetal methylene resonances at δ3.98 - 3.85 p.p.m. and the C-2 dioxolane methine triplet at δ4.95 p.p.m. in the ^{1}H n.m.r. spectrum in addition to the appearance of a new deshielded aldehyde proton signal at δ9.80 p.p.m. The presence of two quaternary carbonyl resonances at δ208.07 and 201.76 p.p.m. in the ^{13}C n.m.r. spectrum and detection of the parent ion MH^{+} (327) and the tropylium ion completed characterisation of the product.

An effort was made to force the deprotection equilibrium to product (**390**). Stirring a solution of dioxolane (**388**) in a two phase ether-dilute hydrochloric acid system furnished predominantly unreacted starting material in 79 % yield, with only a trace of the desired product (**390**). Utilising a stronger catalyst, trifluoroacetic acid, and repeating the reaction still returned predominantly unreacted starting material but caused appreciable degradation of material.

Repeating the *p*-toluenesulphonic acid deprotection and refluxing the mixture for a total of 48 hours still failed to force the deacetalisation equilibrium to completion and reduced the product yield to 85 %. However the failure to effect total conversion was solved by changing the purification procedure. Chromatographic separation on neutral alumina, eluting with ethyl acetate-light petroleum (b.p. 30-40°C), enabled isolation of pure aldehyde (**390**) but in only 50 % yield, reflecting the instability of the product under these conditions. Hence, due to the problem in effecting both the exclusive and efficient formation of aldehyde (**390**), it was decided to proceed with the contaminated substrate, generated in 95 % yield (**Scheme 155**), for dienophilic elaboration. It was hoped that dioxolane (**388**) would be unreactive under nucleophilic addition in the presence of the aldehyde (**390**) and so would not interfere in the conversion.

In order to establish the synthetic methodology an initial attempt was made to generate the mono-activated IMDAF substrate (**328**). Vinylmagnesium bromide was added to a solution of aldehyde (**390**) in tetrahydrofuran at -35°C. Warming the mixture to room temperature overnight afforded a complex mixture of products that contained unreacted starting material and the desired allylic alcohol (**391**), identified by observation of olefinic proton resonances at δ5.91, 5.26, and 5.10 p.p.m. (**Figure 6**).



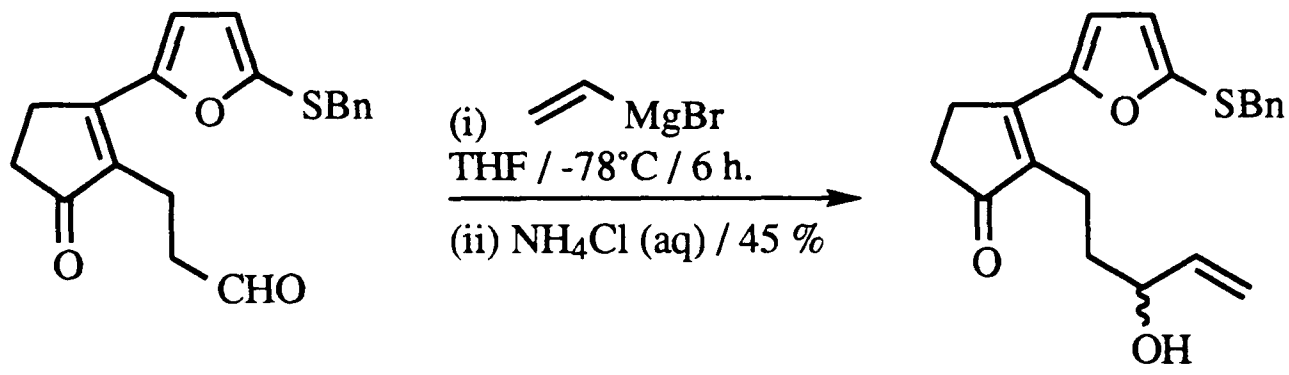
(**391**)

H_a : 5.91 (1H, ddd, *J* 17.3, *J'* 10.5, *J"* 5.4 Hz)
H_b : 5.26 (1H, dd, J_{vic} 17.3, J_{gem} 1.5 Hz)
H_c : 5.10 (1H, dd, J_{vic} 10.5, J_{gem} 1.5 Hz)

Figure 6

Repeating the procedure and conducting the addition at -78°C indicated by ^{1}H n.m.r. spectroscopic analysis of reaction aliquots that, although the reaction was slow, formation of the desired product (**391**) was exclusive in precedence to 1, 2- or 1, 4- cyclopentenone addition over the first 5 hours at this temperature. However as the temperature was raised to

-60°C an alternative product started to form. Thus in order to prevent chemoselectivity problems evident at higher temperatures, the vinylation was repeated rigorously maintaining the reaction temperature at -78°C for 6 hours. Following aqueous work up the allylic alcohol (**391**) was formed in quantitative crude yield, with only minimal contamination from unreacted starting material (**390**) and the unidentified side product present in only a trace concentration. Although the purity of the product was satisfactory for synthetic progression, it was insufficient to allow accurate combustion analysis. Purification by flash chromatography on silica resulted in appreciable degradation of material but did facilitate isolation of analytically pure allylic alcohol (**391**) in 45 % yield (**Scheme 156**).



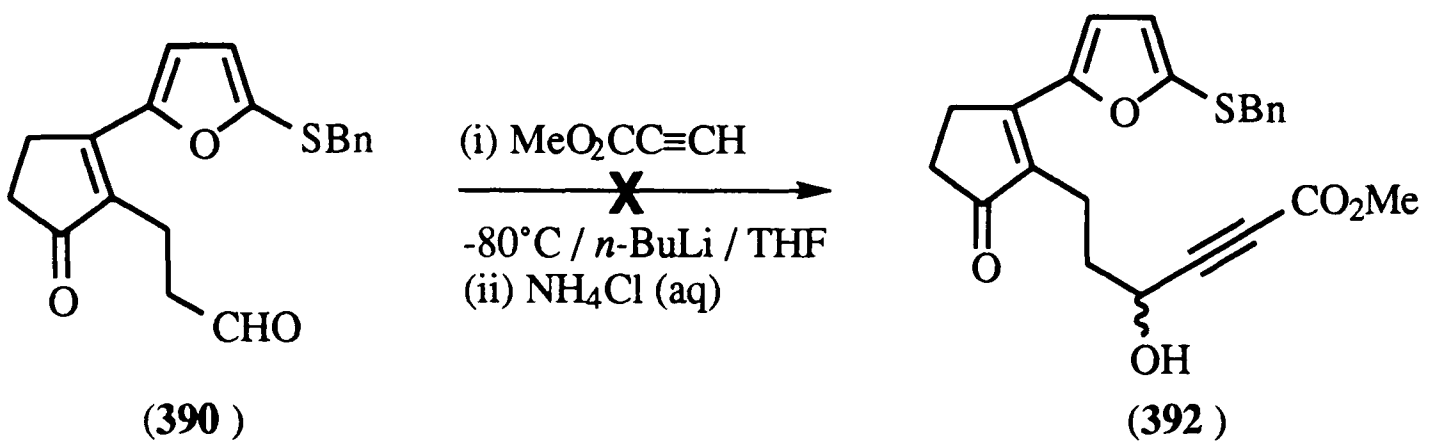
(**390**) (**391**)

Scheme 156

The product was identified by the appearance of a hydroxyl absorption at 3 429 cm^{-1} in the i.r. spectrum and observation of an allylic methine multiplet resonance at δ4.04 p.p.m. and three olefinic resonances in the ^1H n.m.r. spectrum. Detection of the parent ion MH^+ (355) by mass spectrometric analysis completed the characterisation and confirmed that introduction of the mono-activated dienophilic skeleton had been successful.

An attempt was made to construct a di-activated dienophile by similar protocol. Lithiated acetylide, generated by the deprotonation of methyl propiolate with *n*-butyllithium in tetrahydrofuran at -80°C, was added to aldehyde (**390**) according to the procedure of Midland.[95] However, only a 92 % recovery of unreacted starting material (**390**) was obtained from the reaction mixture after 2 hours at -95 to -80°C. Allowing the reaction to warm slowly to room temperature resulted in degradation of the acetylide and formation of a complex mixture of products containing unreacted starting material and none of the required alkynyl

alcohol (**392**) (**Scheme 157**). Evidently at temperatures at which the lithium acetylide reagent was stable, addition was unable to occur.

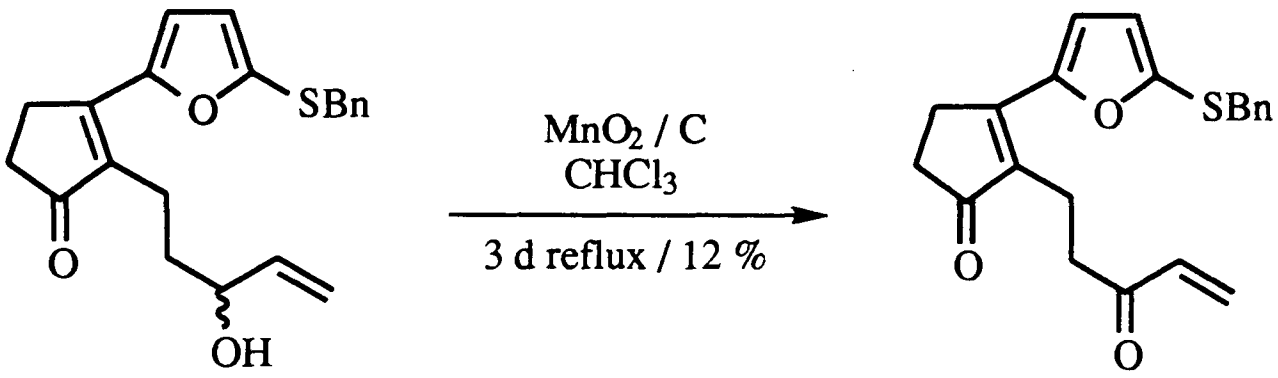


(**390**) (**392**)

Scheme 157

Experiencing difficulties in the synthesis of alkynyl derivatives, it was decided to elaborate the mono-activated dienophile constructed by vinylic addition. Submitting allylic alcohol (**391**) to conditions for Swern oxidation[137] and exposing the substrate to the mild action of "activated" dimethylsulphoxide at -30°C, followed by treatment with triethylamine, resulted in complete polymerisation of material.

Employing alternative oxidation conditions and stirring the alcohol (**391**) in a solution of chloroform in the presence of activated manganese dioxide on charcoal for 3 days at room temperature afforded only a trace of enone (**328**) and returned predominantly unreacted starting material. An attempt was made to speed up the rate of reaction in this heterogeneous system by submitting the substrate to reflux. T.l.c. analysis indicated that formation of the oxidised species (**328**) was extremely sluggish, even in the presence of a large excess of the oxidant (approximately 2 g/mmol). After 3 days at reflux only a 12 % yield of α, β-unsaturated ketone (**328**) was obtained, with a 4 % return of unreacted starting material (**391**) (**Scheme 158**).



(**391**) (**328**)

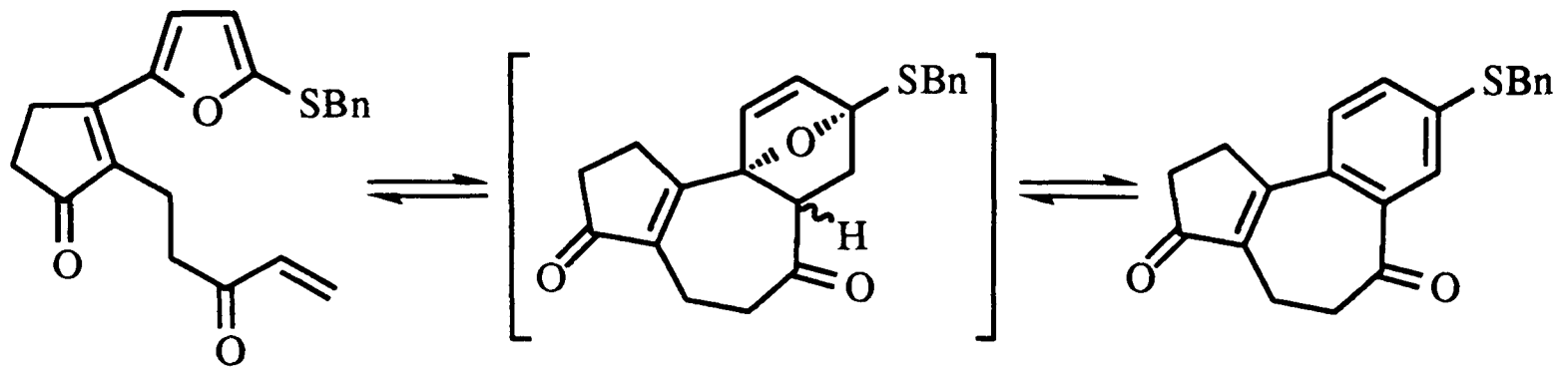
Scheme 158

The product was identified by absorptions in the i.r. spectrum at 1 692 and 1 621 cm^{-1}, that corresponded to enone vibration, and disappearance of the hydroxyl absorption at 3 429 cm^{-1}. It was confirmed that oxidation had been successful by ^1H n.m.r. spectroscopy, observing deshielding of the olefinic proton resonance as a result of electron withdrawal to the newly formed carbonyl moiety. Additionally, disappearance of the allylic proton resonance was accompanied by removal of its vicinal couplings, the olefinic methine signal now being observed as a simple double-doublet. Detection of the parent ion MH^+ (353) by mass spectrometric analysis completed the characterisation of the product.

Submitting the allylic alcohol (**391**) crude into the manganese dioxide oxidation afforded little improvement in yield over the two synthetic steps and resulted in contamination of the product (**328**) by a trace of aldehyde starting material (**390**) that could not be removed by chromatographic purification techniques. For this reason, despite the high degree of purity of crude allylic alcohol (**391**) and its instability to silica, separation at this stage was demanded and led to some loss of material.

Employing alternative oxidative conditions and refluxing a solution of the allylic alcohol (**391**) in toluene overnight in the presence of Fetizon's reagent precipitated the reduced silver metal and appeared to cause an appreciable loss of material. A mixture of unreacted alcohol (**391**), the oxidised product (**328**), and a side product (**393**) was isolated from the reaction, the latter elucidated by ^1H n.m.r. spectroscopy to contain 3 aromatic protons that appeared as a singlet at δ8.82 p.p.m. and 2 doublets at δ8.35 and 7.88 p.p.m.. Upon this evidence it was proposed that the consumption of material was occuring through cycloadducts (**394**) that were degrading under the reaction conditions. It could be expected

that cleavage of the oxygen bridge would be more facile in this system, not only because of the release of strain inherent in the tetracyclic diterpene adduct (**394a**) but on account of dehydration producing extended conjugation in the aromatised product (**393**) (**Scheme 159**).

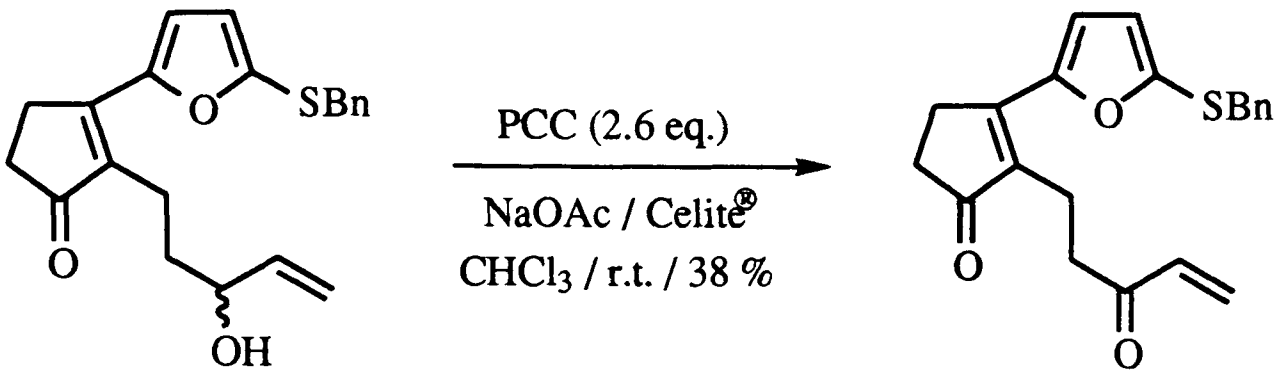


(**328**) (**394a**) (**393**)

Scheme 159

Although this hypothesis explained the observed loss of reaction material and the presence of aromatic resonances in the ^1H n.m.r. spectrum of the product, it did not account convincingly for the absence of cycloadduct (**394a**) and the aromatised species (**393**) from other allylic oxidation systems. It was however evident that some degradation mechanism was operating that destroyed the substrate in Swern oxidation and drastically lowered the efficiency of other oxidants.

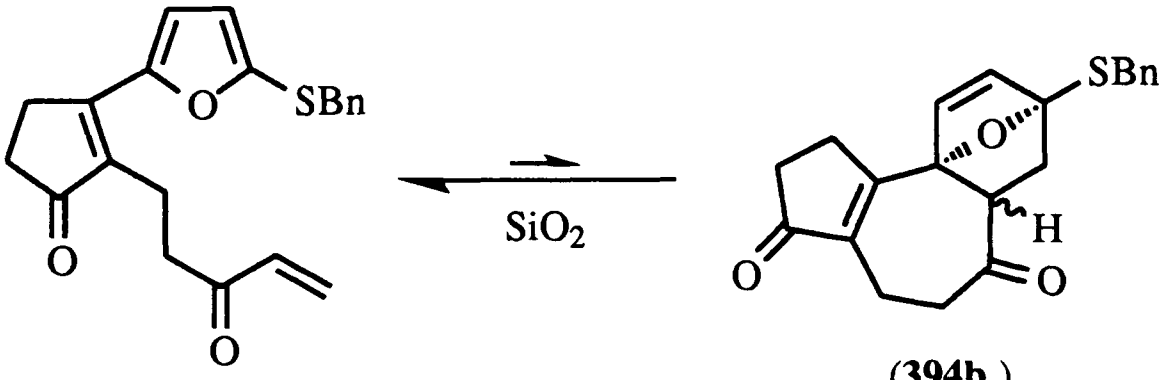
As a final effort to optimise the transformation a solution of alcohol (**391**) in chloroform was treated with pyridinium chlorochromate in the presence of anhydrous sodium acetate buffer and Celite®. The oxidant was added in small portions and the course of reaction followed by t.l.c. analysis. Halting the procedure after the addition of 2.6 equivalents of reagent, enone (**328**) was isolated exclusively in 38 % yield (**Scheme 160**), an efficiency that surpassed any of the heterogeneous oxidants. Although this marked increase in yield could have been a consequence of the buffer, the convenience, reproducibility and ease of monitoring of this system resulted in the adoption of this procedure for allylic oxidation.



(**391**) (**328**)

Scheme 160

Subjecting a solution of the IMDAF precursor (**328**) in dichloromethane to 18 kbar pressure at 20°C for 1 day afforded predominantly unreacted starting material and a new product that reverted to enone (**328**) on attempted silica purification. ^{1}H n.m.r. spectroscopic analysis of the crude reaction mixture elucidated the identity of the trace product as the desired cycloadduct (**394b**) that was in an unfavourable equilibrium with the starting material (**328**), the cycloreversion catalysed by exposure to silica (**Scheme 161**).

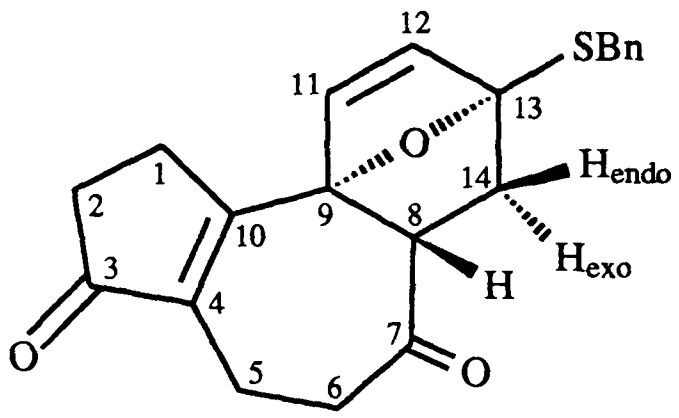


(**328**) (**394b**)

Scheme 161

The product was identified by observation of 2 new olefinic doublet resonances at δ6.78 and 6.01 p.p.m., confirming formation of a 7-oxabicyclo[2.2.1]heptene with a coupling constant magnitude (*J* 5 Hz) typical of the system, a double-doublet resonance at δ3.58 p.p.m. arising from the B-C ring junction proton, and two double-doublet resonances at δ2.26 and 2.06 p.p.m., corresponding to *exo* and *endo* C-14 cycloadduct protons (tigliane numbering). Comparison of spectroscopic data with reported information[82,94] supported the assignment and confirmed the presence of the cycloadduct (**394b**) in the reaction equilibrium.

Due to the close proximity of *exo* and *endo* oxabicyclo[2.2.1]heptyl proton signals and the absence of W-couplings in the unsaturated system, it was not possible to categorically specify the stereochemistry of the cycloaddition. Based on the assumption that the high field double-doublet signal corresponded to resonance of the C-14 *endo* proton (tigliane numbering), the *syn* orientated B-C bridgehead proton (*J* 8 Hz) would occupy an *endo*-stereochemical environment, implying *exo* cycloaddition (**Figure 7**). Spectroscopic data for the *exo* adduct (**394b**) compared favourably with results from previous studies within the group[82,94] and corresponded well to formation of the kinetic reaction product under conditions of high pressure.



(394b)

3.58 (1H, dd, *J* 8.3, *J'* 4.0 Hz, 8-H)
2.26 (1H, dd, J_{gem} 11.7, J_{vic} 4.0 Hz, 14 $_{exo}$-H)
2.06 (1H, dd, J_{gem} 11.7, J_{vic} 8.3 Hz, 14 $_{endo}$-H)

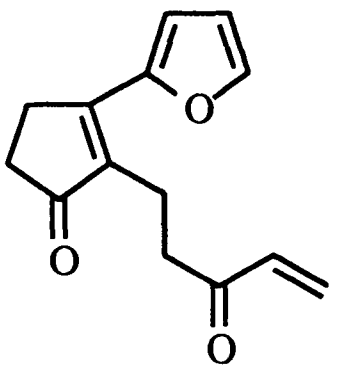
Figure 7

Evidently activation of the dienophile had successfully favoured IMDAF and allowed observation of a single cycloadduct (**394b**). However isolation and characterisation of the product was not possible as a consequence of the steroelectronic effect of the cyclopentenone and the unfavourable configurational change upon sp^2 hybridisation at the A-B ring junction. Enforced adoption of 120° bond angles at this junction would introduce strain into the cycloadduct that can be relieved by cycloreversion. This would produce an unfavourable reaction equilibrium and prevent isolation of product (**394b**). The change in configuration at the A-B ring junction could also be the factor responsible for formation of the kinetic cycloadduct with an increase in the activation barrier to reaction.

Increasing the pressurisation time of the IMDAF and subjecting enone (**328**) to 18 kbar pressure for 4 days did not improve the yield of cycloadduct (**394b**) and resulted in a marked decrease in the concentration of both starting material and product, with formation of

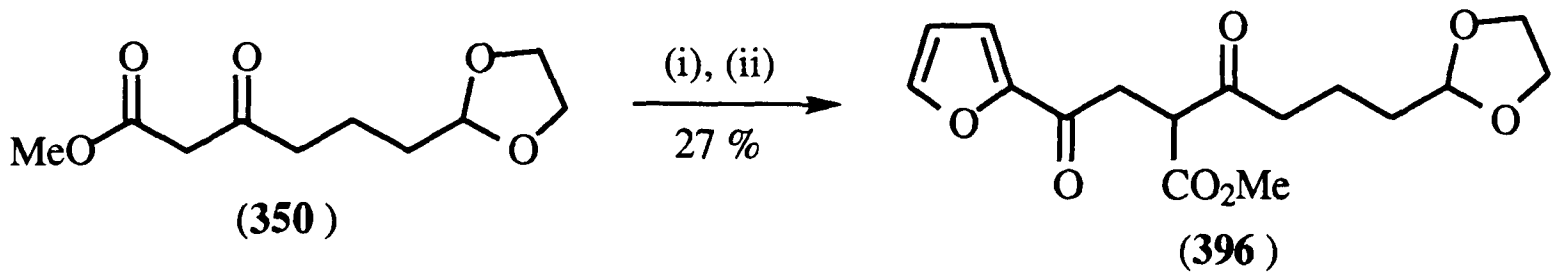
a number of new derivatives. Silica purification indicated that the mixture predominantly consisted of degraded material but succeeded in isolating a single unidentified reaction product, elucidated by ^{13}C n.m.r. to have incorporated 2 extra carbon atoms into its molecular skeleton and thus to be the product of an intermolecular reaction. This observation was supported by evidence from mass spectrometric and 500 MHz ^{1}H n.m.r. spectroscopic analysis, that suggested consumption of the dienophilic enone moiety, preservation of the benzylthiofurylcyclopentenone function, and curious incorporation of an ethyl substituent. This result not only implied that an intermolecular process was occuring but that redox chemistry had effectively reduced the dienophilic enone. Based on this evidence it was deduced that a route to phorboid cycloadducts by IMDAF of benzylthiocyclopentenone (**328**) was not synthetically viable. It was also postulated that the degradative mechanism that had prevented cycloadduct (**394b**) isolation had been responsible for the destruction of the methyl substituted cyclopentenone (**387**) (**Scheme 152**).

In order to compare system behaviour under high pressure conditions, an effort was made to synthesise the analogous furyl substrate (**395**). Not only would this examine the necessity of the benzylthio diene activating group for cycloadduct (**394b**) generation but it would probe the role of this substituent in the degradative process.



(**395**)

Following the established protocol, (2-bromoacetyl)furan (**227**) was alkylated with the anion generated from the methyl acetoacetate derivative (**350**) to furnish the (furoylmethyl)acetoacetate (**396**) in 27 % yield (**Scheme 162**). The product was identified by comparison of spectroscopic data with those of the benzylthiofuroyl derivative (**376**).

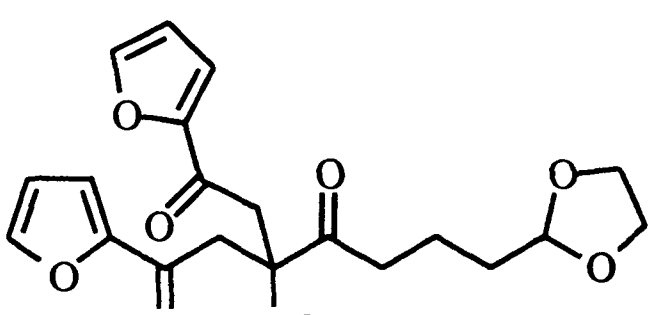


(**350**) (**396**)

(i) NaH / THF / 0°C; (ii) 2-(Bromoacetyl)furan (**227**).

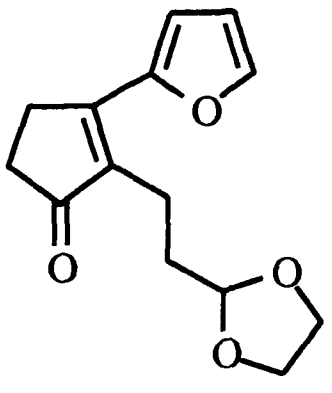
Scheme 162

Not only did a large degree of polymerisation accompany the reaction but a 20 % yield of the diaddition product (**397**) was formed that was separated by chromatographic purification on silica. ^{1}H n.m.r. spectroscopic analysis identified the side product, observing an absence of signals at δ4.2 p.p.m. due to the acetoacetate methine proton and appearance of a four proton singlet at δ3.83 p.p.m. as a consequence of incorporation of two furoylmethylene groups.

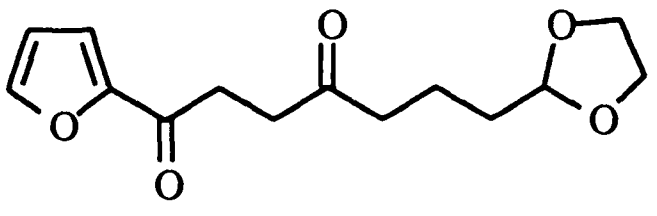


(**397**)

Subjecting substrate (**396**) to conditions for intramolecular cyclisation and refluxing for 6 hours led to isolation of a mixture of cyclopentenone (**398**) and its 1, 4-diketone precursor (**399**). Resubmission for a further 24 hours reflux still did not drive the reaction equilibrium to completion, alicyclic furan (**399**) dominating the isolated mixture.



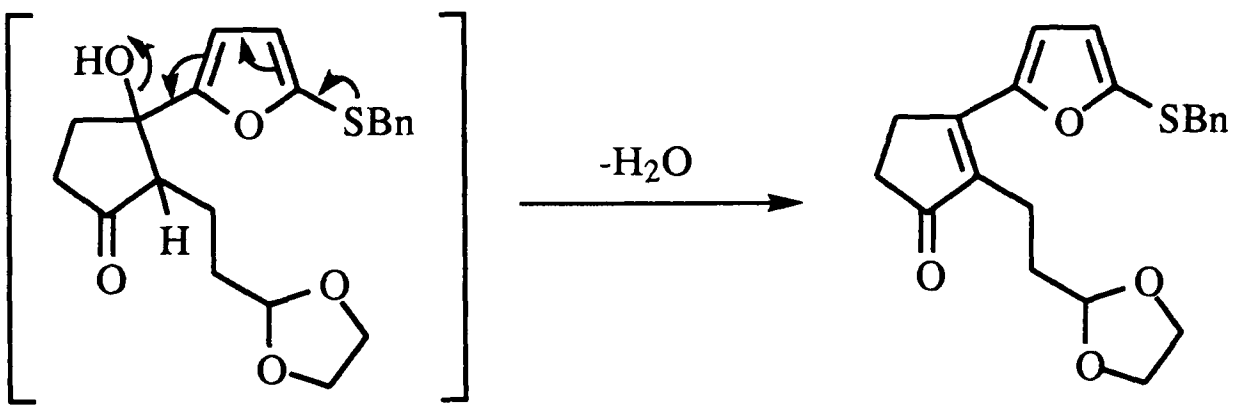
(**398**)



(**399**)

Flash chromatographic purification proved incapable of separating 1, 4-diketone (**399**) from the required product (**398**) whereas recrystallisation from ethanol at -12°C allowed isolation of the pure material in 30 % yield. The product was identified by comparison of spectroscopic data with that of benzylthiofurylcyclopentenone (**388**).

It was apparent that the cyclisation of the furyl substrate (**396**) was less facile than the condensation of benzylthiofuran (**376**). In the latter instance, dehydration of the cyclised intermediate (**400**) was anchimerically assisted by the sulphide substituent to furnish benzylthiofurylcyclopentenone (**388**) (**Scheme 163**).

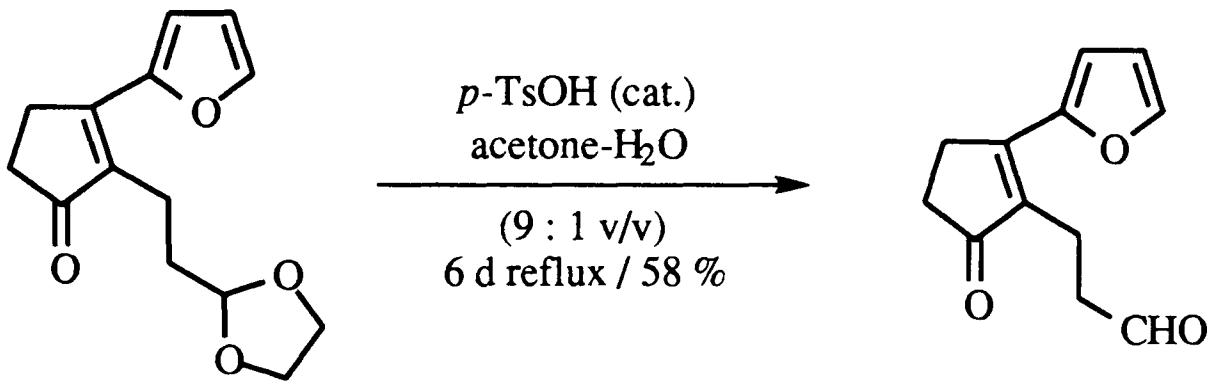


(**400**) (**388**)

Scheme 163

Repeating the procedure and diluting the reaction by a factor of five appeared to accelerate the intramolecular cyclisation dramatically, furnishing cyclopentenone (**398**) in 56 % yield with only minimal contamination from diketone (**399**).

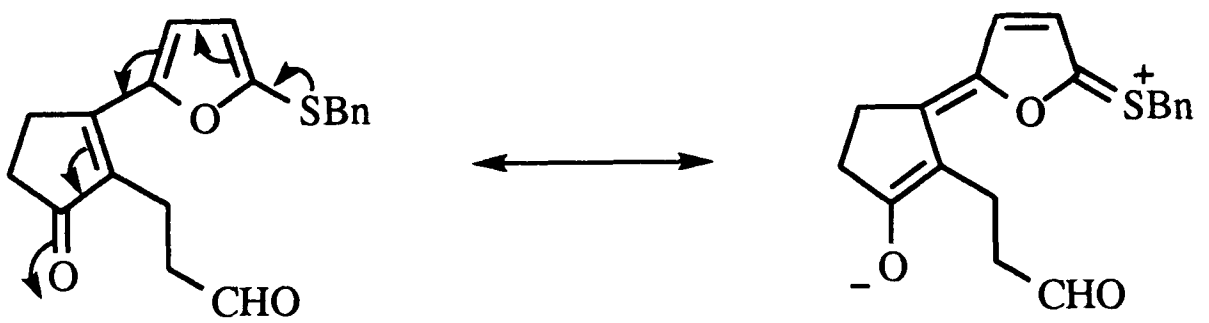
Deprotecting the dioxolane (**398**) under standard conditions and refluxing in an acetone-water solution in the presence of *p*-toluenesulphonic acid for 2 days afforded aldehyde (**401**) as the minor product, predominantly returning unreacted starting material. Resubmission to the deacetalisation conditions and refluxing for a further 4 days successfully unmasked the product in 58 % yield (**Scheme 164**). Although no explanation could be offered for the unusually sluggish deprotection, the loss of material was attributed to acid catalysed polymerisation over the extended reaction period.



(398) **(401)**

Scheme 164

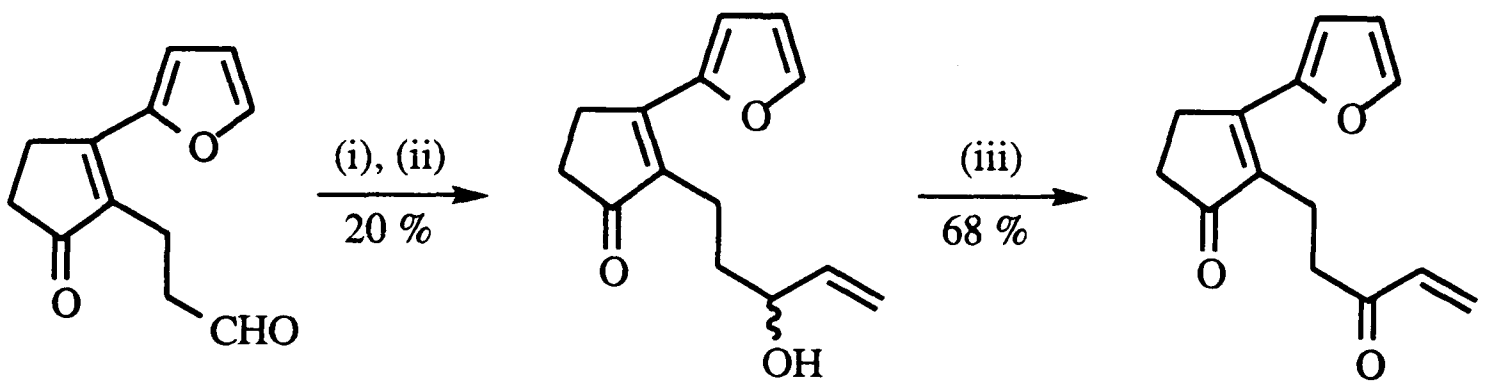
The treatment of a solution of aldehyde (**401**) in tetrahydrofuran with vinylmagnesium bromide at -78°C for 6 hours resulted in isolation of the allylic alcohol (**402**) in only 20 % yield (**Scheme 166**). This reflected instability of the product to silica purification and a loss in the chemoselectivity of reaction, determined by the appearance of alternative alkene signals at δ6.40 and 5.35 p.p.m. in the crude ^{1}H n.m.r. spectrum. Mesomeric donation by the sulphide substituent in the benzylthiofuryl substituted aldehyde (**390**) would reduce the electrophilicity of the cyclopentenone and so inhibit 1, 2-addition at the alternative reaction site (**Scheme 165**) favouring a chemoselective attack of the aldehyde moiety.



(390) **(403)**

Scheme 165

The allylic oxidation with pyridinium chlorochromate in chloroform, in the presence of Celite® and anhydrous sodium acetate, was followed closely by t.l.c. analysis and halted after addition of 2.6 equivalents of oxidant. Enone (**395**) was furnished in 68 % yield (**Scheme 166**) and identified by comparison of spectroscopic data with those of the benzylthiofuryl IMDAF substrate (**328**).



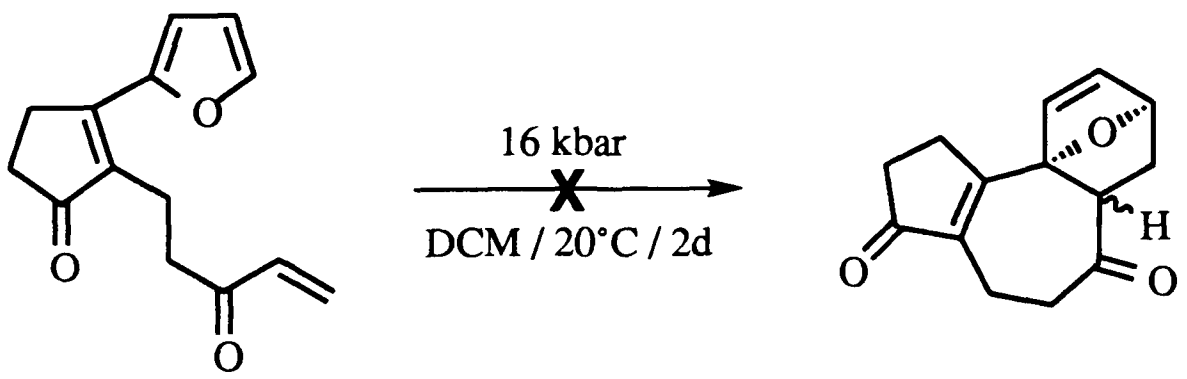
(**401**) (**402**) (**395**)

(i) Vinylmagnesium bromide / THF / -78°C / 6 h; (ii) NH_4Cl (aq); (iii) PCC (2.6 eq.) / NaOAc / Celite® / $CHCl_3$ / 24 h.

Scheme 166

It was noted that the efficiency of the oxidation had improved over oxidation of the benzylthiofuryl system (**391**). Evidently degradation of a more electron rich thiofuran system under oxidative reaction conditions had resulted in an appreciable loss of material in the previous instance.

Subjecting a solution of the furyl IMDAF substrate (**395**) in dichloromethane to 16 kbar pressure at 20°C for 2 days led to no isolation of cycloadduct (**404**) or recovery of starting material (**Scheme 167**). The degradation was identical to that of benzylthiofuran (**328**) under high pressure conditions, the unidentified product being shown by ^1H n.m.r. spectroscopy to be the result of an intermolecular reaction with disappearance of the terminal enone resonance and appearance of ethyl signals. Evidently debenzylthiolation had had no effect on the course of the degradation and the required product (**404**) was not observed.



(**395**) (**404**)

Scheme 167

Comparing furyl and benzylthiofuryl substrates it was apparent that, although a great synthetic effort had been required to introduce what originally appeared as an easily

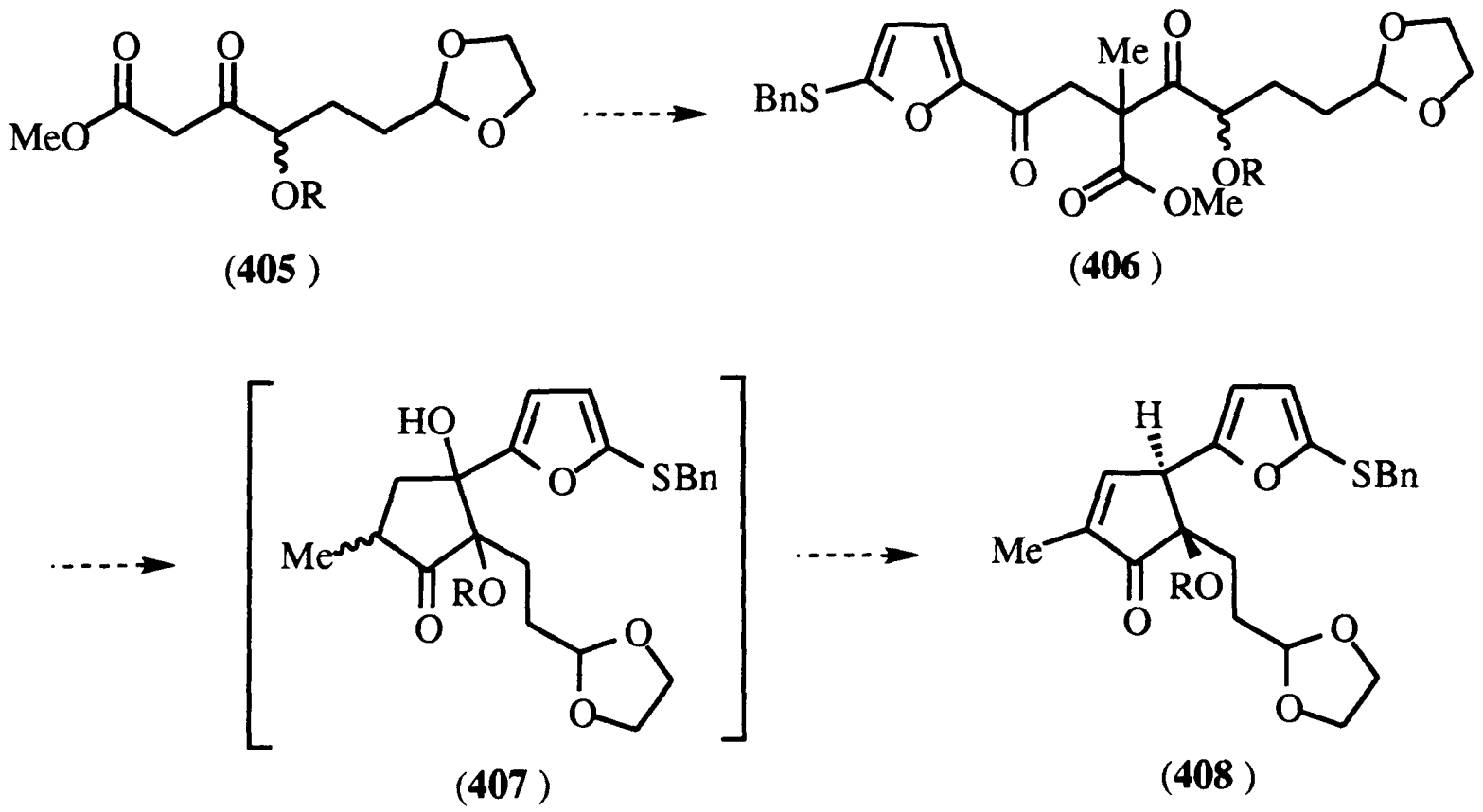
incorporated diene activating substituent, the rewards had been substantial. Not only had the observation of a single cycloadduct been facilitated but chemoselectivity in the Grignard vinylation had been optimised and other transformations, such as deacetalisation and intramolecular aldol cyclisation accelerated.

To conclude, although intramolecular cycloaddition had been observed in the IMDAF of benzylthiofuran (**328**), an alternative degradative process had occured preventing the build up and isolation of product (**394b**). This was undoubtably a consequence of the unsaturation at the A-B ring junction, its deactivation of the furan diene and unfavourable steric influence and configurational effect on the cycloaddition transition state. Based upon this evidence, further success in the intramolecular aldol approach to A-ring construction would only be obtained if the unsaturation at the ring junction could be removed and replaced with functionality that facilitated the IMDAF and enabled cycloadduct elaboration.

4.4. Introduction of the C-4 Hydroxyl Functionality.

It has already been shown that olefinic reduction in benzylthiofurylcyclopentenone systems is problematic, hydrogenation with a variety of catalysts only returning unreacted starting material and with sodium in liquid ammonia chemoselectivity problems are introduced (**Scheme 80**) with preferential electron delivery to the furyl aromatic ring. As it was evident that sp^3 hybridisation at the A-B ring junction was necessary to facilitate cycloaddition, it was proposed to attempt to introduce the tigliane C-4 hydroxyl in the ring forming step.

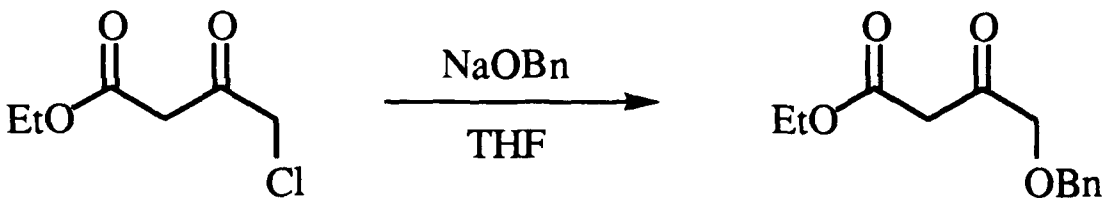
If a suitable alkoxyacetoacetate derivative (**405**) was substituted for dioxolane (**350**) in (bromoacetyl)furan (**249**) alkylation then oxygenation would be in place at the ring junction forming carbon of the generated aldol precursor (**406**). Additionally, the inability of the intramolecularly cyclised intermediate (**407**) to dehydrate across the A-B junction could facilitate an alternative elimination. Isomerisation to *trans*-dialkylcyclopentenone (**408**) (**Scheme 168**) should be encouraged by steric interaction between the bulky furan and dioxolane alkyl tethers and would establish an A-ring that was representative of the phorbol natural product (**1**).



(**405**) (**406**) (**407**) (**408**)

Scheme 168

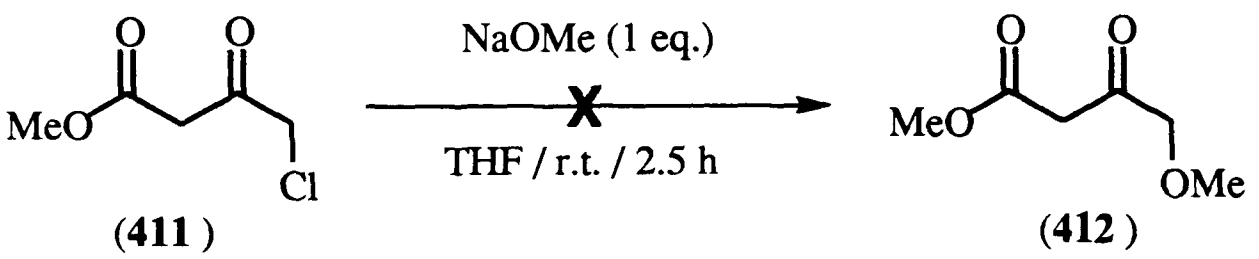
In a report by Miller and Tenud,[146] ethyl 4-benzyloxyacetoacetate (**410**), a suitable precursor to the alkoxyacetoacetate derivative (**406**), was generated by halogen displacement on the commercially available ethyl 4-chloroacetoacetate (**409**) (**Scheme 169**).



(**409**) (**410**)

Scheme 169

A methoxy alcoholic protecting species was chosen as, although it would be problematic to remove, it should allow develop ment of the synthetic protocol, be stable to all reaction conditions, and be of sufficiently small steric bulk to facilitate preferential formation of the *trans*-dialkyl product (**408**).

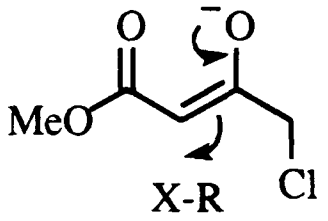


(**411**) (**412**)

Scheme 170

The addition of methyl 4-chloroacetoacetate (**411**) to one equivalent of a stirred suspension of sodium methoxide in tetrahydrofuran resulted in an instantaneous exothermic reaction. ^{1}H n.m.r. spectroscopic analysis of an evaporated aliquot after 2.5 hours at room temperature indicated that starting material (**411**) had been consumed and that a complex mixture of products had been formed. However, upon aqueous work up only a 75 % recovery of unreacted chloride (**411**) was obtained (**Scheme 170**). Conducting the reaction at 40°C still led to no isolation of product (**412**) but starting material (**411**) was consumed, alkylation at the acidic position evidenced by observation of acetoacetate methine coupling in the ^{1}H n.m.r. spectrum. Evidently under the reaction conditions sodium methoxide was functioning as a base and deprotonating the β-ketoester acidic methylene site. At the higher reaction

temperature the deprotonated substrate (**413**) was capable of attacking another enolate anion leading to the consumption of starting material (**Figure 8**).



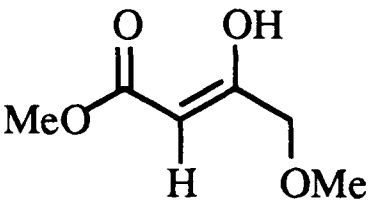
(**413**)

Figure 8

Based on this hypothesis, the reaction was repeated with 2 equivalents of sodium methoxide at 40°C to furnish methoxyacetoacetate (**412**) in 25 % yield. Evidently at the elevated reaction temperature the methoxide anion was capable of displacing chloride from the chloromethyl enolate (**413**) although the low efficiency was a result of anionic competition.

The product was identified by the appearance of carbonyl absorptions at 1 751 and 1 728 cm^{-1} in the i.r. spectrum and observation of higher field methylene singlet signals at δ4.09 and 3.53 p.p.m. as a consequence of precursor (**411**) resonances being deshielded by the action of the more powerful chlorine inductive withdrawal. The presence of six signals in the ^{13}C n.m.r. spectrum and detection of the parent ion MNH_4^+ (164) by mass spectrometry completed characterisation of the product.

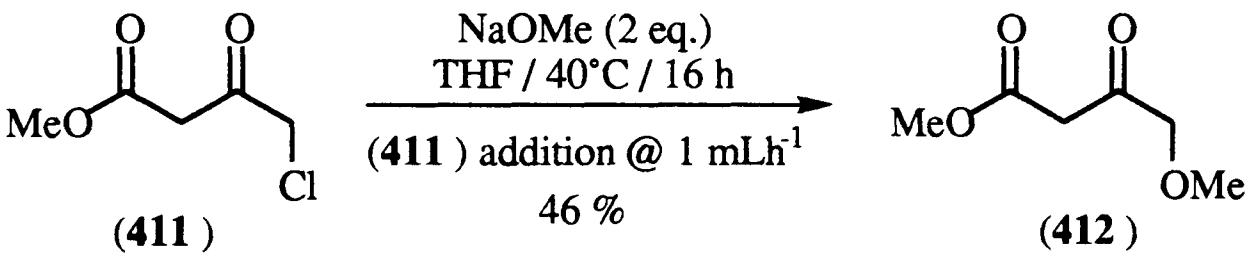
Closer analysis of the spectroscopic data elucidated that (**412**) was contaminated by a minor reaction product (**414**) that was inseparable by chromatographic purification on silica and was only removed to a small extent by reduced pressure distillation. I.r. spectroscopy indicated the presence of side product absorptions at 3 459, 1 671, and 1 624 cm^{-1} corresponding to vibration of hydroxyl, α, β-unsaturated ester carbonyl and olefinic functions. The detection of a singlet resonance at δ11.89 p.p.m. in the ^1H n.m.r. spectrum affirmed that the side product (**414**) was an equilibrium concentration of the enol tautomer. Confirmation was obtained by accurate combustion analysis and the observation that the 'contaminated' sample of (**412**) was purified by distillation when the fore-run was discarded, indicating preferential keto (**412**) formation at a higher temperature.



(**414**)

O-H : 3 459 cm^{-1}
C=O : 1 671 cm^{-1}
C=C : 1 624 cm^{-1}

Since the low yield was probably a consequence of problems in chemoselectivity in chloroenolate displacement, an attempt was made to minimise the concentration of this intermediate by the slow addition of chloroacteoacetate (**411**) to a suspension of sodium methoxide in tetrahydrofuran. This, coupled with an acidic aqueous work up, succeeded in optimising the reaction and furnished the product (**412**) in 46 % yield (**Scheme 171**).

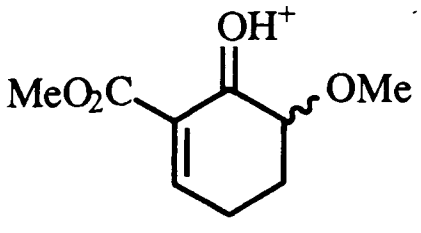


(**411**) (**412**)

Scheme 171

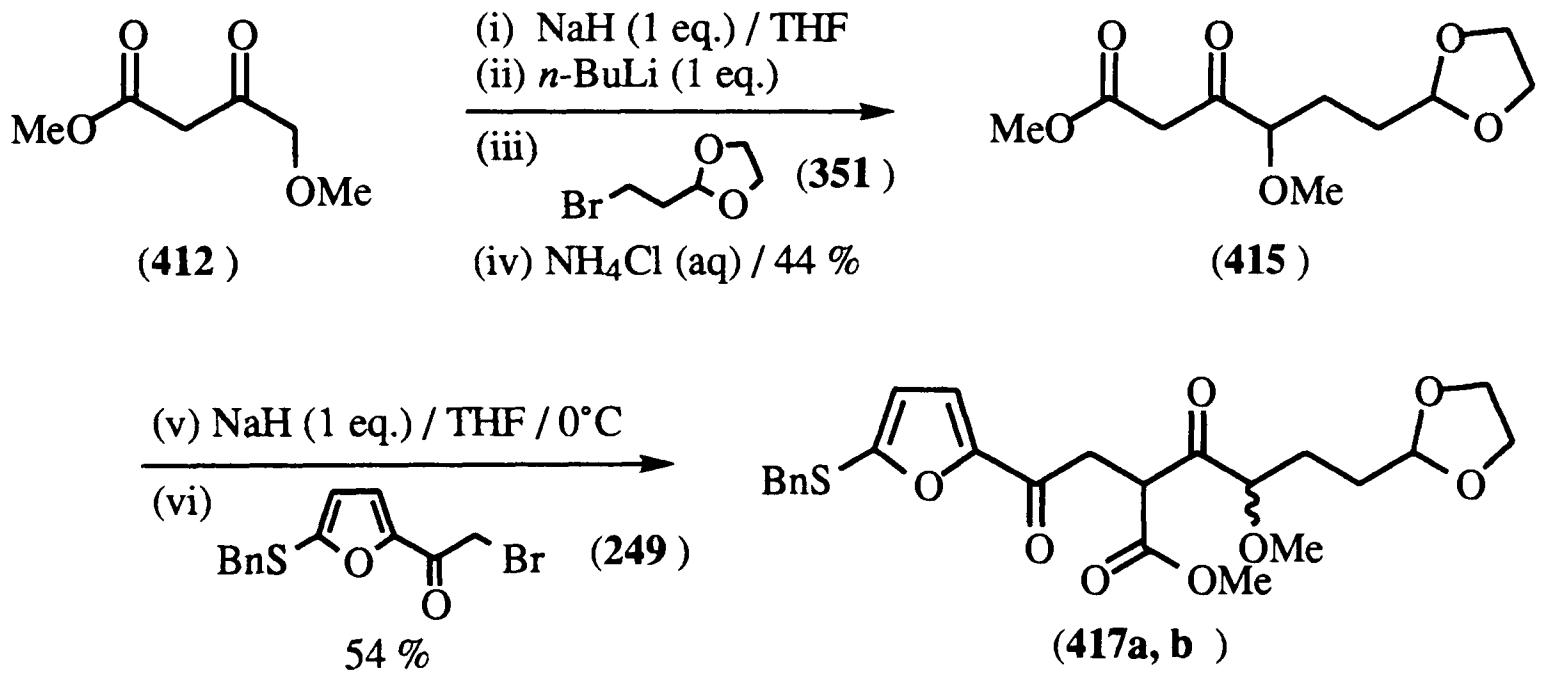
With successful generation of the methoxyacetoacetate (**412**) it was now necessary to introduce the dioxolane containing component by dianion addition. Successive deprotonation with sodium hydride and *n*-butyllithium in tetrahydrofuran, quenching the more nucleophilic terminal anion with (bromoethyl)dioxolane (**351**) furnished derivative (**415**) in 44 % yield (**Scheme 172**).

The product was identified by comparison of spectroscopic data with (**350**). However, as a consequence of methoxy substitution, the acetoacetate methylene protons were now diastereotopic, appearing as doublets in the 500 MHz ^1H n.m.r. spectrum and exhibiting a geminal coupling of 16.2 Hz. Mass spectrometric analysis confirmed that transformation had been successful, detecting the parent ion MH^+ (247), the dioxonium ion (**352**) (73), and the ion species (**416**) (185) generated by intramolecular condensation.



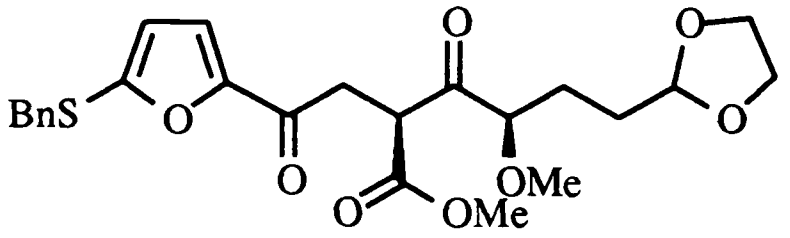
(**416**)

Deprotonation with sodium hydride in tetrahydrofuran at 0°C according to the established protocol followed by substitution with benzylthio(bromoacetyl)furan (**249**) furnished the aldol cyclisation precursor (**417a, b**) in 47 % yield. The reduced efficiency of alkylation could have been a consequence of starting material degradation under the reaction conditions. Repeating the procedure with deprotonation at -78°C, allowing the mixture to warm to room temperature after (benzylthio)bromoacetylfuran (**249**) addition, increased the reaction yield to 54 % (**Scheme 172**).

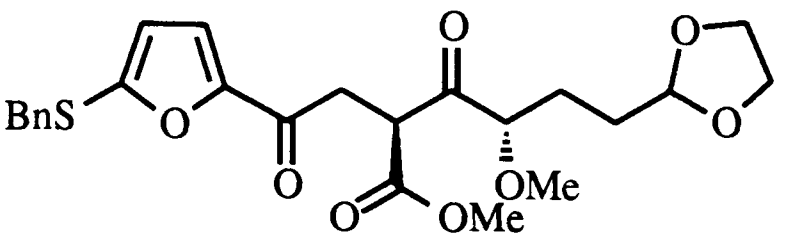


Scheme 172

The success of the conversion was confirmed by comparison of spectroscopic data with (**376**). ^{1}H and ^{13}C n.m.r. spectroscopic analysis indicated that the product actually consisted of an approximate 1 : 1 ratio of *cis*-(**418**) and *trans*-(**419**) (furoylmethyl)hexanoates which were inseparable by chromatographic purification on silica. As the integrity of the acetoacetate methine stereocentre would be lost on decarboxylation, no effort was made to identify the major (**417a**) or minor (**417b**) isomers although presumably alkylation of the enolate anion would preferentially occur from the opposite face to the methoxy substituent. For a small alkoxy group, steric interactions are minimal and so only minor diastereoselectivity was observed.

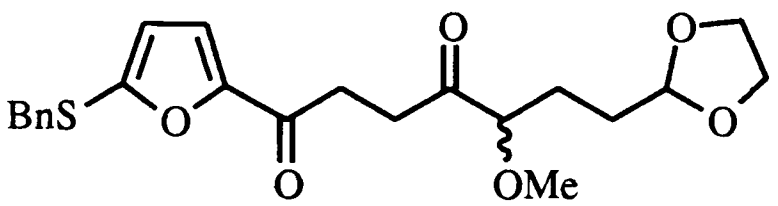


cis-(**418**)



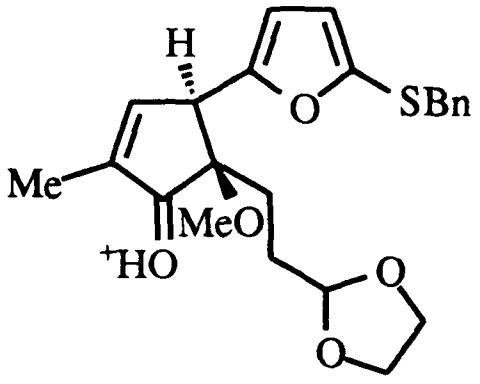
trans-(**419**)

Submitting an aqueous ethanolic solution of (**417a,b**) to conditions for intramolecular aldol cyclisation resulted in rapid consumption of starting material by t.l.c. analysis. Reaction was complete after only 2 hours and the single product identified as 1, 4-diketone (**420**), formed in 55 % yield.

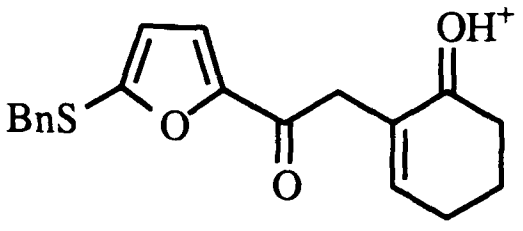


(420)

The product was identified by disappearance of the ester carbonyl vibration at 1 746 cm^{-1} in the i.r. spectrum and appearance of absorptions at 1 723 and 1 675 cm^{-1} corresponding to keto and furoyl functionality. ^1H n.m.r. spectroscopy indicated that the *cis/trans*- diastereoisomerism had been removed, the acetoacetate methine resonance at δ4.5 p.p.m. being replaced with diastereotopic methylene doublet of triplet signals at δ2.95 and 2.90 p.p.m.. Detection of the parent ion MH^+ (419) by mass spectrometry completed the characterisation of the product but absence of the dehydrated ion species $(MH\text{-}H_2O)^+$ (**421**) (401), corresponding to intramolecular cyclisation, was noted. The dehydrated and deprotected fragment ion (357) was observed, but it was assumed that this was the product of an alternative intramolecular aldol condensation (**422**).



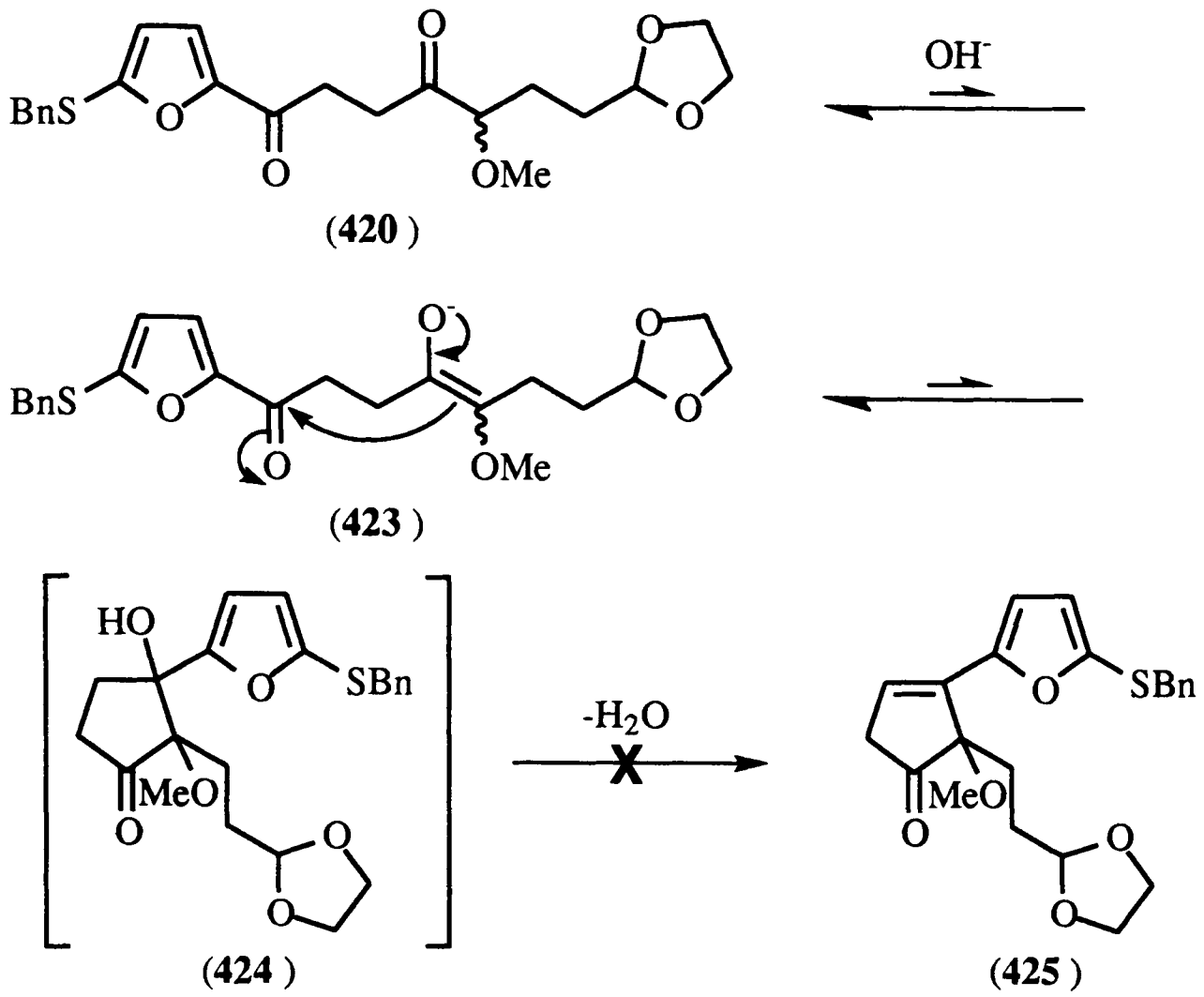
(**421**)



(**422**)

The rapid hydrolysis and concomitant decarboxylation under the reaction conditions was in accordance with observation of the 1, 4-diketone (**389**) in cyclisation of the demethoxylated substrate (**376**). The presence of the C-2 cyclopentanone alkoxy substituent prevented dehydration to generate α, β-unsaturation at the ring junction and this facilitated isolation of the diketone (**420**). Resubmission to the intramolecular aldol cyclisation conditions and refluxing (**420**) for 24 hours in aqueous ethanolic solvent afforded only an incomplete recovery of starting material. This result was unchanged by employing alternative conditions, refluxing the substrate in methanolic potassium hydroxide or heating to 120°C in quinoline returning unreacted diketone (**420**) in the presence of polymeric residue.

Evidently, without the ability to form a conjugated system, the dehydration of (**424**) was not as facile, producing an unfavourable aldol condensation equilibrium and preventing product (**425**) isolation (**Scheme 173**). Additionally mesomeric donation by the methoxy substituent would serve to destabilise the enolate anion cyclisation precursor (**423**) and disfavour further the intramolecular closure.



Scheme 173

Based on this evidence it appeared that the approach was not applicable for introducing C-4 hydroxylation.

4.5. Conclusion.

Without the capability of dehydrating to a 3-furyl-2-cyclopentenone, the aldol equilibrium prevented construction of the A-ring. However, with unsaturation present at the A-B ring junction, although cyclopentenone formation is facilitated, the intramolecular Diels-Alder addition is disfavoured sufficiently to prevent the isolation of cycloadducts, even with activated diene and dienophilic components. Evidently further success will only be achieved by establishing a more favourable IMDAF equilibrium with removal of the problematic α, β-unsaturation, introduction of the tigliane C-4 hydroxylation, and incorporation of a diactivated dienophilic tether. In spite of cycloadduct isolation being prevented by this unforeseen phenomenon, the intramolecular aldol approach to A-ring construction has been successful in introducing A-ring functionality with potential for elaboration and has allowed

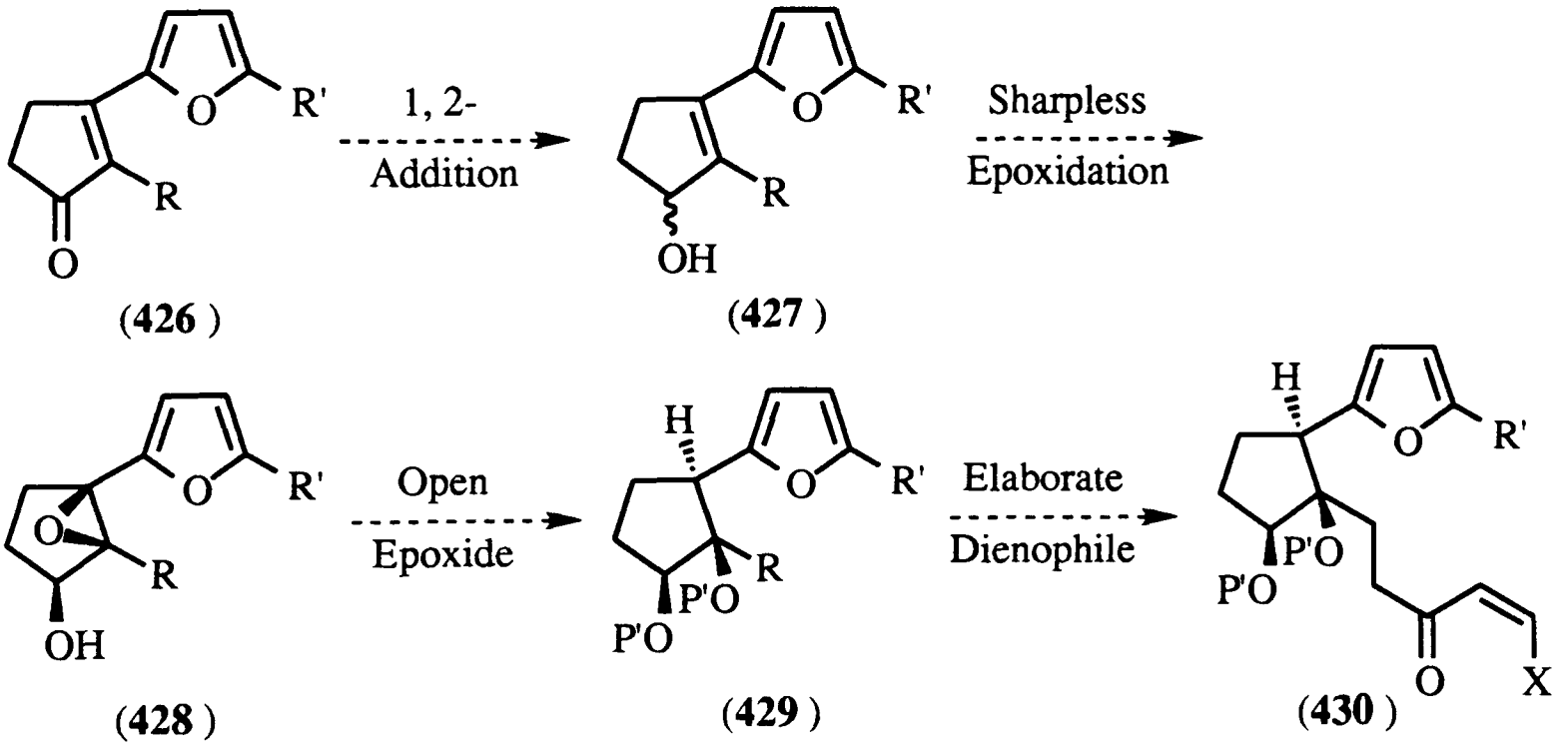
observation of a phorboid adduct (**394b**) in the IMDAF of (**328**) where the furyl diene component is activated by a sulphide substituent.

Based on these observations it seems likely that further success will be enjoyed by this approach (see 4.6.) facilitating the generation of analogues of phorbol (**1**) that more closely resemble the target system and lending more weight to the IMDAF strategy of natural product synthesis in the face of a considerable synthetic challenge.

4.6. Future Work

Although the intramolecular aldol cyclisation approach had established an IMDAF precursor (**328**) that contained unsaturation at the A-B ring junction, the unfavourable cycloaddition equilibrium had prevented product (**394b**) isolation. In order to develop the strategy it was therefore necessary to oxygenate the C-4 position and establish the stereochemistry at the A-B ring junction prior to the IMDAF.

Initial studies on the epoxidation of furylcyclopentenones indicated that standard sodium hydroxide / hydrogen peroxide epoxidation conditions were incapable of effecting the required transformation as a consequence of the increased conjugation in the substrate. To circumvent this problem it was proposed that 1, 2-reduction of cyclopentenone (**426**) would establish the allylic alcohol (**427**) that would be suitable for directed epoxidation under Sharpless conditions.[75] Regiospecific opening of epoxide (**428**) and elaboration of the dienophilic tether should generate an IMDAF precursor (**430**) that contained the required C-4 oxygenation and correct stereochemistry across the A-B ring junction (**Scheme 174**).



Scheme 174

The successful cycloaddition of the oxygenated substrate (**430**) would validate the intramolecular aldol cyclisation approach and facilitate the introduction of the C-2 and C-11 methyl substituents in an approach towards phorbol natural products.

CHAPTER FIVE

CHAPTER 5 - EXPERIMENTAL

5.1. Experimental Techniques.

Reagents were obtained from Aldrich, BDH, Fisons, Fluka, Janssen, Lancaster, Rathburn, and Rectapur chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin and Armarego.[147] Dichloromethane was dried by refluxing over, and distilling from calcium hydride. *N, N*-Dimethylformamide was dried over magnesium sulphate and refluxed over and distilled from calcium hydride. Tetrahydrofuran and diethyl ether were obtained dry and oxygen-free by distillation from sodium-benzophenone ketyl under nitrogen. Benzene and toluene were dried over sodium wire. Furan was distilled from potassium hydroxide. Triethylamine was distilled from calcium hydride and dried over potassium hydroxide. Di-*iso*propylamine was distilled from sodium hydroxide. Light petroleum (b.p. 30-40°C), acetic anhydride, quinoline and methyl acetoacetate were distilled before use. Benzyl bromide and allyl bromide were distilled before use and stored in the dark at -12°C. All other reagents were used as supplied.

The concentrations of *n*- and *t*-butyllithium and methyllithium were determined by titration against a solution of diphenyl acetic acid in tetrahydrofuran.

T.l.c. analysis refers to analytical thin-layer chromatography, using either Merck plastic or aluminium backed plates, coated with 0.2 mm silica $60F_{254}$. Product spots were viewed either by the quenching of u.v. fluorescence, or by staining with iodine vapour, a solution of 2 % aqueous potassium permanganate, a solution of vanillin in acidic methanol (0.3 M), or a solution of ceric sulphate / ammonium molybdate in 5 % aqueous sulphuric acid.

Flash chromatography refers to column chromatography using head pressure by means of compressed air according to the procedure of Still.[148] Dry flash chromatography refers to column chromatography on Merck 60H silica gel using suction rather than head pressure according to the procedure of Harwood.[149]

Short-path distillation (bulb-to-bulb) was performed using a horizontal Kugelröhr apparatus, recording the uncorrected bath temperature.

Melting points were recorded using a Koffler heated-stage microscope and are uncorrected.

Micro-analyses were performed in the Dyson-Perrins laboratory by Mrs. V. Lamb urn .

Infra-red spectra were recorded on a Perkin-Elmer 781 or a Perkin-Elmer 297 instrument either as a thin film between sodium chloride plates, in solution (usually in chloroform) within a sodium chloride cell (path length 0.1 mm), in a nujol mull, or as a KBr disk. The abbreviation w. denotes a weak absorption. All absorptions are quoted in cm^{-1}.

^1H n.m.r. spectra (δ_H) were recorded in deuteriochloroform (unless otherwise stated) and referenced to the solvent peak. Instruments used were a Varian Gemini (200 MHz), a Bruker AC200 (200 MHz), a Bruker WH300 (300 MHz), and a Bruker AM500 (500 MHz). Peak positions were recorded in δ p.p.m. with the abbreviations **s**, **d**, **t**, **q**, and **m** denoting singlet, doublet, triplet, quartet, and multiplet resonances respectively.

Mass-spectrometric data were recorded on a ZAB1F or TRIO 1 G.C. Mass Spectrometer, under conditions of chemical ionisation (C.I.), using ammonia as the ionising source.

5.2. General Procedures.

(a) Formation of Acetoacetate Dianions.

The acetoacetate (1 equiv.) was added dropwise to a stirred suspension of sodium hydride (50 - 80 % dispersion in mineral oil, ≥ 1 equiv.) in anhydrous THF (≥ 2 mL/mmol) under an inert atmosphere, maintaining the temperature below 0°C (ice-salt bath), and the reaction mixture was stirred at this temperature for 10 min. *n*-Butyllithium (solution in hexane, ≥ 1 equiv.) was added dropwise and the resultant yellow solution stirred for 10 min.

(b) Alkylation of Acetoacetate Dianions.

The appropriate bromide alkylating agent (≤ 1.0 equiv.) was added dropwise to a stirred solution of the dianion (1 equiv.) in anhydrous THF, prepared by the above general procedure (a). The reaction mixture was allowed to warm slowly to room temperature overnight, quenched by the addition of saturated aqueous ammonium chloride solution and extracted with diethyl ether. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude product as an oil.

(c) α-Monobromination of 2- or 5-Acetylfurans.

According to the procedure reported by King and Ostrum,[101] a suspension of powdered copper (II) bromide (≤ 2.0 equiv.) in ethyl acetate (≈ 5 mL/mmol) was refluxed for 20 min under N_2. The mixture was briefly allowed to cool, a solution of the 2- or 5-acetylfuran (1 equiv.) in chloroform (≈ 5 mL/mmol) was added and the reaction mixture refluxed for 4 - 6 h, neutralising the evolved hydrogen bromide by bubbling the gas through 1M aqueous ammonium hydroxide solution. The reaction was allowed to cool, filtered, the grey precipitate washed with ethyl acetate, and the filtrate evaporated *in vacuo* to afford the crude 2- or 5-(bromoacetyl)furan as an oil.

(d) Alkylation of (Bromoacetyl)furans.

The β-keto ester (≈ 1.1 equiv.) was added dropwise to a stirred suspension of sodium hydride (dispersion in mineral oil, 1.1 equiv.) in anhydrous THF (≥ 5 mL/mmol) under an inert atmosphere, maintaining the temperature below 0°C (ice-salt bath), and the reaction mixture was stirred at this temperature for 15 min. A solution of the 2-(bromoacetyl)furan (1.0 equiv.) in anhydrous THF (1 mL/mmol) was added by syringe, the mixture was allowed to warm slowly to room temperature over 6 h, and was quenched by the addition of saturated aqueous ammonium chloride solution. The reaction was extracted with diethyl ether, washed successively with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude product as an oil.

(e) Base Catalysed Intramolecular Aldol Cyclisation.

According to a procedure adapted from Büchi and Wüest,[99] a solution of the methyl ester (1 equiv.) and 0.5 M aqueous sodium hydroxide solution (4 - 7 equiv.) in ethanol-water (1 : 2 (v/v)) (≈ 20 mL/mmol) was refluxed for up to 6 d under N_2. The reaction was allowed to cool and was partitioned between diethyl ether and water. The organic layer was washed successively with saturated aqueous ammonium chloride solution, saturated sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude cyclopentenone as an oil.

(f) 5-Lithiation of 2-Substituted Furans.

n-Butyllithium (solution in hexane, ≥ 1 equiv.) was added dropwise to a stirred solution of the furan (1 equiv.) in anhydrous THF (≥ 2 mL/mmol) under an inert atmosphere, maintaining the temperature between -20 and -30°C, and the reaction mixture was stirred at this temperature for 2.5 h.

(g) Benzylthiolation of 2-Substituted 5-Lithiofurans.

According to the procedure reported by Niwa,[108] a solution of the 5-lithiofuran (1 equiv.) in anhydrous THF, prepared by the above general procedure, was cooled to -65°C and sulphur

(≥ 1 equiv.) was added in one portion under increased Ar or N_2 flow. The reaction mixture was warmed to -40°C, stirred for 45 min, maintaining the temperature between -40 and -30°C, and then recooled to -65°C. Benzyl bromide (≥ 1 equiv.) was added dropwise by syringe and the reaction mixture slowly warmed to room temperature. Ice-water was added and the mixture extracted with diethyl ether. The aqueous phase was further extracted with diethyl ether (3 times) and the ethereal extracts combined, washed successively with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution (2 times), and brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude benzylthiofuran as an oil.

(h) Phenylthiolation of 2-Substituted 5-Lithiofurans.

According to a procedure adapted from Niwa,[108] a solution of the lithiofuran (1 equiv.) in anhydrous THF, prepared by the above general procedure, was cooled to -60°C and phenyl disulphide (1.05 equiv.) was added in one portion under increased N_2 flow. The reaction mixture was allowed to warm slowly to room temperature and was quenched by the addition of 1 M aqueous sodium hydroxide solution and extracted with diethyl ether. The aqueous phase was further extracted with diethyl ether and the ethereal extracts combined, washed successively with water and brine (2 times), dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude 2-phenylthiofuran as an oil.

(i) Deprotection of Acetals and Ketals under Acid Catalysis.

A solution of the aldehyde or ketone (1.0 equiv.) and *p*-toluenesulphonic acid monohydrate (0.3 equiv.) in acetone-water (9 : 1 (v/v)) (≈ 10 mL/mmol) was heated to reflux for between 2.5 h and 6 d. The reaction mixture was allowed to cool and the acetone removed *in vacuo*. The residue was extracted with diethyl ether, washed successively with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude ketone.

(j) Grignard Addition to 2-Furaldehyde (**276**).

A suspension of magnesium turnings (0.21 g, 8.6 mmol, 5 equiv.) in anhydrous diethyl ether (15 mL) was stirred vigorously for 2 d under N_2 at room temperature. The bromoalkene (1.2 equiv.) was added dropwise and the solution warmed intermittently to maintain a gentle reflux for 45 min. The mixture was cooled to room temperature, stirred for 2 h, and cooled to 0°C. 2-Furaldehyde (1.0 equiv.) was added dropwise by syringe and the reaction mixture allowed to warm slowly to room temperature overnight. Saturated aqueous ammonium chloride solution (20 mL) was added and the solution decanted once the evolution of hydrogen had subsided. The supernatant was diluted with diethyl ether (20 mL) and the organic layer was separated, washed successively with saturated aqueous ammonium chloride solution (30 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude alcohol as a yellow oil. Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 4) furnished the pure product.

(k) *tert*-Butyldimethylsilyl Protection of Alcohols.

Imidazole (1.1 equiv.), *tert*-butyldimethylsilyl chloride (2.5 equiv.), and *N, N*-dimethylaminopyridine (0.1 equiv.) were added to a solution of the furfuryl alcohol (1.0 equiv.) in anhydrous DMF (5 mL) under N_2 at room temperature and the solution was stirred for 3 days. *tert*-Butyldimethylsilyl chloride (2.5 equiv.) and *N, N*-dimethylaminopyridine (0.1 equiv.) were added, the solution stirred for another 2 d, quenched by the addition of water (10 mL) and extracted with diethyl ether (10 mL). The aqueous phase was further extracted with diethyl ether (10 mL) and the ethereal extracts combined, washed successively with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude silyl ether as an oil.

(l) 2-Lithiation of 1, 3-Dithianes.

n-Butyllithium (1.5 M solution in hexane, 1.1 equiv.) was added dropwise to a stirred solution of 1, 3-dithiane (1.0 equiv.) in anhydrous THF under N_2, maintaining the

temperature below 0°C (bath temperature -23°C). The solution was stirred at -23°C for 2 h and cooled to -78°C.

(m) High Pressure Mediated Diels-Alder Cycloaddition.

A solution of the substrate (15 μmol - 1.3 mmol) in anhydrous dichloromethane (5 or 10 mL) was subjected to high pressure (17 - 19 kbar) for 24 h at 20 °C. The solution was returned to ambient pressure, filtered through a plug of cotton wool, and evaporated *in vacuo* to afford the crude cycloadduct.

(n) Preparation of Activated Manganese Dioxide on Charcoal.

According to the procedure reported by Harwood and Moody,[152] potassium permanganate (24.0 g, 0.15 mmol, 1.0 equiv.) was dissolved in boiling water (300 mL) and the solution allowed to briefly cool. Activated charcoal (7.5 g) was added portionwise over 10 min, the mixture stirred at 85°C for 15 min, and filtered through a sinter funnel. The residue was washed with water (4 x 50 mL), stirring the slurry during filtration, dried under suction for 5 min, suspended in toluene (150 mL), and refluxed overnight with the azeotropic removal of water using a Dean-Stark apparatus. The mixture was allowed to cool, filtered, and the residue dried by suction for 10 min, *in vacuo* under water aspirator pressure (bath temperature 85°C), and *in vacuo* under high vacuum reduced pressure (4 mmHg) to afford the title compound (20.7 g).

(o) Grignard Addition to 2-(3-Oxopropyl)cyclopent-2-enones.

Vinylmagnesium bromide (1.0 M solution in THF, 1.3 equiv.) was added dropwise to a stirred solution of the 2-(3-oxopropyl)cyclopent-2-enone (1.0 equiv.) in anhydrous THF (20 mL) under N_2 at -78°C. The reaction mixture was stirred for 6 h, quenched at -78°C by the addition of saturated aqueous ammonium chloride solution (30 mL), and extracted with diethyl ether (25 mL). The aqueous phase was further extracted with diethyl ether (25 mL), the ethereal extracts combined, washed successively with water (40 mL) and brine (40 mL),

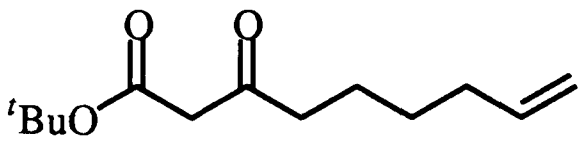
dried ($MgSO_4$), and evaporated *in vacuo*. Purification by dry flash chromatography on silica, eluting with ethyl acetate-dichloromethane (1 : 4), furnished the pure product as an oil.

(p) Pyridinium Chlorochromate Mediated Allylic Oxidation.

Pyridinium chlorochromate (1.3 equiv.) was add ed to a stirred suspension of anhydrous sodium acetate (3.0 equiv.) and Celite® (1.5 times mass of PCC) in chloroform under an inert atmosphere at room temperature and the mixture homogenised by stirring vigorously for 3 - 4 min. A solution of the allylic alcohol (1.0 equiv.) in chloroform was added by syringe and the reaction mixture stirred overnight. Pyridinium chlorochromate (1.3 equiv.) was added, the reaction mixture was stirred for 2 h, filtered through a pad of silica, washing the residual cake successively with chloroform and diethyl ether, and evaporated *in vacuo* to afford the crude enone as an oil.

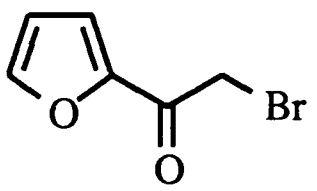
5.3. Experimental Procedures.

Preparation of tert-*Butyl 3-oxonon-8-enoate* (**226**).



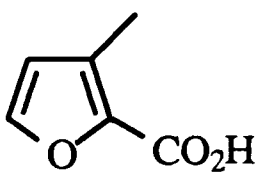
The title compound was prepared according to the general procedure for the alkylation of acetoacetate dianions given in section 5.2.b. The reaction was carried out with *tert*-butyl acetoacetate (9.5 g, 60 mmol, 1.2 equiv.), sodium hydride (80 % dispersion in mineral oil, 1.8 g, 60 mmol, 1.2 equiv.), *n*-butyllithium (1.5 M solution in hexane, 40 mL, 60 mmol, 1.2 equiv.), anhydrous THF (125 mL), and 5-bromopent-1-ene (**228**) (6 mL, 51 mmol, 1.0 equiv.) to afford crude *tert*-butyl 3-oxonon-8-enoate (**226**) as a yellow oil (12.2 g). Purification by dry flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 8), furnished the pure product as a pale yellow oil (6.1 g, 53 %) (Found C, 69.3, H, 9.60; $C_{13}H_{22}O_3$ requires C, 69.0, H, 9.80 %); ν_{max} (thin film) 3 087, 2 979, 2 945, 2 871, 1 742 (C=O ester), 1 722 (C=O), 1 642 (C=C), 1 369, 1 253, and 1 150 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.83 - 5.75 (1H, ddt, J_{tr} 17, J_{cis} 10.3, J 6.7 Hz, $CH_2C\underline{H}=CH_2$), 5.01 (1H, ddt, $J_{vic,tr}$ 17, J_{gem} 1.7, J_w 1.7 Hz, RCH=C$\underline{H}$H *cis* to R), 4.95 (1H, m, $J_{vic,cis}$ 10, J 1 Hz, RCH=CH$\underline{H}$ *trans* to R), 3.34 (2H, s, O_2CCH_2CO), 2.54 (2H, t, J 7.3 Hz, $OCCH_2CH_2$), 2.06 (2H, m, J 7, J_w 1.3 Hz, $CH_2C\underline{H}_2CH=CH_2$), 1.61 (2H, m, J 7 Hz, $OCCH_2C\underline{H}_2$), 1.55 - 1.37 (2H, m, J 7, J' 2.5 Hz, $C\underline{H}_2CH_2CH=CH_2$), and 1.47 (9H, s, $C(CH_3)_3$); $^m/_z$ (C.I.) 244 (7 %, MNH_4^+), 227 (6 %, MH^+), 216 (5 %, $^t BuO_2CC_6H_9ONH_4^+$), 199 (10 %, $^t BuO_2CC_6H_9OH^+$), 188 (72 %, $HO_2CCH_2COC_6H_{11}NH_4^+$), 171 (17 %, $HO_2CCH_2COC_6H_{11}H^+$), 170 (14 %), 153 (100 %, M^+-^{t}BuO), 111 ($C_2H_3C_4H_8CO^+$), and 55 (7 %).

Preparation of *2-(Bromoacetyl)furan* (**227**).



The title compound was prepared according to the general procedure for the α-monobromination of acetylfurans given in section 5.2.c. The reaction was carried out with copper (II) bromide (48.9 g, 0.22 mol, 2.0 equiv.), ethyl acetate (350 mL), 2-acetylfuran (**229**) (12.1 g, 0.11 mol, 1.0 equiv.), and chloroform (350 mL) to afford, after 4 h reflux, crude 2-(bromoacetyl)furan (**227**) as a dark green oil (23.0 g). Purification by dry flash chromatography on silica, gradient eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 4 - 1 : 2), followed by crystallisation at -12°C, furnished the pure product as colourless plates, m.p. 33-34°C after recrystallisation at low temperature (diethyl ether-light petroleum (b.p. 30-40°C)) (4.9 g, 24 %) (Found C, 38.2, H, 2.30; $C_6H_5BrO_2$ requires C, 38.1, H, 2.65 %); ν_{max} (KBr disk) 3 142, 3 124, 2 999, 2 942, 1 681 (C=O), 1 559, 1 463, 1 392, 1 224, 1 042, 998, 791, 663, and 594 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.66 (1H, d, $J_{5,4}$ 1.7 Hz, 5-FuH), 7.35 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 6.62 (1H, dd, $J_{4,3}$ 3.6 Hz, 4-FuH), and 4.33 (2H, s, CH_2Br); $m/_z$ (C.I.) 111 (100 %, MH^+-Br), 95 (87 %, $FuCO^+$), and 81 (98 %, $FuCH_2^+$).

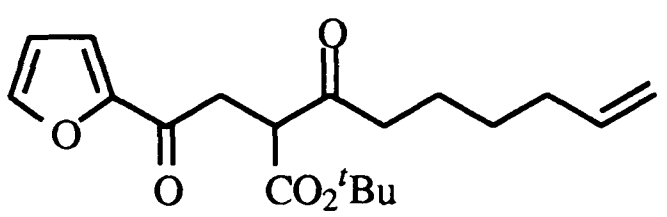
Preparation of *3-Methyl-2-furoic acid* (**232**).



According to an adapted procedure of Burness,[102] a solution of methyl 3-methyl-2-furoate (0.59 g, 42 mmol, 1.0 equiv.) and potassium hydroxide (0.76 g, 12.7 mmol, 3.2 equiv.) in methanol-water (1 : 2 v/v) was refluxed for 2.5 h under N_2. The reaction was allowed to cool and the methanol evaporated *in vacuo*. The solution was washed with diethyl ether (40 mL), acidified to pH 1 with concentrated hydrochloric acid, and extracted with diethyl ether (30 mL). The aqueous phase was further extracted with diethyl ether (2 x 30 mL) and the ethereal

extracts combined, washed successively with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 3-methyl-2-furoic acid (**232**) as pale yellow prisms, m.p. 130-131°C that could be used without further purification (0.42 g, 78 %). A small portion was purified by trituration with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 50 v/v) to afford the pure product as pale yellow prisms, m.p. 133-134.5°C (lit[102] 134-135°C) (Found C, 56.9, H, 4.85; $C_6H_6O_3$ calculated C, 57.1, H, 4.80 %); ν_{max} (KBr disk) 2 868, 2 662, 2 574, 1 670 (C=O), 1 599, 1 489, 1 450, 1 387, 1 301, 1 190, 1 137, 1 101, 890, and 784 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.53 (1H, d, $J_{5,4}$ 1.3 Hz, 5-FuH), 6.42 (1H, d, $J_{4,5}$ 1.3 Hz, 4-FuH), and 2.41 (3H, s, CH_3); $^m/_z$ (C.I.) 144 (100 %, MNH_4^+), 127 (7 %, MH^+), 126 (20 %, M^+), 109 (15 %, MeFu'CO^+), and 81 (12 %, $FuCH_2^+$).

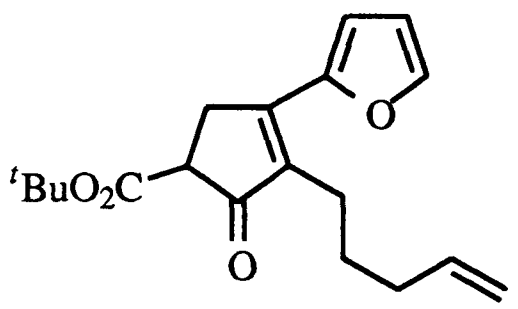
Preparation of tert-*Butyl 2-(2-furoylmethyl)-3-oxonon-8-enoate* (**240**).



The title compound was prepared according to the general procedure for the alkylation of (bromoacetyl)furans given in section 5.2.d. The reaction was carried out with sodium hydride (60 % dispersion in mineral oil, 0.22 g, 5.4 mmol, 1.0 equiv.), anhydrous THF (100 mL), *tert*-butyl 3-oxonon-8-enoate (**226**) (1.23 g, 5.4 mmol, 1.0 equiv.), and a solution of 2-(bromoacetyl)furan (**227**) (1.03 g, 5.4 mmol, 1.0 equiv.) in anhydrous THF (1 mL) to afford crude *tert*-butyl 2-(2-furoylmethyl)-3-oxonon-8-enoate (**240**) as a brown oil (1.97 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 4), furnished the pure product as a pale yellow oil (1.44 g, 79 %) (Found C, 68.0, H, 7.55; $C_{19}H_{26}O_5$ requires C, 68.2, H, 7.85 %); ν_{max} (thin film) 2 978, 2 933, 2 871, 1 738 (C=O ester), 1 715 (C=O), 1679 (Fu-C=O), 1 641 (w) (C=C), 1 572, 1 470, 1 396, 1 370, 1 282, 1 257, 1 153, and 766 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.38 (1H, dd, $J_{5,4}$ 1.7, $J_{5,3}$ 0.8 Hz, 5-FuH), 7.23 (1H, dd, $J_{3,4}$ 3.6, $J_{3,5}$ 0.8 Hz, 3-FuH), 6.54 (1H, dd, $J_{4,3}$ 3.6, $J_{4,5}$ 1.7 Hz, 4-FuH), 5.80 (1H, ddt, J_{tr} 17.0, J_{cis} 10.3, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.01

(1H, m, $J_{vic,tr}$ 17.0 Hz, RCH=C<u>H</u>H *cis* to R), 4.92 (1H, m, $J_{vic,cis}$ 10.3 Hz, RCH=CH<u>H</u> *trans* to R), 4.11 (1H, dd, *J* 8.2, *J'* 5.9 Hz, C<u>H</u>CH$_2$COFu), 3.51 (1H, dd, J_{gem} 18.2, J_{vic} 8.2 Hz, CHC<u>H</u>HCOFu), 3.32 (1H, dd, J_{gem} 18.2, J_{vic} 5.9 Hz, CHCH<u>H</u>COFu), 2.80 (1H, dt, J_{gem} 17.7, J_{vic} 7.3 Hz, OCC<u>H</u>HCH$_2$), 2.69 (1H, dt, J_{gem} 17.7, J_{vic} 7.0 Hz, OCCH<u>H</u>CH$_2$), 2.08 (2H, dt, *J* 7, *J'* 7 Hz, CH$_2$C<u>H</u>$_2$CH=CH$_2$), 1.77 - 1.33 (4H, m, CH$_2$C$_2$<u>H</u>$_4$CH$_2$), and 1.46 (9H, s, C(CH$_3$)$_3$); δ_C (50.3 MHz, $CDCl_3$) 204.65 (s), 186.23 (s), 167.78 (s), 151.97 (s), 146.55 (d), 138.41 (d), 117.43 (d), 114.57 (t), 112.24 (d), 82.31 (s), 53.74 (d), 42.68 (t), 36.75 (t), 33.45 (t), 28.23 (t), 27.81 (q), and 22.84 (t); $^m/_z$ (C.I.) 335 (20 %, MH$^+$), 279 (100 %, MH$^+$-C$_4$H$_8$), 261 (53 %, M$^+$-^{t}BuO), 235 (42 %, MH$^+$-CO$_2$C$_4$H$_8$), 217 (4 %, MH$^+$-CO$_2$C$_4$H$_8$-H$_2$O), 151 (12 %), 95 (7 %, FuCO$^+$), and 55 (3 %, C$_2$H$_3$CO$^+$).

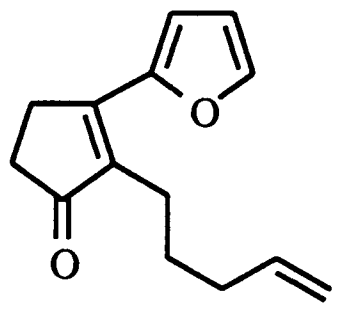
Preparation of tert-*Butyl 4-(2-furyl)-3-(pent-4-enyl)-2-oxocyclopent-3-enoate* (**241**).



The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with *tert*-butyl 2-(2-furoylmethyl)-3-oxonon-8-enoate (**240**) (0.11 g, 0.34 mmol, 1.0 equiv.), ethanol (6 mL), water (9 mL), and 0.5 M aqueous sodium hydroxide solution (2.8 mL, 1.4 mmol, 4.1 equiv.) to afford, after 2 h reflux, a yellow oil (87 mg). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C), furnished pure *3-(2-furyl)-2-(pent-4-enyl)cyclopent-2-enone* (**221**) (R_f 0.10) as a pale yellow oil (26 mg, 35 %) and the pure product (**241**) (R_f 0.21) as a pale yellow oil (40 mg, 37 %) (Found C, 71.7, H, 7.15; $C_{19}H_{24}O_4$ requires C, 72.1, H, 7.65 %); ν_{max} (thin film) 3 123, 3 078, 2 978, 2 932, 2 863, 1 729 (C=O ester), 1 697 (C=O), 1 625 (C=C), 1 475, 1 398, 1 369, 1 334, 1 227, 1 151, 1 024, 991, and 753 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.38 (1H, d, $J_{5,4}$ 1.7 Hz, 5-FuH), 6.85 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.58 (1H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 1.7 Hz,

4-FuH), 5.84 (1H, ddt, J_{tr} 17.0, J_{cis} 10, J 6.6 Hz, $CH_2C\underline{H}=CH_2$), 5.02 (1H, m, RCH=C$\underline{H}$H *cis* to R), 4.96 (1H, m, $J_{vic,cis}$ 10 Hz, RCH=CH$\underline{H}$ *trans* to R), 3.43 (1H, dd, J 7.3, J' 3.1 Hz, C$\underline{H}CH_2$CFu), 3.20 (1H, dd, J_{gem} 17.4, J_{vic} 3.1 Hz, CHC$\underline{H}$HCFu), 3.02 (1H, dd, J_{gem} 17.4, J_{vic} 7.3 Hz, CHCH$\underline{H}$CFu), 2.59 (2H, t, J 8 Hz, OCCC$\underline{H_2}CH_2$), 2.11 (2H, dt, J 7, J' 7 Hz, CHC$\underline{H_2}CH_2$), 1.59 (2H, m, $CH_2C\underline{H_2}CH_2$), and 1.49 (9H, s, $C(CH_3)_3$); $^m/_z$ (C.I.) 261 (9 %, MH^+-C_4H_8), 217 (100 %, MH^+-$CO_2C_4H_8$), 215 (8 %), 187 (10 %, M^+-$CO_2C_4H_8$-C_2H_5), 162 (4 %), and 161 (3 %, M^+-$CO_2C_4H_8$-$C_2H_3C_2H_4$).

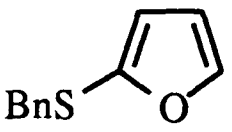
Preparation of 3-(2-Furyl)-2-(pent-4-enyl)cyclopent-2-enone (**221**).



The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with *tert*-butyl 2-(2-furoylmethyl)-3-oxonon-8-enoate (**240**) (1.12 g, 3.34 mmol, 1.0 equiv.), ethanol (20 mL), water (13 mL), and 0.5 M aqueous sodium hydroxide solution (27 mL, 13.5 mmol, 4.0 equiv.) to afford crude 3-(2-furyl)-2-(pent-4-enyl)cyclopent-2-enone (**221**) as a pale yellow oil that could be used without further purification (0.63 g, 87 %). A small portion was purified by crystallisation at -12°C to afford the title compound as colourless prisms, m.p. 130.5-133.5°C after recrystallisation at low temperature (light petroleum (b.p. 30-40°C)) (Found C, 77.5, H, 7.55; $C_{14}H_{16}O_2$ requires C, 77.8, H, 7.45 %); ν_{max} (thin film) 3 119, 3 077, 2 976, 2 928, 2 861, 1 693 (C=O), 1 625 (C=C), 1 474, 1 399, 1 360, 1 302, 1 225, 1 015, 915, and 751 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.63 (1H, d, $J_{5,4}$ 1.8 Hz, 5-FuH), 6.81 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.57 (1H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 1.8 Hz, 4-FuH), 5.86 (1H, ddt, J_{tr} 17.1, J_{cis} 10.2, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.03 (1H, ddt, $J_{vic,tr}$ 17.1, J_{gem} 1.8, J_w 1.7 Hz, RCH=C$\underline{H}$H *cis* to R), 4.97 (1H, m, $J_{vic,cis}$ 10.2, J_{gem} 1.8 Hz, RCH=CH$\underline{H}$ *trans* to R), 2.87 (2H, m, J 5 Hz, $OCCH_2CH_2$), 2.58 (2H, m, J 8 Hz, OCCC$\underline{H_2}CH_2$), 2.50 (2H, m, FuCC$\underline{H_2}CH_2$), 2.14 (2H, m,

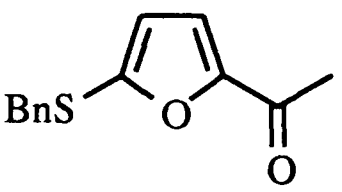
$HCC\underline{H}_2CH_2$), and 1.57 (2H, m, $CH_2C\underline{H}_2CH_2$); $^{m}/_{z}$ (C.I.) 217 (100 %, MH^+), 215 (8 %, MH^+-2H), 201 (14 %), 187 (3 %, M^+-C_2H_5), and 161 (4 %, M^+-C_4H_7).

Preparation of *2-Benzylthiofuran* (**248**).



The title compound was prepared according to the general procedure for the benzylthiolation of lithiofurans given in section 5.2.g. The reaction was carried out with *n*-butyllithium (1.6 M solution in hexane, 52 mL, 83 mmol, 1.05 equiv.), furan (**246**) (5.4 g, 79 mmol, 1.0 equiv.), anhydrous THF (160 mL), sulphur (2.6 g, 82 mmol, 1.04 equiv.), and benzyl bromide (9.7 mL, 81 mmol, 1.03 equiv.) to afford crude 2-benzylthiofuran (**248**) as a red-brown oil (16.3 g). Purification by bulb-to-bulb distillation under reduced pressure furnished the pure product as a pale yellow oil, b.p. 103-120°C (bath temperature) / 4 mmHg (lit[150] 67-71°C / 0.07 Torr) (10.4 g, 69 %); ν_{max} (thin film) 3 130, 3 086, 3 063, 3 030, 2 960, 2 929, 1 495, 1 455, 1 152, 1 008, 907, 744, 697, and 598 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.51 (1H, s, 5-FuH), 7.31 - 7.21 (3H, m, *o,p*-PhH), 7.18 - 7.13 (2H, m, *m*-PhH), 6.34 (1H, s, 4-FuH or 3-FuH), 6.33 (1H, s, 3-FuH or 4-FuH), and 3.97 (2H, s, $PhCH_2S$); $^{m}/_{z}$ (C.I.) 191 (100 %, MH^+), 190 (14 %, M^+), 108 (9 %, $C_7H_7NH_3^+$), 91 (60 %, $C_7H_7^+$), and 55 (3 %, $C_2H_3CO^+$).

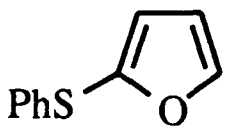
Preparation of *5-Acetyl-2-benzylthiofuran* (**251**) by Friedel-Crafts Acylation.



2-Benzylthiofuran (**248**) (1.4 g, 7.1 mmol, 1.0 equiv.), acetic anhydride (**250**) (0.85 mL, 9.0 mmol, 1.25 equiv.) and iron (III) chloride (22 mg, 0.22 mmol, 0.03 equiv.) were heated to reflux for 1 h under N_2. The solution was allowed to cool, diluted with diethyl ether (30 mL), washed successively with brine (30 mL) and saturated aqueous sodium hydrogen carbonate

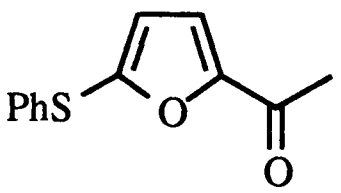
solution (30 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 5-acetyl-2-benzylthiofuran (**251**) as a dark brown oil (0.73 g). Purification by flash chromatography on silica, eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (1 : 5), furnished the pure product as a red oil (0.24 g, 14 %); further data on page 172.

Preparation of *2-Phenylthiofuran* (**253**).



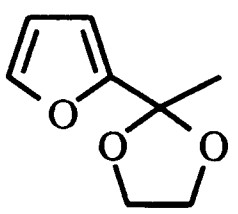
The title compound was prepared according to the general procedure for the phenylthiolation of lithiofurans given in section 5.2.h. The reaction was carried out with *n*-butyllithium (1.5 M solution in hexane, 29 mL, 43 mmol, 1.05 equiv.), furan (**246**) (3.0 mL, 41 mmol, 1.0 equiv.), anhydrous THF (160 mL), and phenyl disulphide (9.4 g, 43 mmol, 1.05 equiv.) to afford crude 2-phenylthiofuran (**253**) as a yellow oil (7.3 g). Purification by bulb-to-bulb distillation under reduced pressure furnished the pure product as a colourless oil, b.p. 87-90°C (bath temperature) / 0.8 mmHg (lit[151] 97-98°C / 25 mmHg) (5.0 g, 69 %) (Found C, 68.2, H, 4.50, S, 18.2; $C_{10}H_8OS$ calculated C, 68.2, H, 4.60, S, 18.2 %); ν_{max} (thin film) 3 130, 3 061, 1 584 (furan), 1 554, 1 479, 1 459, 1 441, 1 152, 1 005, 908, 740, and 690 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.60 (1H, d, $J_{5,4}$ 1.9 Hz, 5-FuH), 7.35 - 7.27 (2H, m, *o*-PhH), 7.27 - 7.15 (3H, m, *m,p*-PhH), 6.76 (1H, d, $J_{3,4}$ 3.3 Hz, 3-FuH), and 6.49 (1H, dd, $J_{4,3}$ 3.3, $J_{4,5}$ 1.9 Hz, 4-FuH); $m/_z$ (C.I.) 177 (100 %, MH^+), 176 (67 %, M^+), 147 (17 %), 115 (20 %), 77 (2 %, $C_6H_5^+$), 69 (4 %, $C_4H_4OH^+$), and 55 (6 %, $C_2H_3CO^+$).

Preparation of *5-Acetyl-2-phenylthiofuran* (**254**) by Friedel-Crafts Acylation.



2-Phenylthiofuran (**253**) (0.38 g, 2.2 mmol, 1.0 equiv.), acetic anhydride (**250**) (0.60 mL, 6.3 mmol, 2.9 equiv.) and iron (III) chloride (10 mg, 0.22 mmol, 0.03 equiv.) were heated to reflux for 1 h under N_2. The solution was allowed to cool, diluted with diethyl ether (20 mL), washed successively with brine (20 mL), saturated aqueous sodium hydrogen carbonate solution (2 x 20 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 5-acetyl-2-phenylthiofuran (**254**) as a dark brown oil (0.73 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 9), furnished the pure product as a pale yellow solid (0.17 g, 35 %). A small portion was further purified to afford the title compound as pale yellow needles, m.p. 63-63.5°C after recrystallisation (CH_2Cl_2-light petroleum (b.p. 30-40°C)) (Found C, 65.8, H, 4.45, S, 14.5; $C_{12}H_{10}O_2S$ requires C, 66.0, H, 4.60, S, 14.7 %); ν_{max} (KBr disk) 3 128, 3 087, 1 666 (C=O), 1 647, 1 578, 1 556, 1 466, 1 441, 1 036, 941, 741, and 691 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.34 - 7.27 (5H, m, PhH), 7.19 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 6.64 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), and 2.47 (3H, s, CH_3); $^m/_z$ (C.I.) 236 (7 %, MNH_4^+), 219 (100 %, MH^+), 203 (7 %, PhSFu'CO^+), and 176 (2 %, $PhSFu^+$).

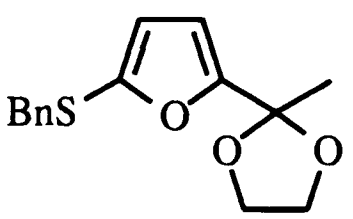
Preparation of *2-(2-Furyl)-2-methyl-1, 3-dioxolane* (**255**).



A solution of 2-acetylfuran (**229**) (8.6 g, 78 mmol, 1.0 equiv.), ethane-1, 2-diol (7.5 mL, 130 mmol, 1.7 equiv.), and *p*-toluenesulphonic acid monohydrate (0.74 g, 3.9 mmol, 0.05 equiv.) in benzene (150 mL) was refluxed for 3 d under N_2 with the azeotropic removal of water

using a Dean-Stark apparatus. The solution was allowed to cool, washed successively with 1 M aqueous potassium hydroxide solution (3 x 70 mL) and brine (2 x 70 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 2-(2-furyl)-2-methyl-1, 3-dioxolane (**255**) as a brown oil (15.7 g). Purification by distillation under reduced pressure furnished the pure product as a colourless oil, b.p. 106°C / 10 mmHg (9.5 g, 79 %) (Found C, 62.5, H, 6.65; $C_8H_{10}O_3$ requires C, 62.3, H, 6.55 %); ν_{max} (thin film) 3 121, 2 994, 2 892, 1 503, 1 475, 1 442, 1 040, 1 008, 870, and 743 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37 (1H, d, $J_{5,4}$ 1.5 Hz, 5-FuH), 6.32 (2H, m, 3-FuH and 4-FuH), 4.04 (4H, m, OCH_2CH_2O), and 1.75 (3H, s, CH_3); $^m/_z$ (C.I.) 155 (100 %, MH^+), 139 (19 %, M^+-CH_3), 111 (5 %, $FuAcH^+$), 95 (8 %, $FuCO^+$), and 87 (3 %, $C_3H_4O_2CH_3^+$).

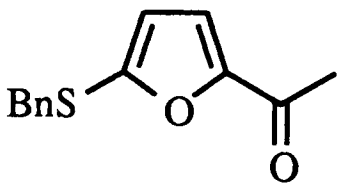
Preparation of *2-[5-(2-Benzylthio)furyl]-2-methyl-1, 3-dioxolane* (**256**).



The title compound was prepared according to the general procedure for the benzylthiolation of lithiofurans given in section 5.2.g. The reaction was carried out with *n*-butyllithium (1.6 M solution in hexane, 40 mL, 64 mmol, 1.2 equiv.), 2-(2-furyl)-2-methyl-1, 3-dioxolane (**255**) (8.1 g, 53 mmol, 1.0 equiv.), anhydrous THF (180 mL), sulphur (1.9 g, 58 mmol, 1.1 equiv.), and benzyl bromide (6.5 mL, 55 mmol, 1.04 equiv.) to afford crude 2-[5-(2-benzylthio)furyl]-2-methyl-1, 3-dioxolane (**256**) as a brown oil (16.5 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 5), furnished the pure product as a pale yellow oil (10.7 g, 73 %). A small portion was further purified by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 5), and solidified at -12°C to afford the title compound as colourless needles, m.p. 18-21°C after recrystallisation at low temperature (CH_2Cl_2-light petroleum (b.p. 30-40°C)) (Found C, 65.5, H, 5.80, S, 11.4; $C_{15}H_{16}O_3S$ requires C, 65.2, H, 5.85, S, 11.6 %); ν_{max} (thin film) 3 062, 3 029, 2 992, 2 890, 1 602, 1 495, 1 475, 1 455, 1 041, and

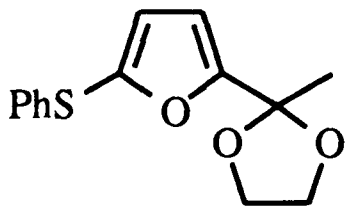
700 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35 - 7.20 (3H, m, *o*-PhH and *p*-PhH), 7.16 (2H, m, *m*-PhH), 6.25 (2H, m, 3-FuH and 4-FuH), 4.09 - 3.91 (4H, m, OCH_2CH_2O), 3.98 (2H, s, $PhCH_2S$), and 1.72 (3H, s, CH_3); $^m/_z$ (C.I.) 277 (100 %, MH^+), 261 (5 %, M^+-CH_3), 233 (6 %, BnSFu'AcH^+), 108 (4 %, $C_7H_7NH_3^+$), 91 (27 %, $C_7H_7^+$), and 87 (10 %, $C_3H_4O_2CH_3^+$).

Preparation of 5-Acetyl-2-benzylthiofuran (**251**).



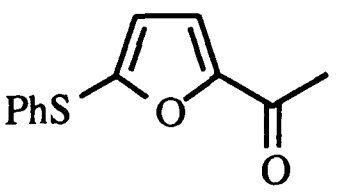
The title compound was prepared according to the general procedure for the deprotection of ketals under acid catalysis given in section 5.2.i. The reaction was carried out with 2-[5-(2-benzylthio)furyl]-2-methyl-1, 3-dioxolane (**256**) (10.1 g, 37 mmol, 1.0 equiv.), *p*-toluenesulphonic acid monohydrate (2.1 g, 11 mmol, 0.3 equiv.), and acetone-water (9 : 1 v/v) (300 mL) to afford, after 2 h reflux, crude 5-acetyl-2-benzylthiofuran (**251**) as a pale yellow oil (8.9 g). Purification by crystallisation overnight at -12°C furnished the pure product as colourless needles, m.p. 41-41.5°C after recrystallisation at low temperature (CH_2Cl_2-light petroleum (b.p. 30-40°C)) (7.4 g, 87 %) (Found C, 67.3, H, 5.30, S, 13.7; $C_{13}H_{12}O_2S$ requires C, 67.2, H, 5.20, S, 13.8 %); ν_{max} (KBr disk) 3 122, 3 086, 1 662 (C=O), 1 557, 1 494, 1 455, 1 360, 1 293, 1 031, 942, and 700 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.34 - 7.21 (5H, m, PhH), 7.09 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.36 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.14 (2H, s, $PhCH_2S$), and 2.44 (3H, s, CH_3); $^m/_z$ (C.I.) 233 (68 %, MH^+), 108 (7 %, $C_7H_7NH_3^+$), 91 (100 %, $C_7H_7^+$), and 65 (5 %, $C_5H_5^+$).

Preparation of *2-[5-(2-Phenylthio)furyl]-2-methyl-1, 3-dioxolane* (**257**).



The title compound was prepared according to the general procedure for the phenylthiolation of lithiofurans given in section 5.2.h. The reaction was carried out with *n*-butyllithium (1.5 M solution in hexane, 4.5 mL, 6.8 mmol, 1.04 equiv.), 2-(2-furyl)-2-methyl-1, 3-dioxolane (**255**) (1.0 g, 6.5 mmol, 1.0 equiv.), anhydrous THF (50 mL), and phenyl disulphide (1.5 g, 6.8 mmol, 1.05 equiv.) to afford crude 2-[5-(2-phenylthio)furyl]-2-methyl-1, 3-dioxolane (**257**) as a brown oil (1.7 g). Purification by flash chromatography on silica, gradient eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 8 to 1 : 7), furnished phenyl disulphide starting material (0.79 g, 53 %) and the pure product as colourless needles, m.p. 56-57°C after recrystallisation at low temperature (diethyl ether-light petroleum (b.p. 30-40°C)) (0.41 g, 24 %) (Found C, 64.5, H, 5.35, S, 12.0; $C_{14}H_{14}O_3$ requires C, 64.1, H, 5.40, S, 12.2 %); ν_{max} (KBr disk) 3 121, 3 112, 3 001, 2 907, 1 580, 1 493, 1 479, 1 442, 1 378, 1 245, 1 210, 1 191, 1 037, 858, and 739 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.30 - 7.15 (5H, m, PhH), 6.66 (1H, d, $J_{4,3}$ 3.2 Hz, 4-FuH), 6.40 (1H, d, $J_{3,4}$ 3.2 Hz, 3-FuH), 4.11 - 3.96 (4H, m, OCH_2CH_2O), and 1.74 (3H, s, CH_3); $^m/_z$ (C.I.) 263 (100 %, MH^+), 247 (13 %, M^+-CH_3), 219 (10 %, PhSFu'AcH^+), 203 (5 %, PhSFu'CO^+), 155 (3 %, $FuC_3H_4O_2^+$), and 87 (3 %, $C_3H_4O_2CH_3^+$).

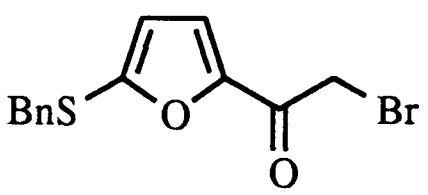
Preparation of 5-Acetyl-2-phenylthiofuran (**254**).



The title compound was prepared according to the general procedure for the deprotection of ketals under acid catalysis given in section 5.2.i. The reaction was carried out with 2-[5-(2-phenylthio)furyl]-2-methyl-1, 3-dioxolane (**257**) (390 mg, 1.5 mmol, 1.0 equiv.),

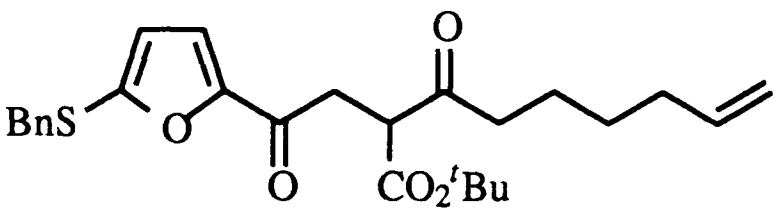
p-toluenesulphonic acid monohydrate (85 mg, 0.45 mmol, 0.3 equiv.), and acetone-water (9 : 1 v/v) (20 mL) to afford crude 5-acetyl-2-phenylthiofuran (**254**) as a pale yellow solid that could be used without further purification (313 mg, 96 %). Purification by recrystallisation (CH_2Cl_2-light petroleum (b.p. 30-40°C)) furnished the pure product as colourless needles, m.p. 63-63.5°C (130 mg, 39 %) (Found C, 66.4, H, 4.55, S, 14.5; $C_{12}H_{10}O_2S$ requires C, 66.0, H, 4.60, S, 14.7 %); further data on page 170.

Preparation of *2-Benzylthio-5-(bromoacetyl)furan* (**249**).



The title compound was prepared according to the general procedure for the α-monobromination of acetylfurans given in section 5.2.c. The reaction was carried out with copper (II) bromide (27.6 g, 124 mmol, 2.0 equiv.), ethyl acetate (350 mL), 5-acetyl-2-benzylthiofuran (**251**) (14.3 g, 62 mmol, 1.0 equiv.), and chloroform (350 mL) to afford, after 6 h reflux, crude 2-benzylthio-5-(bromoacetyl)furan (**249**) as a dark brown oil (20.4 g). Purification by dry flash chromatography on silica, gradient eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (1 : 8 - 1 : 5), followed by crystallisation at -12°C, furnished the pure product as pale yellow needles, m.p. 44.5-45.5°C, after recrystallisation at low temperature (CH_2Cl_2-light petroleum (b.p. 30-40°C)) (8.9 g, 46 %). A small portion was further purified by recrystallisation at low temperature (CH_2Cl_2-light petroleum (b.p. 30-40°C)) to afford the title compound as colourless needles, m.p. 49.5-50.5°C (Found C, 50.2, H, 3.40, S, 9.9; $C_{13}H_{11}BrO_2S$ requires C, 50.2, H, 3.55, S, 10.3 %); ν_{max} (KBr disk) 3 136, 3 086, 3 062, 3 030, 3 004, 2 979, 2 943, 1 669 (C=O), 1 602, 1 584, 1 561, 1 495, 1 451, 1 357, 1 292, 1 048, 1 020, and 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35 - 7.23 (5H, m, PhH), 7.26 (1H, d, $J_{4,3}$ 3.6 Hz, 4-FuH), 6.42 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 4.24 (2H, s, CH_2Br), and 4.18 (2H, s, $PhCH_2S$); $^m/_z$ (C.I.) 313 and 311 (3 %, MH^+), 233 (32 %, MH^+-Br), 108 (3 %, $C_7H_7NH_3^+$), 91 (100 %, $C_7H_7^+$), and 65 (7 %, $C_5H_5^+$).

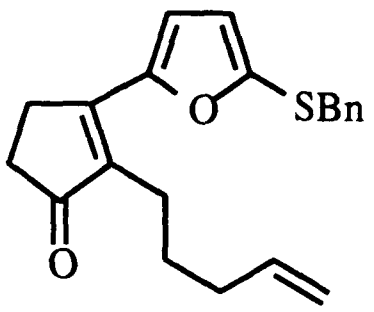
Preparation of tert-*Butyl 2-[2-(5-benzylthiofuroyl)methyl]-3-oxonon-8-enoate* (**258**).



The title compound was prepared according to the general procedure for the alkylation of (bromoacetyl)furans given in section 5.2.d. The reaction was carried out with sodium hydride (60 % dispersion in mineral oil, 0.21 g, 5.3 mmol, 1.05 equiv.), anhydrous THF (40 mL), *tert*-butyl 3-oxonon-8-enoate (**226**) (1.21 g, 5.3 mmol, 1.05 equiv.), and a solution of 2-benzylthio-5-(bromoacetyl)furan (**249**) (1.28 g, 5.1 mmol, 1.0 equiv.) in anhydrous THF (6 mL) to afford crude *tert*-butyl 2-[2-(5-benzylthiofuroyl)methyl]-3-oxonon-8-enoate (**258**) as a brown oil (2.52 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 4), furnished the pure product as a yellow oil (1.76 g, 76 %). A small portion was further purified by crystallisation overnight at -12°C to afford the title compound as colourless prisms, m.p. 42.5-43.5°C after recrystallisation at low temperature (diethyl ether-light petroleum (b.p. 30-40°C)) (Found C, 68.5, H, 6.90, S, 7.1; $C_{26}H_{32}O_5S$ requires C, 68.4, H, 7.05, S, 7.0 %); ν_{max} (thin film) 3 065, 2 978, 2 932, 2 872, 1 738 (C=O ester), 1 714 (C=O), 1675 (Fu-C=O), 1 645 (C=C), 1 609, 1 564, 1 455, 1 370, 1 278, 1 255, 1 153, 914, 757, 735, and 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32 - 7.24 (5H, m, PhH), 7.12 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.35 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 5.81 (1H, ddt, J_{tr} 17, J_{cis} 10, J 6.7 Hz, $CH_2C\underline{H}=CH_2$), 5.02 (1H, ddt, $J_{vic,tr}$ 17, J_{gem} 1.7, J_w 1.7 Hz, RCH=C$\underline{H}$H *cis* to R), 4.96 (1H, m, RCH=CH$\underline{H}$ *trans* to R), 4.15 (2H, s, $PhCH_2S$), 4.09 (1H, dd, J 8.3, J' 5.7 Hz, C$\underline{H}CH_2COFu$), 3.45 (1H, dd, J_{gem} 18.2, J_{vic} 8.3 Hz, CHC$\underline{H}$HCOFu), 3.27 (1H, dd, J_{gem} 18.2, J_{vic} 5.7 Hz, CHCH$\underline{H}$COFu), 2.78 (1H, dt, J_{gem} 17.6, J_{vic} 7.2 Hz, OCC$\underline{H}$HCH$_2$), 2.71 (1H, dt, J_{gem} 17.6, J_{vic} 7.2 Hz, OCCH$\underline{H}$CH$_2$), 2.09 (2H, m, $CH_2C\underline{H}_2CH=CH_2$), 1.66 (2H, m, $OCCH_2C\underline{H}_2$), 1.50 - 1.39 (2H, m, $C\underline{H}_2CH_2CH=CH_2$), and 1.47 (9H, s, $C(CH_3)_3$); δ_C (50.3 MHz, $CDCl_3$) 185.5 (s), 168.0 (s), 153.5 (s), 152.0 (s), 138.5 (d), 137.0 (s), 129.0 (d), 128.5 (d), 127.5 (d), 119.0 (d), 117.0 (d), 114.5 (t), 82.5 (s), 54.0 (d), 43.0 (t), 39.0 (t), 36.5 (t), 33.5 (t), 28.5 (t), 28.0 (q), and 23.0 (t); $m/_z$ (C.I.) 457 (1 %, MH^+),

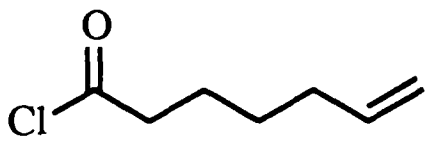
456 (1 %, M^+), 401 (8 %, MH^+-C_4H_8), 383 (8 %, M^+-^tBuO), 357 (8 %, MH^+-$CO_2C_4H_8$), 233 (8 %, BnSFu'$COMeH^+$), 223 (13 %, $^tBuO_2CCH_2C(O)C_6H_8^+$), 188 (41 %), 172 (12 %), 108 (4 %, $C_7H_7NH_3^+$), 91 (100 %, $C_7H_7^+$), 65 (8 %, $C_5H_5^+$), and 55 (2 %, $C_2H_3CO^+$).

Preparation of *3-[2-(5-Benzylthio)furyl]-2-(pent-4-enyl)cyclopent-2-enone* (**245**).



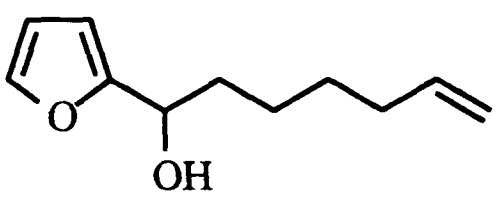
The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with *tert*-butyl 2-[2-(5-benzylthiofuroyl)methyl]-3-oxonon-8-enoate (**258**) (1.78 g, 3.9 mmol, 1.0 equiv.), ethanol (20 mL), water (8 mL), and 0.5 M aqueous sodium hydroxide solution (32 mL, 16 mmol, 4.2 equiv.) to afford crude 3-[2-(5-benzylthio)furyl]-2-(pent-4-enyl)cyclopent-2-enone (**245**) as a brown oil (1.36 g). Purification by crystallisation at -12°C furnished the pure product as yellow needles, m.p. 48.5-49.5°C after recrystallisation at low temperature (ethanol) (0.55 g, 42 %); ν_{max} (thin film) 3 064, 3 029, 2 927, 2 859, 1 693 (C=O), 1622 (C=C), 1 465, 1 376, 1 300, 1 240, 1 018, 913, 793, and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.27 (3H, m, *m, p*-PhH), 7.20 (2H, m, *o*-PhH), 6.71 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.44 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 5.87 (1H, ddt, J_{tr} 17.1, J_{cis} 10.2, J 6.7 Hz, $CH_2C\underline{H}=CH_2$), 5.04 (1H, ddt, $J_{vic,tr}$ 17.1, J_{gem} 1.7, J_w 1.7 Hz, RCH=C$\underline{H}$H *cis* to R), 4.97 (1H, m, $J_{vic,cis}$ 10.2, J_{gem} 1.7 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.08 (2H, s, $PhCH_2S$), 2.81 (2H, m, $OCC\underline{H}_2CH_2$), 2.55 (2H, m, $OCCC\underline{H}_2CH_2$), 2.50 (2H, m, $FuCC\underline{H}_2CH_2$), 2.15 (2H, m, $CHC\underline{H}_2CH_2$), and 1.58 (2H, m, $CH_2C\underline{H}_2CH_2$); δ_C (50.3 MHz, $CDCl_3$) 208.58 (s), 153.64 (s), 152.34 (s), 149.38 (s), 138.49 (d), 138.27 (s), 137.30 (s), 128.75 (d), 128.58 (d), 127.46 (d), 118.02 (d), 114.77 (d), 114.77 (t), 39.97 (t), 34.04 (t), 33.54 (t), 27.42 (t), 25.75 (t), and 23.63 (t); $m/_z$ (C.I.) 339 (19 %, MH^+), 217 (100 %, MH^+-PhCHS), 201 (22 %, MH^+-PhCHS-CH_2-2H), and 91 (18 %, $C_7H_7^+$).

Preparation of *6-Heptenoyl chloride* (**269**).



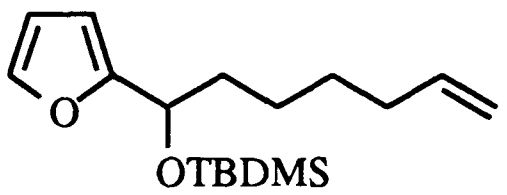
Oxalyl chloride (0.90 mL, 10.3 mmol, 1.4 equiv.) was added dropwise to 6-heptenoic acid (**268**) (1 mL, 7.6 mmol, 1.0 equiv.) at 0°C under N_2. The mixture was warmed rapidly to room temperature, stirred for 2 h, and left to stand for 2 h to afford 6-heptenoyl chloride (**269**) that was used without further purification.

Preparation of *7-(2-Furyl)hept-1-en-7-ol* (**278**).



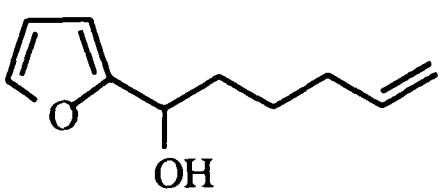
The title compound was prepared according to the general preparation for the Grignard addition to 2-furaldehyde (**276**) given in section 5.2.j. The reaction was carried out with 2-furaldehyde (**276**) (0.13 mL, 1.5 mmol, 1.0 equiv.) and 6-bromohex-1-ene (0.28 mL, 2.1 mmol, 1.4 equiv.) to afford the pure product (**278**) as a pale yellow oil (0.19 g, 70 %) (Found C, 72.9, H, 9.15; $C_{11}H_{16}O_2$ requires C, 73.3, H, 8.95 %); ν_{max} (thin film) 3 368 (O-H), 3 077, 2 976, 2 932, 2 860, 1 641 (C=C), 1 505, 1 151, 1 072, 1 009, 913, and 737 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.38 (1H, dd, $J_{5,4}$ 1.8, $J_{5,3}$ 0.9 Hz, 5-FuH), 6.34 (1H, dd, $J_{4,3}$ 3.2, $J_{4,5}$ 1.8 Hz, 4-FuH), 6.24 (1H, dd, $J_{3,4}$ 3.2, $J_{3,5}$ 0.9 Hz, 3-FuH), 5.81 (1H, ddt, J_{tr} 17, J_{cis} 10.3, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.01 (1H, m, $J_{vic,tr}$ 17, J_{gem} 1.6 Hz, RCH=C$\underline{H}$H *cis* to R), 4.96 (1H, m, $J_{vic,cis}$ 10.3 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.68 (1H, dd, J 7, J' 5.3 Hz, OC$\underline{H}CH_2$), 2.08 (2H, m, J 7 Hz, $CH_2C\underline{H}_2CH=CH_2$), 1.87 (3H, m, $\underline{H}OCHC\underline{H}_2CH_2$), and 1.44 (4H, m, $CH_2C_2\underline{H}_4CH_2$); $^m/_z$ (C.I.) 181 (3 %, MH^+), 180 (3 %, MNH_4^+-H_2O), 179 (16 %), 163 (100 %, MH^+-H_2O), 95 (9 %, $FuCO^+$), and 81 (26 %, $FuCH_2^+$).

Preparation of *7-(2-Furyl)hept-1-enyl* tert-*butyldimethylsilyl ether* (**282**).



The title compound was prepared according to the general preparation for the *tert*-butyldimethylsilyl protection of alcohols given in section 5.2.k. The reaction was carried out with 7-(2-furyl)hept-1-en-7-ol (**278**) (0.15 g, 0.84 mmol, 1.0 equiv.) to afford crude 7-(2-furyl)hept-1-enyl *tert*-butyldimethylsilyl ether (**282**) as a yellow oil (0.41 g). Purification by flash chromatography on silica, eluting sequentially with light petroleum (b.p. 30-40°C), diethyl ether-light petroleum (b.p. 30-40°C) (1 : 200) (R_f 0.12), and diethyl ether, furnished the alcoholic starting material (**278**) (46 mg, 30 %) and the pure product (**282**) as a pale yellow oil (96 mg, 39 %) (Found C, 69.4, H, 9.95; $C_{17}H_{30}O_2Si$ requires C, 69.3, H, 10.25 %); ν_{max} (thin film) 2 930, 2 858, 1 642 (C=C), 1 473, 1 463, 1 256, 1 152, 1 098, 1 007, 911, 838, 777, and 735 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35 (1H, dd, $J_{5,4}$ 1.9, $J_{5,3}$ 0.9 Hz, 5-FuH), 6.32 (1H, dd, $J_{4,3}$ 3.1, $J_{4,5}$ 1.9 Hz, 4-FuH), 6.17 (1H, d, $J_{3,4}$ 3.1, 3-FuH), 5.81 (1H, ddt, J_{tr} 17, J_{cis} 10, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.00 (1H, m, $J_{vic,tr}$ 17, J_{gem} 2, J_w 1 Hz, RCH=C$\underline{H}$H *cis* to R), 4.94 (1H, m, $J_{vic,cis}$ 10 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.67 (1H, t, J 6.5 Hz, OC$\underline{H}CH_2$), 2.05 (2H, m, $CH_2C\underline{H}_2CH=CH_2$), 1.79 (2H, m, $OCHC\underline{H}_2CH_2$), 1.45 - 1.30 (4H, m, $CH_2C_2\underline{H}_4CH_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $C\underline{H}_3SiMe$), and -0.06 (3H, s, $MeSiC\underline{H}_3$); $^m/_z$ (C.I.) 295 (0.4 %, MH^+), 254 (3 %, MNH_3^+-C_4H_9), 237 (7 %, M^+-C_4H_9), 163 (100 %, M^+-TBDMSO), and 81 (5 %, $FuCH_2^+$).

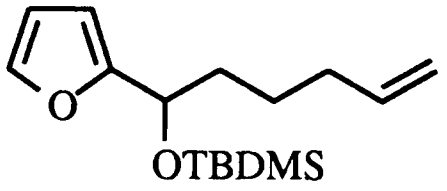
Preparation of *6-(2-Furyl)hex-1-en-6-ol* (**285**).



The title compound was prepared according to the general preparation for the Grignard addition to 2-furaldehyde (**276**) given in section 5.2.j. The reaction was carried out with

2-furaldehyde (**276**) (0.15 mL, 1.8 mmol, 1.0 equiv.) and 5-bromopent-1-ene (**228**) (0.25 mL, 2.1 mmol, 1.4 equiv.) to afford the pure product (**285**) as a pale yellow oil (0.21 g, 69 %) (Found C, 71.9, H, 8.80; $C_{10}H_{14}O_2$ requires C, 72.3, H, 8.50 %); ν_{max} (thin film) 3 368 (O-H), 3 077, 2 977, 2 938, 2 863, 1 641 (C=C), 1 505, 1 150, 1 070, 1 009, 913, and 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.38 (1H, d, $J_{5,4}$ 1.9 Hz, 5-FuH), 6.34 (1H, dd, $J_{4,3}$ 3.2, $J_{4,5}$ 1.9 Hz, 4-FuH), 6.24 (1H, d, $J_{3,4}$ 3.2 Hz, 3-FuH), 5.81 (1H, ddt, J_{tr} 17.1, J_{cis} 10.2, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.02 (1H, ddt, $J_{vic,tr}$ 17.1, J_{gem} 1.7, J_w 1.7 Hz, RCH=C$\underline{H}$H *cis* to R), 4.97 (1H, ddt, $J_{vic,cis}$ 10.2, J_{gem} 1.7, J_w 1.4 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.70 (1H, dd, J 7, J' 5.5 Hz, OC$\underline{H}CH_2$), 2.11 (2H, dt, J 7, J' 7 Hz, $CH_2C\underline{H}_2CH=CH_2$), 1.88 (2H, m, $OCHC\underline{H}_2CH_2$), 1.85 (1H, d, J 5.5 Hz, CHO$\underline{H}$), 1.57 (1H, m, $CH_2C\underline{H}HCH_2$), and 1.44 (1H, m, $CH_2CH\underline{H}CH_2$); $^m/_z$ (C.I.) 166 (3 %, MNH_4^+-H_2O), 149 (100 %, MH^+-H_2O), and 81 (22 %, $FuCH_2^+$).

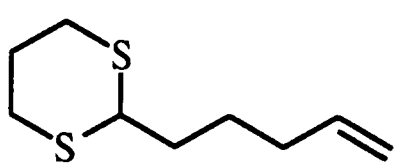
Preparation of *6-(2-Furyl)hex-1-enyl* tert-*butyldimethylsilyl ether* (**286**).



The title compound was prepared according to the general preparation for the *tert*-butyldimethylsilyl protection of alcohols given in section 5.2.k. The reaction was carried out with 6-(2-furyl)hex-1-en-6-ol (**285**) (0.16 g, 0.95 mmol, 1.0 equiv.) to afford crude 6-(2-furyl)hex-1-enyl *tert*-butyldimethylsilyl ether (**286**) as a yellow oil (0.34 g). Purification by flash chromatography on silica, eluting sequentially with light petroleum (b.p. 30-40°C), diethyl ether-light petroleum (b.p. 30-40°C) (1 : 100), and diethyl ether, furnished the alcoholic starting material (**285**) (17 mg, 11 %) and the pure product as a pale yellow oil (0.13 g, 49 %) (Found C, 68.3, H, 10.00; $C_{16}H_{28}O_2Si$ requires C, 68.5, H, 10.05 %); ν_{max} (thin film) 2 951, 2 930, 2 858, 1 642 (C=C), 1 473, 1 463, 1 257, 1 152, 1 096, 1 007, 911, 837, 777, and 735 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.34 (1H, dd, $J_{5,4}$ 1.8, $J_{5,3}$ 0.5 Hz, 5-FuH), 6.30 (1H, dd, $J_{4,3}$ 3.2, $J_{4,5}$ 1.8 Hz, 4-FuH), 6.16 (1H, d, $J_{3,4}$ 3.2, 3-FuH), 5.80 (1H, ddt,

J_{tr} 17.0, J_{cis} 10.2, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.00 (1H, ddt, $J_{vic,tr}$ 17.1, J_{gem} 1.7, J_w 1.7 Hz, RCH=C$\underline{H}$H *cis* to R), 4.95 (1H, m, $J_{vic,cis}$ 10.2 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.68 (1H, dd, J 7, J' 5.9 Hz, OC$\underline{H}CH_2$), 2.07 (2H, dt, J 7, J' 7 Hz, $CH_2C\underline{H}_2CH=CH_2$), 1.81 (2H, m, $OCHC\underline{H}_2CH_2$), 1.49 (1H, m, $CH_2C\underline{H}HCH_2$), 1.39 (1H, m, $CH_2CH\underline{H}CH_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $C\underline{H}_3SiMe$), and -0.06 (3H, s, $MeSiC\underline{H}_3$); $^m/_z$(C.I.) 281 (1 %, MH^+), 265 (0.5 %, M^+-CH_3), 240 (1.5 %, MNH_3^+-C_4H_9), 223 (18 %, M^+-C_4H_9), 149 (100 %, M^+-TBDMSO), and 81 (4 %, $FuCH_2^+$).

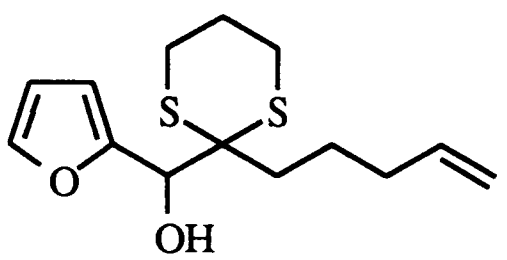
Preparation of *2-(5-Pent-1-enyl)-1, 3-dithiane* (**295**).



5-Bromopent-1-ene (**228**) (3 mL, 25 mmol, 1.2 equiv.) was added dropwise to a stirred solution of 2-lithio-1, 3-dithiane (**294**) prepared according to the general procedure given in section 5.2.1.[120] The reaction was carried out with *n*-butyllithium (1.5 M solution in hexane, 16 mL, 24 mmol, 1.1 equiv.), 1, 3-dithiane (**293**) (2.5 g, 21 mmol, 1.0 equiv.), and anhydrous THF (20 mL). The mixture was allowed to warm slowly to room temperature overnight and was partitioned between diethyl ether (75 mL) and saturated aqueous ammonium chloride solution (50 mL). The ethereal layer was washed successively with saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 2-(5-pent-1-enyl)-1, 3-dithiane (**295**) as a brown oil (4.82 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 18) (R_f 0.20) furnished the pure product as a pale yellow oil (3.67 g, 93 %) (Found C, 57.5, H, 8.80, S, 34.0; $C_9H_{16}S_2$ requires[120] C, 57.4, H, 8.55, S, 34.1 %); ν_{max} (thin film) 3 075, 2 975, 2 934, 2 899, 2 857, 1 640 (C=C), 1 423, 1 276, 1 243, 1 183, 993, and 910 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.81 (1H, ddt, J_{tr} 17, J_{cis} 10.3, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.04 (1H, m, $J_{vic,tr}$ 17, J 1.8 Hz, RCH=C$\underline{H}$H *cis* to R), 4.98 (1H, m, $J_{vic,cis}$ 10.3 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.06 (1H, t, J 7 Hz, $S_2C\underline{H}CH_2$), 2.88 (4H, m, $CH(SC\underline{H}_2)_2$), and 2.21

- 1.58 (8H, m, C<u>H</u>$_2$CH$_2$S and CHC$_3$<u>H</u>$_6$CH); $^m/_z$ (C.I.) 191 (9 %, MH$^+$+2H), 189 (100 %, MH$^+$), 188 (8 %, M$^+$), and 119 (10 %, C$_3$H$_6$S$_2$CH$^+$).

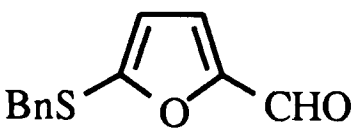
Preparation of *2-(2-Furylhydroxymethyl)-2-(pent-4-enyl)-1, 3-dithiane* (**297**).



2-Furaldehyde (**276**) (0.50 mL, 6.0 mmol, 1.1 equiv.) was added dropwise to a stirred solution of 2-lithio-2-(5-pent-1-enyl)-1, 3-dithiane (**296**) prepared according to the general procedure given in section 5.2.1.[121] The reaction was carried out with *n*-butyllithium (1.5 M solution in hexane, 4.0 mL, 6.0 mmol, 1.1 equiv.), 2-(5-pent-1-enyl)-1, 3-dithiane (**295**) (1.0 g, 5.5 mmol, 1.0 equiv.), and anhydrous THF (50 mL). The mixture was allowed to warm slowly to room temperature overnight and was partitioned between diethyl ether (75 mL) and saturated aqueous ammonium chloride solution (50 mL). The ethereal layer was washed successively with saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 2-(2-furylhydroxymethyl)-2-(pent-4-enyl)-1, 3-dithiane (**297**) as a yellow oil (1.47 g). Purification by flash chromatography on silica, gradient eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 5 to 1 : 4) furnished the pure product as a pale yellow oil (1.08 g, 69 %) (Found C, 59.2, H, 7.25, S, 22.5; $C_{14}H_{20}O_2S_2$ calculated[124] C, 59.1, H, 7.10, S, 22.6 %); ν_{max} (thin film) 3 451 (O-H), 3 075, 2 933, 2 867, 1 640 (C=C), 1 502, 1 423, 1 365, 1 276, 1 243, 1 148, 1 043, 1 010, 911, and 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.42 (1H, d, *J* 0.9 Hz, 5-FuH), 6.41 (1H, d, $J_{3,4}$ 3.2, 3-FuH), 6.39 (1H, dd, $J_{4,3}$ 3.2, *J* 1.8 Hz, 4-FuH), 5.79 (1H, ddt, J_{tr} 17.1, J_{cis} 10.2, *J* 7 Hz, CH$_2$C<u>H</u>=CH$_2$), 5.13 (1H, d, $J_{H\text{-}OH}$ 3.4 Hz, C<u>H</u>OH), 5.01 (1H, ddt, $J_{vic,tr}$ 17.1, J_{gem} 1.7, J_w 1.7 Hz, RCH=C<u>H</u>H *cis* to R), 4.95 (1H, dd, $J_{vic,cis}$ 10.2, J_{gem} 1.7 Hz, RCH=CH<u>H</u> *trans* to R), 3.14 (1H, d, $J_{HO\text{-}H}$ 3.4 Hz, exchanges in D_2O, CHO<u>H</u>), 3.06 (1H, ddd, J_{gem} 14, $J_{vic,ax\text{-}ax}$ 11.5, $J_{vic,ax\text{-}eq}$ 3.0 Hz, SC<u>H</u>$_{ax}$HCH$_2$CH$_2$S), 2.86 (1H, ddd, J_{gem} 14, $J_{vic,ax\text{-}ax}$ 11.5, $J_{vic,ax\text{-}eq}$ 3.0 Hz, SCH$_2$CH$_2$C<u>H</u>$_{ax}$HS), 2.65 (2H, m, J_{gem} 14, $J_{vic,eq\text{-}ax}$

3.0 Hz, SCH$\underline{H}_{eq}$CH$_2$CH$\underline{H}_{eq}$S), 2.07 (1H, m, $J_{vic,eq\text{-}ax}$ 3.0 Hz, SCH$_2$CH$\underline{H}_{eq}$), 2.03 (2H, m, CH$_2$C$\underline{H}_2$CH=CH$_2$), 1.94 (1H, m, SCC$\underline{H}$HCH$_2$), 1.85 (1H, m, $J_{vic,ax\text{-}ax}$ 11.5, $J_{vic,ax\text{-}eq}$ 3.0 Hz, SCH$_2$C$\underline{H}_{ax}$H), and 1.72 - 1.63 (3H, m, SCCH$\underline{H}$C$\underline{H}_2$); δ_C (50.3 MHz, $CDCl_3$) 152.26 (s), 141.96 (d), 138.45 (d), 115.06 (t), 110.55 (d), 109.19 (d), 70.29 (d), 35.28 (t), 33.91 (t), 26.08 (t), 25.52 (t), 24.11 (t), and 23.53 (t); $^m/_z$ (C.I.) 267 (100 %, MH$^+$-H$_2$O), 235 (4 %), 211 (4 %, MH$^+$-C$_3$H$_6$S), 196 (21 %, C$_2$H$_5$C$_4$H$_6$S$_2$CH$_2$ONH$_4^+$), 187 (61 %, M$^+$-FuCHOH), 179 (51 %, C$_2$H$_5$C$_4$H$_6$S$_2$CH$_2$OH$_2^+$), 163 (22 %, C$_2$H$_5$C$_4$H$_6$S$_2$CH$_4^+$), 161 (71 %, C$_2$H$_3$C$_4$H$_6$S$_2$CH$_4^+$), 145 (25 %, C$_4$H$_6$S$_2$C$_2$H$_3^+$), 119 (8 %, C$_3$H$_6$S$_2$CH$^+$), and 81 (12 %, FuCH$_2^+$).

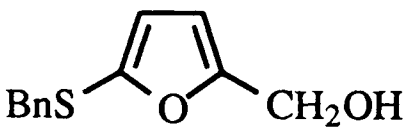
Preparation of *5-(2-Benzylthio)furaldehyde* (**298**).



According to a procedure adapted from Vilsmeier and Haack,[122] phosphorus oxychloride (0.25 mL, 2.7 mmol, 1.1 equiv.) was added dropwise by syringe to *N, N*-dimethylformamide (0.80 mL, 10.4 mmol, 4.4 equiv.) under N_2, maintaining the temperature below 0°C (ice-salt bath), and the reaction was stirred for 30 min. A solution of 2-benzylthiofuran (**248**) (0.45 g, 2.4 mmol, 1.0 equiv.) in *N, N*-dimethylformamide (0.28 mL, 3.5 mmol, 1.5 equiv.) was added dropwise, maintaining the temperature below 10°C. The solution was warmed to 35°C, stirred for 1 h, and allowed to cool. Ice was added to the resultant canary yellow paste with cooling, the mixture stirred carefully, and the brown solution decanted. 1 M Aqueous sodium hydroxide (26 mL, 26 mmol, 11.0 equiv.) was added to the supernatant, the mixture refluxed for 1.5 h, allowed to cool, and extracted with diethyl ether (40 mL). The aqueous phase was further extracted with diethyl ether (3 x 10 mL), the ethereal extracts combined, washed successively with water (30 mL), saturated aqueous ammonium chloride solution (30 mL), and brine (30 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 5-(2-benzylthio)furaldehyde (**298**) as a dark red-brown oil. Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p.30-40°C) (1 : 3) (R_f

0.20) furnished the pure product as a red-brown oil (0.24 g, 47 %) (Found C, 66.3, H, 4.40, S, 14.4; $C_{12}H_{10}O_2S$ requires C, 66.0, H, 4.60, S, 14.7 %); ν_{max} (thin film) 3 136, 3 087, 3 062, 3 030, 1 675 (HC=O), 1 562, 1 455, 1 378, 1 023, 763, and 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.56 (1H, s, CHO), 7.31 (5H, m, PhH), 7.17 (1H, d, $J_{4,3}$ 3.6 Hz, 4-FuH), 6.40 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), and 4.22 (2H, s, $PhCH_2S$); δ_C (50.3 MHz, $CDCl_3$) 176.75 (d), 155.16 (s), 154.32 (s), 136.65 (s), 129.06 (d), 128.89 (d), 127.91 (d), 123.25 (d), 115.60 (d), and 38.44 (t); m/z (C.I.) 236 (2 %, MNH_4^+), 219 (100 %, MH^+), 114 (17 %, MNH_4^+-$PhCH_2S$), 108 (9 %, $C_7H_7NH_3^+$), and 91 (18 %, $C_7H_7^+$).

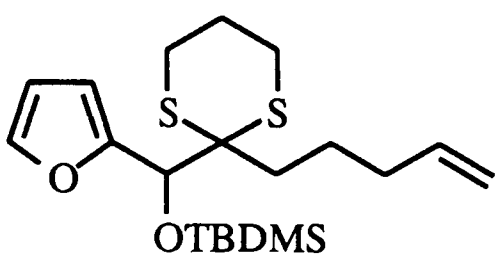
Preparation of *5-(2-Benzylthio)furfuryl alcohol* (**301**).



A solution of 5-(2-benzylthio)furaldehyde (**298**) (0.22 g, 0.99 mmol, 1.04 equiv.) in anhydrous THF (5 mL) was added to a stirred solution of 2-lithio-2-(5-pent-1-enyl)-1, 3-dithiane (**296**) prepared according to the general procedure given in section 5.2.1. The reaction was carried out with *n*-butyllithium (1.5 M solution in hexane, 0.65 mL, 0.98 mmol, 1.02 equiv.), 2-(5-pent-1-enyl)-1,3-dithiane (**295**) (0.18 g, 0.95 mmol, 1.0 equiv.), and anhydrous THF (20 mL). The mixture was allowed to warm slowly to room temperature overnight and was partitioned between diethyl ether (75 mL) and saturated aqueous ammonium chloride solution (75 mL). The ethereal layer was washed successively with saturated aqueous sodium hydrogen carbonate solution (80 mL) and brine (80 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford a brown oil (0.30 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 2) furnished dithiane starting material (**295**) (0.16 g, 87 %), aldehyde starting material (**298**) (13 mg, 6 %), and pure 5-(2-benzylthio)furfuryl alcohol (**301**) as a yellow oil (92 mg, 44 %); ν_{max} (thin film) 3 350 (O-H), 3 126, 3 086, 3 062, 3 029, 2 928, 2 869, 1 602, 1 495, 1 454, 1 011, 796, and 699 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.30 - 7.14 (5H, m, PhH), 6.31 (1H, d, $J_{4,3}$ 3.2 Hz, 4-FuH), 6.23 (1H, d, $J_{3,4}$ 3.2 Hz, 3-FuH), 4.57 (2H, d, $J_{H\text{-}OH}$ 6.3 Hz, $C\underline{H}_2OH$),

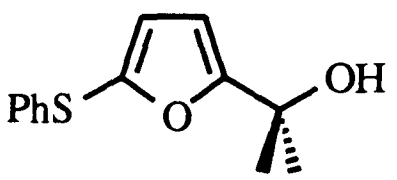
3.98 (2H, s, $PhCH_2S$), and 1.70 (1H, t, J_{HO-H} 6.3 Hz, exchanges in D_2O, $CH_2O\underline{H}$); $^m/_z$ (C.I.) 221 (6 %, MH^+), 220 (4 %, M^+), 203 (100 %, M^+-OH), 113 (10 %, $FuSCH_2^+$), 108 (8 %, $C_7H_7NH_3^+$), and 91 (17 %, $C_7H_7^+$).

Preparation of *2-(2-Furylmethyl)-2-(pent-4-enyl)-1, 3-dithiane*-tert-*butyldimethylsilyl ether* (**305**).



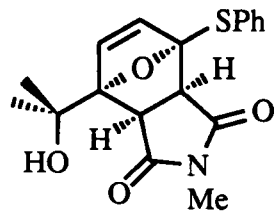
The title compound was prepared according to the general procedure for the *tert*-butyldimethylsilyl protection of alcohols given in section 5.2.k. The reaction was carried out with 2-(2-furylhydroxymethyl)-2-(pent-4-enyl)-1, 3-dithiane (**297**) (0.34 g, 1.2 mmol, 1.0 equiv.) to afford crude 2-(2-furylmethyl)-2-(pent-4-enyl)-1, 3-dithiane-tert-butyldimethylsilyl ether (**305**) as a pale yellow oil (0.60 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 30), furnished alcoholic starting material (**297**) (0.13 g, 39 %) and the pure product (**305**) as a colourless oil (0.15 g, 32 %) (Found C, 60.2, H, 8.90, S, 15.8; $C_{20}H_{34}O_2S_2Si$ requires C, 60.3, H, 8.60, S, 16.1 %); ν_{max} (thin film) 2 953, 2 929, 2 857, 1 641 (C=C), 1 499, 1 472, 1 463, 1 256, 1 150, 1 094, 1 011, 911, 890, 839, 778, and 735 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.39 (1H, s, 5-FuH), 6.36 (2H, m, 3-FuH and 4-FuH), 5.83 (1H, ddt, J_{tr} 17, J_{cis} 10, J 7 Hz, $CH_2C\underline{H}=CH_2$), 5.07 (1H, s, J_{H-OH} 3.4 Hz, $C\underline{H}OTBDMS$), 5.03 (1H, d, J 17 Hz, $RCH=C\underline{H}H$ *cis* to R), 4.96 (1H, d, J 10 Hz, $RCH=CH\underline{H}$ *trans* to R), 3.05 - 2.62 (4H, m, $C(SCH_2)_2$), 2.11 - 1.59 (8H, m, $SCH_2C\underline{H}_2$ and $C_3\underline{H}_6CH=CH_2$), 0.89 (9H, s, $C(CH_3)_3$), 0.07 (3H, s, $C\underline{H}_3SiMe$), and -0.21 (3H, s, $MeSiC\underline{H}_3$); $^m/_z$ (C.I.) 399 (0.3 %, MH^+), 383 (0.7 %, MH^+-CH_3), 293 (67 %, $C_2H_5C_4H_6S_2CH_2OTBDMSH^+$), 267 (91 %, M^+-TBDMSO), 235 (22 %), 211 (41 %, MH^+-$C_4H_8SiMe_2$-C_3H_6S), 187 (100 %, M^+-FuCHOTBDMS), 161 (77 %, $C_2H_3C_4H_6S_2CH_4^+$), 145 (61 %, $C_4H_6S_2C_2H_3^+$), 81 (42 %, $FuCH_2^+$), and 75 (63 %, Me_2SiOH^+).

Preparation of *5-[1-(1-Hydroxy-1-methyl)ethyl]-2-phenylthiofuran* (**312**).



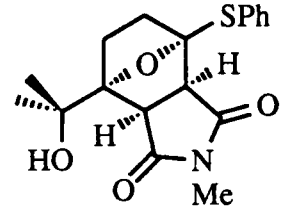
n-Butyllithium (1.5 M solution in hexane, 9.5 mL, 14 mmol, 1.3 equiv.) was added dropwise to a stirred solution of 2-phenylthiofuran (**253**) (1.92 g, 11 mmol, 1.0 equiv.) in anhydrous THF (35 mL) under N_2 at -78°C. The dark brown solution was stirred at this temperature for 1.5 h, warmed rapidly to -20°C and acetone (1.0 mL, 14 mmol, 1.3 equiv.) was added dropwise. The reaction mixture was stirred for 3 h, quenched at -20°C by the addition of saturated aqueous ammonium chloride solution (5 mL), and extracted with diethyl ether (20 mL). The aqueous phase was further extracted with diethyl ether (2 x 20 mL), the ethereal extracts combined, washed with brine (30 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 5-[1-(1-hydroxy-1-methyl)ethyl]-2-phenylthiofuran (**312**) as a brown solid (2.4 g). The pure product was obtained as brown needles after recrystallisation (ethyl acetate-hexane (10 : 1)) (1.4 g, 53 %). A small portion was further purified by recrystallisation (ethyl acetate-hexane (10 : 1)) to afford the title compound as brown needles, m.p. 57.5-59.5°C (Found C, 66.4, H, 6.20; $C_{13}H_{14}O_2S$ requires C, 66.6, H, 6.00 %); ν_{max} (KBr disk) 3 246 (O-H), 3 165, 3 072, 2 983, 2 930, 1 583, 1 478, 1 173, 805, 736, and 686 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.29 (2H, m, *o*-PhH), 7.26 - 7.14 (3H, m, *m, p*-PhH), 6.69 (1H, d, $J_{4,3}$ 3.2 Hz, 4-FuH), 6.30 (1H, d, $J_{3,4}$ 3.2 Hz, 3-FuH), 2.14 (1H, s, exchanges in D_2O, OH), and 1.60 (6H, s, $C(CH_3)_2$); $^m/_z$ (C.I.) 219 (100 %, M^+-CH_3), 218 (87 %), 217 (12 %, MH^+-H_2O), 203 (7 %, PhSFu'CO^+), 176 (14 %, MNH_4^+-C_6H_4), 147 (35 %), 110 (15 %), 89 (12 %), and 77 (3 %, $C_6H_5^+$).

Preparation of endo-*7-[1-(1-hydroxy-1-methyl)ethyl]*-N-*methyl-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3,5-dione* (**314**).



The title compound was prepared according to the general procedure for high pressure mediated Diels-Alder cycloaddition given in section 5.2.m. The reaction was carried out with 5-[1-(1-hydroxy-1-methyl)ethyl]-2-phenylthiofuran (**312**) (0.30 g, 1.3 mmol, 1.0 equiv.) and *N*-methylmaleimide (0.22 g, 1.9 mmol, 1.5 equiv.) to afford crude *endo*-7-[1-(1-hydroxy -1-methyl)ethyl]-*N*-methyl-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3,5-dione (**314**) as a brown foam that was used without purification (0.50 g, quant.); δ_H (200 MHz, $CDCl_3$) 7.65 (3H, m, *m,p*-PhH), 7.34 (2H, m, *o*-PhH), 6.42 (1H, d, *J* 5.6 Hz, 8-H or 9-H), 6.16 (1H, d, *J* 5.6 Hz, 9-H or 8-H), 3.76 (1H, d, $J_{6,2}$ 7.5 Hz, 6-H), 3.48 (1H, d, $J_{2,6}$ 7.5 Hz, 2-H), 2.87 (3H, s, NCH_3), 2.47 (1H, s, OH), 1.48 (3H, s, $C\underline{H}_3CCH_3$), and 1.44 (3H, s, $CH_3C\underline{CH}_3$).

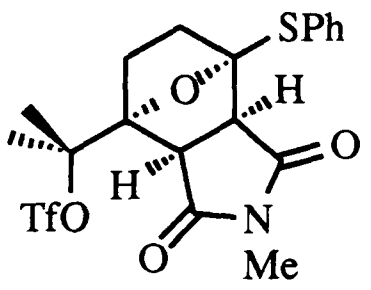
Preparation of endo-*7-[1-(1-hydroxy-1-methyl)ethyl]*-N-*methyl-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.0^{2,6}]deca-3,5-dione* (**317**).



A solution of crude *endo*-7-[1-(1-hydroxy-1-methyl)ethyl]-*N*-methyl-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3,5-dione (**314**) (0.50 g, 1.29 mmol, 1.0 equiv.) in ethyl acetate (10 mL) containing 10 % palladium on carbon (0.50 g, 100 % by weight) was stirred for 3 d under hydrogen (1 atmosphere) at room temperature. The solution was filtered

through a pad of silica and evaporated *in vacuo* to afford crude *endo*-7-[1-(1-hydroxy-1-methyl)ethyl]-*N*-methyl-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.$0^{2,6}$]deca-3,5-dione (**317**) as a pale yellow foam (0.41 g). Purification by dry flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (3 : 1) (R_f 0.20) furnished the pure product as colourless prisms, m.p. 104-106°C (0.39 g, 87 %) (Found C, 62.2, H, 6.40, N, 3.95, S, 9.45; $C_{18}H_{21}NO_4S$ requires C, 62.2, H, 6.10, N, 4.05, S, 9.25 %); ν_{max} (KBr disk) 3 501 (O-H), 3 058, 2 980, 1 775 (5 ring imide C=O), 1 703 (w) (5 ring imide C=O), 1 433, 1 379, 1 289, and 1 024 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.68 (2H, m, *o*-PhH), 7.41 - 7.35 (3H, m, *m,p*-PhH), 3.65 (1H, dd, J_{vic} 10.0, J_w 2.3 Hz, 6-H), 3.26 (1H, dd, J_{vic} 10.0, J_w 2.1 Hz, 2-H), 2.99 (3H, s, NCH_3), 2.09 (1H, s, OH), 1.98 (1H, dddd, *J* 12.4, *J'* 5, *J"* 2.3 Hz, 8_{exo}-H), 1.92 (1H, dddd, *J* 12.0, *J'* 4, *J"* 2.1 Hz, 9_{exo}-H), 1.86 (1H, ddd, *J* 12.4, *J'* 8, *J"* 5 Hz, 9_{endo}-H), 1.64 (1H, ddd, *J* 12.0, *J'* 8, *J"* 4 Hz, 8_{endo}-H), 1.42 (3H, s, $C\underline{H}_3CCH_3$), and 1.41 (3H, s, $CH_3CC\underline{H}_3$); δ_C (50.3 MHz, $CDCl_3$) 175.64 (s), 174.13 (s), 135.79 (d), 130.16 (s), 129.47 (d), 129.26 (d), 93.36 (s), 93.10 (s), 71.31 (s), 54.63 (d), 51.26 (d), 32.49 (t), 27.61 (t), 25.11 (q), and 24.87 (q); $^m/_z$ (C.I.) 348 (100 %, MH^+), 330 (95 %, MH^+-H_2O), 289 (10 %, M^+-HC(O)NMe), 261 (15 %, M^+-HC(O)NMeCO), 217 (72 %), 192 (48 %), and 77 (5 %, $C_6H_5^+$).

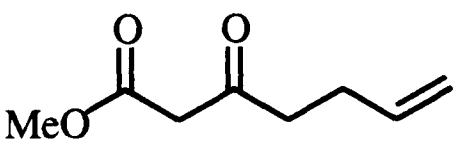
Preparation of *2-{*endo*-7-(N-methyl-3,5-dioxo-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.$0^{2,6}$] decanyl)}-1-(1-methyl)ethyl trifluoroacetate* (**320**).



A solution of *endo*-7-[1-(1-hydroxy-1-methyl)ethyl]-*N*-methyl-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.$0^{2,6}$]deca-3,5-dione (**317**) (63 mg, 0.18 mmol, 1.0 equiv.) and trifluoroacetic anhydride (0.37 g, 1.8 mmol, 1.0 equiv.) in 1, 2-dichloroethane (5 mL) was refluxed for 7 h under Ar. The reaction mixture was allowed to cool and was partitioned

between diethyl ether (15 mL) and water (10 mL). The ethereal extract was washed with brine (20 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 2-{*endo*-7-(*N*-methyl-3,5-dioxo-1-phenylthio-4-aza-10-oxatricyclo[5.2.1.$0^{2,6}$]decanyl)}-1-(1-methyl)ethyl trifluoroacetate (**320**) as a yellow foam (90 mg). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 1) furnished the pure product as a pale yellow foam (68 mg, 85 %); ν_{max} (thin film) 3 070, 2 994, 2 960, 1 780 (C=O), 1 708 (w) (5 ring imide C=O), 1 587, 1 433, 1 378, 1 289, 1 222, 1 176, 1 138, and 1 034 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.68 (2H, m, *o*-PhH), 7.36 (3H, m, *m,p*-PhH), 3.60 (1H, dd, J_{vic} 10.1, J_w 1.7 Hz, 6-H), 3.28 (1H, dd, J_{vic} 10.1, J_w 1.7 Hz, 2-H), 2.99 (3H, s, NCH_3), 1.96 - 1.70 (4H, m, 8_{exo}-H, 9_{exo}-H, 9_{endo}-H, and 8_{endo}-H), 1.83 (3H, s, $C\underline{H}_3CCH_3$), and 1.82 (3H, s, $CH_3CC\underline{H}_3$); δ_C (50.3 MHz, $CDCl_3$) 175.00 (s), 173.66 (s), 135.44 (d), 130.11 (s), 129.44 (d), 129.21 (d), 93.01 (s), 91.24 (s), 87.77 (s), 54.02 (d), 51.36 (d), 31.97 (s), 28.10 (q), 24.85 (t), 21.26 (q), and 20.80 (t); $^m/_z$ (C.I.) 461 (15 %, MNH_3^+), 444 (10 %, MH^+), 443 (10 %, M^+), 330 (100 %, MH^+-CF_3CO_2H), 237 (13 %, MNH_4^+-PhSH-CF_3CO_2H), and 220 (39 %, MH^+-PhSH-CF_3CO_2H).

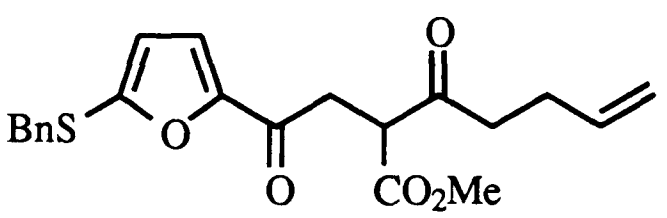
Preparation of *Methyl 3-oxohept-6-enoate* (**331**).



The title compound was prepared according to the general procedure for the alkylation of acetoacetate dianions given in section 5.2.b. The reaction was carried out with methyl acetoacetate (**332**) (0.45 mL, 4.2 mmol, 1.0 equiv.), sodium hydride (50 % dispersion in mineral oil, 0.21 g, 4.3 mmol, 1.02 equiv.), *n*-butyllithium (1.6 M solution in hexane, 4 mL, 6.4 mmol, 1.5 equiv.), anhydrous THF (50 mL), and allyl bromide (0.4 mL, 4.6 mmol, 1.1 equiv.) to afford crude methyl 3-oxohept-6-enoate (**331**) as a yellow oil (0.66 g). Purification by dry flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 1), furnished the pure product as a pale yellow oil, b.p. 100-105°C (bath temperature) / 2 mmHg (0.35 g, 54 %); ν_{max} (thin film) 3 080, 2 956, 1 751 (C=O ester),

1 718 (C=O), 1 643 (C=C), 1 438, 1 409, 1 322, 1 159, 1 001, and 918 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.92 - 5.71 (1H, ddt, J_{tr} 17, J_{cis} 10, J 6.7 Hz, $CH_2C\underline{H}=CH_2$), 5.05 (1H, m, $J_{vic,tr}$ 17, J_{gem} 1.6 Hz, RCH=C$\underline{H}$H *cis* to R), 4.99 (1H, m, $J_{vic,cis}$ 10, J_{gem} 1.6 Hz, RCH=CH$\underline{H}$ *trans* to R), 3.74 (3H, s, CH_3O), 3.46 (2H, s, O_2CCH_2CO), 2.65 (2H, t, J 7.4 Hz, $OCC\underline{H}_2CH_2$), and 2.35 (2H, m, $CH_2C\underline{H}_2CH=CH_2$); $^m/_z$ (C.I.) 174 (12 %, MNH_4^+), 157 (100 %, MH^+), 156 (13 %, M^+), 125 (40 %, M^+-MeO), 124 (25 %, $C_7H_8O_2^+$), 101 (14 %, $MeO_2CCH_2CO^+$), 84 (28 %, $C_4H_4O_2^+$), 83 (31 %, $C_2H_3C_2H_4CO^+$), 82 (94 %), and 55 (57 %, $C_4H_7^+$).

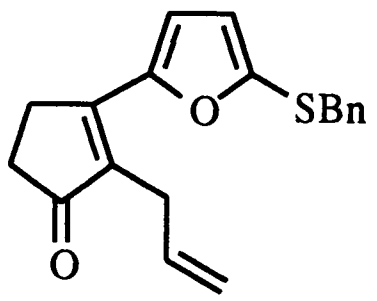
Preparation of *Methyl 2-[2-(5-benzylthiofuroyl)methyl]-3-oxohept-6-enoate* (**330**).



The title compound was prepared according to the general procedure for the alkylation of (bromoacetyl)furans given in section 5.2.d. The reaction was carried out with sodium hydride (50 % dispersion in mineral oil, 32 mg, 0.66 mmol, 1.1 equiv.), anhydrous THF (10 mL), a solution of methyl 3-oxohept-6-enoate (**331**) (99 mg, 0.63 mmol, 1.0 equiv.) in anhydrous THF (3 mL), and 2-benzylthio-5-(bromoacetyl)furan (**249**) (190 mg, 0.62 mmol, 1.0 equiv.) to afford crude methyl 2-[2-(5-benzylthiofuroyl)methyl]-3-oxohept-6-enoate (**330**) as a brown oil (310 mg). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 2), furnished the pure product as a yellow oil (123 mg, 51 %); ν_{max} (thin film) 3 143, 3 085, 3 065, 3 038, 3 008, 2 953, 2 930, 1 746 (C=O ester), 1 721 (C=O), 1674 (Fu-C=O), 1 643 (terminal C=C), 1 602, 1 564, 1 455, 1 260, 914, 734, and 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.35 - 7.22 (5H, m, PhH), 7.15 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.38 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 5.95 - 5.75 (1H, ddt, J_{tr} 17, J_{cis} 10, J 6.7 Hz, $CH_2C\underline{H}=CH_2$), 5.09 (1H, m, $J_{vic,tr}$ 17, J_{gem} 1.7 Hz, RCH=C$\underline{H}$H *cis* to R), 5.02 (1H, m, $J_{vic,cis}$ 10, J_{gem} 1.7 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.20 (1H, dd, J 8.4, J' 5.7 Hz, $C\underline{H}CH_2COFu$), 4.16 (2H, s, $PhCH_2S$), 3.79 (3H, s, CH_3O), 3.55 (1H, dd, J_{gem} 18.4, J_{vic} 8.4 Hz, $CHC\underline{H}HCOFu$), 3.34 (1H, dd, J_{gem} 18.4, J_{vic} 5.7 Hz, $CHCH\underline{H}COFu$), 2.88 (2H, dt, J_{vic}

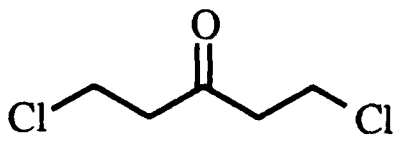
7, *J* 3 Hz, OCC<u>H</u>$_2$CH$_2$), and 2.40 (2H, dt, *J* 7 Hz, CH$_2$C<u>H</u>$_2$CH=CH$_2$),; $^m/_z$ (C.I.) 387 (100 %, MH$^+$), 233 (25 %, BnSFu'COMeH$^+$), 197 (2 %, $C_8H_{12}O_3CH_2CO^+$), 157 (3 %, $C_8H_{13}O_3^+$), 108 (28 %, $C_7H_7NH_3^+$), 91 (49 %, $C_7H_7^+$), 65 (2 %, $C_5H_5^+$), and 55 (2 %, $C_2H_3CO^+$).

Preparation of *2-(Prop-2-enyl)-3-(2-(5-benzylthio)furyl)cyclopent-2-enone* (**329**).



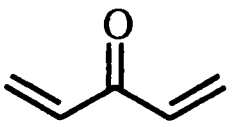
The title compound was prepared according to the general procedure for the base catalysed intramolecular Aldol cyclisation given in section 5.2.e. The reaction was carried out with methyl 2-[2-(5-benzylthiofuroyl)methyl]-3-oxohept-6-enoate (**330**) (57 mg, 0.15 mmol, 1.0 equiv.), ethanol (1 mL), and 0.5 M aqueous sodium hydroxide solution (2 mL, 1.0 mmol, 6.7 equiv.) to afford crude 2-(prop-2-enyl)-3-(2-(5-benzylthio)furyl)cyclopent-2-enone (**329**) as a brown oil (32 mg). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 1) furnished the pure product as a yellow oil (16 mg, 35 %). A small portion was further purified by crystallisation at -12°C to obtain the title compound as yellow needles, m.p. 62-63°C, after recrystallisation at low temperature (CH_2Cl_2-light petroleum (b.p. 30-40°C)) (Found C, 73.8, H, 6.00, S, 10.5; $C_{19}H_{18}O_2S$ requires C, 73.5, H, 5.85, S, 10.3 %); ν_{max} (thin film) 3 127, 3 108, 3 030, 3 006, 2 974, 2 961, 2 936, 2 914, , 2 833, 1 684 (C=O), 1625 (C=C), 1 546, 1 494, 1 462, 1 374, 1 207, 916, 809, and 703 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.34 - 7.17 (5H, m, PhH), 6.76 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.45 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 5.86 (1H, ddt, J_{tr} 17.0, J_{cis} 10.0, *J* 6 Hz, CH$_2$C<u>H</u>=CH$_2$), 5.10 (1H, ddt, $J_{vic,tr}$ 17.0, J_{gem} 1.6, J_w 1.6 Hz, RCH=C<u>H</u>H *cis* to R), 5.02 (1H, m, $J_{vic,cis}$ 10.0, J_{gem} 1.6, J_w 1.6 Hz, RCH=CH<u>H</u> *trans* to R), 4.09 (2H, s, PhCH$_2$S), 3.31 (2H, d, *J* 6 Hz, C=CHC<u>H</u>$_2$C=C), 2.87 (2H, t, *J* 5 Hz, OCCH$_2$), and 2.53 (2H, dt, *J* 5 Hz, C<u>H</u>$_2$CFu); $^m/_z$ (C.I.) 311 (100 %, MH$^+$), 310 (8 %, M$^+$), 189 (35 %, FuSCHPh$^+$), 108 (22 %, $C_7H_7NH_3^+$), and 91 (50 %, $C_7H_7^+$).

Preparation of *1,5-Dichloro-3-pentanone* (**345**).



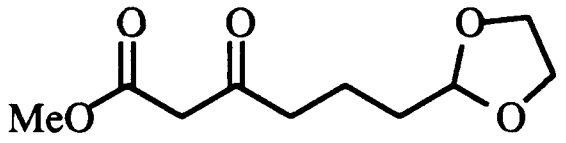
According to a procedure adapted from Baddeley, Taylor, and Pickles,[136] 3-chloropropanoyl chloride (**344**) (2.5 mL, 26 mmol, 1.0 equiv.) was added dropwise by syringe to a stirred suspension of aluminium chloride (4.0 g, 30 mmol, 1.1 equiv.) in anhydrous dichloromethane (150 mL) at room temperature under Ar. The solution was stirred for 15 min, allowed to stand for 10 min, decanted from the residual solid *via* cannula to a pre-dried flask, and cooled to -10°C. Dry ethene was passed through the agitated solution for 3 h, maintaining reaction temperature between -10 and -5°C. 1 M Aqueous hydrochloric acid (100 mL) was added and the organic layer was separated, washed successively with 1 M aqueous hydrochloric acid (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude 1,5-dichloro-3-pentanone (**345**) as a brown oil (2.9 g). Purification by dry flash column chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 4), furnished the pure product as a colourless oil (1.8 g, 45 %) (Found C, 38.7, H, 5.25; $C_5H_8Cl_2O$ calculated C, 38.7, H, 5.25 %); ν_{max} (thin film) 2 973, 2 910, 1 719 (C=O), 1 435, 1 396, 1 372, 1 339, 1 301, 1 092, 721, and 666 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.75 (4H, t, *J* 6.5 Hz, CH_2CO), and 2.95 (4H, t, *J* 6.5 Hz, CH_2Cl); $^m/_z$ (C.I.) 174 (65 %, $C_5H_8{}^{37}Cl{}^{35}ClONH_4{}^+$), 172 (92 %, $C_5H_8{}^{35}Cl_2ONH_4{}^+$), 157 (3 %, $C_5H_8{}^{37}Cl{}^{35}ClOH^+$), 155 (5 %, $C_5H_8{}^{35}Cl_2OH^+$), 138 (6 %, $C_5H_8{}^{37}ClONH_3{}^+$), 136 (12 %, $C_5H_8{}^{35}ClONH_3{}^+$), 121 (7 %, $C_5H_8{}^{37}ClO^+$), 119 (20 %, $C_5H_8{}^{35}ClO^+$), 93 (32 %, $^{37}ClC_2H_4CO^+$), 91 (100 %, $^{35}ClC_2H_4CO^+$), 83 (22 %, MH^+-2Cl), 82 (21 %, $C_2H_3{}^{37}ClH^+$), 80 (57 %, $C_2H_3{}^{35}ClH^+$), 65 (21 %, $C_2H_3{}^{37}ClH^+$), 63 (31 %, $C_2H_3{}^{35}ClH^+$), and 55 (79 %, $C_2H_3CO^+$).

Preparation of *Divinyl ketone* (**343**).



According to a procedure of Jung,[137] the distillation of 1,5-dichloro-3-pentanone (**345**) (0.46 g, 3.0 mmol, 1.0 equiv.) from quinoline (0.75 mL, 6.4 mmol, 2.1 equiv.) under reduced pressure (110-140°C (bath temperature) / 30 mmHg), trapping the distillate in a liquid nitrogen cold finger, furnished crude divinyl ketone (**343**) as a pale yellow oil that was used without further purification (0.20 g, 39 %); ν_{max} (thin film) 3 099, 3 020, 1 674 (C=O), 1 611 (C=C), 1 414, 1 217, 1 102, 988, 968, 827, and 758 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.65 (2H, dd, J_{tr} 17.5, J_{cis} 10.5 Hz, OCC<u>H</u>=CH_2), 6.32 (2H, dd, $J_{vic,tr}$ 17.5, J_{gem} 1.3 Hz, RCH=C<u>H</u>H *cis* to R), and 5.89 (2H, dd, $J_{vic,cis}$ 10.5, J_{gem} 1.3 Hz, RCH=C<u>H</u>H *trans* to R).

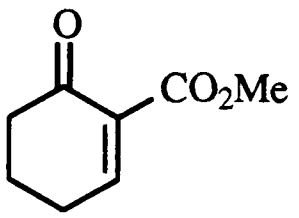
Preparation of *Methyl 6-(1, 3-dioxolanyl)-3-oxohexanoate* (**350**).



The title compound was prepared according to the general procedure for the alkylation of acetoacetate dianions given in section 5.2.b. The reaction was carried out with methyl acetoacetate (9.39 g, 81 mmol, 1.1 equiv.), sodium hydride (80 % dispersion in mineral oil, 3.3 g, 0.11 mol, 1.5 equiv.), *n*-butyllithium (1.5 M solution in hexane, 49.5 mL, 74 mmol, 1.0 equiv.), anhydrous THF (220 mL), and 2-(2-bromoethyl)-1, 3-dioxolane (**351**) (13.4 g, 74 mmol, 1.0 equiv.) to afford crude methyl 6-(1, 3-dioxolanyl)-3-oxohexanoate (**350**) as a yellow oil (15.1 g). Purification by dry flash chromatography on silica, gradient eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 2 - 2 : 1), furnished the pure product as a pale yellow oil, b.p. 145-165°C (bath temperature) / 2 mmHg (6.4 g, 40 %) (Found C, 55.6, H, 7.45; $C_{10}H_{16}O_5$ calculated C, 55.6, H, 7.45 %); ν_{max} (thin film) 2 955, 2 888, 1 747 (C=O ester), 1 718 (C=O), 1 439, 1 411, 1 322, 1 264, and 1 143 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.83 (1H, t, *J* 4.2 Hz, CHOO), 3.89 (4H, m, OCH_2CH_2O), 3.72 (3H, s, CH_3O), 3.44 (2H, s,

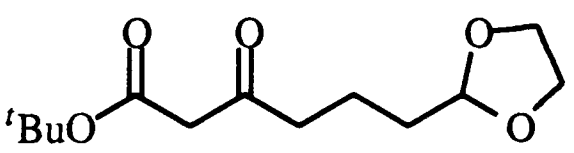
O_2CCH_2CO), 2.60 (2H, t, $J_{4,5}$ 7 Hz, $OCC\underline{H}_2CH_2$), and 1.80 - 1.62 (4H, m, $CH_2C_2\underline{H}_4CHOO$); $^m/_z$ (C.I.) 234 (40 %, MNH_4^+), 217 (100 %, MH^+), 172 (30 %, $MeO_2CC_6H_7ONH_4^+$), 159 (4 %, MH^+-CO_2CH_2), 155 (90 %, $MeO_2CC_6H_7OH^+$), 143 (10 %, $C_3H_5O_2C_3H_6CO^+$), 99 (13 %, $C_3H_4O_2C_2H_3^+$), and 73 (86 %, $C_3H_5O_2^+$).

Preparation of *Methyl 6-oxocyclohex-1-enoate* (**353**).



The title compound was prepared according to the general procedure for the deprotection of acetals and ketals under acid catalysis given in section 5.2.i. The reaction was carried out with methyl 6-(1,3-dioxolyl)-3-oxohexanoate (**350**) (4.1 g, 10.9 mmol, 1.0 equiv.), *p*-toluenesulphonic acid monohydrate (0.64 g, 3.4 mmol, 0.3 equiv.), and acetone-water (9 : 1 v/v) (200 mL) to afford, after 14 h reflux, crude methyl 6-oxocyclohex-1-enoate (**353**) as a pale yellow oil (1.6 g, quant.); ν_{max} (thin film) 2 954, 2 879, 1 746 (C=O ester), 1 689 (C=O), 1 619 (C=C), 1 436, 1 371, 1 273, 1 227, and 1 062 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.73 (1H, t, *J* 4.1 Hz, C=CH), 3.82 (3H, s, CH_3O), 2.58 - 2.45 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), and 2.15 - 2.01 (2H, m, $CH_2C\underline{H}_2CH_2$); $^m/_z$ (C.I.) 172 (20 %, MNH_4^+), 155 (100 %, MH^+), 153 (4 %, MH^+-2H), 140 (4 %, MH^+-2H-CH_2), 123 (4 %, M^+-MeO), and 55 (3 %, $C_2H_3CO^+$).

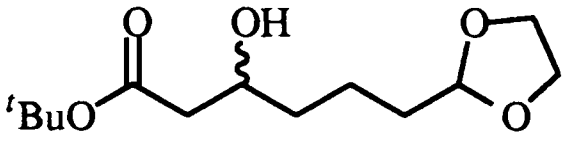
Preparation of tert-*Butyl 6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate* (**354**).



The title compound was prepared according to the general procedure for the alkylation of acetoacetate dianions given in section 5.2.b. The reaction was carried out with *tert*-butyl acetoacetate (19.1 g, 0.12 mol, 1.2 equiv.), sodium hydride (80 % dispersion in mineral oil, 3.6 g, 0.12 mol, 1.2 equiv.), *n*-butyllithium (1.5 M solution in hexane, 82 mL, 0.12 mol, 1.2

equiv.), anhydrous THF (250 mL), and 2-(2-bromoethyl)-1,3-dioxolane (18.5 g, 0.10 mol, 1.0 equiv.) to afford crude *tert*-butyl 6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**354**) as a pale yellow oil (27.2 g). Purification by dry flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 2), furnished the pure product as a pale yellow oil (18.4 g, 70 %) (Found C, 60.4, H, 8.65; $C_{13}H_{22}O_5$ calculated C, 60.5, H, 8.60 %); ν_{max} (thin film) 2 978, 2 886, 1 737 (C=O ester), 1 714 (C=O), 1 369, 1 319, 1 255, and 1 146 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.85 (1H, t, *J* 4.1 Hz, CHOO), 3.90 (4H, m, OCH_2CH_2O), 3.34 (2H, s, O_2CCH_2CO), 2.60 (2H, t, $J_{4,5}$ 7 Hz, $OCC\underline{H}_2CH_2$), 1.80 - 1.61 (4H, m, $CH_2C_2\underline{H}_4CHOO$), and 1.47 (9H, s, $C(CH_3)_3$); $^m/_z$ (C.I.) 276 (8 %, MNH_4^+), 259 (3 %, MH^+), 220 (88 %, MNH_4^+-C_4H_8), 203 (92 %, MH^+-C_4H_8), 185 (35 %, M^+-C_4H_9O), 159 (30 %), 158 (18 %, MH^+-C_4H_9OCO), 143 (7 %, $C_3H_5O_2C_3H_6CO^+$), 141 (28 %), 99 (10 %, $C_3H_4O_2C_2H_3^+$), and 73 (100 %, $C_3H_5O_2^+$).

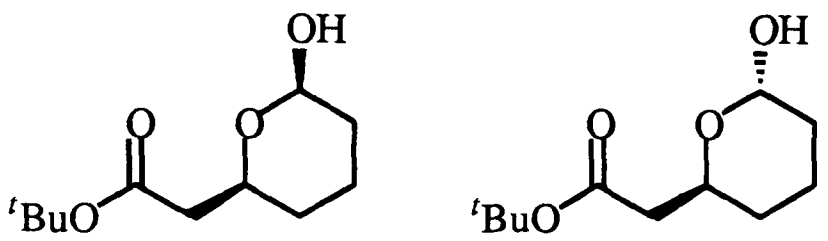
Preparation of tert-*Butyl 6-[2-(1, 3-dioxolanyl)]-3-hydroxyhexanoate* (**357**).



A solution of sodium borohydride (2.9 g, 77 mmol, 1.1 equiv.) in water (25 mL) was added dropwise to a stirred solution of *tert*-butyl 6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**354**) (18.0 g, 70 mmol, 1.0 equiv.) in ethanol (50 mL) at 0°C. The reaction mixture was stirred for 5 min, warmed to room temperature, stirred for 45 min, acidified to pH 1 with 1 M aqueous hydrochloric acid (≈ 20 mL), and extracted with diethyl ether (50 mL). The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford *tert*-butyl 6-[2-(1, 3-dioxolanyl)]-3-hydroxyhexanoate (**357**) as a pale yellow oil (19.0 g, quant.) that was used without further purification (Found C, 60.0, H, 9.60; $C_{13}H_{24}O_5$ requires C, 60.0, H, 9.30 %); ν_{max} (thin film) 3 474 (sharp, intramolecular H-bonded O-H), 2 985, 2 934, 2 891, 1 727 (intramolecular H-bonded C=O ester), 1 368, and 1 151 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.88 (1H, t, *J* 4 Hz, CHOO), 3.92 (4H, m, OCH_2CH_2O), 3.14 (1H, d, *J* 2 Hz, exchanges in D_2O,

CHOH), 2.45 (1H, dd, J_{gem} 16.5 , J_{vic} 3.6 Hz, $O_2CCHHCHOH$), 2.32 (1H, dd, J_{gem} 16.5 , J_{vic} 8.6 Hz, $O_2CCHHCHOH$), 1.71 - 1.50 (6H, m, C_3H_6CHOO), and 1.47 (9H, s, $C(CH_3)_3$); $^{m}/_{z}$ (C.I.) 278 (4 %, MNH_4^+), 261 (18 %, MH^+), 243 (5 %, MH^+-H_2O), 205 (5 %, MH^+-C_4H_8), 199 (100 %, MH^+-C_2H_4O-H_2O), 187 (11 %, M^+-^{t}BuO), 160 (93 %, $C_3H_5O_2C_3H_6CONH_3^+$), 143 (53 %, $C_3H_5O_2C_3H_6CO^+$), 125 (5 %, M^+-C_2H_4O-H_2O-C_4H_9O), 99 (4 %, $C_3H_4O_2C_2H_3^+$), and 73 (70 %, $C_3H_5O_2^+$).

Preparation of tert-*Butyl 3-hydroxy-2-oxacyclohexylacetate* (**359**).

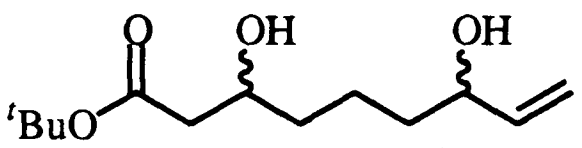


(359 a) **(359 b)**

The title compound was prepared according to the general procedure for the deprotection of acetals and ketals under acid catalysis given in section 5.2.i. The reaction was carried out with *tert*-butyl 6-[2-(1, 3-dioxolanyl)]-3-hydroxyhexanoate (**357**) (6.9 g, 26 mmol, 1.0 equiv.), *p*-toluenesulphonic acid monohydrate (1.5 g, 8 mmol, 0.3 equiv.), and acetone-water (10 : 1 v/v) (125 mL) to afford crude *tert*-butyl 3-hydroxy-2-oxacyclohexylacetate (**359**) as a pale yellow oil (5.1 g). Purification by dry flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 1), furnished the pure product (**359**) as a pale yellow oil (3.6 g, 63 %) (Found C, 61.1, H, 9.40; $C_{11}H_{20}O_4$ requires C, 61.1, H, 9.30 %); ν_{max} (thin film) 3 430 (O-H), 2 987, 2 940, 2 875, 1 732 (C=O ester), 1 369, 1 300, 1 153, 1 038, and 989 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.29 (1H, s, $CH_{eq}OO$ (**359b**)), 4.76 (1H, dd, J_{ax-ax} 8.6, J 1.2 Hz, $CH_{ax}OO$ (**359a**)), 4.38 (1H, m, CH_2CHOCH_2 (**359a**)), 3.87 (1H, m, CH_2CHOCH_2 (**359b**)), 2.56 (1H, dd, J_{gem} 15.5, J_{vic} 7.4 Hz, $O_2CCHHCHO$ (**359b**)), 2.46 - 2.24 (3H, m, J_{gem} 15.5 Hz, $O_2CCHHCHO$ (**359a**) and $O_2CCHHCHO$), 1.97 - 1.02 (14 H, m, $CH_2CHOC_3H_6CHOO$), and 1.45 (18H, s, $C(CH_3)_3$); $^{m}/_{z}$ (C.I.) 234 (22 %, MNH_4^+), 217 (4 %, MH^+), 199 (66 %, MH^+-H_2O), 178 (29 %, MNH_4^+-C_4H_8), 160 (100 %, MNH_4^+-C_4H_8-

H_2O), 143 (81 %, MH^+-C_4H_8-H_2O), 142 (4 %, MNH_3^+-^tBuO-H_2O), 125 (6 %, M^+-^tBuO-H_2O), and 57 (3 %, $C_4H_9^+$).

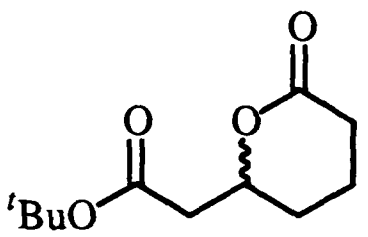
Preparation of tert-*Butyl 3, 7-dihydroxynon-8-enoate* (**360**).



Vinylmagnesium bromide (1.0 M solution in THF, 31 mL, 31 mmol, 2.6 equiv.) was added dropwise to a stirred solution of *tert*-butyl 3-hydroxy-2-oxacyclohexylacetate (**359**) (2.6 g, 12 mmol, 1.0 equiv.) in anhydrous THF (60 mL) under N_2 at 0°C. The mixture was stirred at this temperature for 1.5 h, quenched by the addition of saturated aqueous ammonium chloride solution (50 mL) and extracted with diethyl ether (50 mL). The aqueous layer was further extracted with diethyl ether (50 mL), the ethereal extracts combined, washed with brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude *tert*-butyl 3, 7-dihydroxynon-8-enoate (**360**) as a yellow oil (2.9 g, 99 %) that could be used without further purification. A small portion (0.84 g) was purified by dry flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (2 : 1), to afford the title compound as a colourless oil (0.33 g, 39 %) (Found C, 64.0, H, 9.80; $C_{13}H_{24}O_4$ requires C, 63.9, H, 9.90 %); ν_{max} (thin film) 3 398 (O-H), 2 979, 2 934, 2 878, 1 728 (intramolecular H-bonded C=O ester), 1 651 (C=C), 1 394, 1 369, 1 305, 1 258, and 1 154 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.88 (1H, ddd, J_{tr} 17, J_{cis} 10.4, J 6.3 Hz, $CHC\underline{H}=CH_2$), 5.23 (1H, m, $J_{vic,tr}$ 17.2, J 1.4 Hz, $RCH=C\underline{H}H$ *cis* to R), 5.12 (1H, d, $J_{vic,cis}$ 10.4 Hz, $RCH=CH\underline{H}$ *trans* to R), 4.12 (1H, m, $CH_2C\underline{H}(OH)CH=C$), 3.97 (1H, m, $CH_2C\underline{H}(OH)CH_2$), 2.44 (1H, dd, J_{gem} 16.5 , J_{vic} 3.7 Hz, $O_2CC\underline{H}HCHO$), 2.32 (1H, dd, J_{gem} 16.5 , J_{vic} 8.6 Hz, $O_2CCH\underline{H}CHO$), 2.04 (2H, s, exchanges in D_2O, OH), 1.60 - 1.33 (6H, m, $CHC_3\underline{H}_6CH$), and 1.46 (9H, s, $C(CH_3)_3$); δ_C (50.3 MHz, $CDCl_3$) 172.80 (s), 141.43 (d), 114.68 (t), 81.25 (s), 72.83 (d), 67.94 (d), 42.27 (t), 36.61 (t), 36.07 (t), 27.99 (q), and 21.09 (t); $^m/_z$ (C.I.) 262 (13 %, MNH_4^+), 245 (100 %, MH^+), 227 (3 %, MH^+-H_2O), 206 (3 %, MNH_4^+-C_4H_8), 189 (26 %, MH^+-C_4H_8), 171 (10 %,

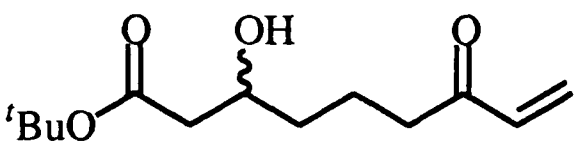
MH^+-C_4H_8-H_2O), 153 (5 %, MH^+-C_4H_8-$2H_2O$), 111 (3 %, M^+-^{t}BuOC(O)CH_2-H_2O), 93 (2 %, M^+-^{t}BuOC(O)CH_2-$2H_2O$), and 57 (6 %, $C_4H_9^+$).

Preparation of tert-*Butyl 3-oxo-2-oxacyclohexylacetate* (**362**).



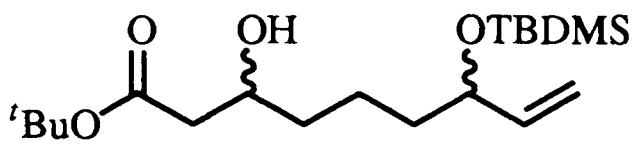
Pyridinium chlorochromate (0.92 g, 4.3 mmol, 4.0 equiv.) was added in one portion to a stirred suspension of anhydrous sodium acetate (0.35 g, 4.3 mmol, 4 equiv.) and Celite® (1.4 g, 1.5 times mass of PCC) in chloroform (50 mL) at room temperature under N_2 and the mixture homogenised by stirring vigorously for 15 min. A solution of *tert*-butyl 3, 7-dihydroxynon-8-enoate (**360**) (0.23 g, 1.1 mmol, 1.0 equiv.) in chloroform (2 mL) was added by syringe and the resultant solution stirred overnight. The mixture was filtered through a plug of silica, washing the residual cake successively with chloroform and diethyl ether, and evaporated *in vacuo* to afford crude *tert*-butyl 3-oxo-2-oxacyclohexylacetate (**362**) as a pale yellow oil (0.20 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (5 : 4), furnished the pure product as a colourless oil (92 mg, 43 %); ν_{max} (thin film) 2 978, 2 944, 1 746 (C=O ester), 1 394, 1 369, 1 344, 1 299, 1 241, 1 149 and 1 050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.71 (1H, m, $CH_2C\underline{H}(O)CH_2$), 2.73 (1H, dd, J_{gem} 15.8 , J_{vic} 6.5 Hz, $O_2CC\underline{H}HCHO$), 2.63 - 2.45 (3H, m, $O_2CCH\underline{H}CHO$ and $O_2CC\underline{H}_2CH_2$), 2.08 - 1.87 (3H, m, $OCHC\underline{H}_2CH_2$ and $CH_2C\underline{H}HCH_2$), 1.69 - 1.51 (1H, m, $CH_2CH\underline{H}CH_2$), and 1.47 (9H, s, $C(CH_3)_3$); δ_H (500 MHz, C_6D_6) 4.25 (1H, m, $CH_2C\underline{H}(O)CH_2$), 2.37 (1H, dd, J_{gem} 15.5 , J_{vic} 7.1 Hz, $O_2CC\underline{H}HCHO$), 2.05 (1H, dd, J_{gem} 15.5 , J_{vic} 5.9 Hz, $O_2CCH\underline{H}CHO$), 1.95 (1H, ddt, J_{gem} 17 , J_{vic} 6, J_w 1 Hz, $O_2CC\underline{H}HCH_2$), 1.86 (1H, ddt, J_{gem} 17 , J_{vic} 7.7, J_w 1 Hz, $O_2CC\underline{H}HCH_2$), 1.35 (9H, s, $C(CH_3)_3$), 1.17 (1H, m, $OCHC\underline{H}HCH_2$), 1.01 (1H, m, $OCHCH\underline{H}CH_2$), 0.93 (1H, m, $CH_2C\underline{H}HCH_2$), and 0.83 (1H, m, $CH_2CH\underline{H}CH_2$); $^m/_z$ (C.I.) 232 (30 %, MNH_4^+), 176 (100 %, MNH_4^+-C_4H_8), 159 (8 %, MNH_4^+-^{t}BuO), and 99 (3 %, M^+-^{t}BuOC(O)CH_2).

Preparation of tert-*Butyl 3-hydroxy-7-oxonon-8-enoate* (**363**).

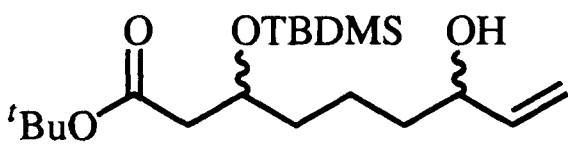


A suspension of anhydrous sodium acetate (0.35 g, 4.3 mmol, 10 equiv.) and active manganese dioxide on carbon (1.0 g, 10 times by weight), prepared by the general procedure given in section 5.1.n, in a solution of *tert*-butyl 3, 7-dihydroxynon-8-enoate (**360**) (0.11 g, 0.43 mmol, 1.0 equiv.) in chloroform (40 mL) was stirred overnight under N_2 at room temperature. The reaction mixture was filtered through a pad of Celite®, washing with chloroform, and evaporated *in vacuo* to afford crude *tert*-butyl 3-hydroxy-7-oxonon-8-enoate (**363**) as a pale-yellow oil (73 mg). Purification by flash chromatography on silica, eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (1 : 2), furnished the pure product as a colourless oil (62 mg, 59 %) (Found C, 64.2, H, 9.30; $C_{13}H_{22}O_4$ requires C, 64.4, H, 9.15 %); ν_{max} (thin film) 3 462 (O-H), 2 979, 2 934, 1 728 (intramolecular H-bonded C=O ester), 1 684 (C=O), 1 616 (C=C), 1 403, 1 369, 1 257, and 1 153 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.39 (1H, dd, J_{tr} 17.6, J_{cis} 9.8 Hz, C$\underline{H}$=CH_2), 6.24 (1H, dd, $J_{vic,tr}$ 17.6, J_{gem} 1.8 Hz, RCH=C$\underline{H}$H *cis* to R), 5.85 (1H, dd, $J_{vic,cis}$ 9.8, J_{gem} 1.8 Hz, RCH=CH$\underline{H}$ *trans* to R), 3.97 (1H, m, $CH_2C\underline{H}(OH)CH_2$), 3.22 (1H, d, $J_{HO\text{-}H}$ 3.7 Hz, exchanges in D_2O, OH), 2.66 (2H, t, J 7.1 Hz, O=C$C\underline{H}_2CH_2$), 2.46 (1H, dd, J_{gem} 16.5 , J_{vic} 3.8 Hz, $O_2CC\underline{H}HCHO$), 2.34 (1H, dd, J_{gem} 16.5 , J_{vic} 8.5 Hz, $O_2CCH\underline{H}CHO$), 1.83 - 1.40 (4H, m, $OCHC_2\underline{H}_4$), and 1.48 (9H, s, $C(CH_3)_3$); δ_C (50.3 MHz, $CDCl_3$) 200.65 (s), 172.37 (s), 136.43 (d), 128.08 (t), 81.21 (s), 67.69 (d), 42.22 (t), 39.15 (t), 35.65 (t), 28.04 (q), and 19.74 (t); $^m/_z$ (C.I.) 260 (5 %, MNH_4^+), 243 (4 %, MH^+), 242 (8 %, MH^+-H_2O), 225 (22 %, MH^+-H_2O), 204 (25 %, MNH_4^+-C_4H_8), 187 (14 %, MH^+-C_4H_8), 169 (100 %, MH^+-C_4H_8-H_2O or M^+-^{t}BuO), and 55 (6 %, $C_2H_3CO^+$).

Preparation of tert-*Butyl 3-hydroxy-7*-tert-*butyldimethylsilyloxynon-8-enoate* (**371**) and tert-*Butyl 7-hydroxy-3*-tert-*butyldimethylsilyloxynon-8-enoate* (**372**).

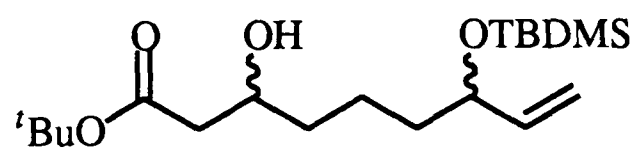


(**371**)



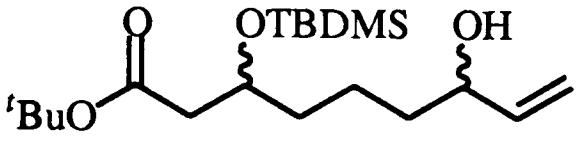
(**372**)

A solution of *tert*-butyl 3, 7-dihydroxynon-8-enoate (**360**) (0.26 g, 1.1 mmol, 1.0 equiv.), imidazole (74 mg, 1.1 mmol, 1.0 equiv.), and *tert*-butyldimethylsilyl chloride (0.17 g, 1.1 mmol, 1.0 equiv.) in anhydrous DMF (10 mL) was stirred for 24 h under N_2 at room temperature. The solution was partitioned between water (10 mL) and diethyl ether (20 mL), the aqueous layer further extracted with diethyl ether (20 mL), the ethereal extracts combined, washed successively with water (25 mL) and brine (25 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford a yellow oil (0.31 g). Purification by dry flash chromatography on silica, gradient eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 4) - (1 : 2), furnished *tert*-butyl 3, 7-dihydroxynon-8-enoate starting material (**360**) (58 mg, 22 %) and the title compounds.



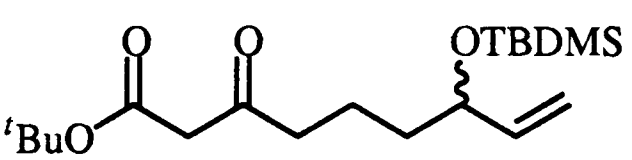
tert-Butyl 3-hydroxy-7-*tert*-butyldimethylsilyloxynon-8-enoate (**371**) was obtained as a colourless oil (87 mg, 23 %) (Found C, 63.7, H, 10.75; $C_{19}H_{38}O_4Si$ requires C, 63.6, H, 10.70 %); ν_{max} (thin film) 3 447 (O-H), 2 931, 2 858, 1 729 (C=O ester), 1 645 (C=C), 1 369, 1 255, 1 154, 1 089, 1 031, 837, and 776 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.80 (1H, ddd, J_{tr} 17, J_{cis} 10.3, J 6 Hz, CHC<u>H</u>=CH_2), 5.14 (1H, ddd, $J_{vic,tr}$ 17, J_{gem} 1.8, J_w 1.4 Hz, RCH=C<u>H</u>H *cis* to R), 5.03 (1H, ddd, $J_{vic,cis}$ 10.3, J_{gem} 1.8 Hz, RCH=CH<u>H</u> *trans* to R), 4.08 (1H, m, CHO), 3.95 (1H, m, CHOTBDMS), 3.12 (1H, d, J 4 Hz, exchanges in D_2O, OH), 2.43 (1H, dd, J_{gem} 16.5 , J_{vic} 3.5 Hz, O_2CC<u>H</u>HCHO), 2.30 (1H, dd, J_{gem} 16.5 , J_{vic} 8.6 Hz, O_2CCH<u>H</u>CHO), 1.70 - 1.30 (6H, m, CHC<u>$_3$H$_6$</u>CH), 1.47 (9H, s, C(CH_3)$_3$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.05 (3H, s, C<u>H_3</u>SiCH_3), and 0.03 (3H, s, CH_3SiC<u>H_3</u>); $^m/_z$ (C.I.) 359 (32 %,

MH$^+$), 303 (32 %, MH$^+$-C_4H_8), 227 (30 %, MH$^+$-TBDMSOH), 188 (33 %, MNH_4^+-TBDMSOH-C_4H_8 or $C_2H_3CH(OTBDMS)CH_2^+$), 171 (100 %, MH$^+$-TBDMSOH-C_4H_8 or $C_2H_3CH(OTBDMS)CH_2^+$), 111 (18 %, M$^+$-^{t}BuOC(O)CH_2-TBDMSOH), 93 (28 %, M$^+$-^{t}BuOC(O)CH_2-H_2O-TBDMSOH), 75 (13 %, Me_2SiOH^+), 74 (13 %, $C_4H_9NH_3^+$), and 57 (7 %, $C_4H_9^+$).



tert-Butyl 7-hydroxy-3-*tert*-butyldimethylsilyloxynon-8-enoate (**372**) was obtained as a colourless oil (37 mg, 10 %); ν_{max} (thin film) 3 425 (O-H), 2 954, 2 931, 2 858, 1 730 (C=O ester), 1 644 (C=C), 1 369, 1 256, 1 156, 1 093, 837, 776, and 759 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.87 (1H, ddd, J_{tr} 17, J_{cis} 10.4, J 6.3 Hz, CHC$\underline{H}$=CH_2), 5.22 (1H, ddd, $J_{vic,tr}$ 17.2, J_{gem} 1.4, J_w 1.4 Hz, RCH=C$\underline{H}$H *cis* to R), 5.11 (1H, dd, $J_{vic,cis}$ 10.4, J_{gem} 1.4 Hz, RCH=CH$\underline{H}$ *trans* to R), 4.09 (2H, m, 2CHO), 2.42 (1H, dd, J_{gem} 13 , J_{vic} 4.3 Hz, $O_2CC\underline{H}HCHO$), 2.31 (1H, dd, J_{gem} 13 , J_{vic} 4.3 Hz, $O_2CCH\underline{H}CHO$), 1.71 - 1.40 (6H, m, $CHC_3\underline{H}_6CH$), 1.45 (9H, s, $C(CH_3)_3$), 0.87 (9H, s, $SiC(CH_3)_3$), and 0.06 (6H, s, $Si(CH_3)_2$); $^m/_z$ (C.I.) 359 (30 %, MH$^+$), 303 (98 %, MH$^+$-C_4H_8), 285 (100 %, M$^+$-^{t}BuO), 227 (91 %, MH$^+$-TBDMSOH), 209 (25 %, MH$^+$-TBDMSOH-H_2O), 199 (50 %, M$^+$-$C_4H_8SiMe_2$-C_2H_3-H_2O), 185 (22 %, $C_2H_3CH(OTBDMS)CH_2^+$), 171 (23 %, MH$^+$-TBDMSOH-C_4H_8 or $C_2H_3CH(OTBDMS)CH_2^+$), 160 (48 %), 143 (50 %), 111 (40 %, M$^+$-^{t}BuOC(O)CH_2-TBDMSOH), 93 (46 %, M$^+$-^{t}BuOC(O)CH_2-H_2O-TBDMSOH), 75 (27 %, Me_2SiOH^+), 74 (41 %, $C_4H_9NH_3^+$), and 57 (16 %, $C_4H_9^+$).

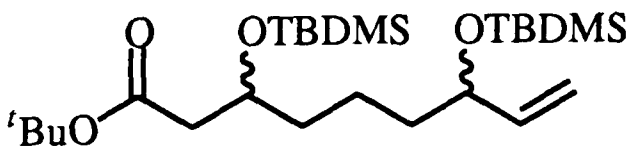
Preparation of tert-*Butyl 3-oxo-7*-tert-*butyldimethylsilyloxynon-8-enoate* (**373**).



Pyridinium chlorochromate (64 mg, 0.30 mmol, 1.3 equiv.) was added in one portion to a stirred suspension of anhydrous sodium acetate (24 mg, 0.30 mmol, 1.3 equiv.) and Celite®

(96 mg, 1.5 times mass of PCC) in chloroform (5 mL) at room temperature under N_2 and the mixture homogenised by stirring vigorously for 20 min. A solution of *tert*-butyl 3-hydroxy-7-*tert*-butyldimethylsilyloxynon-8-enoate (**371**) (82 mg, 0.23 mmol, 1.0 equiv.) in chloroform (3 mL) was added by syringe and the resultant solution stirred for 4 d. Pyridinium chlorochromate (49 mg, 0.23 mmol, 1.0 equiv.) was added in one portion and the mixture was stirred for 2 h, filtered through a plug of silica, washing the residual cake successively with chloroform and diethyl ether, and evaporated *in vacuo* to afford crude *tert*-butyl 3-oxo-7-*tert*-butyldimethylsilyloxynon-8-enoate (**373**) as a yellow oil (82 mg). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 10), furnished the pure product as a colourless oil (75 mg, 92 %) (Found C, 63.8, H, 10.15; $C_{19}H_{36}O_4Si$ requires C, 64.0, H, 10.20 %); ν_{max} (thin film) 2 957, 2 931, 2 858, 1 738 (C=O ester), 1 718 (C=O), 1 645 (C=C), 1 369, 1 319, 1 253, 1 149, 1 088, 1 028, 837, and 777 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.80 (1H, dd, J_{tr} 17, J_{cis} 10.4, J 6 Hz, CHC<u>H</u>=CH_2), 5.14 (1H, ddd, $J_{vic,tr}$ 17, J 1.6 Hz, RCH=C<u>H</u>H *cis* to R), 5.03 (1H, ddd, $J_{vic,cis}$ 10.4, J 1.6 Hz, RCH=CH<u>H</u> *trans* to R), 4.10 (1H, dt, J 6, J' 6 Hz, CH_2C<u>H</u>O), 3.33 (2H, s, OCCH_2CO), 2.53 (2H, t, J 7 Hz, O=C$C\underline{H}_2CH_2$), 1.68 - 1.40 (4H, m, O$CCH_2C_2\underline{H}_4$CHO), 1.46 (9H, s, O$C(CH_3)_3$), 0.89 (9H, s, Si$C(CH_3)_3$), 0.05 (3H, s, Me$SiCH_3$), and 0.03 (3H, s, CH_3SiMe); $m/_z$ (C.I.) 357 (6 %, MH^+), 301 (13 %, MH^+-C_4H_8), 243 (20 %, MH^+-$C_4H_8SiMe_2$), 225 (43 %, MH^+-TBDMSOH), 186 (14 %, MNH_4^+-C_4H_8-TBDMSOH), 171 (15 %, C_2H_3CHOTBDMS$^+$), 169 (100 %, MH^+-C_4H_8-TBDMSOH), 151 (13 %, M^+-TBDMSOH-^{t}BuO), 125 (18 %, MH^+-TBDMSOH-C_4H_8OCO), 75 (5 %, Me_2SiOH^+), 74 (8 %, $C_4H_9NH_3^+$), and 57 (6 %, $C_4H_9^+$).

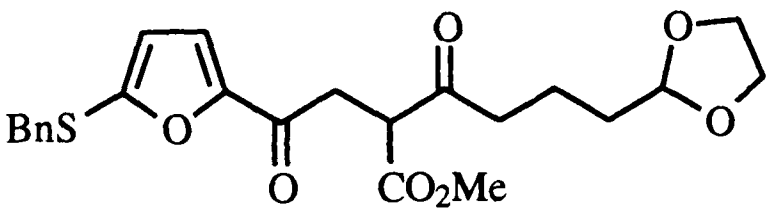
Preparation of tert-*Butyl 3, 7-di*-tert-*butyldimethylsilyloxynon-8-enoate* (**375**).



A solution of *tert*-Butyldimethylsilyl chloride (88 mg, 0.59 mmol, 5.0 equiv.), triethylamine (50 μL, 0.36 mmol, 3.1 equiv.), *N, N*-dimethylaminopyridine (7 mg, 0.06 mmol, 0.5 equiv.),

and *tert*-butyl 3, 7-dihydroxynon-8-enoate (**360**) (29 mg, 0.12 mmol, 1.0 equiv.) in anhydrous DMF (5 mL) was stirred for 2 d under N_2 at room temperature. *tert*-Butyldimethylsilyl chloride (44 mg, 0.29 mmol, 2.5 equiv.) and triethylamine (50 µL, 0.36 mmol, 3.1 equiv.) were added, the solution stirred for 1.5 h and partitioned between water (10 mL) and diethyl ether (10 mL). The aqueous phase was further extracted with diethyl ether (10 mL), the ethereal extracts combined, washed successively with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude *tert*-butyl 3, 7-di-*tert*-butyldimethylsilyloxynon-8-enoate (**375**) as a yellow oil (37 mg). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 40) (R_f 0.13), furnished the pure product as a colourless oil (15 mg, 27 %); ν_{max} (thin film) 2 960, 2 930, 2 858, 1 733 (C=O ester), 1 644 (C=C), 1 368, 1 255, 1 155, 1 094, 836, and 775 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.79 (1H, ddd, J_{tr} 17, J_{cis} 10.4, J 6 Hz, $CHC\underline{H}=CH_2$), 5.13 (1H, ddd, $J_{vic,tr}$ 17, J_{gem} 1.7, J_w 1.4 Hz, $RCH=C\underline{H}H$ *cis* to R), 5.02 (1H, dd, $J_{vic,cis}$ 10.4, J_{gem} 1.7 Hz, $RCH=CH\underline{H}$ *trans* to R), 4.08 (2H, m, 2CHO), 2.40 (1H, dd, J_{gem} 13 , J_{vic} 4.3 Hz, $O_2CC\underline{H}HCHO$), 2.30 (1H, dd, J_{gem} 13, J_{vic} 4.3 Hz, $O_2CCH\underline{H}CHO$), 1.45 - 1.13 (6H, m, $CHC_3\underline{H}_6CH$), 1.45 (9H, s, $OC(CH_3)_3$), 0.90 (9H, s, $C(CH_3)_3Si^tBu$), 0.88 (9H, s, $^tBuSi(CH_3)_3$), and 0.06 (12H, s, $Si(CH_3)_2$); $^m/_z$ (C.I.) 417 (8 %, MH^+-C_4H_8), 359 (15 %, MH^+-$C_4H_8SiMe_2$), 285 (100 %, MH^+-TBDMSOH-C_4H_8), 227 (44 %, MH^+-TBDMSOH-$C_4H_8SiMe_2$), 209 (11 %, MH^+-2TBDMSOH), 75 (11 %, Me_2SiOH^+), 74 (48 %, $C_4H_9NH_3^+$), and 57 (6 %, $C_4H_9^+$).

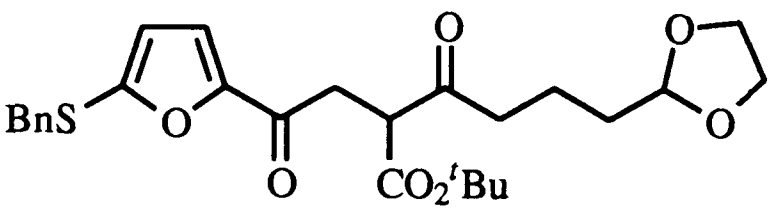
Preparation of *Methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate* (**376**).



The title compound was prepared according to the general procedure for the alkylation of (bromoacetyl)furans given in section 5.2.d. The reaction was carried out with sodium hydride

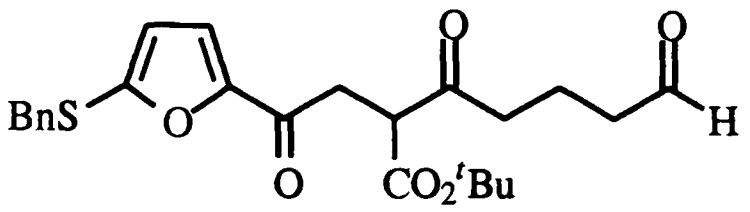
(80 % dispersion in mineral oil, 0.83 g, 28 mmol, 1.2 equiv.), anhydrous THF (40 mL), a solution of methyl 6-(1, 3-dioxolanyl)-3-oxohexanoate (**350**) (6.0 g, 28 mmol, 1.2 equiv.) in anhydrous THF (15 mL), and a solution of 2-benzylthio-5-(bromoacetyl)furan (**249**) (7.2 g, 23 mmol, 1.0 equiv.) in anhydrous THF (40 mL) to afford crude methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**376**) as a brown oil (10.7 g). Purification by dry flash chromatography on silica, eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (1 : 2), furnished the pure product as a yellow oil (7.2 g, 69 %). A small portion was further purified by crystallisation overnight at -12°C, followed by trituration with pentane and diethyl ether (3 times), to afford the title compound as colourless prisms, m.p. 62-63°C after recrystallisation at low temperature (ethanol) (Found C, 61.9, H, 6.05, S, 7.40; $C_{23}H_{26}O_7S$ requires C, 61.9, H, 5.85, S, 7.20 %); ν_{max} (thin film) 3 137, 3 066, 3 037, 2 966, 2 902, 1 746 (C=O ester), 1 720 (C=O), 1 675 (Fu-C=O), 1 603, 1 564, 1 451, 1 245, 1 045, 944, 806, and 702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32 - 7.24 (5H, m, PhH), 7.12 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 6.36 (1H, d, $J_{4,3}$ 3.6 Hz, 4-FuH), 4.87 (1H, t, J 4.5 Hz, $CH_2C\underline{H}(OCH_2CH_2O)$), 4.17 (1H, dd, J 8.3, J' 5.7 Hz, $C\underline{H}CH_2COFu$), 4.15 (2H, s, $PhCH_2S$), 3.98 - 3.83 (4H, m, OCH_2CH_2O), 3.76 (3H, s, CH_3O), 3.51 (1H, dd, J_{gem} 18.3, J_{vic} 8.3 Hz, $CHC\underline{H}HCOFu$), 3.32 (1H, dd, J_{gem} 18.3, J_{vic} 5.7 Hz, $CHCH\underline{H}COFu$), 2.85 (1H, dt, J_{gem} 18, J_{vic} 7 Hz, $OCC\underline{H}HCH_2CH_2$), 2.79 (1H, dt, J_{gem} 18, J_{vic} 7 Hz, $OCCH\underline{H}CH_2CH_2$), and 1.81 - 1.67 (4H, m, J 7, J' 7, J'' 4.5 Hz, $CH_2C_2\underline{H}_4CHOO$); $^m/_z$ (C.I.) 447 (100 %, MH^+), 429 (4 %, MH^+-CH_2), 415 (8 %, M^+-MeO), 217 (7 %, MH^+-BnSFu'C(O)CH), 143 (15 %, $C_3H_5O_2C_3H_6CO^+$), 108 (42 %, $C_7H_7NH_3^+$), 99 (16 %, $C_3H_4O_2C_2H_3^+$), 91 (93 %, $C_7H_7^+$), 73 (53 %, $C_3H_5O_2^+$), and 55 (8 %, $C_2H_3CO^+$).

Preparation of tert-*Butyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate* (**380**).



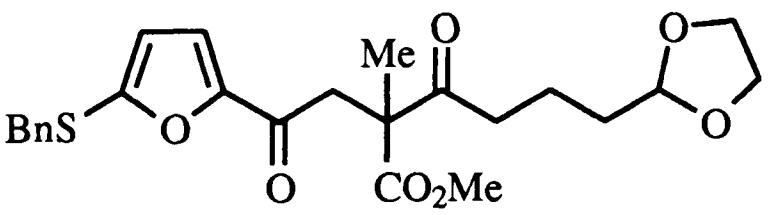
The title compound was prepared according to the general procedure for the alkylation of 5-(bromoacetyl)furans given in section 5.2.d. The reaction was carried out with sodium hydride (80 % dispersion in mineral oil, 0.13 g, 4.2 mmol, 1.3 equiv.), anhydrous THF (40 mL), a solution of *tert*-butyl 6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**354**) (1.1 g, 4.2 mmol, 1.3 equiv.) in anhydrous THF (15 mL), and a solution of 2-benzylthio-5-(bromoacetyl)furan (**249**) (1.0 g, 3.2 mmol, 1.0 equiv.) in anhydrous THF (40 mL) to afford crude *tert*-butyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**380**) as a dark green oil (1.71 g). Purification by dry flash chromatography on silica, gradient eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (1 : 2 - 1 : 1), furnished the pure product as a yellow oil (0.77 g, 49 %) (Found C, 63.8, H, 6.75; $C_{26}H_{32}O_7S$ requires C, 63.9, H, 6.60 %); ν_{max} (thin film) 2 976, 2 939, 2 891, 1 737 (C=O ester), 1 714 (C=O), 1 675 (Fu-C=O), 1 564, 1 455, 1 369, 1 152, and 1 041 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.34 - 7.19 (5H, m, PhH), 7.12 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.35 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.87 (1H, t, J 4.3 Hz, $CH_2C\underline{H}(OCH_2CH_2O)$), 4.14 (2H, s, $PhCH_2S$), 4.09 (1H, dd, J 8.1, J' 6.0 Hz, $C\underline{H}CH_2COFu$), 4.01 - 3.81 (4H, m, OCH_2CH_2O), 3.45 (1H, dd, J_{gem} 18.2, J_{vic} 8.1 Hz, $CHC\underline{H}HCOFu$), 3.27 (1H, dd, J_{gem} 18.2, J_{vic} 6.0 Hz, $CHCH\underline{H}COFu$), 2.82 (2H, m, $OCC\underline{H}_2CH_2$), 1.81 - 1.66 (4H, m, $OCCH_2C_2\underline{H}_4CHOO$), and 1.47 (9 H, s, $C(CH_3)_3$); $^m/_z$ (C.I.) 489 (15 %, MH^+), 433 (80 %, MH^+-C_4H_8), 415 (10 %, M^+-^{t}BuO), 389 (30 %, MH^+-$CO_2C_4H_8$), 143 (16 %, $C_3H_5O_2C_3H_6CO^+$), 108 (22 %, $C_7H_7NH_3^+$), 99 (14 %, $C_3H_4O_2C_2H_3^+$), 91 (100 %, $C_7H_7^+$), 73 (44 %, $C_3H_5O_2^+$), and 55 (5 %, $C_2H_3CO^+$).

Preparation of tert-*Butyl 2-[2-(5-benzylthiofuroyl)methyl]-3, 7-dioxoheptanoate* (**381**).



The title compound was prepared according to the general procedure for the deprotection of acetals and ketals under acid catalysis given in section 5.2.i. The reaction was carried out with *tert*-butyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**380**) (0.66 g, 1.35 mmol, 1.0 equiv.), *p*-toluenesulphonic acid monohydrate (80 mg, 0.40 mmol, 0.3 equiv.), and acetone-water (10 : 1 v/v) (165 mL) to afford, after 2 days reflux, crude *tert*-butyl 2-[2-(5-benzylthiofuroyl)methyl]-3, 7-dioxoheptanoate (**381**) as a yellow oil that was used without further purification (0.55 g, 91 %); ν_{max} (thin film) 3 139, 3 063, 2 977, 2 934, 1 737 (C=O ester), 1 717 (C=O), 1 674 (Fu-C=O), 1 563, 1 455, 1 370, 1 256, 1 153, 1 043, 756, and 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.80 (1H, t, *J* 1.2 Hz, O=CH), 7.27 (5H, m, PhH), 7.13 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 6.35 (1H, d, $J_{4,3}$ 3.6 Hz, 4-FuH), 4.15 (2H, s, $PhCH_2S$), 4.06 (1H, dd, *J* 8.9, *J'* 5.2 Hz, C<u>H</u>CH_2COFu), 3.51 (1H, dd, J_{gem} 17.9, J_{vic} 8.9 Hz, CHC<u>H</u>HCOFu), 3.27 (1H, dd, J_{gem} 17.9, J_{vic} 5.1 Hz, CHCH<u>H</u>COFu), 2.84 (2H, m, *J* 7 Hz, CHC(=O)C<u>H</u>$_2CH_2$), 2.51 (2H, m, *J* 7 Hz, CH_2C<u>H</u>$_2$CHO), 1.96 (2H, m, *J* 7 Hz, CH_2C<u>H</u>$_2CH_2$), and 1.52 (9H, s, $C(CH_3)_3$); $^m/_z$ (C.I.) 445 (53 %, MH^+), 427 (21 %, MH^+-H_2O), 389 (72 %, MH^+-C_4H_8), 108 (25 %, $C_7H_7NH_3^+$), and 91 (100 %, $C_7H_7^+$).

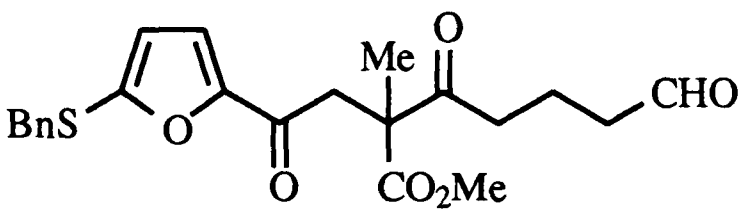
Preparation of *Methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-2-methyl-3-oxohexanoate* (**383**).



A solution of methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**376**) (0.82 g, 1.8 mmol, 1.0 equiv.) in anhydrous THF (2 mL) was added

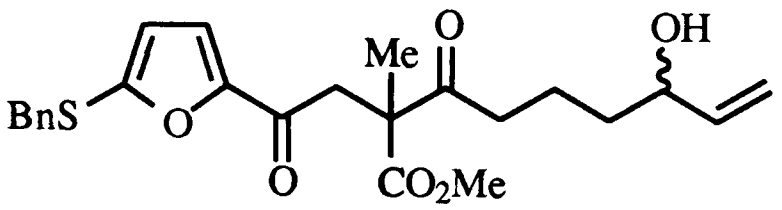
dropwise to a stirred suspension of sodium hydride (60 % dispersion in mineral oil, 81 mg, 2.0 mmol, 1.1 equiv.) in anhydrous THF (30 mL) under N_2, maintaining the temperature below 0°C (ice-salt bath), and the solution stirred at this temperature for 15 min. Iodomethane (1.2 mL, 18.5 mmol, 10.1 equiv.) was added by syringe and the mixture allowed to warm slowly to room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (30 mL) and was extracted with ethyl acetate (30 mL). The aqueous phase was further extracted with ethyl acetate (30 mL), the organic phases combined, washed with brine (2 x 30 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-2-methyl-3-oxohexanoate (**383**) as a brown oil (0.90 g). Purification by flash chromatography on silica, eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (1 : 2), furnished the pure product as a yellow oil (0.63 g, 75 %) (Found C, 62.3, H, 6.30, S, 6.75; $C_{24}H_{28}O_7S$ requires C, 62.6, H, 6.15, S, 6.95 %); ν_{max} (thin film) 3 139, 3 063, 3 030, 2 951, 2 886, 1 739 (C=O ester), 1 713 (C=O), 1 674 (Fu-C=O), 1 563, 1 455, 1 366, 1 238, 1 201, 1 142, 1 039, 944, and 702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.29 (5H, m, PhH), 7.12 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.38 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.89 (1H, t, J 4.2 Hz, $CH_2C\underline{H}(OCH_2CH_2O)$), 4.16 (2H, s, $PhCH_2S$), 3.93 (4H, m, OCH_2CH_2O), 3.77 (3H, s, CH_3O), 3.44 (2H, s, $C\underline{H}_2COFu$), 2.72 (2H, m, $OCC\underline{H}_2CH_2$), 1.71 (4H, m, $CH_2C_2\underline{H}_4CH$), and 1.55 (3H, s, CH_3C); δ_C (50.3 MHz, $CDCl_3$) 207.11 (s), 185.65 (s), 173.07 (s), 154.07 (s), 152.37 (s), 136.93 (s), 129.07 (d), 128.84 (d), 127.83 (d), 118.80 (d), 116.64 (d), 104.43 (d), 64.87 (t), 56.88 (s), 52.68 (q), 43.83 (t), 39.13 (t), 37.91 (t), 32.77 (t), 20.38 (q), and 17.95 (t); $^m/_z$ (C.I.) 461 (100 %, MH^+), 399 (5 %, MH^+-C_2H_4O-H_2O), 339 (23 %, MH^+-PhCHS), 231 (28 %, MH^+-BnSFu'C(O)CH), 160 (7 %, $C_3H_5O_2C_3H_6CONH_3^+$), 143 (18 %, $C_3H_5O_2C_3H_6CO^+$), 108 (12 %, $C_7H_7NH_3^+$), 99 (9 %, $C_3H_4O_2C_2H_3^+$), 91 (15 %, $C_7H_7^+$), 73 (14 %, $C_3H_5O_2^+$), and 55 (2 %, $C_2H_3CO^+$).

Preparation of *Methyl 2-[2-(5-benzylthiofuroyl)methyl]-2-methyl-3, 7-dioxoheptanoate* (**384**).



The title compound was prepared according to the general procedure for the deprotection of acetals and ketals under acid catalysis given in section 5.2.i. The reaction was carried out with methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-2-methyl-3-oxohexanoate (**383**) (0.31 g, 0.66 mmol, 1.0 equiv.), *p*-toluenesulphonic acid monohydrate (38 mg, 0.20 mmol, 0.3 equiv.), and acetone-water (9 : 1 v/v) (30 mL) to afford, after 24 h reflux, crude methyl 2-[2-(5-benzylthiofuroyl)methyl]-2-methyl-3, 7-dioxoheptanoate (**384**) as a yellow oil that was used without further purification (0.26 g, 93 %) (Found C, 63.4, H, 5.85, S, 7.45; $C_{22}H_{24}O_6S$ requires C, 63.4, H, 5.80, S, 7.70 %); ν_{max} (thin film) 3 138, 3 062, 3 030, 2 952, 2 726, 1 738 (C=O ester), 1 715 (C=O), 1 673 (Fu-C=O), 1 603, 1 562, 1 455, 1 367, 1 266, 1 238, 1 201, 1 176, 1 047, 1 019, 805, and 702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.78 (1H, t, *J* 1.2 Hz, O=CH), 7.29 (5H, m, PhH), 7.10 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.36 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.14 (2H, s, $PhCH_2S$), 3.75 (3H, s, CH_3O), 3.49 (1H, d, J_{gem} 17.9 Hz, C<u>H</u>HCOFu), 3.37 (1H, d, J_{gem} 17.9 Hz, CH<u>H</u>COFu), 2.74 (2H, m, OCC<u>H</u>$_2$$CH_2$), 2.52 (2H, dt, *J* 7, *J'* 1.2 Hz, CH_2C<u>H</u>$_2$CHO), 1.96 (2H, m, CH_2C<u>H</u>$_2$$CH_2$), and 1.54 (3H, s, CH_3C); δ_C (50.3 MHz, $CDCl_3$) 207.00 (s), 202.48 (s), 185.52 (s), 172.97 (s), 153.86 (s), 152.55 (s), 136.90 (s), 129.03 (d), 128.81 (d), 127.80 (d), 118.99 (d), 116.55 (d), 56.67 (s), 52.71 (q), 44.07 (t), 42.59 (t), 39.03 (t), 37.24 (t), 20.54 (q), and 15.91 (t); $^m/_z$ (C.I.) 434 (3 %, MNH_4^+), 417 (100 %, MH^+), 399 (10 %, MH^+-H_2O), 108 (14 %, $C_7H_7NH_3^+$), and 91 (16 %, $C_7H_7^+$).

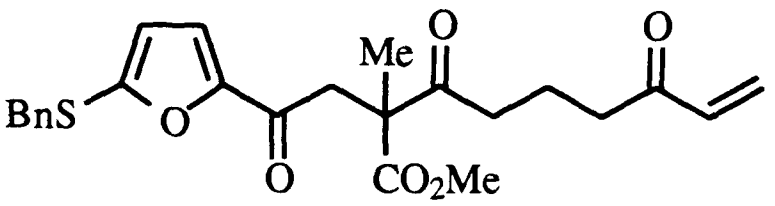
Preparation of *Methyl 2-[2-(5-benzylthiofuroyl)methyl]-7-hydroxy-2-methyl-3-oxonon-8-enoate* (**385**).



Vinylmagnesium bromide (1.0 M solution in THF, 0.60 mL, 0.60 mmol, 1.0 equiv.) was added dropwise to a stirred solution of methyl 2-[2-(5-benzylthiofuroyl)methyl]-2-methyl-3, 7-dioxoheptanoate (**384**) (0.25 g, 0.59 mmol, 1.0 equiv.) in anhydrous THF (60 mL) under N_2 at -78°C. The reaction mixture was stirred for 30 min, quenched at -78°C by the addition of saturated aqueous ammonium chloride solution (40 mL) and extracted with ethyl acetate (50 mL). The aqueous phase was further extracted with ethyl acetate (50 mL), the organic extracts combined, washed with brine (2 x 80 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude methyl 2-[2-(5-benzylthiofuroyl)methyl]-7-hydroxy-2-methyl-3-oxonon-8-enoate (**385**) as a yellow oil (0.27 g). Purification by flash chromatography on silica, eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (2 : 3) (R_f 0.18), furnished aldehyde starting material (**384**) (76 mg, 31 %) and the pure product as a pale yellow oil (86 mg, 32 %); ν_{max} (thin film) 3 500 (O-H), 3 139, 3 087, 3 064, 3 029, 2 951, 1 733 (C=O ester), 1 714 (C=O), 1 674 (Fu-C=O), 1 603, 1 563, 1 455, 1 366, 1 266, 1 238, 1 202, 1 175, 1 048, 1 019, 920, 804, 759, and 702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.27 (5H, m, PhH), 7.10 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 6.36 (1H, d, $J_{4,3}$ 3.6 Hz, 4-FuH), 5.88 (1H, ddd, J_{tr} 17, J_{cis} 10.5, J 6.5 Hz, CHC<u>H</u>=CH_2), 5.24 (1H, m, $J_{vic,tr}$ 17, J_{gem} 1.4 Hz, RCH=C<u>H</u>H *cis* to R), 5.12 (1H, m, $J_{vic,cis}$ 10.5, J_{gem} 1.4 Hz, RCH=CH<u>H</u> *trans* to R), 4.14 (2H, s, $PhCH_2S$), 4.09 (1H, m, C<u>H</u>OH), 3.75 (3H, s, CH_3O), 3.43 (2H, s, CH_2COFu), 2.70 (2H, m, OCC<u>H</u>$_2CH_2$), 1.88 (1H, s, exchanges in D_2O, CHO<u>H</u>), 1.80 - 1.48 (4H, m, CH_2C_2<u>H</u>$_4CHO$), and 1.54 (3H, s, CH_3C); δ_C (50.3 MHz, $CDCl_3$) 207.11 (s), 185.27 (s), 172.74 (s), 154.02 (s), 152.18 (s), 140.96 (d), 136.66 (s), 128.85 (d), 128.62 (d), 127.61 (d), 118.72 (d), 116.43 (d), 114.69 (t), 72.74 (d), 56.84 (s), 52.72 (q), 43.94 (t), 39.13 (t), 38.08 (t), 36.05 (t), 20.56 (q), and 19.35 (t); $^m/_z$ (C.I.) 445 (2 %, MH^+), 429 (12 %, M^+-CH_3), 427 (100 %, MH^+-H_2O), 417 (12 %, M^+-C_2H_3), 319

(17 %, M^+-$OCC_4H_8OC_2H_3$), 305 (10 %, M^+-$OCC_4H_8OC_2H_3$-CH_2), 287 (5 %, M^+-$OCC_4H_8OC_2H_3$-MeO), 197 (4 %, MH^+-BnSFu'C(O)CH_2-OH), 144 (12 %, $C_2H_3CH(OH)C_3H_6CONH_3^+$), 127 (11 %, $C_2H_3CH(OH)C_3H_6CO^+$), 108 (11 %, $C_7H_7NH_3^+$), 91 (17 %, $C_7H_7^+$), and 55 (3 %, $C_2H_3CO^+$).

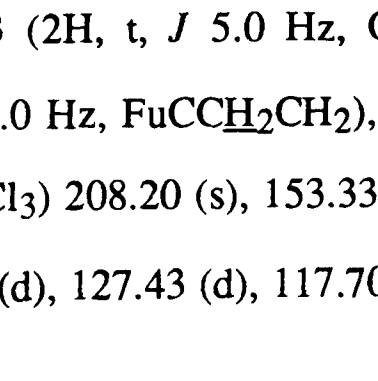
Preparation of *Methyl 2-[2-(5-benzylthiofuroyl)methyl]-2-methyl-3, 7-dioxonon-8-enoate* (**386**).



A suspension of active manganese dioxide on carbon (0.35 g, 4 times by weight), prepared by the general procedure given in section 5.2.n, in a solution of methyl 2-[2-(5-benzylthiofuroyl)methyl]-7-hydroxy-2-methyl-3-oxonon-8-enoate (**385**) (84 mg, 0.19 mmol, 1.0 equiv.) in chloroform (20 mL) was stirred overnight under N_2 at room temperature. The reaction mixture was filtered through a pad of Celite®, which was washed with chloroform and the solvent evaporated *in vacuo* to afford crude methyl 2-[2-(5-benzylthiofuroyl)methyl]-2-methyl-3, 7-dioxonon-8-enoate (**386**) as a pale yellow oil (70 mg). Purification by flash chromatography on silica, eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (2 : 3), furnished allylic alcohol starting material (**385**) (34 mg, 40 %) and the pure product (**386**) as a pale yellow oil (20 mg, 24 %); ν_{max} (thin film) 3 139, 3 089, 3 062, 3 026, 2 951, 1 733 (C=O ester), 1 714 (C=O), 1 681 (C=C-C=O), 1 673 (Fu-C=O), 1 616 (C=C), 1 563, 1 455, 1 404, 1 367, 1 268, 1 238, 1 201, 1 047, 1 019, 805, 768, 736, and 702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.27 (5H, m, PhH), 7.10 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 6.37 (1H, dd, J_{tr} 17.6, J_{cis} 9.6 Hz, C<u>H</u>=CH_2), 6.36 (1H, d, $J_{4,3}$ 3.6 Hz, 4-FuH), 6.23 (1H, dd, $J_{vic,tr}$ 17.6, J_{gem} 2.2 Hz, RCH=C<u>H</u>H *cis* to R), 5.84 (1H, dd, $J_{vic,cis}$ 9.6, J_{gem} 2.2 Hz, RCH=CH<u>H</u> *trans* to R), 4.14 (2H, s, $PhCH_2S$), 3.74 (3H, s, CH_3O), 3.48 (1H, d, J_{gem} 17.9 Hz, FuC(O)C<u>H</u>H), 3.38 (1H, d, J_{gem} 17.9 Hz, FuC(O)CH<u>H</u>), 2.72 (2H, m, CC(O)C<u>H</u>$_2$CH_2), 2.66 (2H, t, J 7.0 Hz, $C_2H_3C(O)C\underline{H}_2CH_2$), 1.95 (2H, tt, J 7.0, J' 7 Hz, $CH_2C\underline{H}_2CH_2$), and 1.53 (3H, s, CCH_3); $^m/_z$

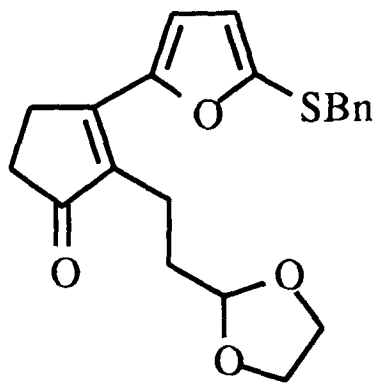
(C.I.) 445 (32 %, MH^++2H), 443 (100 %, MH^+), 429 (12 %, M^+-CH_3), 417 (15 %), 411 (4 %, M^+-MeO), 319 (13 %, M^+-$OCC_4H_6OC_2H_3$), 387 (6 %, M^+-$OCC_4H_6OC_2H_3$-MeO), 233 (8 %, BnSFu'C(O)CH_4^+), 108 (26 %, $C_7H_7NH_3^+$), 91 (49 %, $C_7H_7^+$), and 55 (11 %, $C_2H_3CO^+$).

Preparation of *3-[5-(2-Benzylthio)furyl]-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone* (**388**).



The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**376**) (1.35 g, 3.0 mmol, 1.0 equiv.), ethanol (13 mL), and 0.5 M aqueous sodium hydroxide solution (25 mL, 12.5 mmol, 4.1 equiv.) to afford crude 3-[5-(2-benzylthio)furyl]-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**388**) as a yellow oil (1.0 g). Purification by crystallisation at -12°C furnished the pure product as yellow needles, m.p. 61-62°C, after recrystallisation at low temperature (ethanol) (0.56 g, 50 %) (Found C, 68.1, H, 6.00, S, 8.50; $C_{21}H_{22}O_4S$ requires C, 68.1, H, 6.00, S, 8.65 %); ν_{max} (thin film) 3 070, 3 030, 2 929, 2 885, 1 692 (C=O), 1 620 (C=C), 1 562, 1 495, 1 456, 1 378, 1 141, 1 073, 1 029, 736, and 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.24 (5H, m, PhH), 6.82 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.44 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.95 (1H, t, J 4.6 Hz, OOC$\underline{H}CH_2$), 4.14 (2H, s, $PhCH_2S$), 3.98 - 3.85 (4H, m, OCH_2CH_2O), 2.83 (2H, t, J 5.0 Hz, $OCCH_2$), 2.68 (2H, t, J 8.0 Hz, $O_2CHCH_2C\underline{H}_2$), 2.50 (2H, m, J 5.0 Hz, $FuCC\underline{H}_2CH_2$), and 1.85 (2H, m, J 8, J' 4.6 Hz, $CHC\underline{H}_2CH_2$); δ_C (50.3 MHz, $CDCl_3$) 208.20 (s), 153.33 (s), 152.71 (s), 149.41 (s), 137.35 (s), 137.14 (s), 128.79 (d), 128.56 (d), 127.43 (d), 117.70 (d), 115.14 (d), 104.14 (d), 64.91

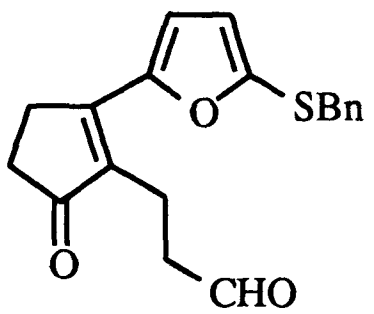
Preparation of 3-[5-(2-Benzylthio)furyl]-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**388**) under Conditions of High Dilution.



The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**376**) (0.46 g, 1.0 mmol, 1.0 equiv.), ethanol (20 mL), water (32 mL), and 0.5 M aqueous sodium hydroxide solution (8 mL, 4.0 mmol, 4 equiv.) to afford crude 3-[5-(2-benzylthio)furyl]-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**388**) as a yellow oil (0.34 g, 89 %) that could be used without further purification.

(t), 39.49 (t), 33.50 (t), 31.95 (t), 25.78 (t), and 18.53 (t); $^{m}/_{z}$ (C.I.) 371 (100 %, MH^+), 327 (10 %, MH^+-C_2H_4O), 281 (22 %, MH^+-PhCH), 279 (15 %, MH^+-PhCH-2H), 265 (4 %, MH^+-$C_3H_4O_2$-2H), 249 (10 %, MH^+-PhCHS), 234 (8 %, MNH_4^+-PhCH-$C_2H_4O_2$), 217 (29 %, MH^+-PhCH-$C_2H_4O_2$), 181 (35 %, MH^+-$BnSC_4HO$-2H), 108 (43 %, $C_7H_7NH_3^+$), 99 (18 %, $C_3H_4O_2C_2H_3^+$), 91 (65 %, $C_7H_7^+$), and 73 (42 %, $C_3H_5O_2^+$).

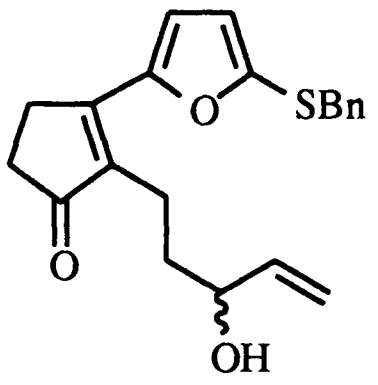
Preparation of *3-[5-(2-Benzylthio)furyl]-2-(3-oxopropyl)cyclopent-2-enone* (**390**).



The title compound was prepared according to the general procedure for the deprotection of acetals and ketals under acid catalysis given in section 5.2.i. The reaction was carried out with 3-[5-(2-benzylthio)furyl]-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**388**) (0.50 g, 1.3 mmol, 1.0 equiv.), *p*-toluenesulphonic acid monohydrate (0.10 g, 0.40 mmol, 0.3 equiv.), and acetone-water (9 : 1 v/v) (60 mL) to afford, after 24 h reflux, crude 3-[5-(2-benzylthio)furyl]-2-(3-oxopropyl)cyclopent-2-enone (**390**) as a brown oil (0.56 g). Purification by flash chromatography on silica, eluting with ethyl acetate-light petroleum (b.p. 30-40°C) (11 : 14) (R_f 0.31), furnished the product (**390**) polluted with a trace of (388) as pale yellow prisms, m.p. 70.5-71.5°C (0.40 g, 95 %) (Found C, 69.7, H, 5.45, S, 9.90; $C_{19}H_{18}O_3S$ requires C, 69.9, H, 5.55, S, 9.80 %); ν_{max} (thin film) 3 069, 3 033, 2 926, 2 864, 2 835, 2 733, 1 720 (C=O aldehyde), 1 691 (C=O), 1 622 (C=C), 1 566, 1 549, 1 498, 1 464, 1 377, 1 240, 1 019, 799, and 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.80 (1H, t, *J* 1.5 Hz, O=CH), 7.31 - 7.18 (5H, m, PhH), 6.75 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.46 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.07 (2H, s, $PhCH_2S$), 2.85 (4H, m, 2 x $OCCH_2$), 2.61 (2H, dt, *J* 7.0, *J* 1.5 Hz, CH_2C=CFu), and 2.51 (2H, m, Fu$CC\underline{H}_2CH_2$); δ_C (50.3 MHz, $CDCl_3$) 208.07 (s), 201.76 (s), 153.13 (s), 149.93 (s), 137.04 (s), 135.73 (s), 128.73 (d), 128.57 (d), 127.46 (d), 117.93 (d), 115.48 (d), 41.97 (t),

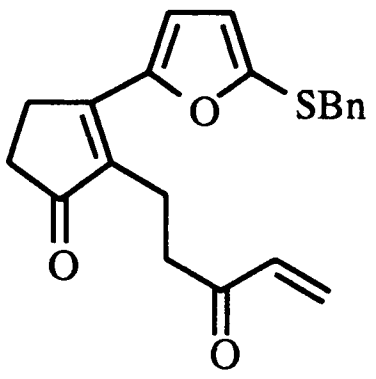
39.89 (t), 33.48 (t), 25.78 (t), and 17.04 (t); $^{m}/_{z}$ (C.I.) 327 (100 %, MH^+), 237 (8 %, MH^+-PhCH), 108 (10 %, $C_7H_7NH_3^+$), and 91 (20 %, $C_7H_7^+$).

Preparation of *3-[5-(2-Benzylthio)furyl]-2-(3-hydroxypent-4-enyl)cyclopent-2-enone* (**391**).



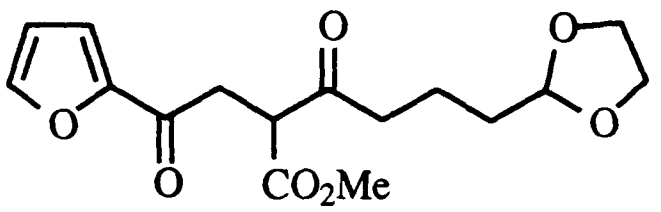
The title compound was prepared according to the general procedure for the Grignard addition to 2-(3-oxopropyl)cyclopent-2-enones given in section 5.2.o. The reaction was carried out with vinylmagnesium bromide (1.0 M solution in THF, 0.50 mL, 0.50 mmol, 1.3 equiv.) and 3-[5-(2-benzylthio)furyl]-2-(3-oxopropyl)cyclopent-2-enone (**390**) (0.12 g, 0.37 mmol, 1.0 equiv.) to afford the pure product as a brown oil (60 mg, 45 %) (Found C, 71.0, H, 6.00, S, 8.80; $C_{21}H_{22}O_3S$ requires C, 71.2, H, 6.25, S, 9.05 %); ν_{max} (thin film) 3 429 (O-H), 3 129, 3 085, 3 063, 3 029, 2 927, 2 862, 1 690 (C=O), 1 615 (C=C), 1 463, 1 456, 1 378, 1 304, 1 241, 1 020, and 700 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.27 (5H, m, PhH), 6.81 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.47 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 5.91 (1H, ddd, J_{tr} 17.3, J_{cis} 10.5, J 5.4 Hz, $CHC\underline{H}=CH_2$), 5.26 (1H, dd, $J_{vic,tr}$ 17.3, J_{gem} 1.5 Hz, $RCH=C\underline{H}H$ *cis* to R), 5.10 (1H, dd, $J_{vic,cis}$ 10.5, J_{gem} 1.5 Hz, $RCH=CH\underline{H}$ *trans* to R), 4.10 (2H, s, $PhCH_2S$), 4.04 (1H, m, $CH_2C\underline{H}(OH)CH$), 2.86 (2H, m, $OCC\underline{H}_2CH_2$), 2.67 (2H, t, J 7.4 Hz, $FuC=CC\underline{H}_2CH_2$), 2.54 (2H, m, $FuCC\underline{H}_2CH_2$), and 1.70 (2H, m, $OCHC\underline{H}_2CH_2$); δ_C (50.3 MHz, $CDCl_3$) 209.69 (s), 153.53 (s), 153.23 (s), 140.81 (d), 137.39 (s), 137.06 (s), 128.76 (d), 128.57 (d), 127.47 (d), 118.02 (d), 115.62 (d), 114.21 (t), 71.53 (d), 39.84 (t), 35.33 (t), 33.46 (t), 25.91 (t), and 19.74 (t); $^{m}/_{z}$ (C.I.) 372 (7 %, MNH_4^+), 371 (33 %, MNH_3^+), 355 (100 %, MH^+), 337 (28 %, MH^+-H_2O), 108 (19 %, $C_7H_7NH_3^+$), and 91 (58 %, $C_7H_7^+$).

Preparation of *3-[5-(2-Benzylthio)furyl]-2-(3-oxopent-4-enyl)cyclopent-2-enone* (**328**).



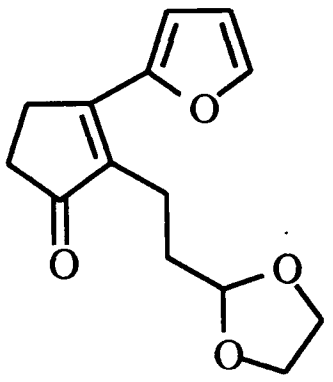
The title compound was prepared according to the general procedure for the pyridinium chlorochromate mediated allylic oxidation given in section 5.2.p. The reaction was carried out with 3-[5-(2-benzylthio)furyl]-2-(3-hydroxypent-4-enyl)cyclopent-2-enone (**391**) (55 mg, 0.16 mmol, 1.0 equiv.), anhydrous sodium acetate (24 mg, 0.29 mmol, 1.9 equiv.), 2 portions of PCC (44 mg, 0.20 mmol, 1.3 equiv.), Celite® (66 mg), and chloroform (6 mL) to afford crude 3-[5-(2-benzylthio)furyl]-2-(3-oxopent-4-enyl)cyclopent-2-enone (**328**) as a brown oil (37 mg). Purification by flash chromatography on silica, eluting with ethyl acetate-dichloromethane (1 : 20) (R_f 0.20), furnished the pure product as a yellow oil (21 mg, 38 %) (Found C, 71.8, H, 6.00, S, 8.90; $C_{21}H_{20}O_3S$ requires C, 71.6, H, 5.70, S, 9.10 %); ν_{max} (thin film) 3 126, 3 087, 3 062, 3 029, 2 926, 2 860, 1 692 (C=O), 1 621 (C=C), 1 464, 1 405, 1 377, 1 304, 1 239, 1 022, and 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.28 (5H, m, PhH), 6.79 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.44 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 6.39 (1H, dd, J_{tr} 17.7, J_{cis} 9.6 Hz, C<u>H</u>=CH_2), 6.25 (1H, dd, $J_{vic,tr}$ 17.7, J_{gem} 2.0 Hz, RCH=C<u>H</u>H *cis* to R), 5.86 (1H, dd, $J_{vic,cis}$ 9.6, J_{gem} 2.0 Hz, RCH=CH<u>H</u> *trans* to R), 4.09 (2H, s, $PhCH_2S$), 2.84 (6H, m, FuC=C(C(O)CH_2)C_2H_4CO), and 2.51 (2H, m, FuC$C\underline{H}_2CH_2$); $^m/_z$ (C.I.) 353 (100 %, MH^+), 263 (3 %, MH^+-PhCH), 108 (24 %, $C_7H_7NH_3^+$), 91 (53 %, $C_7H_7^+$), and 55 (11 %, $C_2H_3CO^+$).

Preparation of *Methyl 2-(2-furoylmethyl)-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate* (**396**).



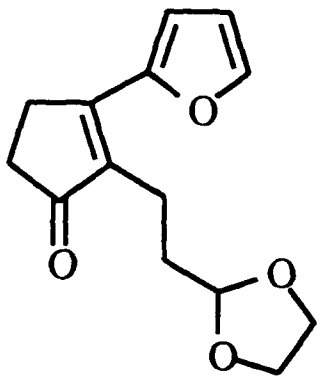
The title compound was prepared according to the general procedure for the alkylation of (bromoacetyl)furans given in section 5.2.d. The reaction was carried out with sodium hydride (60 % dispersion in mineral oil, 0.36 g, 9.1 mmol, 1.0 equiv.), anhydrous THF (125 mL), a solution of methyl 6-(1, 3-dioxolanyl)-3-oxohexanoate (**350**) (2.0 g, 9.1 mmol, 1.0 equiv.) in anhydrous THF (5 mL), and a solution of 2-(bromoacetyl)furan (**227**) (1.7 g, 9.1 mmol, 1.0 equiv.) in anhydrous THF (10 mL) to afford crude methyl 2-(2-furoylmethyl)-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**396**) as a brown oil (3.0 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (6 : 1) (R_f 0.17), furnished the pure product as a yellow oil (0.81 g, 27 %) (Found C, 59.4, H, 6.20; $C_{16}H_{20}O_7$ requires C, 59.3, H, 6.20 %); ν_{max} (thin film) 3 134, 2 955, 2 886, 1 744 (C=O ester), 1 717 (C=O), 1677 (Fu-C=O), 1 572, 1 470, 1 399, 1 256, 1 228, 1 163, 1 142, 1 038, 884, and 771 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.61 (1H, d, $J_{5,4}$ 1.6 Hz, 5-FuH), 7.25 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 6.56 (1H, dd, $J_{4,3}$ 3.6 Hz, 4-FuH), 4.87 (1H, t, J 4.3 Hz, $CH_2C\underline{H}(OCH_2CH_2O)$), 4.20 (1H, dd, J 8.2, J' 5.9 Hz, $C\underline{H}CH_2COFu$), 3.91 (4H, m, OCH_2CH_2O), 3.76 (3H, s, CH_3O), 3.59 (1H, dd, J_{gem} 18.3, J_{vic} 8.2 Hz, $CHC\underline{H}HCOFu$), 3.39 (1H, dd, J_{gem} 18.3, J_{vic} 5.9 Hz, $CHCH\underline{H}COFu$), 2.83 (2H, m, J 7 Hz, $OCC\underline{H}_2CH_2CH_2$), and 1.74 (4H, m, $CH_2C_2\underline{H}_4CHOO$); δ_C (50.3 MHz, $CDCl_3$) 204.23 (s), 186.23 (s), 169.50 (s), 152.04 (s), 146.96 (d), 117.74 (d), 112.45 (d), 104.21 (d), 64.72 (t), 52.56 (q), 52.38 (d), 42.32 (t), 36.70 (t), 32.55 (t), and 17.56 (t); $^m/_z$ (C.I.) 342 (10 %, MNH_4^+), 325 (100 %, MH^+), 293 (21 %, M^+-MeO), 281 (4 %, MH^+-C_2H_4O), 263 (13 %, MH^+-C_2H_4O-H_2O), 217 (7 %, MH^+-FuC(O)CH), 159 (36 %, MH^+-FuC(O)CH-CO_2CH_2), 143 (8 %, $C_3H_5O_2C_3H_6CO^+$), and 73 (42 %, $C_3H_5O_2^+$).

Preparation of 3-(2-Furyl)-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**398**) under Conditions of High Dilution.



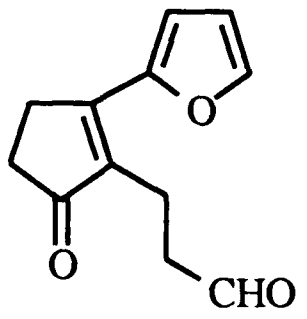
The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with methyl 2-(2-furoylmethyl)-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**396**) (85 mg, 0.26 mmol, 1.0 equiv.), ethanol (20 mL), water (22 mL), and 1.0 M aqueous sodium hydroxide solution (1.1 mL, 1.1 mmol, 4.2 equiv.) to afford, after 24 h reflux, crude 3-(2-furyl)-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**398**) as a yellow oil (37 mg, 56 %) that could be used without further purification.

Preparation of *3-(2-Furyl)-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone* (**398**).



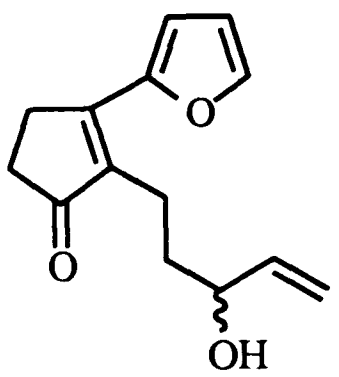
The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with methyl 2-(2-furoylmethyl)-6-[2-(1, 3-dioxolanyl)]-3-oxohexanoate (**396**) (0.70 g, 2.2 mmol, 1.0 equiv.), ethanol (20 mL), water (22 mL), and 0.5 M aqueous sodium hydroxide solution (18 mL, 9.0 mmol, 4.2 equiv.) to afford, after 24 h reflux, crude 3-(2-furyl)-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**398**) as a brown oil (0.24 g). Purification by crystallisation at -12°C furnished the pure product as light brown prisms, m.p. 60.5-61.5°C, after recrystallisation at low temperature (ethanol) (0.16 g, 30 %) (Found C, 67.7, H, 6.40; $C_{14}H_{16}O_4$ requires C, 67.7, H, 6.50 %); ν_{max} (KBr disk) 3 140, 3 123, 2 931, 2 887, 2 861, 1 675 (C=O), 1 613 (C=C), 1 562, 1 477, 1 385, 1 368, 1 341, 1 176, 1 137, 1 051, 1 017, 882, 779, and 598 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.59 (1H, d, $J_{5,4}$ 1.7 Hz, 5-FuH), 6.88 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.53 (1H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 1.7 Hz, 4-FuH), 4.88 (1H, t, J 4.6 Hz, $OOC\underline{H}CH_2$), 3.87 (4H, m, OCH_2CH_2O), 2.84 (2H, m, $OCCH_2$), 2.63 (2H, m, $O_2CHCH_2C\underline{H}_2$), 2.44 (2H, m, $FuCC\underline{H}_2CH_2$), and 1.78 (2H, m, $CHC\underline{H}_2CH_2$); δ_C (50.3 MHz, $CDCl_3$) 208.67 (s), 153.95 (s), 151.33 (s), 145.11 (d), 137.06 (s), 113.78 (d), 112.36 (d), 104.18 (d), 64.83 (t), 33.34 (t), 31.67 (t), 28.87 (t), and 18.19 (t); $^m/_z$ (C.I.) 249 (100 %, MH^+), 100 (11 %, $C_3H_5NH_3^+$), and 73 (15 %, $C_3H_5O_2^+$).

Preparation of *3-(2-furyl)-2-(3-oxopropyl)cyclopent-2-enone* (**401**).



The title compound was prepared according to the general procedure for the deprotection of acetals and ketals under acid catalysis given in section 5.2.i. The reaction was carried out with 3-(2-furyl)-2-{2-[2-(1, 3-dioxolanyl)]ethyl}cyclopent-2-enone (**398**) (75 mg, 0.3 mmol, 1.0 equiv.), *p*-toluenesulphonic acid monohydrate (17 mg, 0.09 mmol, 0.3 equiv.), and acetone-water (9 : 1 v/v) (20 mL) to afford, after 6 d reflux, crude 3-(2-furyl)-2-(3-oxopropyl)cyclopent-2-enone (**401**) as pale yellow prisms, m.p. 60-62°C that was used without further purification (36 mg, 58 %) (Found C, 70.3, H, 6.20; $C_{12}H_{12}O_3$ requires C, 70.6, H, 5.90 %); ν_{max} (thin film) 3 123, 2 972, 2 929, 2 870, 1 692 (C=O), 1 621 (C=C), 1 477, 1 442, 1 400, 1 362, 1 306, 1 243, 1 226, 1 183, 1 072, 1 014, 885, 757, and 595 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.81 (1H, t, *J* 1.4 Hz, O=CH), 7.63 (1H, d, $J_{5,4}$ 1.6 Hz, 5-FuH), 6.84 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.57 (1H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 1.6 Hz, 4-FuH), 2.93 (2H, t, *J* 7.3 Hz, $OCC\underline{H}_2CH_2$), 2.88 (2H, m, $FuCCH_2C\underline{H}_2$), 2.63 (2H, m, $HOCC\underline{H}_2CH_2$), and 2.51 (2H, m, $FuCC\underline{H}_2CH_2$); $m/_z$ (C.I.) 205 (100 %, MH^+), 176 (8 %), and 175 (3 %, MH^+-CH_2O).

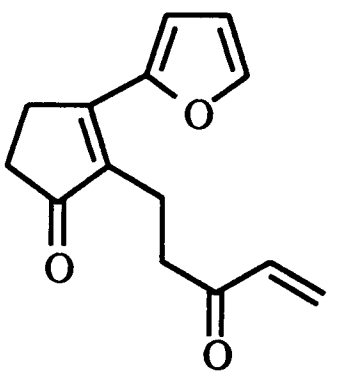
Preparation of *3-(2-Furyl)-2-(3-hydroxypent-4-enyl)cyclopent-2-enone* (**402**).



The title compound was prepared according to the general procedure for the Grignard addition to 2-(3-oxopropyl)cyclopent-2-enones given in section 5.2.o. The reaction was

carried out with vinylmagnesium bromide (1.0 M solution in THF, 0.25 mL, 0.25 mmol, 1.4 equiv.) and 3-(2-furyl)-2-(3-oxopropyl)cyclopent-2-enone (**401**) (36 mg, 0.18 mmol, 1.0 equiv.) to afford the pure product as a pale brown oil (8 mg, 20 %); ν_{max} (thin film) 3 418 (O-H), 3 121, 3 086, 2 927, 2 862, 1 683 (C=O), 1 620 (C=C), 1 478, 1 400, 1 362, 1 305, 1 013, and 754 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.65 (1H, d, $J_{5,4}$ 1.8 Hz, 5-FuH), 6.91 (1H, d, $J_{3,4}$ 3.4 Hz, 3-FuH), 6.57 (1H, dd, $J_{4,3}$ 3.4, $J_{4,5}$ 1.8 Hz, 4-FuH), 5.89 (1H, ddd, J_{tr} 17.2, J_{cis} 10.5, J 5.4 Hz, CHC<u>H</u>=CH_2), 5.25 (1H, dd, $J_{vic,tr}$ 17.2, J_{gem} 1.5 Hz, RCH=C<u>H</u>H *cis* to R), 5.09 (1H, dd, $J_{vic,cis}$ 10.5, J_{gem} 1.5 Hz, RCH=CH<u>H</u> *trans* to R), 4.01 (1H, m, CH_2C<u>H</u>(OH)CH), 3.09 (1H, d, J_{HO-H} 4 Hz, exchanges in D_2O, CHO<u>H</u>), 2.92 (2H, m, OCC<u>H_2</u>CH_2), 2.71 (2H, m, FuC=CC<u>H_2</u>CH_2), 2.54 (2H, m, FuCC<u>H_2</u>CH_2), and 1.72 (2H, m, OCHC<u>H_2</u>CH_2); $^m/_z$ (C.I.) 250 (2 %, MNH_4^+), 233 (65 %, MH^+), 217 (100 %, MH^++2H-H_2O), 215 (66 %, MH^+-H_2O), 205 (9 %, M^+-C_2H_3), 175 (10 %, M^+-$C_2H_3CH_2O$), and 149 (7 %, $FuC_5H_5OH^+$).

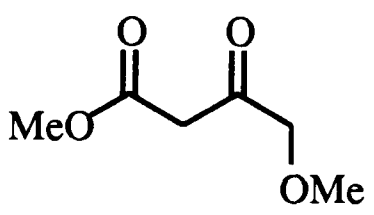
Preparation of *3-(2-Furyl)-2-(3-oxopent-4-enyl)cyclopent-2-enone* (**395**).



The title compound was prepared according to the general procedure for the pyridinium chlorochromate mediated allylic oxidation given in section 5.2.p. The reaction was carried out with 3-(2-furyl)-2-(3-hydroxypent-4-enyl)cyclopent-2-enone (**402**) (8 mg, 34 μmol, 1.0 equiv.), anhydrous sodium acetate (8 mg, 0.10 mmol, 3.0 equiv.), 2 portions of PCC (10 mg, 45 μmol, 1.3 equiv.), Celite® (30 mg, 1.5 times mass of PCC), and chloroform (2 mL) to afford crude 3-(2-furyl)-2-(3-oxopent-4-enyl)cyclopent-2-enone (**395**) as a brown oil (7 mg). Purification by flash chromatography on silica, eluting with ethyl acetate-dichloromethane (1 : 10) (R_f 0.21), furnished the pure product as pale yellow prisms, m.p.

44.5-46°C (5 mg, 68 %); ν_{max} (thin film) 3 120, 2 927, 2 866, 1 690 (C=O), 1 625 (C=C), 1 474, 1 441, 1 400, 1 349, 1 304, 1 241, 1 023, and 756 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.63 (1H, d, $J_{5,4}$ 1.7 Hz, 5-FuH), 6.89 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.57 (1H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 1.7 Hz, 4-FuH), 6.38 (1H, dd, J_{tr} 17.7, J_{cis} 9.6 Hz, C<u>H</u>=CH_2), 6.24 (1H, dd, $J_{vic,tr}$ 17.7, J_{gem} 2.1 Hz, RCH=C<u>H</u>H *cis* to R), 5.86 (1H, dd, $J_{vic,cis}$ 9.6, J_{gem} 2.1 Hz, RCH=CH<u>H</u> *trans* to R), 2.92 - 2.75 (6H, m, FuC=C(C(O)CH_2)C_2H_4CO), and 2.52 (2H, m, FuCC<u>H_2</u>CH_2); $^m/_z$ (C.I.) 248 (2 %, MNH_4^+), 233 (41 %, M+2H+H^+), 231 (100 %, MH^+), 215 (12 %, MH^++2H-H_2O), 175 (10 %, M^+-C_2H_3CO), 149 (4 %, $FuC_5H_5OH^+$-C_2H_3), and 55 (3 %, $C_2H_3CO^+$).

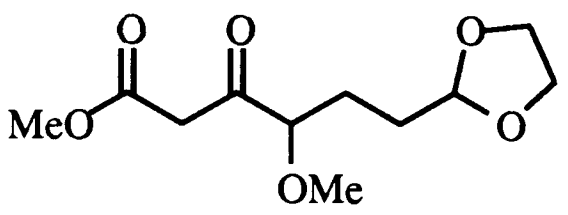
Preparation of *Methyl 4-methoxyacetoacetate* (**412**).



According to a procedure adapted from Miller and Tenud,[146] methyl 4-chloroacetate (5 mL, 43 mmol, 1.0 equiv.) was added dropwise at a rate of 1 mLh^{-1} to a stirred suspension of sodium methoxide (4.8 g, 89 mmol, 2.1 equiv.) in anhydrous THF (50 mL) under N_2 at 40°C. The mixture was stirred overnight, quenched by the addition of saturated aqueous ammonium chloride solution (50 mL), acidified to pH 1 with concentrated hydrochloric acid (≈ 8 mL), allowed to cool, and extracted with ethyl acetate (50 mL). The aqueous phase was further extracted with ethyl acetate (2 x 50 mL) and the organic extracts combined, washed with brine (2 x 100 mL), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude methyl 4-methoxyacetoacetate (**412**) as a brown oil (4.5 g). Purification by bulb-to-bulb distillation under reduced pressure, discarding the fore-run, furnished the pure product as a pale yellow oil, b.p. 145-160°C (bath temperature) / 10 mmHg (2.89 g, 46 %) (Found C, 49.6, H, 7.10; $C_6H_{10}O_4$ calculated C, 49.3, H, 6.90 %); ν_{max} (thin film) 3 459, 3 342, 2 996, 2 954, 2 829, 1 751 (C=O ester), 1 728 (C=O), 1 671 (C=O enol), 1 624 (C=C enol), 1 569, 1 439, 1 325, 1 272, 1 202, 1 165, 1 104, and 1 030 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.09 (2H, s, C<u>H_2</u>OCH_3),

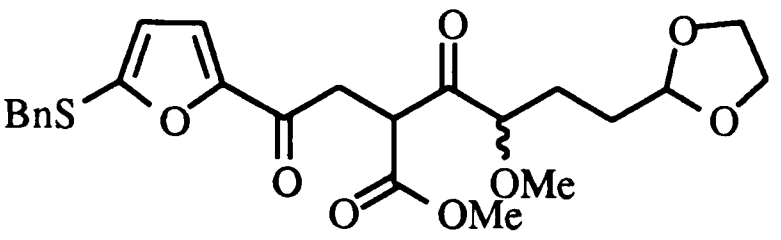
3.75 (3 H, s, CH_3OCO), 3.53 (2H, s, O_2CCH_2CO), and 3.43 (3H, s, $CH_2OC\underline{H}_3$); δ_C (50.3 MHz, $CDCl_3$) 201.21 (s), 167.18 (s), 76.72 (t), 58.63 (q), 51.67 (q), and 44.88 (t); $^m/_z$ (C.I.) 164 (100 %, MNH_4^+), 147 (59 %, MH^+), 146 (16 %, M^+), 134 (28 %, MNH_4^+-CH_2O), 117 (7 %, MH^+-CH_2O), 116 (8 %), 115 (9 %, M^+-MeO), and 59 (9 %, $MeOCO^+$).

Preparation of *Methyl 6-(1, 3-dioxolanyl)-4-methoxy-3-oxohexanoate* (**415**).

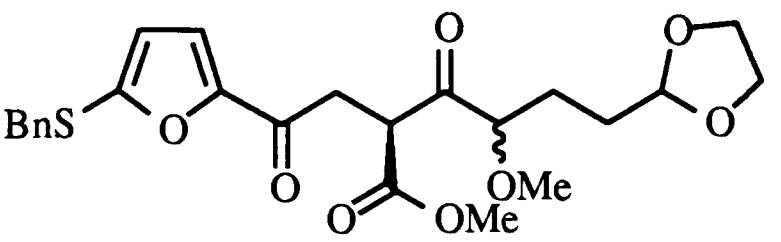


The title compound was prepared according to the general procedure for the alkylation of acetoacetate dianions given in section 5.2.b. The reaction was carried out with methyl 4-methoxyacetoacetate (**412**) (1.3 g, 9.2 mmol, 1.05 equiv.), sodium hydride (60 % dispersion in mineral oil, 0.39 g, 9.7 mmol, 1.1 equiv.), *n*-butyllithium (0.97 M solution in hexane, 11 mL, 10.6 mmol, 1.2 equiv.), anhydrous THF (40 mL), and 2-(2-bromoethyl)-1, 3-dioxolane (**351**) (1.0 mL, 8.8 mmol, 1.0 equiv.) to afford crude methyl 6-(1, 3-dioxolanyl)-4-methoxy-3-oxohexanoate (**415**) as a brown oil (2.3 g). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 1), furnished the pure product as a yellow oil (0.95 g, 44 %) (Found C, 53.8, H, 7.50; $C_{11}H_{18}O_6$ requires C, 53.7, H, 7.35 %); ν_{max} (thin film) 2 954, 2 888, 2 832, 1 752 (C=O ester), 1 723 (C=O), 1 659 (C=O enol), 1 632 (C=C enol), 1 440, 1 403, 1 324, 1 230, 1 142, 1 115, 1 024, 945, and 815 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.89 (1H, t, *J* 4.2 Hz, CHOO), 3.97 - 3.83 (4H, m, OCH_2CH_2O), 3.74 (3H, s, CH_3O), 3.74 (1H, m, *J* 5.2 Hz, $CH_2C\underline{H}OMe$), 3.61 (1H, d, *J* 16.2 Hz, $O_2CC\underline{H}HCO$), 3.54 (1H, d, *J* 16.2 Hz, $O_2CC\underline{H}HCO$), 3.39 (3H, s, $CHOC\underline{H}_3$), and 1.87 - 1.72 (4H, m, $CHC_2\underline{H}_4CH$); δ_C (50.3 MHz, $CDCl_3$) 204.89 (s), 167.47 (s), 103.50 (d), 85.89 (d), 64.65 (t), 57.93 (q), 51.88 (q), 44.34 (t), 28.60 (t), and 24.99 (t); $^m/_z$ (C.I.) 264 (35 %, MNH_4^+), 247 (91 %, MH^+), 215 (17 %, M^+-MeO), 202 (22 %, MNH_4^+-C_2H_4O-H_2O), 185 (100 %, MH^+-C_2H_4O-H_2O), 145 (44 %, M^+-MeO_2CCH_2CO), and 73 (35 %, $C_3H_5O_2^+$).

Preparation of cis- and trans-*Methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-4-methoxy-3-oxohexanoate* (**417a, b**).

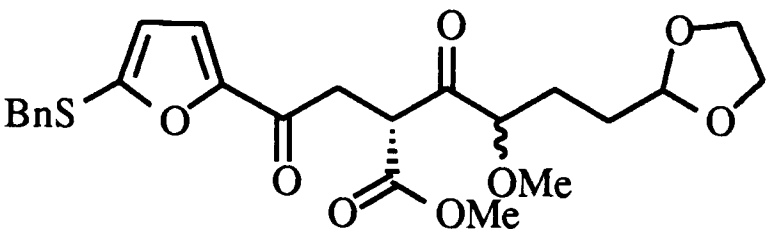


The title compounds were prepared according to the general procedure for the alkylation of (bromoacetyl)furans given in section 5.2.d. The reaction was carried out with sodium hydride (60 % dispersion in mineral oil, 58 mg, 1.5 mmol, 1.05 equiv.), anhydrous THF (15 mL), a solution of methyl 6-(1, 3-dioxolanyl)-4-methoxy-3-oxohexanoate (**415**) (0.36 g, 1.5 mmol, 1.05 equiv.) in anhydrous THF (3 mL), and a solution of 2-benzylthio-5-(bromoacetyl)furan (**249**) (0.43 g, 1.4 mmol, 1.0 equiv.) in anhydrous THF (3 mL) at -78°C to afford crude *cis*- and *trans*-methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-4-methoxy-3-oxohexanoate (**417a, b**) as a brown oil (0.71 g). Purification by flash chromatography on silica, gradient eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 1 - 3 : 2), furnished a diastereomeric mixture of *cis*-(**418**) and *trans*-(**419**) products as a yellow oil (**0·36**g, 54%) (Found C, 61.9, H, 6.05, S, 7.40; $C_{23}H_{26}O_7S$ requires C, 61.9, H, 5.85, S, 7.20 %); ν_{max} (thin film) 3 137, 3 066, 3 037, 2 966, 2 902, 1 746 (C=O ester), 1 720 (C=O), 1 675 (Fu-C=O), 1 603, 1 564, 1 451, 1 245, 1 045, 944, 806, and 702 cm^{-1}; $m/_z$ (C.I.) 477 (77 %, MH^+), 355 (19 %, MH^+-PhCHS), 247 (24 %, MH^+-BnSFu'C(O)CH), 233 (20 %, BnSFu'C(O)CH_4^+), 185 (25 %, MH^+-BnSFu'C(O)CH-C_2H_4O-H_2O), 145 (100 %, $C_3H_5O_2C_2H_4CHOMe^+$), 91 (65 %, $C_7H_7^+$), and 73 (41 %, $C_3H_5O_2^+$).



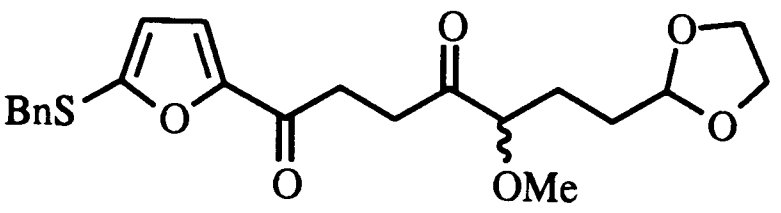
N.m.r. spectroscopic data for the major methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-4-methoxy-3-oxohexanoate isomer (**417a**). δ_H (500 MHz, $CDCl_3$) 7.35 - 7.23 (5H, m, PhH), 7.11 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.36 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.92 (1H, t,

J 4.5 Hz, $CH_2C\underline{H}OO$, 4.48 (1H, dd, *J* 8.8, *J'* 5.2 Hz, $C\underline{H}CH_2C(O)Fu$), 4.14 (2H, s, $PhCH_2S$), 4.00 - 3.82 (4H, m, OCH_2CH_2O), 3.94 (1H, dd, *J* 6.9, *J'* 5.0 Hz, $CH_3OC\underline{H}CH_2$), 3.76 (3H, s, CH_3OCO), 3.48 (1H, dd, J_{gem} 17.9, J_{vic} 8.8 Hz, $CHC\underline{H}HCOFu$), 3.41 (3H, s, $C\underline{H}_3OCH$), 3.22 (1H, dd, J_{gem} 17.9, J_{vic} 5.2 Hz, $CHCH\underline{H}COFu$), and 2.04 - 1.74 (4H, m, $CHC_2\underline{H}_4CH$); δ_C (50.3 MHz, $CDCl_3$) 205.98 (s), 185.01 (s), 169.83 (s), 153.60 (s), 152.58 (s), 136.90 (s), 129.01 (d), 128.79 (d), 127.77 (d), 119.02 (d), 116.62 (d), 104.07 (d), 85.87 (d), 64.83 (t), 58.53 (q), 52.50 (q), 48.53 (d), 39.05 (t), 36.55 (t), 28.65 (t), and 25.03 (t).



N.m.r. spectroscopic data for the minor methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-4-methoxy-3-oxohexanoate isomer (**417b**). δ_H (500 MHz, $CDCl_3$) 7.35 - 7.23 (5H, m, PhH), 7.13 (1H, d, $J_{3,4}$ 3.5 Hz, 3-FuH), 6.36 (1H, d, $J_{4,3}$ 3.5 Hz, 4-FuH), 4.92 (1H, t, *J* 4.5 Hz, $CH_2C\underline{H}OO$, 4.47 (1H, dd, *J* 8.6, *J'* 5.4 Hz, $C\underline{H}CH_2C(O)Fu$), 4.15 (2H, s, $PhCH_2S$), 4.00 - 3.82 (4H, m, OCH_2CH_2O), 4.01 (1H, dd, *J* 7.2, *J'* 4.3 Hz, $CH_3OC\underline{H}CH_2$), 3.75 (3H, s, CH_3OCO), 3.50 (1H, dd, J_{gem} 18.1, J_{vic} 8.6 Hz, $CHC\underline{H}HCOFu$), 3.47 (3H, s, $C\underline{H}_3OCH$), 3.30 (1H, dd, J_{gem} 18.1, J_{vic} 5.4 Hz, $CHCH\underline{H}COFu$), and 2.04 - 1.74 (4H, m, $CHC_2\underline{H}_4CH$); δ_C (50.3 MHz, $CDCl_3$) 205.67 (s), 184.76 (s), 169.47 (s), 153.60 (s), 152.41 (s), 136.90 (s), 129.01 (d), 128.79 (d), 127.77 (d), 118.91 (d), 116.62 (d), 104.07 (d), 85.87 (d), 64.83 (t), 58.36 (q), 52.50 (q), 48.53 (d), 39.05 (t), 36.40 (t), 29.06 (t), and 25.48 (t).

Preparation of *2-{7-[2-(5-Benzylthio)furyl]-3-methoxy-4, 7-dioxoheptyl}-1, 3-dioxolane* (**420**).



The title compound was prepared according to the general procedure for the base catalysed intramolecular aldol cyclisation given in section 5.2.e. The reaction was carried out with a mixture of *cis*- and *trans*-methyl 2-[2-(5-benzylthiofuroyl)methyl]-6-[2-(1, 3-dioxolanyl)]-4-methoxy-3-oxohexanoate (**417a, b**) (55 mg, 0.12 mmol, 1.0 equiv.), ethanol (5 mL), water (5 mL), and 0.5 M aqueous sodium hydroxide solution (0.95 mL, 0.48 mmol, 4.1 equiv.) to afford, after 2 h reflux, crude 2-{7-[2-(5-benzylthio)furyl]-3-methoxy-4, 7-dioxoheptyl}-1, 3-dioxolane (**420**) as an orange-brown oil (46 mg). Purification by flash chromatography on silica, eluting with diethyl ether-light petroleum (b.p. 30-40°C) (1 : 1) furnished the pure product as a yellow oil (27 mg, 55 %) (Found C, 62.8, H, 6.35, S, 7.35; $C_{22}H_{26}O_6S$ requires C, 63.1, H, 6.25, S, 7.65 %); ν_{max} (thin film) 3 138, 3 062, 3 029, 2 932, 2 887, 2 830, 1 723 (C=O), 1 675 (Fu-C=O), 1 563, 1 455, 1 261, 1 201, 1 140, 1 110, 1 029, 944, 803, and 702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.28 (5H, m, PhH), 7.11 (1H, d, $J_{3,4}$ 3.6 Hz, 3-FuH), 6.36 (1H, d, $J_{4,3}$ 3.6 Hz, 4-FuH), 4.91 (1H, t, J 4 Hz, $CH_2C\underline{H}OO$, 4.14 (2H, s, $PhCH_2S$), 3.99 - 3.84 (4H, m, OCH_2CH_2O), 3.76 (1H, dd, J 7, J' 5 Hz, $CH_3OC\underline{H}CH_2$), 3.43 (3H, s, CH_3O), 3.10 (2H, t, J 6.5 Hz, $FuC(O)C\underline{H}_2CH_2$), 2.95 (1H, dt, J_{gem} 18.7, J_{vic} 6.5 Hz, $FuC(O)CH_2C\underline{H}HCO$), 2.90 (1H, dt, J_{gem} 18.7, J_{vic} 6.5 Hz, $FuC(O)CH_2CH\underline{H}CO$), and 1.87 - 1.74 (4H, m, $CHC_2\underline{H}_4CH$); $^m/_z$ (C.I.) 419 (100 %, MH^+), 357 (19 %, MH^+-C_2H_4O-H_2O), 145 (80 %, $C_3H_5O_2C_2H_4CHOMe^+$), 91 (35 %, $C_7H_7^+$), and 73 (18 %, $C_3H_5O_2^+$).

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