FREE RADICAL METHODOLOGY
AND
APPROACHES TO THE SYNTHESIS OF ROSEOPHILIN

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by

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ABSTRACT

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The homolytic Brook rearrangement is discussed and homolytic fragmentations of epoxides and epoxysilane chemistry are reviewed.

Thiyl radical induced isomerisation was performed on spiro alkenylepoxysilanes to generate novel alkenyl-α-trimethylsilylaldehydes rather than the products of radical Brook rearrangement. The trimethylsilylaldehydes were shown to isomerise on heating to silyldienol ethers and, *via* the addition of a Grignard reagent, to act as stereoselective vinyl cation equivalents. Attempts to extend the scope of the isomerisation to non-rigid systems met with failure.

A review of the antibiotic Roseophilin is presented. Cycloaddition-fragmentation approaches to medium and large rings are reviewed as a prelude to our first route, the proposed Michael addition-retro-aldol fragmentation of the Diels-Alder adduct derived from isopropyl-cyclopentadiene and cyclodec-2-yn-1-one. The novel ynone, synthesised *via* the intramolecular Friedel-Crafts acylation of 10-trimethylsilyl-9-decynoyl chloride, was found to isomerise readily to bicyclo[4.4.0]dec-1(6)-en-2-one therefore the model Diels-Alder reaction with cyclopentadiene was effected in one-pot from the cyclisation precursor. Details of the attempted fragmentation of tricyclo[10.2.1.$0^{2,11}$]pentadeca-2(11),13-dien-3-one are then described but, due to inconclusive results, an alternative study was instigated.

The use of free-radical macrocyclisations in the synthesis of large rings is reviewed with particular reference to the synthesis of natural products. Three strategies for the formation of a bicyclo[10.2.1]pentadecanone skeleton are reported, and subsequent model studies described. Cuprate additions to vinyl lactones and epoxides are discussed. The preferred strategy, involving a cycloalkyl tether between the radical donor and radical acceptor groups, was extended to a system which was derived from the addition of various cuprates to 2-oxabicyclo[3.3.0]oct-7-en-3-one The preparation of cuprates derived directly from 6-iodohexan-1-ol and 1-chloro-6-iodohexane is described. The *trans-* cuprate addition products were converted successfully to bicyclo[10.2.1]pentadec-12-en-3-one, and the *cis-* analogues, accessible through a novel regio- and stereoselective hydroboration-fragmentation reaction of 7-(6'-chlorohexyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one, led to bicyclo[10.2.1]pentadec-13-en-3-one. The successful cyclisations of model oximes, to form nitrones having the correct connectivity for the third ring of Roseophilin, are described.

Cuprate additions to 6-(1'-methylethyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one resulted in *anti-* attack; the *cis-* adducts were inaccessible *via* the above methodology but a few intermediates in the *trans-* series were prepared. Future routes and modifications to the methods developed are then discussed.

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Firstly I wish to thank Dr Jeremy Robertson for giving me the opportunity to work in his group, for teaching me so much chemistry over the last three years and for exciting me about the subject. I am extremely grateful to him for his excellent supervision and encouragement, particularly when things weren't going so well. I wish also to thank him for his immense generosity and for painstakingly examining the data in this thesis, along with all the further proof-reading.

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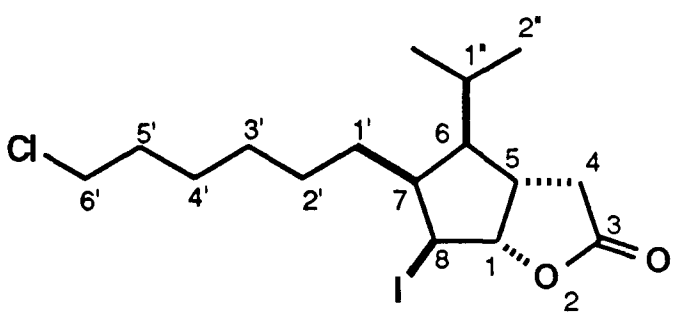
A Note on Nomenclature

- All compounds are named according to the standard IUPAC classifications.
- All molecules are racemic unless otherwise stated.
- The symbols (*R*) and (*S*) have been used to describe the absolute stereochemistry of stereogenic centres in a molecule based on the exact structure shown on the page. The term *rel-* has been included to indicate that these symbols merely describe the relative stereochemistry in each molecule synthesised due to the racemic nature of all transformations reported.
- Numbers in parentheses are given an identification marking (e.g. 6') purely to assist assignments in the reported spectra.

e.g.



rel-(1*S*, 5*S*, 6*S*, 7*S*, 8*S*)-7-(6'-Chlorohexyl)-8-iodo-6-(1"-methylethyl)-2-oxabicyclo[3.3.0]octan-3-one

ABBREVIATIONS

Ac	acetyl
AIBN	2,2-azo-bis(2-methylpropionitrile)
A.P.	atmospheric pressure
aq.	aqueous
atm	atmospheres
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
b.p.	boiling point
Bu	butyl
BVE	butyl vinyl ether
Bz	benzoyl
cat.	catalytic quantity
C.I.	chemical ionisation
conc.	concentrated
COSY	correlation spectroscopy
CSA	camphor sulphonic acid
CTC	chloromethyltrimethylsilyl carbanion
Δ	reflux
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexylurea
DDQ	2,3-dichloro-5,6-dicyanoquinone
d.e.	diastereomeric excess
DEPT	distortionless enhancement by polarisation transfer
DHP	dihydropyran
DIBALH	diisobutylaluminium hydride
DMAP	4-*N*, *N'*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*, *N'*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMS	dimethylsulphide
DMSO	dimethyl sulphoxide
DNP	2,4-dinitrophenylhydrazone
EDA	ethylenediamine
e.e.	enantiomeric excess
ES	electrospray
eq.	equivalents
Et	ethyl
EVE	ethyl vinyl ether
FTIR	fourier transform infrared
GC	gas chromatography
GCMS	gas chromatography mass spectrometry
h	hour(s)
HMBC	hetereonuclear multiple-bond connectivity
HMPA	hexamethylphosphoramide

hν	photolysis
HRMS	high resolution mass spectrometry
i	*iso*
IC_{50}	concentration which causes 50% of maximum possible inhibition
Im	imidazole
KAPA	potassium 3-aminopropylamide
KHMDS	potassim bis(trimethylsilyl)amide
LDA	lithium diisopropylamine
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
min(s)	minute(s)
Mol.S.	molecular sieves
m.p.	melting point
Ms	methane sulphonyl
MS	mass spectrometry
MEK	methylethyl ketone
MVK	methylvinyl ketone
n	normal
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
Np	1-naphthyl
[P]	protecting group
p	*para*
PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulphonate
Pr	propyl
PTC	phase transfer catalysis
py	pyridine
quant.	quantitative
R_f	retention factor
RT	room temperature
SAR	structure activity relationship
sat.	saturated
sec	secondary
t, tert	tertiary
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
t.l.c.	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
tosyl, Ts	*p*-toluene sulphonyl
uv	ultra violet

INTRODUCTION

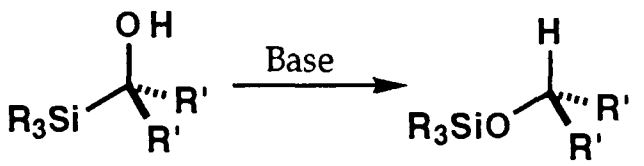
This project is concerned with investigating the feasibility of free-radical induced isomerisation of alkenyl epoxysilanes, *via* a radical Brook rearrangement, to silyl dienol ethers (described in Section **1.7.**).

1.1. Background

There has been an explosion in the use and understanding of silicon chemistry over the last 25 years.[1] The use of silicon in providing the formation of reactive intermediates in a regioselective manner to enable construction of highly prized synthetic processes has been widely exploited.[2] This area has been particularly characterised by the generation and use of silyl enol and dienol ethers as important alkylation and cycloaddition precursors.[3]

1.2. The Brook Rearrangement

Early on, the rearrangement of an α-silylcarbinol to the corresponding silyl ether was observed and characterised by Brook and co-workers[4] as shown in Scheme 1.



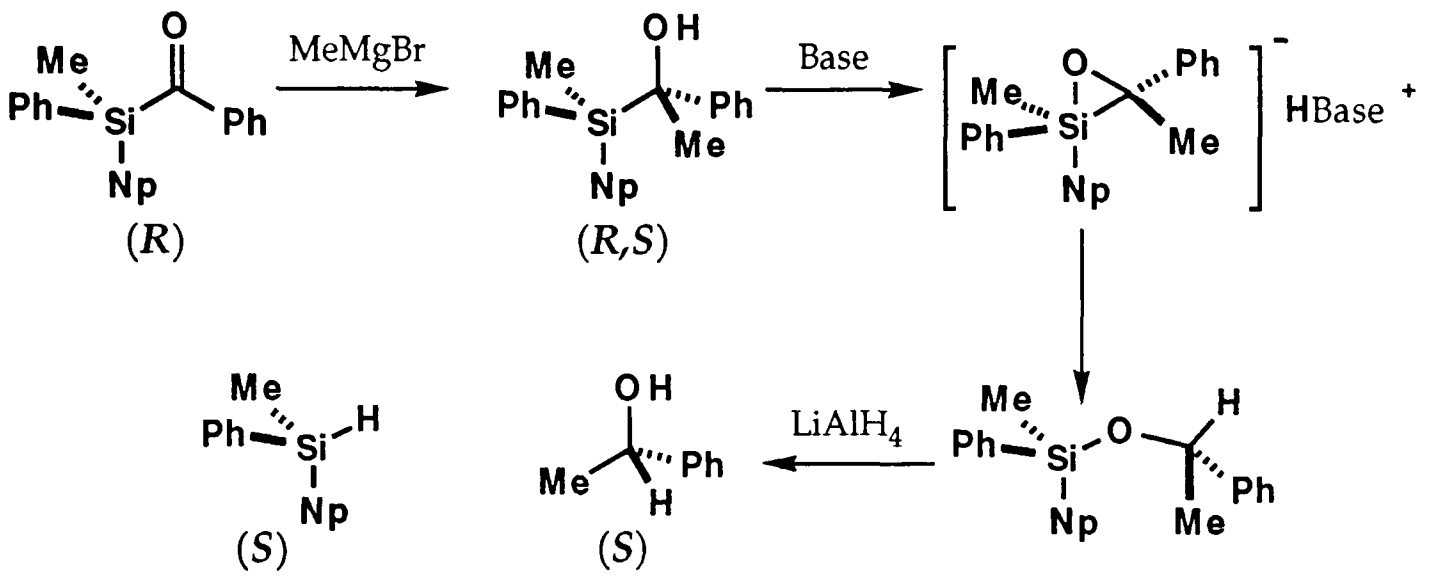
Base = active metals, organometallics, triethylamine and pyridine

Scheme 1

This fascinating sequence was also shown to be facilitated by the formation of an α-silylcarbinol *via* addition of an organometallic reagent to an acyl-silane,[5] and in a series of elegant experiments Brook demonstrated the intramolecular nature of the rearrangement and identified a possible mechanism by examining, in addition to the kinetics of the reaction,[6] the fate of

asymmetric silyl and carbinol fragments under rearrangement conditions. The silyl portion was shown to retain its absolute configuration[7] whereas an asymmetric carbinol centre was shown to undergo a Walden inversion.[5]

Brook noted that these observations are consistent with a mechanism involving a three-membered transition state and an "ate" complex made possible through silicon's ability to stabilise an α-alkoxide. Collapse of this intermediate (the so-called Brook rearrangement[8]) leads to transfer of the formal negative charge to carbon followed by rapid protonation. A summary of this is shown in Scheme 2.

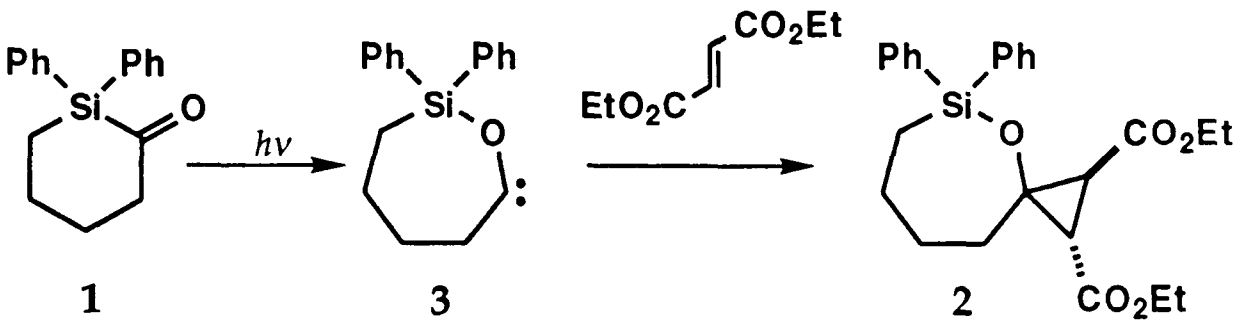


Scheme 2

The reverse retro-Brook reaction is also possible and its feasibility is generally dependent on the functionality and substitution at the α-carbon.

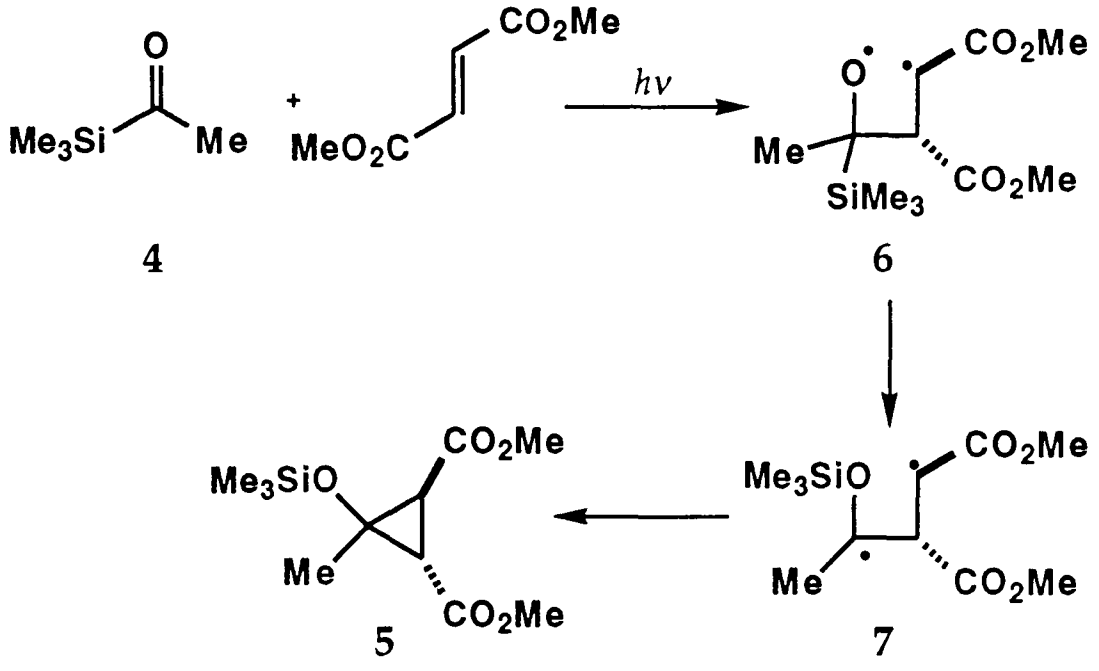
1.3. The Homolytic Brook Rearrangement

1.3.1. In 1981 Dalton and Bourque turned their attention to a photochemical reaction of acylsilanes that Brook had documented several years earlier. Brook observed that photolysis of the acylsilane **1** in the presence of diethyl fumarate gave rise to the cyclopropane **2**, depicted in Scheme 3. He suggested that this could be rationalised through photochemical isomerisation of the acyl silane to siloxycarbene **3** followed by subsequent addition to the alkene.[9]



Scheme 3

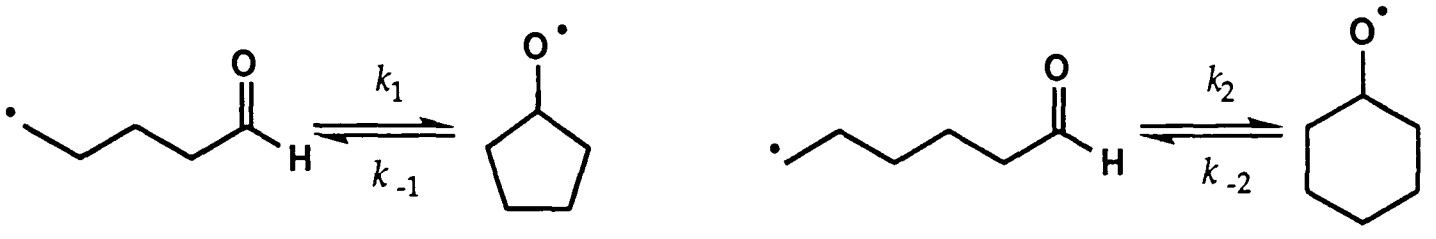
By examining the kinetics and mechanistic detail of the analogous conversion of acylsilane **4** to cyclopropane **5**, Dalton and Bourque confirmed that a siloxycarbene intermediate was not involved and suggested a mechanism shown in Scheme 4, involving interaction of the nucleophilic π system of the carbonyl (^{1}n, π*) state with the electron-deficient alkene to generate a short-lived 1,4-biradical **6**. An intramolecular migration of silicon from carbon to the oxygen radical centre would develop the 1,3-biradical which after ring closure would give the observed product.[10]



Scheme 4

Conversion of **6**, through migration of silicon, to **7** is the radical equivalent of the Brook rearrangement. This homolytic reaction, although potentially of great synthetic value, has seen little investigation in the literature and it is only in recent years that Tsai and co-workers have been instrumental in illustrating the reaction's effectiveness.[11-16]

1.3.2. Tsai was interested in radical additions to carbonyls and suggested that the problems associated with such processes, namely the reversibility of addition and the fact that fragmentation rates are greater than cyclisation rates (Scheme 5), might be overcome by exploitation of the homolytic Brook rearrangement.[11]



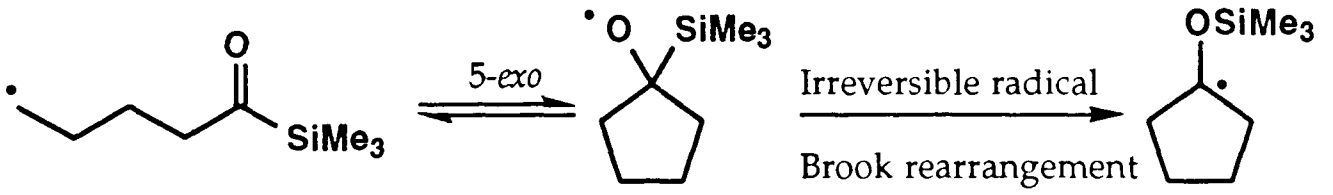
$k_1 = 8.7 \times 10^5\ s^{-1}$ (80°C)
$k_{-1} = 4.7 \times 10^8\ s^{-1}$ (80°C)

$k_2 = 1.0 \times 10^6\ s^{-1}$ (80°C)
$k_{-2} = 1.1 \times 10^7\ s^{-1}$ (80°C)

Scheme 5

Tsai envisaged that transfer of the equilibrium towards the cyclised product could only be achieved through the design of a system which would either greatly enhance the stability of the intermediate alkoxy radical or would kinetically trap the alkoxy radical as soon as it formed.

He identified acylsilanes as the perfect candidates not only because of the silyl group's known ability to stabilise both α-[17] and β-[18] radicals but also because an α-siloxy radical intermediate **8** (analogous to that proposed by Dalton and Bourque), generated *in situ*, could conceivably undergo the radical Brook rearrangement, Scheme 6.

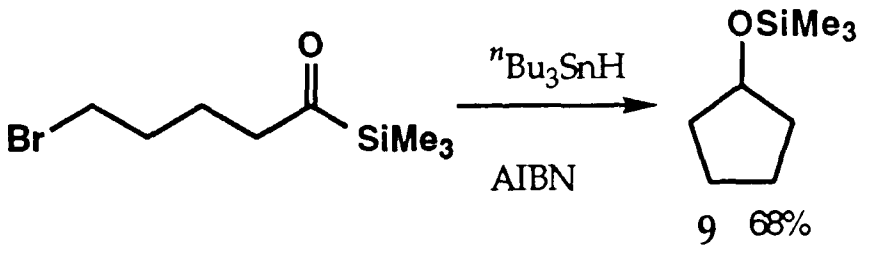


8

Scheme 6

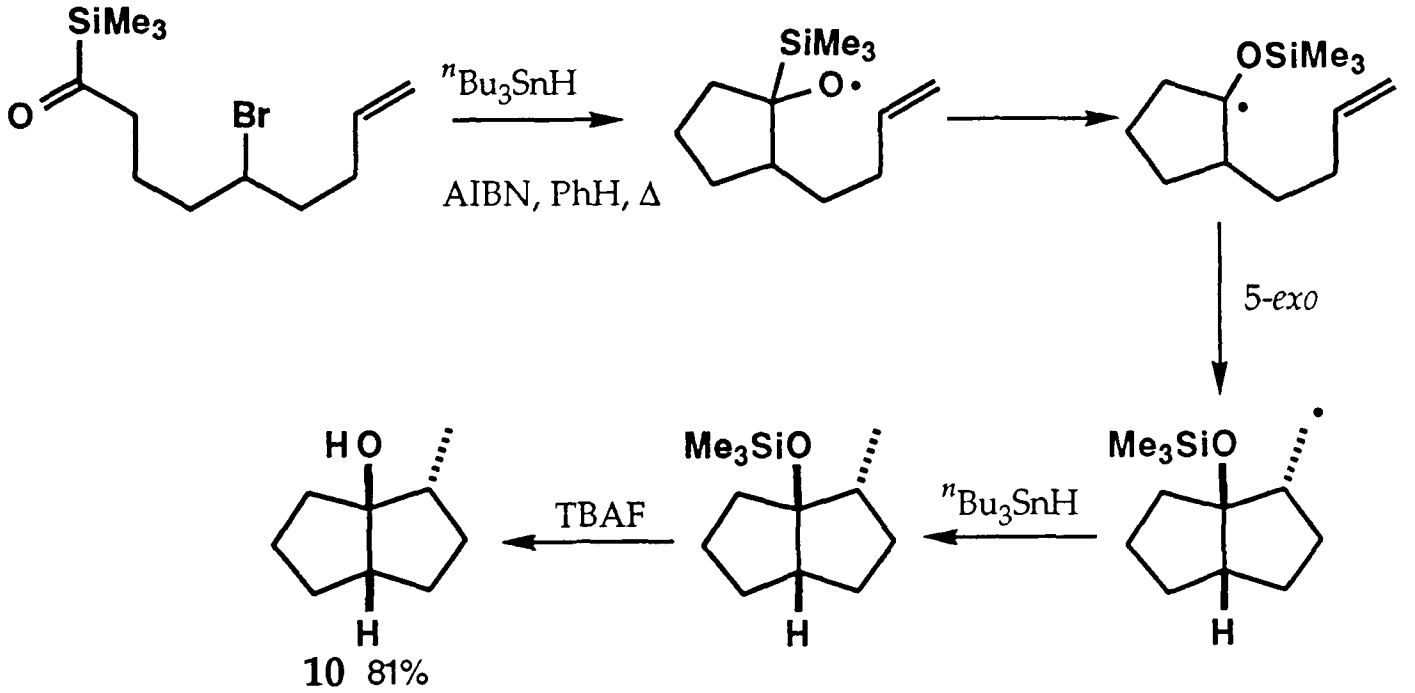
Tsai's hypothesis was shown to work well with primary alkyl radicals and as a result he was able to synthesise a variety of carbocycles (e.g. **9**) where the

carbon-centred radical, formed as a direct consequence of the radical Brook rearrangement, was reduced by tributyltin hydride, Scheme 7.



Scheme 7

Tsai further expanded the scope of this methodology by showing that secondary alkyl radicals also precipitated the rearrangement and he demonstrated that in a carefully constructed system the carbon-centred radical formed after rearrangement, could be used in further tandem cyclisations prior to eventual reduction.[12] An example, that leads to the formation of the bicycle **10**, is summarised in Scheme 8.

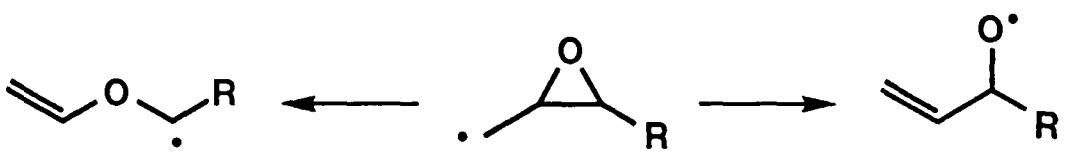


Scheme 8

1.4. Homolytic Epoxide Fragmentations

The generation of radicals α- to epoxides has received a vast amount of attention in recent years.[19-44] Radicals have been positioned at the α- site of an epoxide using a wide variety of approaches. These include abstraction of

thiocarbonyl imidazolide derivatives,[19-23,25-27] abstraction of a halogen at the α- position,[16,24-30,41] addition of a radical to an alkenyl epoxide,[31-36] an epoxy ketone,[37-38] or a protected epoxy enol,[35,39-40] sonication in the presence of metals,[42] and photochemical excitation prior to radical attack on an epoxy ketone.[43] In addition epoxides have been cleaved homolytically by transition metals to generate β-alkoxy radicals[44] and interestingly the homolytic cleavage of aziridines has also been reported.[33,45] In the case of epoxides, both C-O and C-C bond fragmentation have been observed (Scheme 9), with the former predominating.



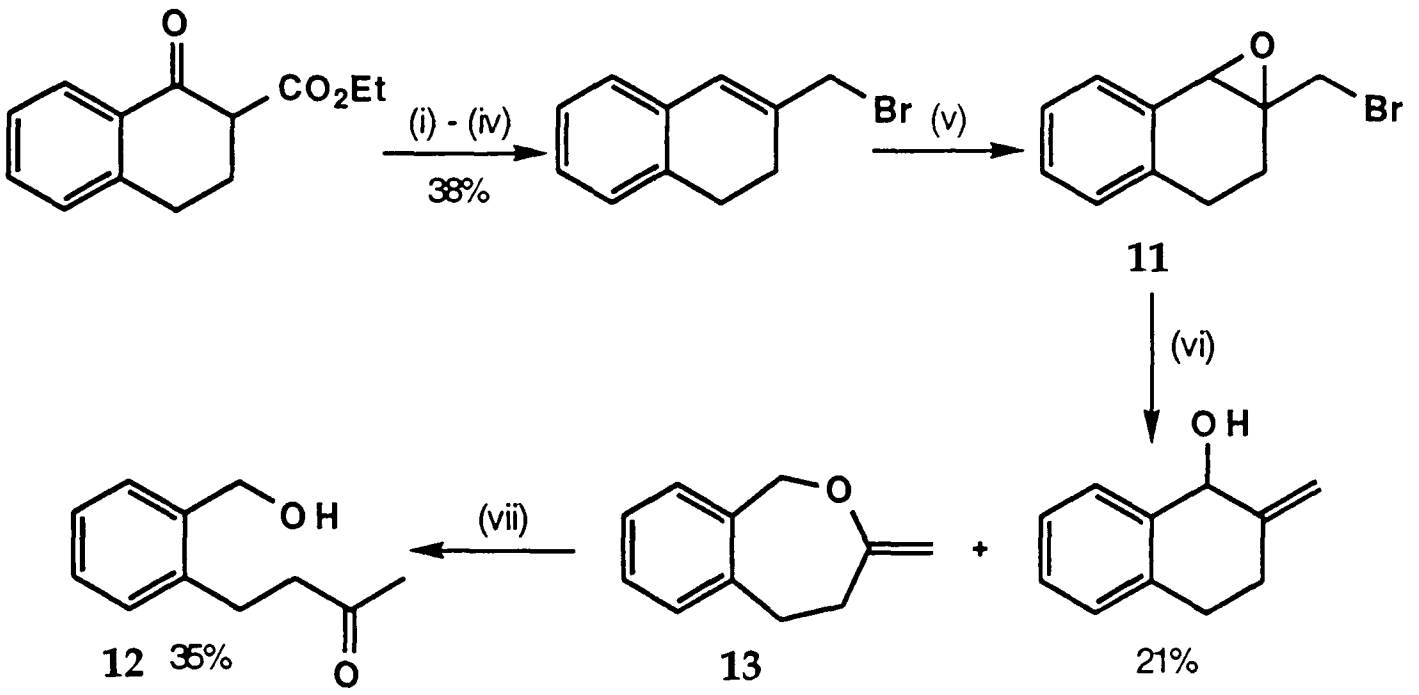
Scheme 9

C-C bond fragmentation results in a carbon-centred radical (**1.4.1.**) whereas C-O bond fragmentation leads to the formation of an alkoxy radical (**1.4.2.**).

1.4.1. Carbon-Carbon Bond Fragmentation

Work by Murphy and co-workers has suggested that a π-system adjacent to the site of the developing radical is important for C-C bond cleavage, and such fragmentations have been reported in aryl epoxides,[24,25] vinyl epoxides[31] and in keto-epoxides.[27]

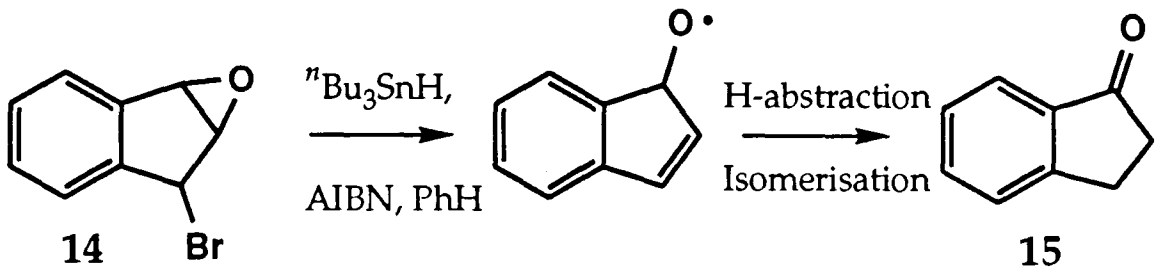
In most cases the radical formed from halogen atom abstraction has the freedom to attain coplanarity with the σ* orbital of either the C-O or C-C bonds ensuring that stereoelectronic effects do not govern the fragmentation pathway. For example, aryl epoxide **11** formed the alcohol **12** after hydrolysis of the oxepane **13**, the major fragmentation product, Scheme 10.



Conditions: (i) $NaBH_4$, EtOH. (ii) TsOH. (iii) DIBALH. (iv) DMS, NBS, DCM. (v) *m*CPBA. (vi) $^nBu_3SnH$, AIBN, PhH. (vii) SiO_2.

Scheme 10

Interestingly, studies on the conformationally constrained aryl epoxide **14** led solely to the exocyclic C-O cleavage[24] product **15** (Scheme 11), as had been previously observed in analogous epoxides without an adjacent π-system.[20a]



Scheme 11

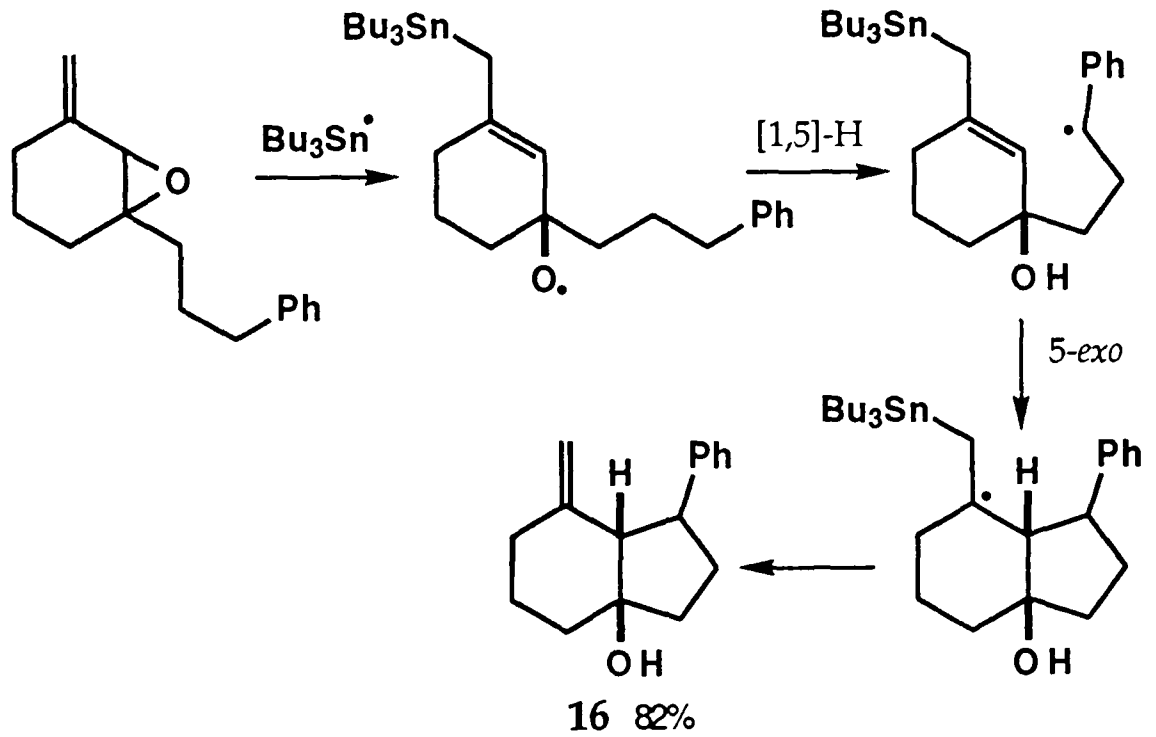
1.4.2. Carbon-Oxygen Bond Fragmentation

In addition to such conformationally constrained epoxides, C-O bond cleavage occurs in epoxides without adjacent π-systems and is by far the major fragmentation route researched. Such a fragmentation pathway generates an alkoxy radical and this short-lived, high-energy intermediate has a tendency, driven by thermodynamics, to either abstract a hydrogen atom in an intra- or intermolecular fashion or undergo a β-scission (although other more unusual atom abstractions and cyclisations are also well known). In all of these

instances a new radical centre is formed and where such a radical is carbon-centred a range of options become apparent.

1.4.2.1. Intramolecular 1,5-Hydrogen Translocation Reactions

Trapping an alkoxy radical, formed from homolytic epoxide fragmentation, by a [1,5]-hydrogen atom abstraction has been used in a number of ingenious examples by Kim and co-workers[32,37,39] and Rawal *et al.*[22,38,40,41] Kim showed that addition of stannyl radical to an alkenyl epoxide resulted in an allyloxy radical. Subsequent [1,5]-hydrogen atom transfer and 5-*exo* cyclisation resulted in smooth elimination of the original stannyl radical and formation of bicyclic system **16**, Scheme 12.[32]

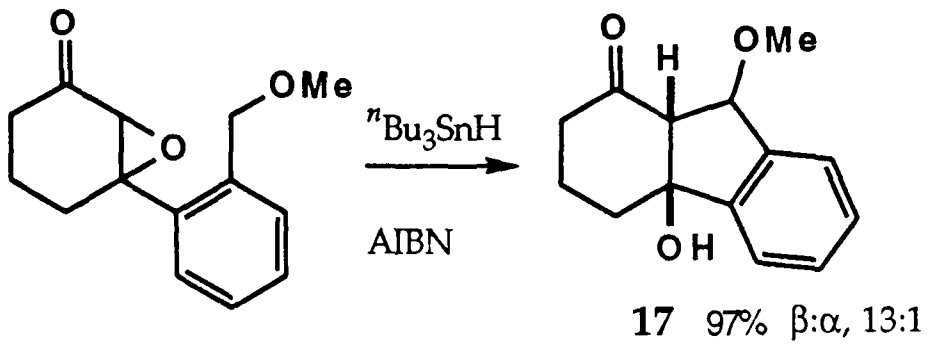


Scheme 12

In a related study Kim showed that the identical sequence could be performed using silyl protected epoxy enols[39] and epoxy ketones.[37]

Related work by Rawal[40] involved the addition of stannyl radical to an epoxy enol acetate followed by an identical sequence of radical steps resulting in the formation of *cis*-fused bicyclic systems. In addition Rawal also identified the versatility of epoxyketones and synthesised a variety of bi- and tricyclic

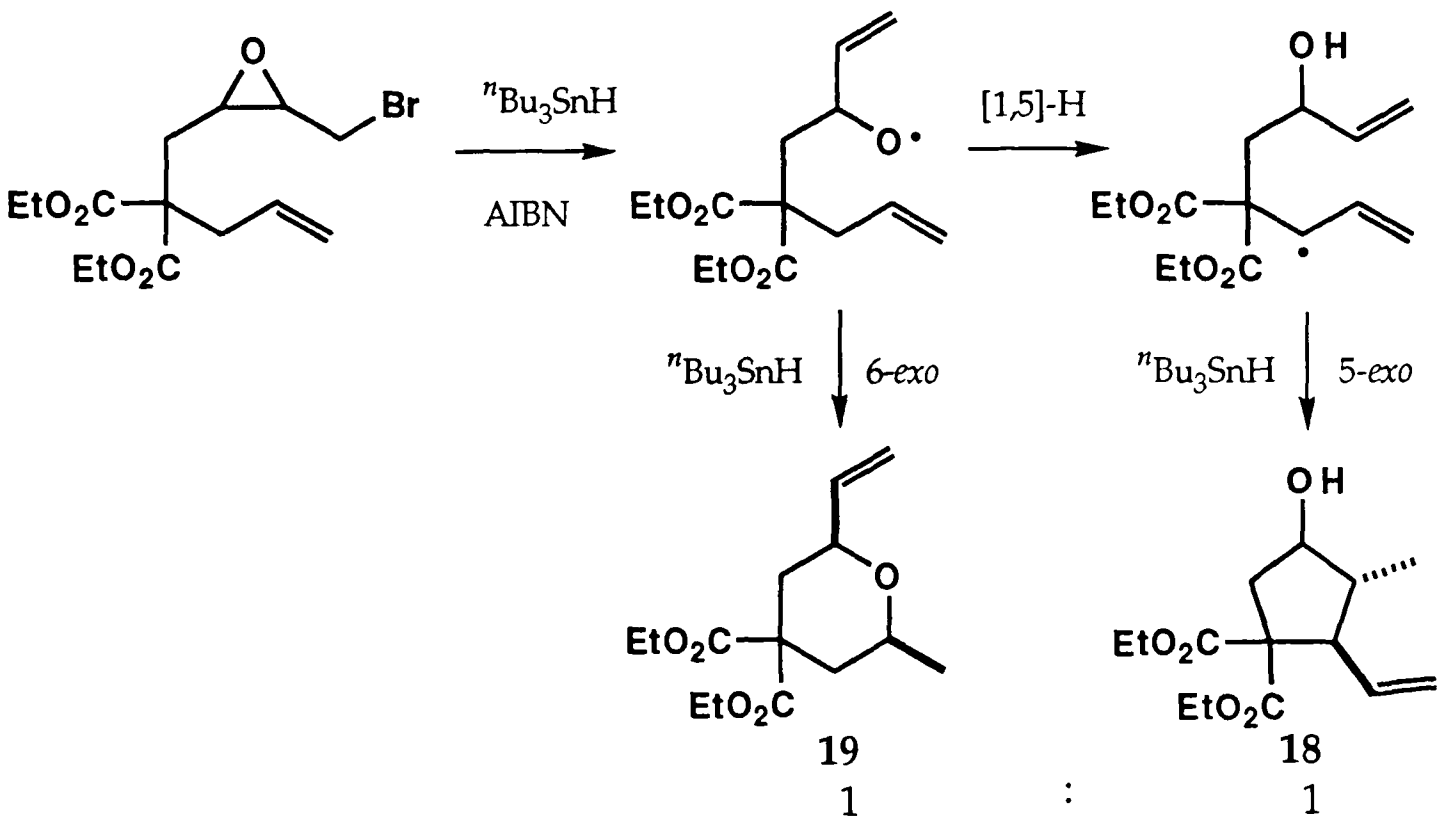
products[38] in an analogous manner. One example is shown to give the tricycle **17** with high diastereoselectivity (Scheme 13).



17 97% β:α, 13:1

Scheme 13

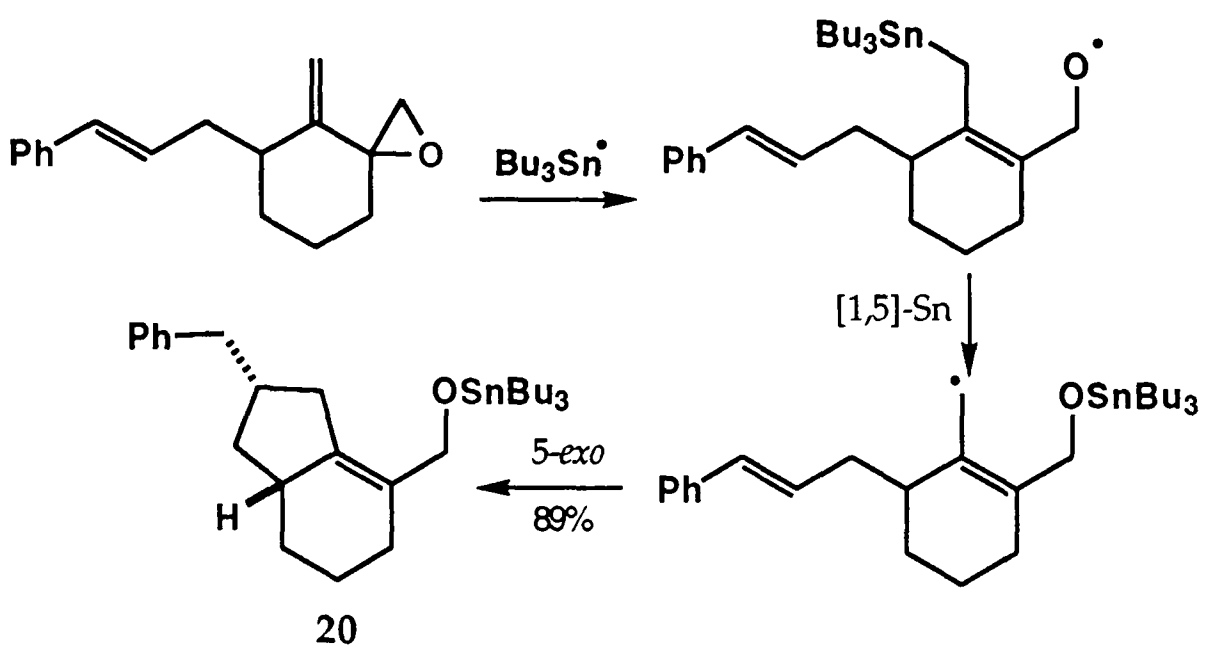
The ability of an alkoxy radical to abstract a hydrogen atom has also been used to great effect by Murphy and co-workers[28] in their formation of cyclopentanes from acyclic epoxides. Scheme 14 shows such a process, in which the carbon-centred radical resulting from hydrogen atom abstraction cyclises on to the alkene generated from epoxide cleavage. Interestingly equal amounts of the cyclopentanol **18** (formed from *trans*- cyclisation) and tetrahydropyran **19** were isolated.



Scheme 14

1.4.2.2. [1,5]-Tin Abstraction Reactions

Alkoxy radicals have also been trapped by the novel 1,5-tin abstraction demonstrated by Kim *et al.*[32,37] This sequence allows the construction of bicyclic systems through addition of stannyl radical to a keto- or alkenyl epoxide as exemplified by the formation of **20** in Scheme 15.



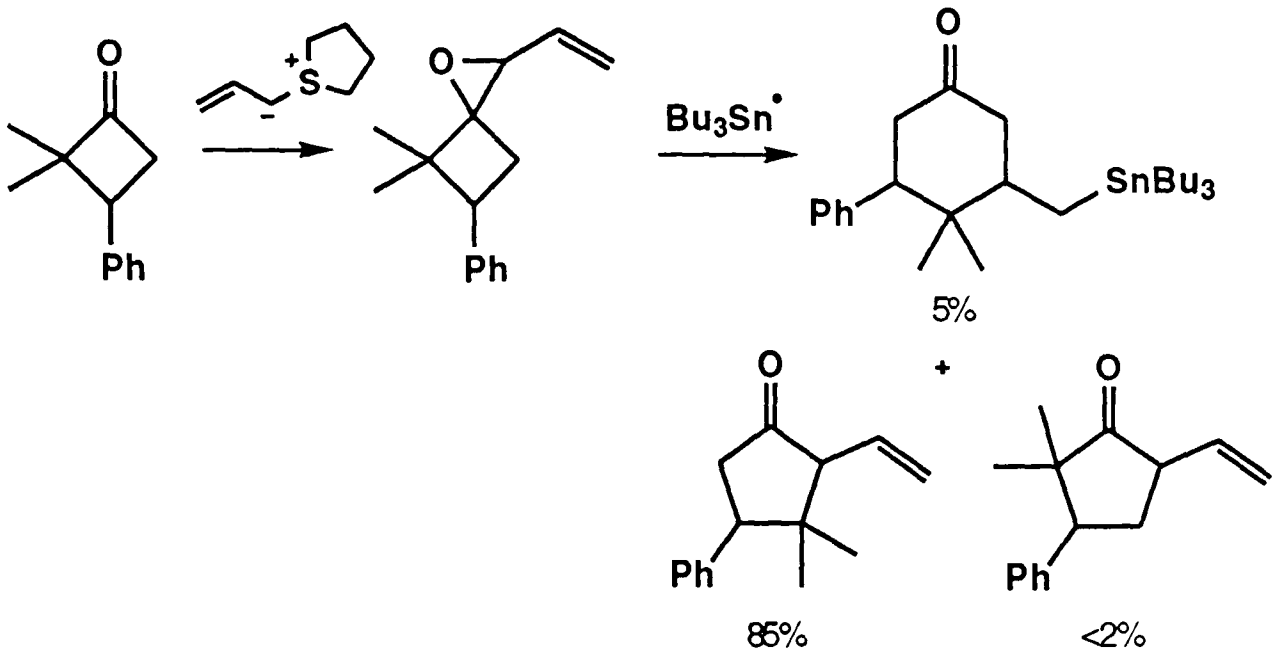
20

Major product (ratio of diastereomers, 3:1)

Scheme 15

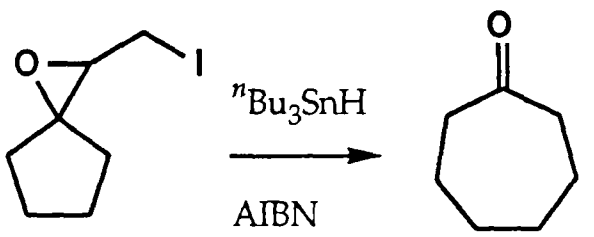
1.4.2.3. Fragmentation Pathways

Employing the allyloxy radical in β-scission processes presents a rapid synthetic route to medium rings through successive ring expansions and also leads, in the case of carefully constructed systems, to interesting bi- and tricycles. Kim showed that the addition of stannyl radical to exocyclic alkenyl spiro-epoxides generated products derived from both one- and two-carbon ring expansions[34] shown in Scheme 16.



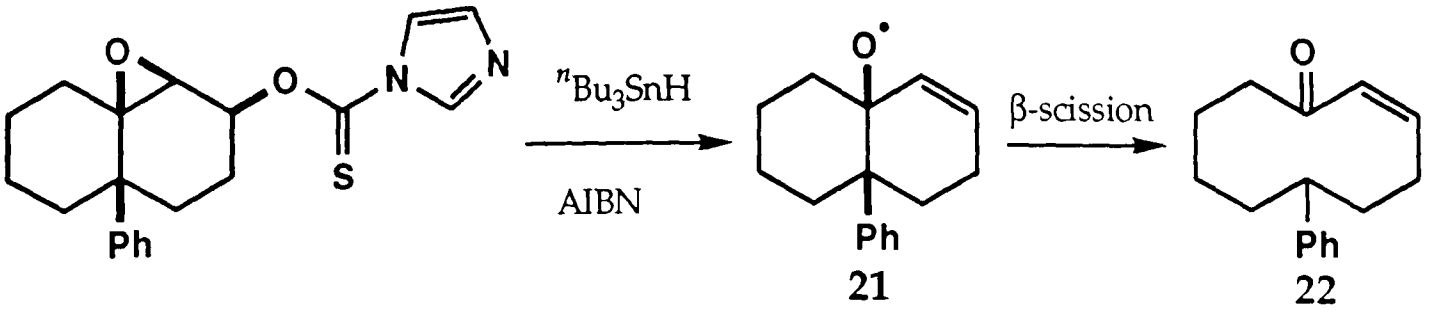
Scheme 16

In an analogous fashion Galatsis reported the synthesis of seven-membered rings from α-iodo spiro-epoxides[29] (Scheme 17).



Scheme 17

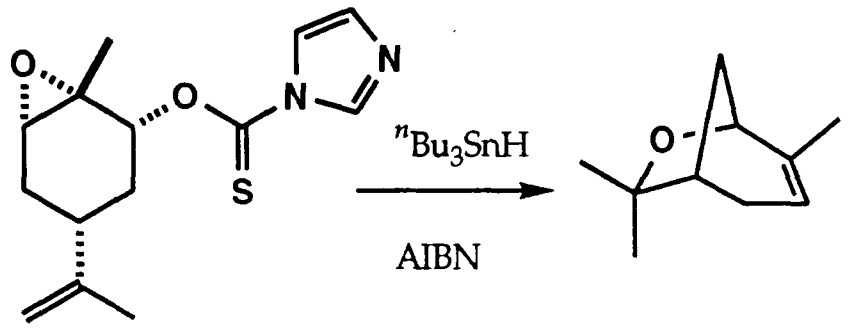
Generation of medium rings by the fragmentation of a bridgehead alkoxy radical is a well established procedure,[46] however, in the majority of cases the parent alcohol is used directly as the radical precursor. Rawal and co-workers[21] established that homolytic cleavage of an epoxide could achieve a similar outcome, as shown by the fragmentation of alkoxy-radical **21** to the cyclodecenone **22** (Scheme 18).



Scheme 18

1.4.2.4. Cyclisations of Alkoxy Radicals

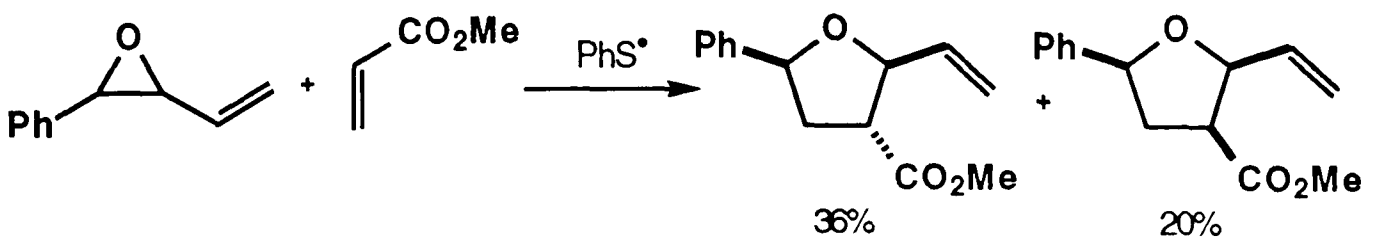
In an attempt to demonstrate an alternative sequence to the Wharton transposition[47] Barton *et al.*[19] took the thiocarbonyl imidazolide **23**, derived from (-)-*cis*-carveol and treated it with tributyltin hydride. To their surprise they observed that, in addition to the desired reduction product, cyclisation to the bicyclic tetrahydrofuran **24** competed, Scheme 19.



Scheme 19

Murphy[23,26] and Walton[30] have similarly demonstrated the effectiveness of this process in forming both monocyclic tetrahydrofurans and also interesting bicycles with bridged oxygens and Murphy[28] has further extended this approach to the generation of tetrahydropyrans *via* 6-*exo* cyclisations.

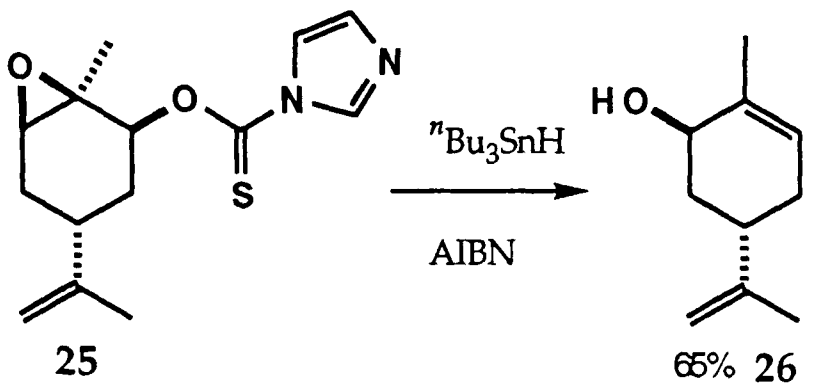
One fascinating example of an intermolecular cyclisation leading again to the synthesis of tetrahydrofurans was reported by Feldman and co-workers.[36] Their approach made use of a [3+2] radical-induced ring expansion of vinyl epoxides, shown in Scheme 20.



Scheme 20

1.4.2.5. Intermolecular Reductive Quenching of the Alkoxy Radical

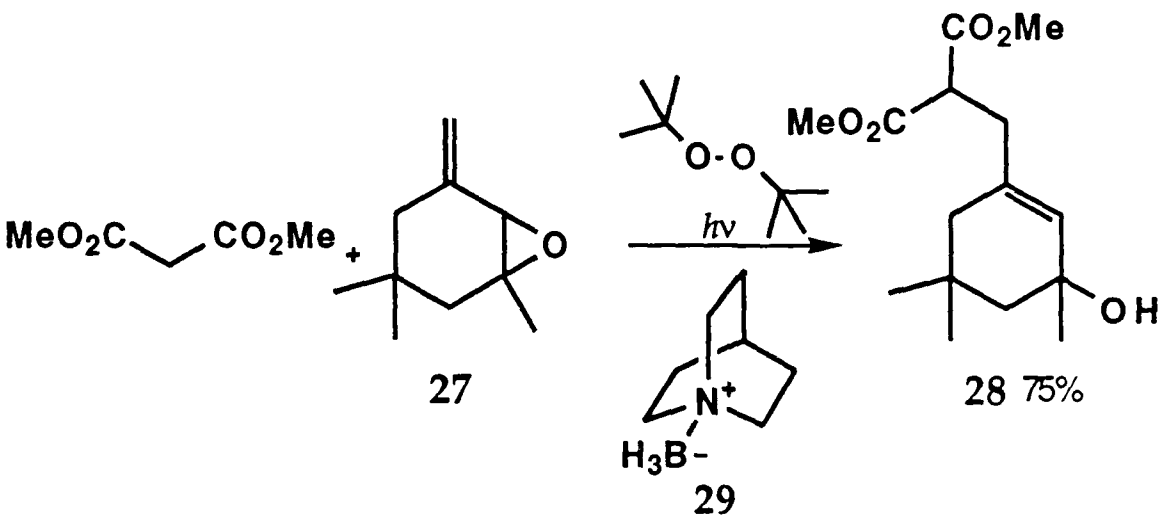
Barton and co-workers[19] showed that treatment of the thiocarbonyl imidazolide derived from (+)-*trans*-carveol **25** (rather than (-)-*cis*-carveol **23**) with tributyltin hydride gave smooth conversion to the desired allylic alcohol **26** as shown in Scheme 21.



25 **65% 26**

Scheme 21

Roberts *et al.*[35] sought to achieve a similar reduction of an alkoxy radical derived from addition of malonyl radical to an alkenyl epoxide or protected epoxy enol. They found that in the presence of an amine-borane catalyst, a radical generated α- to the carbonyl in dimethyl malonate added to the alkenyl epoxide **27** resulting in formation of the allylic alcohol **28**, shown in Scheme 22.



27 **28** 75%

29

Scheme 22

Roberts suggested that the amine-borane (usually quinuclidine-borane **29**) acts as a polarity reversal catalyst enabling regioselective overall transfer of hydrogen from the ester to the alkoxy radical.

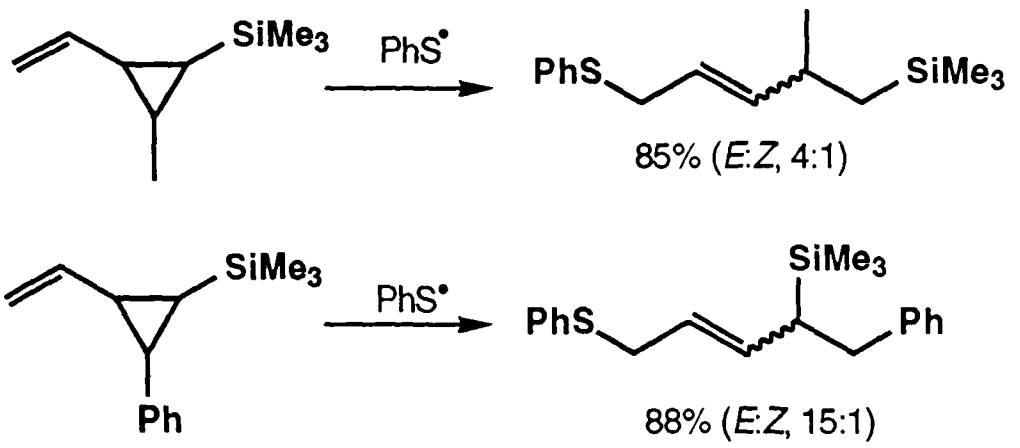
Luche and co-workers[42] demonstrated the effectiveness of single-electron transfer processes that converted α-bromo epoxides to allylic alcohols in the presence of zinc and copper (I) iodide with sonication. Nugent and RajanBabu,[44] in their work on homolytic cleavage of epoxides with transition metal catalysts, reported reduction of the intermediate alkoxy radicals to alcohols.

Murphy[24] has also described an intramolecular hydrogen atom abstraction arising from ring opening of conformationally constrained aryl epoxides and Shimizu *et al.*[43] have developed an interesting formation of β-hydroxy ketones, equivalent to aldol reaction products, *via* addition of tributyltin radical to an epoxyketone.

1.5. Homolytic Cleavage of Epoxysilanes

1.5.1. At the time of initiating our work there were no reports of studies on the radical ring opening of epoxysilanes. Roberts had added a radical to an alkenyl epoxysilane,[35] however it was substituted in such a way as to generate a β-siloxy radical rather than the necessary α-siloxy radical.

1.5.2. Utimoto and Oshima, however, had investigated the analogous homolytic ring opening of cyclopropylsilanes.[48] They showed that in the simple case of mono- or alkyl-substituted cyclopropylsilanes the preferred C-C fragmentation mode led to the product in which the silicon was attached at the terminal carbon; they attributed this to the stabilising effect of silicon on α-radicals. Treatment of aryl- or keto-substituted cyclopropylsilanes with thiyl radical resulted in the opposite fragmentation pathway generating the predicted secondary silane. These examples are summarised in Scheme 23.

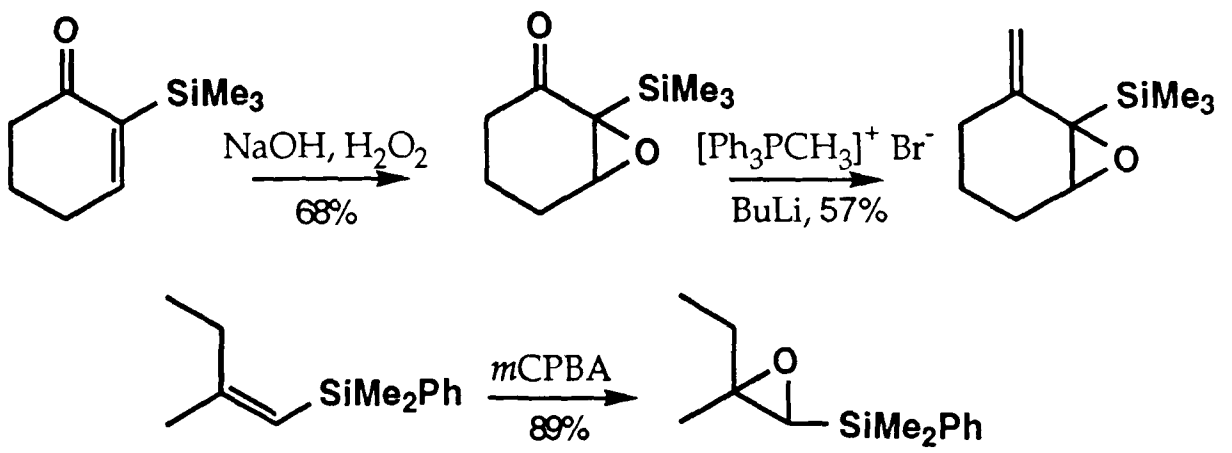


Scheme 23

1.6. Chemistry of Epoxysilanes

1.6.1. Preparation of α,β-Epoxysilanes

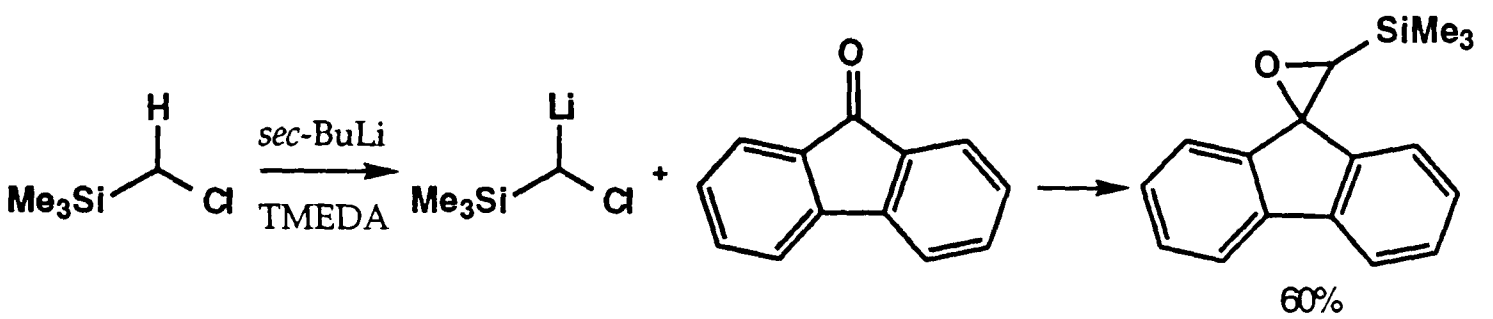
α,β-Epoxysilanes are most commonly synthesised by epoxidation of a parent vinylsilane and, as a result, their synthesis has been traditionally limited by the availability of such precursors.[49] Asymmetric epoxysilane formation works extremely well from the corresponding α-hydroxy vinylsilane[65] using Sharpless' conditions.[50] This use of such hydroxy vinylsilanes and silylated α,β-unsaturated ketones is extremely powerful because alkenyl epoxysilanes may then be easily prepared, using, for example, Wittig chemistry. Several examples are illustrated in Scheme 24.[57,35]



Scheme 24

Magnus and co-workers[51] and more recently Villieras *et al.*[49i] have reported the direct formation of epoxysilanes from saturated and unsaturated ketones. An extremely elegant study by Magnus demonstrated that selective

deprotonation of chloromethyltrimethylsilane with *sec*-butyl lithium develops a silyl carbene synthon which will selectively add to carbonyls forming epoxysilanes. An example is given in Scheme 25.



Scheme 25

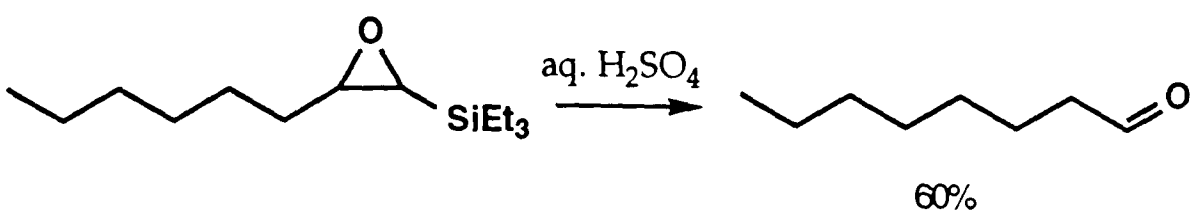
Interestingly, in a related study, Utimoto generated the anion from (dibromomethyl)-*t*-butyldimethylsilane; the dibromolithium species, thus formed, reacted with benzaldehyde, *via* migration of silicon from carbon to oxygen, to give a silyl protected 1,3-diol.[52]

1.6.2. Reactions of α,β-Epoxysilanes

α,β-Epoxysilanes have proven to be versatile synthetic intermediates and their diverse chemistry has been widely explored and exploited.[53-65]

1.6.2.1. Formation of aldehydes and ketones

Stork *et al.*[53] demonstrated that epoxysilanes could be hydrolysed selectively to aldehydes or ketones in the presence of aqueous sulphuric acid. Magnus[51a] then proposed a similar transformation using aqueous perchloric acid. The regiochemistry of C-O fragmentation has been rationalised by invoking silicon's ability to stabilise a β-cation[54] intermediate (Scheme 26).



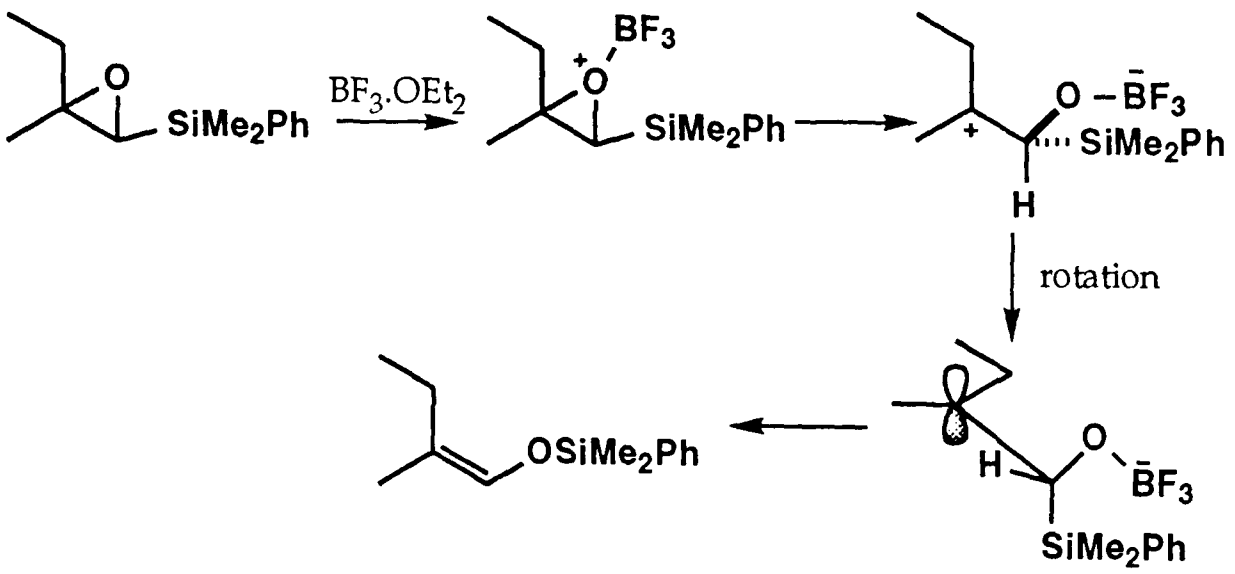
Scheme 26

This powerful transformation allows epoxysilanes (and indeed their most common precursors, vinylsilanes) to act as masked carbonyls.

1.6.2.2. Formation of Silyl Enol Ethers

Hudrlik and co-workers have done a great deal of work on epoxysilanes and related areas of chemistry.[55,56] They have demonstrated the isomerisation of epoxysilanes to silyl enol ethers using Lewis acids[55b,55c,55e] with the exact nature of the products dependant on the conditions used and the degree of substitution in the epoxysilane.

Fleming[57] subsequently reported a valuable stereospecific rearrangement of 2,2-disubstituted epoxysilanes to silyl enol ethers by a novel β-opening of the epoxysilane as shown in Scheme 27.



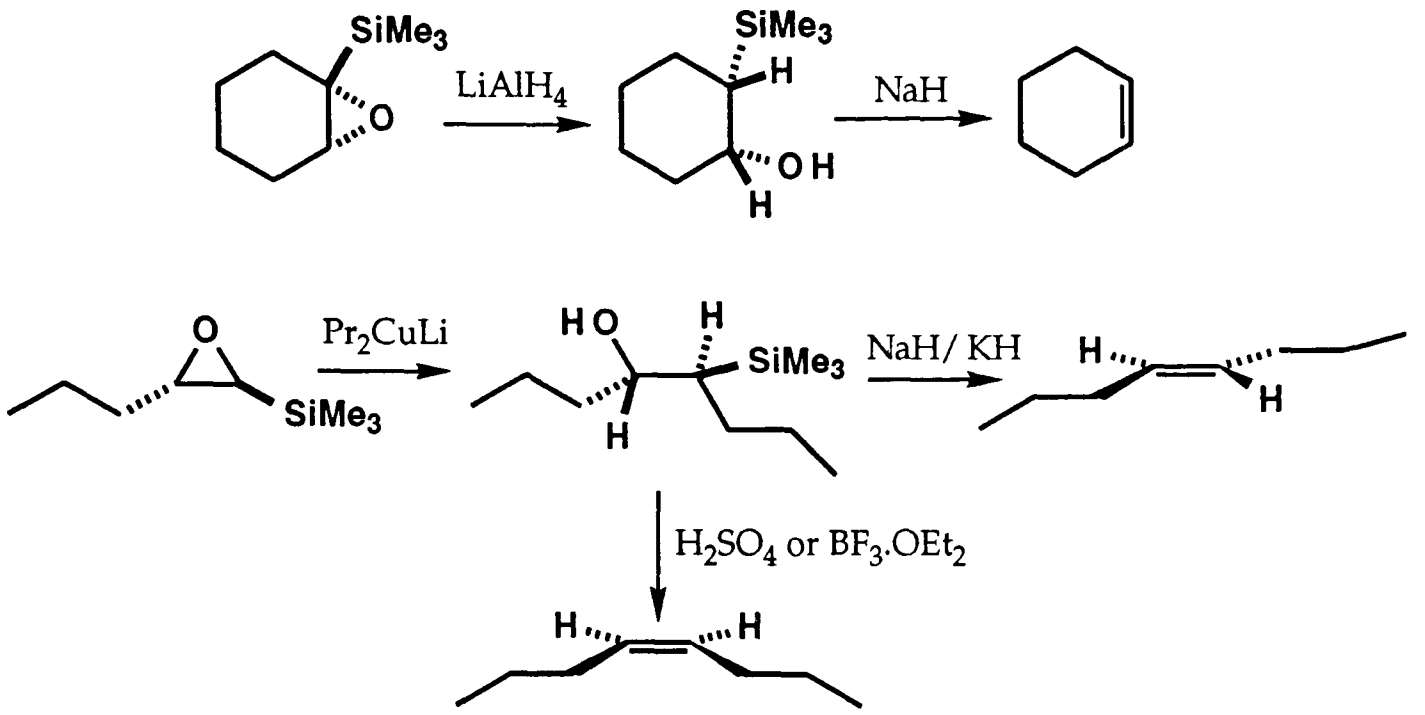
Scheme 27

The thermal rearrangement of epoxysilanes to the corresponding silyl enol ethers has also been observed by Brook.[59]

1.6.2.3. Formation of β-Hydroxy Silanes

Epoxysilanes have proven to be excellent stereospecific vinyl cation equivalents for the synthesis of alkenes[56] and heteroatom-substituted alkenes[55a] thus constituting α-silyl ketone equivalents. This is so because of the ease with which they can be transformed into β-hydroxy silanes. Epoxysilanes

are reduced selectively at the α-position[61,58d] and form alkyl β-hydroxy silanes on addition of dialkylcuprates.[56a,58] Subsequent elimination induced by either acid or base generates the *cis*- or *trans*-alkene stereospecifically.[56,60] These sequences are shown in Scheme 28.



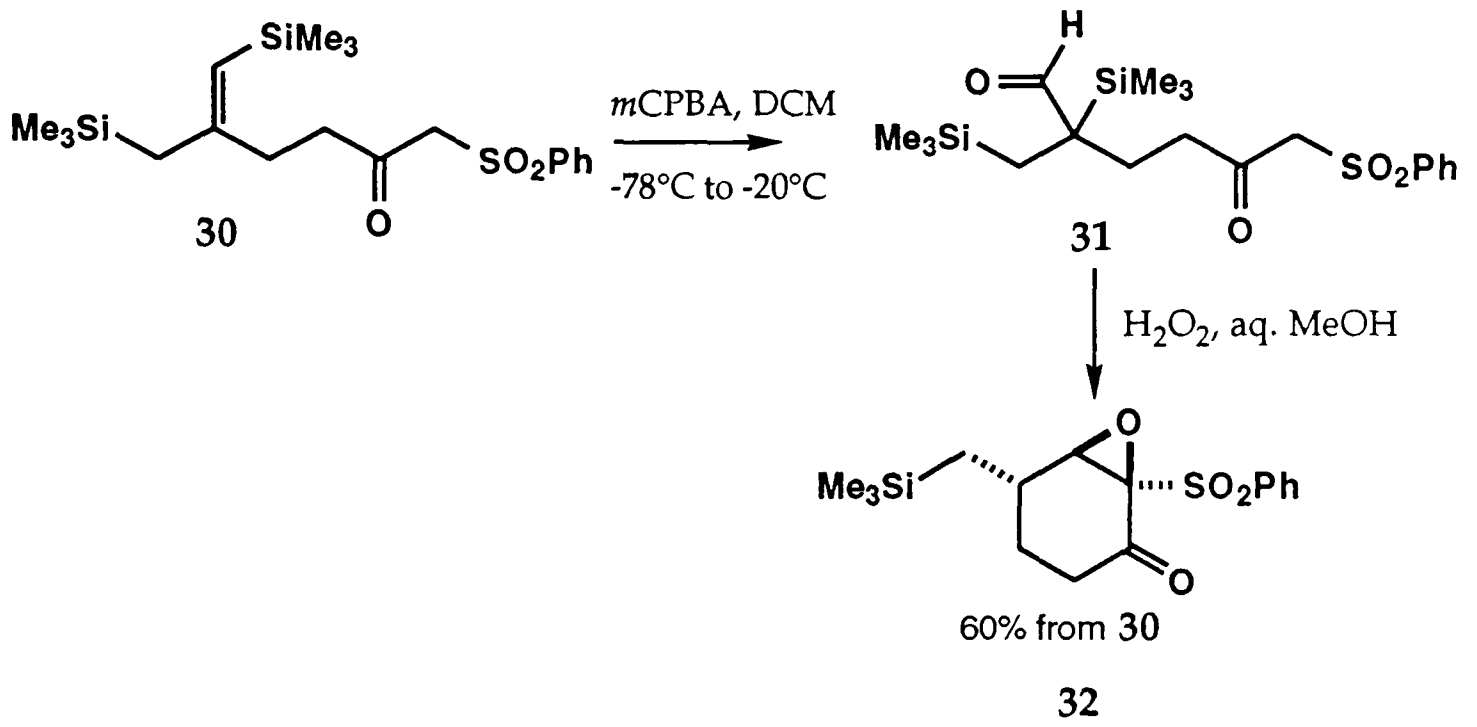
Scheme 28

1.6.2.4. Isomerisation to α-Silylaldehydes

Hudrlik *et al.*[55d,56e,56f] have reported the isolation of β-hydroxysilanes as the products generated from the reaction between epoxysilanes and Grignard reagents. They have suggested that this could arise as a result of Grignard reagent attack at the carbonyl carbon of an *in situ* formed α-silyl aldehyde.

Additionally there have been several other examples of isomerisations towards α-silylaldehydes. Such α-silylaldehydes are reputed to be prone to hydrolysis or facile isomerisation[56e,62] and thus usually bulky groups on silicon are required to enhance the kinetic stability.

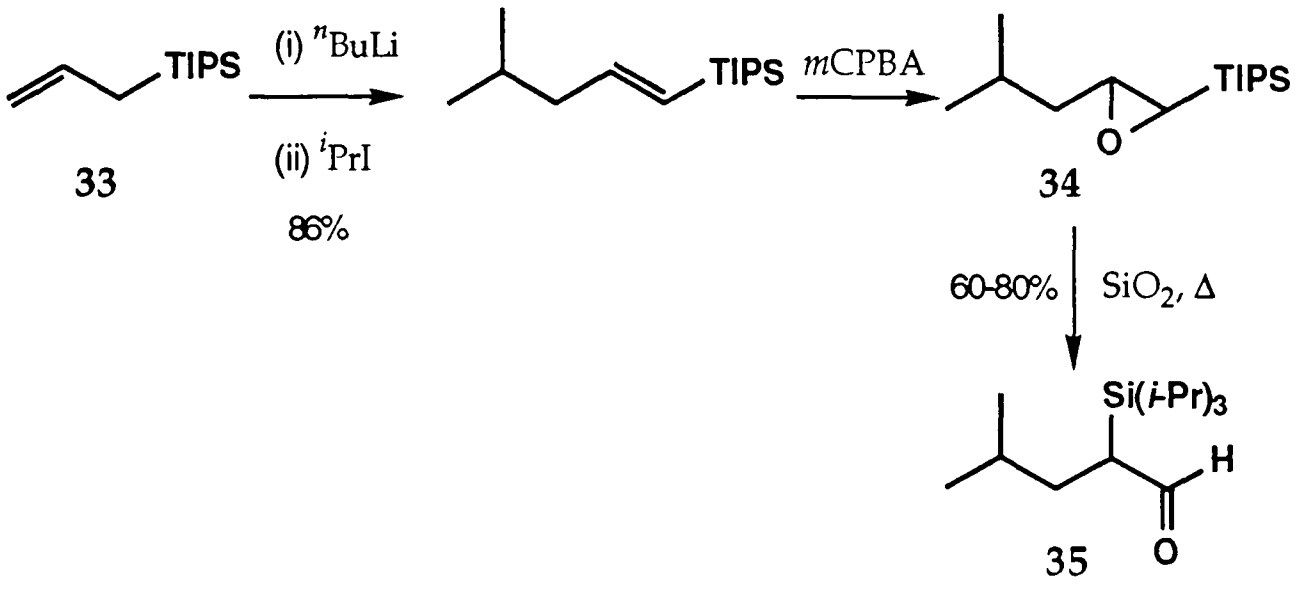
Fujita and co-workers[63] disclosed an *in situ* rearrangement of an epoxysilane generated from the vinylsilane **30** to the α-trimethylsilylaldehyde **31**. This highly reactive and unstable intermediate was then rapidly taken on to the next step in the desired sequence to generate epoxide **32**. This is shown in Scheme 29.



Scheme 29

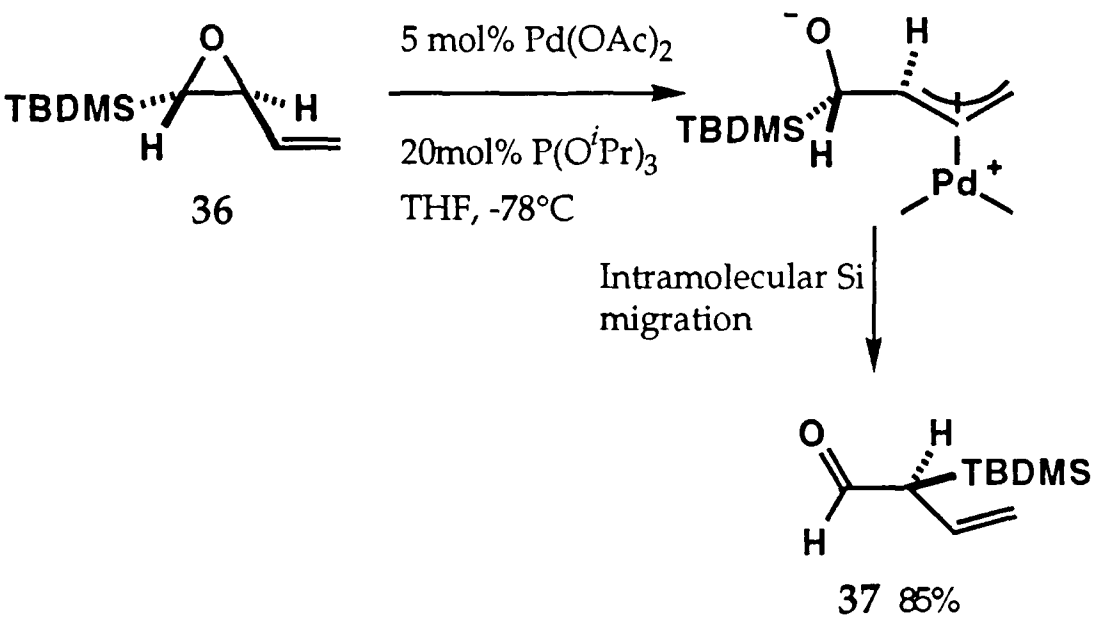
Fujita rather modestly omitted to mention that this was the first reported isolation of an α-trimethylsilylaldehyde, but he does suggest that formation of **31** was possible only by virtue of having two trimethylsilyl groups β- to the cation that must precede migration of silicon.

An analogous rearrangement was observed by Muchowski *et al.*[64] in their synthesis of epoxy-triisopropylsilanes. Muchowski was investigating the γ-alkylation of allyltriisopropylsilane **33**, and noted that heating of the derived epoxysilane **34** with silica gel gave a clean transformation to the corresponding α-triisopropylsilylaldehyde **35**. This is depicted in Scheme 30.



Scheme 30

Elegant work by Malacria and co-workers[65] has illustrated the use of palladium (0) catalysis in the isomerisation of epoxysilanes. Vinyl epoxides had been studied extensively in the presence of palladium (0)[65a] but the epoxides studied had never borne a trialkylsilyl substituent. On discovering this Malacria seized the opportunity to investigate the corresponding vinyl epoxysilanes and observed that when enantiomerically pure **36** (available in five steps [43%] from propargyl alcohol) was treated with palladium (0) the α-*t*-butyldimethylsilylaldehyde **37** shown in Scheme 31 was formed instantaneously.

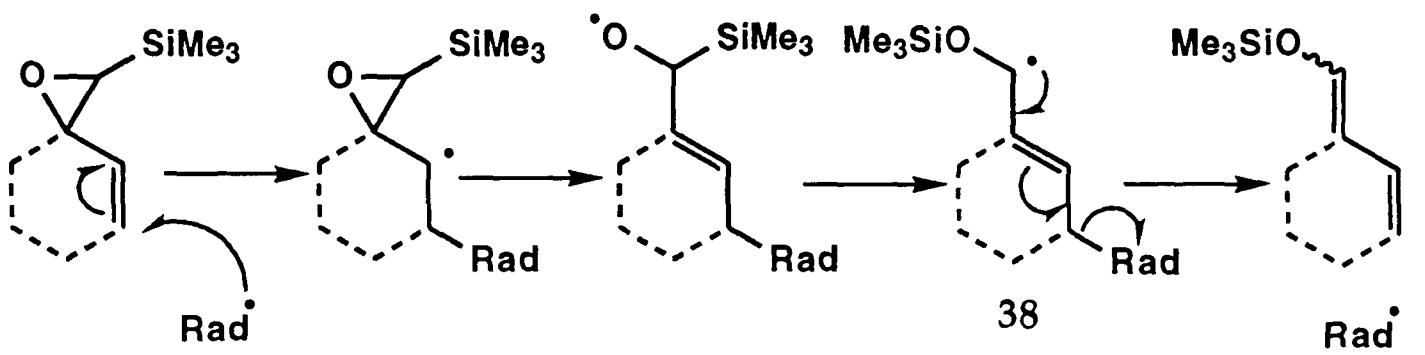


Scheme 31

1.7. Proposed Research: Free Radical Isomerisation of Alkenyl Epoxysilanes

1.7.1. We proposed that an α-siloxy radical could be generated from a carbon-centred radical positioned α- to an epoxysilane.[66] It could be conceived that ring opening of such an epoxide would lead, by analogy (**1.3.2.**), to a new carbon-centred radical **38** formed as a result of a radical Brook rearrangement. Generation of a radical α- to an epoxysilane could come about either by direct abstraction of an atom from the α- site or through addition of a radical to the β-position of an alkenyl epoxysilane.

We were attracted to studies on alkenyl epoxysilanes not only because of their ease of preparation[49i,51] but also because of the added advantage associated with possible elimination of the radical chain carrier subsequent to rearrangement. Indeed such a process would provide an extremely elegant conversion of alkenyl epoxysilanes into silyl dienol ethers under neutral conditions requiring only a catalytic amount of the radical progenitor, shown in Scheme 32.



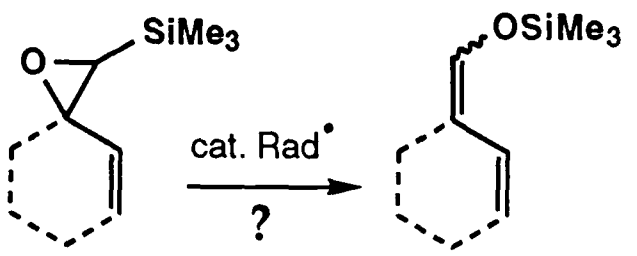
Scheme 32

In addition to such methodology, there would be a wealth of possibilities associated with careful construction of a system in which the carbon-centred radical, generated by the Brook rearrangement, could be subsequently employed in carbon-carbon bond forming processes.

1.7.2. Utimoto's study (**1.5.**) suggested that formation of the α-siloxy radical might be problematic; however, construction of a system where stereoelectronic effects would be important, such as a constrained spiro-alkenyl epoxysilane or other cyclic, rigid alkenyl epoxysilanes would, by analogy (**1.4.1** and **1.4.2.**), promote the desired C-O fragmentation.

1.7.3. Having explored the chemistry associated with epoxysilanes (**1.6.**) and the reported homolytic cleavage reactions of related compounds (**1.4.**), the aim of the project was now to synthesise a variety of alkenyl epoxysilanes and submit them to the necessary free-radical conditions suitable for isomerisation.

Initially a basic system would be studied as a test reaction, Scheme 33, in the hope of generating silyl dienol ethers and most importantly in the hope of observing a radical Brook rearrangement. Further studies to maximise the carbon-carbon bond-forming potential in tandem rearrangement-cyclisation reactions would be implemented on the basis of the initial study.



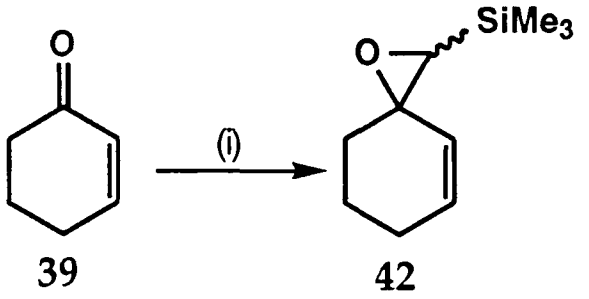
Scheme 33

RESULTS & DISCUSSION ‡

2.1. Preparation of Alkenyl Epoxysilanes

We were attracted to the chloromethyltrimethylsilyl carbanion (CTC) methodology developed by Magnus[51] because of the ease with which alkenyl epoxysilanes may be synthesised from alkenones. We were also keen to initially work with spiro epoxysilanes, to maximise any stereoelectronic control governing the radical ring opening. Cyclohexenone **39**, 4,4-dimethylcyclohexenone **40**, and isophorone **41** were selected as readily available substrates for alkenyl epoxysilane formation.

2.1.1. Treatment of cyclohexenone **39** with CTC, generated *in situ* (Scheme 34), gave a diastereomeric mixture (ratio 3:1) of the known epoxysilanes **42**.[51a]



39 **42**

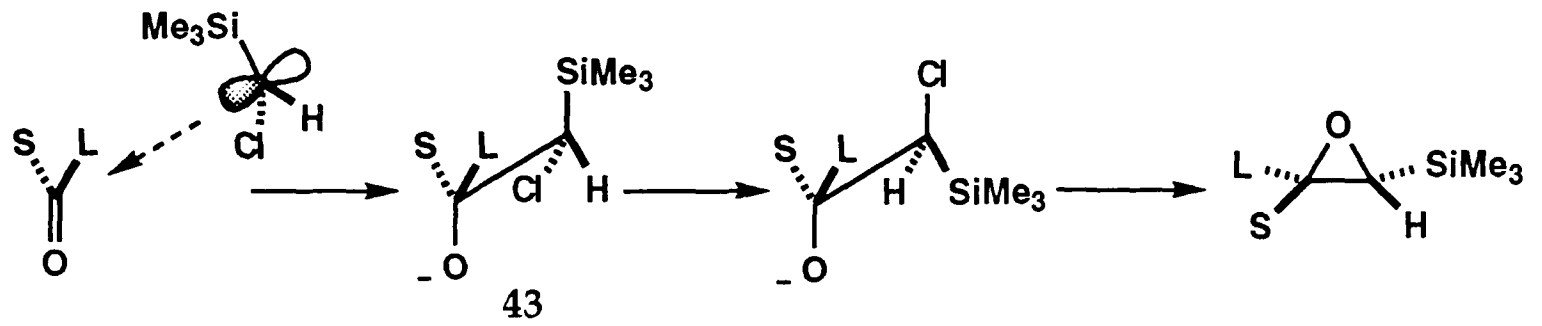
Conditions: (i) Me_3SiCH_2Cl, *sec*-BuLi, TMEDA, THF, -78°C to RT, 2h; 71%.[51a]

Scheme 34

The identity of the major diastereomer was rationalised by Magnus based on transition state modelling, Figure 1. He proposed that kinetic addition of CTC to a prochiral ketone follows a path that arranges atoms in the least sterically demanding conformation. Subsequent rotation of **43** must occur for

‡ This work was presented as a poster at the Pre-doctoral Symposium to the Autumn meeting of the Royal Society of Chemistry at Glasgow University, September 1994 and presented orally at the Oxford University Graduate Symposium, Dyson Perrins Laboratory, September 1996.

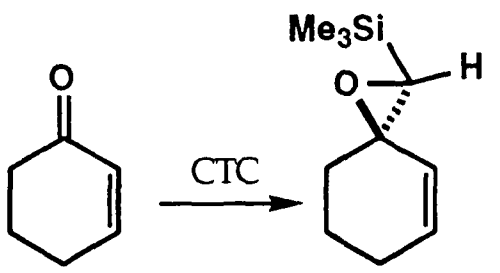
S_N2 displacement of the chloride resulting in the thermodynamically less stable diastereomer as the major product.



L = Larger group attached to carbonyl. S = Smaller group attached to carbonyl.

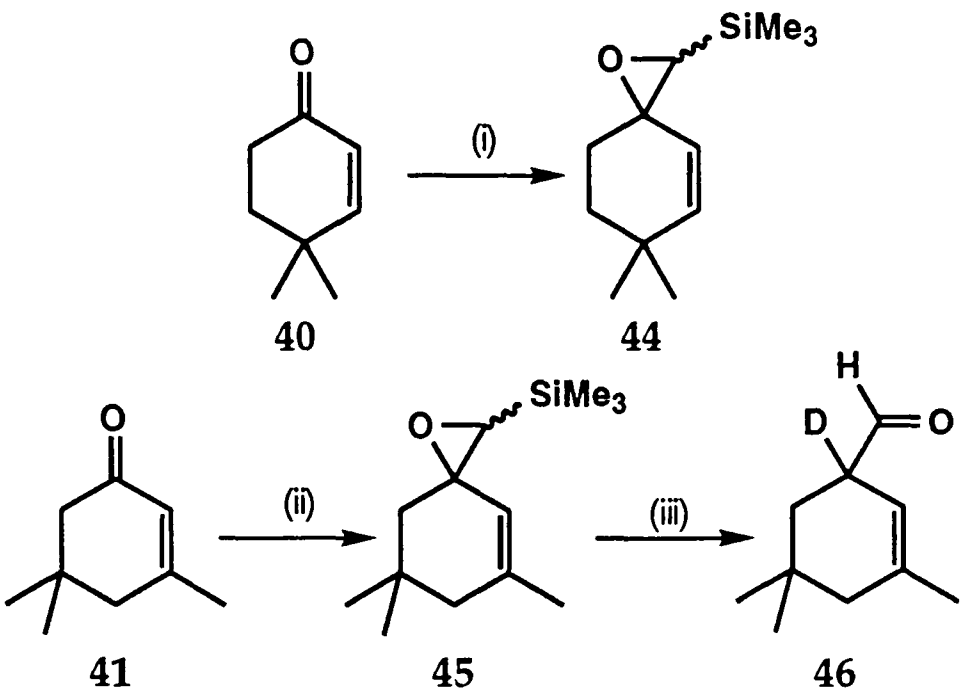
Figure 1

This *suggests* that, in the case of the epoxysilane from cyclohexenone, the major diastereomer is that shown in Scheme 35 but the exact assignment was not proven.



Scheme 35

2.1.2. The syntheses of the unreported epoxysilanes from 4,4-dimethylcyclohexenone **40** and isophorone **41** were then attempted. Formation of dimethylepoxysilane (3:1 ratio of diastereomers) **44** proceeded smoothly, however generation of the trimethylepoxysilane diastereomers **45** from isophorone could not be driven to completion. Further complications arose on discovering the extreme sensitivity and instability of the epoxysilane **45** with respect to rapid hydrolysis in weakly acidic media; indeed full hydrolysis of epoxysilane **45** occurred within 5mins in $CDCl_3$. Neither the epoxysilane **45** nor aldehyde **46** were fully characterised (Appendix A) and it was decided subsequently to avoid the use of β-substituted alkenone substrates. These results are summarised in Scheme 36.



Conditions: (i) Me_3SiCH_2Cl, *sec*-BuLi, TMEDA, THF, -78°C to RT, 2h; 80%. (ii) Me_3SiCH_2Cl, *sec*-BuLi, TMEDA, THF, -78°C to RT, 2h; 60% . (iii) $CDCl_3$, 5mins; quant.

Scheme 36

2.2. Studies on Epoxysilane 42

2.2.1. The Free Radical Isomerisation

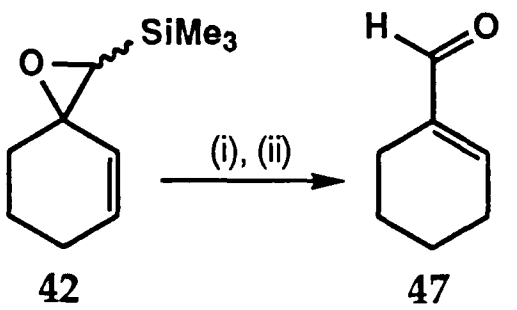
It was decided, as Utimoto had,[48] to make use of thiyl radical addition since the ease with which thiyl radicals add reversibly to multiple bonds is well known;[67] properties that were suitable for our purposes.

The epoxysilane **42** was treated with a catalytic quantity of thiophenol and of AIBN in degassed benzene. Analysis of the reaction mixture by ^1H NMR after 3h unexpectedly showed the clean formation of an aldehyde as the single product. The FTIR spectrum confirmed the presence of a carbonyl, and GCMS identified the compound to be isomeric with the starting-epoxysilane.

2.2.2. Purification of the Intermediate

Initial attempts to isolate the pure compound by flash column chromatography, chromatography using neutral alumina, purification *via* the bisulphite adduct,[68] and Kugelrohr distillation gave mixed results. Purification using the bisulphite methodology or distillation led to a complex mixture,

however column chromatography led to the isolation of aldehyde[69] **47**, the hydrolysis product[53] of the epoxysilane. The unidentified aldehyde also deteriorated over time, even when concentrated and stored under argon at -15°C. This is shown in Scheme 37.



42 **47**

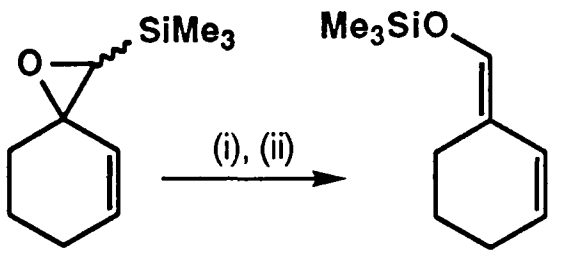
Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ, 3h. (ii) SiO_2; 75% from **42**.[69]

Scheme 37

We were intrigued as to the identity of the unknown aldehyde and tentatively proposed the formation of an allyl-α-trimethylsilylaldehyde **48**, based purely on our interpretation of the spectroscopic and experimental findings. Naturally we were sceptical about such an assignment in light of the reputed instability of such compounds[56e] and the scarcity of their synthesis.[62,63] Therefore we wished to confirm the assignment through further chemical means.

2.2.4. Thermal Isomerisation of the Intermediate

It is well known that α-silyl ketones isomerise to the corresponding silyl enol ethers under both Lewis-acidic and thermal conditions.[8,70] It was hoped, therefore, to achieve an analogous transformation under thermal conditions.[62] The isolated aldehyde was heated in benzene and periodically observed by ^1H NMR. As predicted, conversion to the silyl dienol ether[71] **49** was apparent, shown in Scheme 38.



42 49

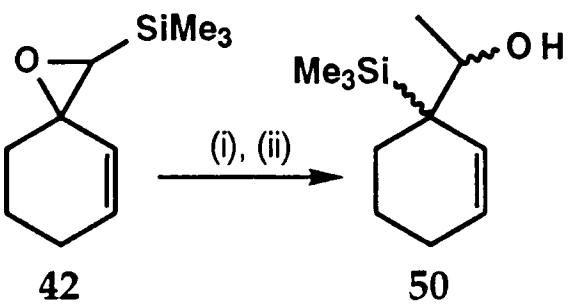
Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ, 3h. (ii) PhH, Δ, 24h.[71]

Scheme 38

Thus our initial aim, the transformation of alkenyl epoxysilanes to silyl dienol ethers had been achieved, albeit through an unexpected intermediate. However, the conversion was not clean enough to be synthetically useful and because of our inability to purify the product a yield could not be reported.

2.2.5. Addition of a Grignard Reagent to the Intermediate

Further evidence for the precise structure of the intermediate came from characterisation of the addition product obtained on reaction of the aldehyde with a Grignard reagent. The isolated aldehyde was treated with methyl magnesium bromide to generate the unreported β-hydroxy-silane **50** of unknown relative stereochemistry, shown in Scheme 39.[56e,62,65b,72]

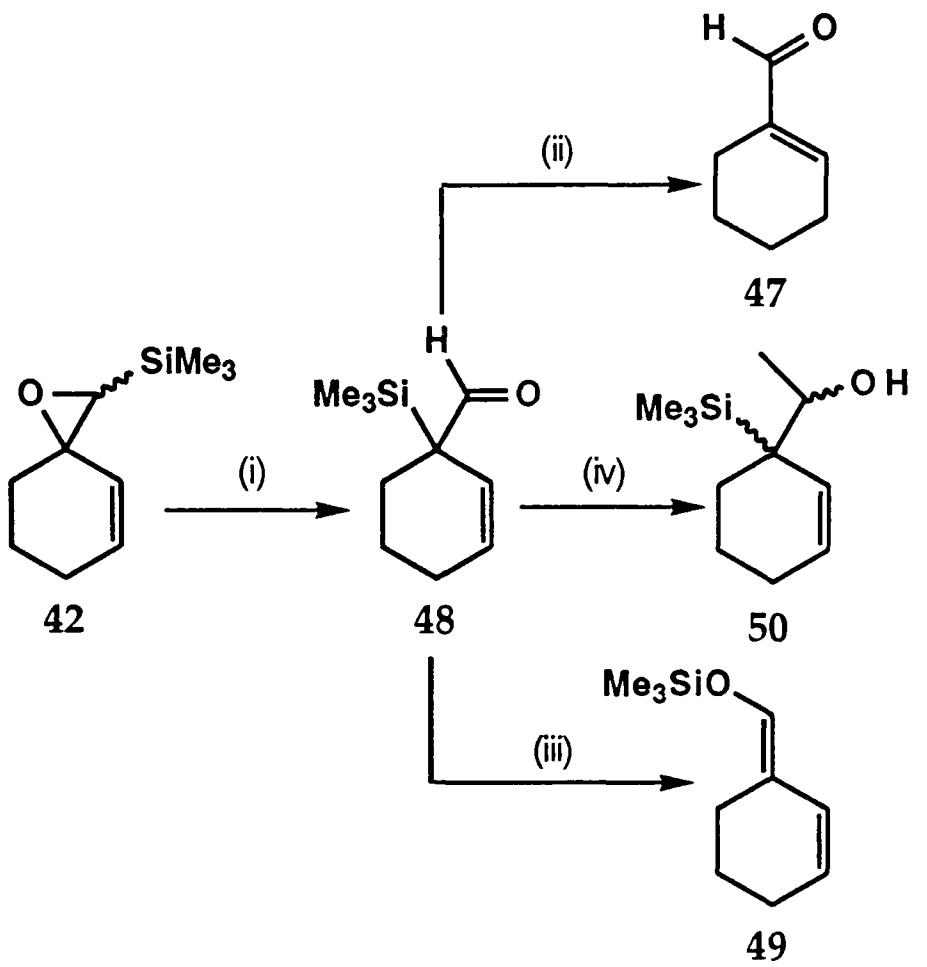


42 50

Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ, 3h. (ii) 1.1 eq. MeMgBr, -78°C to 0°C, 1.5h then 1.2 eq. AcOH, 0°C, 1.5h; 60% from **42**.

Scheme 39

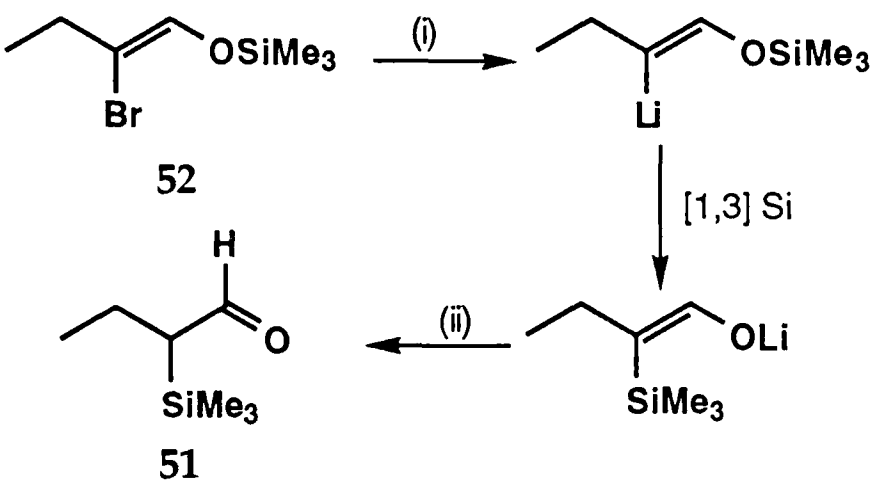
This result strongly supported that the intermediate aldehyde was indeed an allyl-α-trimethylsilylaldehyde **48**, in fact the first ever synthesised.[66] A summary of its formation and reactions is given in Scheme 40.



Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ, 3h. (ii) SiO_2; 75%.[69] (iii) PhH, Δ, 24h.[71] (iv) 1.1 eq. MeMgBr, THF, -78°C to 0°C, 1.5h then 1.2 eq. AcOH, 0°C, 1.5h; 60% from **42**.

Scheme 40

Fujita reported the first isolation of an α-trimethylsilylaldehyde[63] (see Section **1.6.2.4.**) and, more recently, Duhamel published the first general synthesis of pure α-trimethylsilylaldehydes[62] *via* a migration of silicon from oxygen to carbon as exemplified by the formation of **51** in Scheme 41.

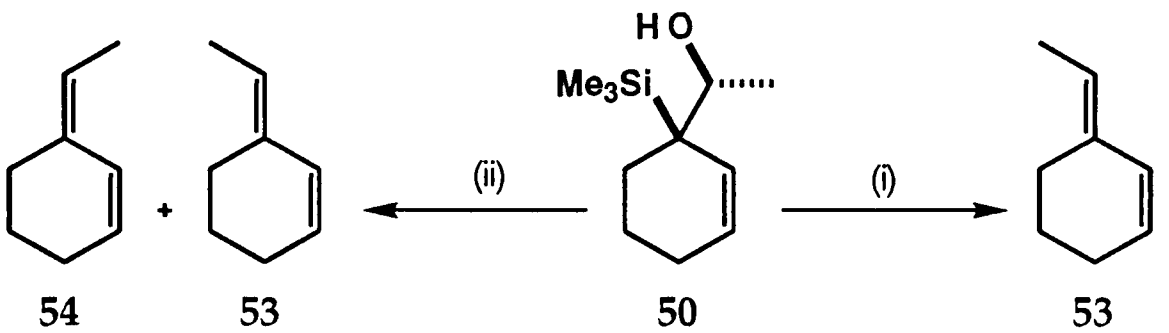


Conditions: (i) ^{t}BuLi, THF, -70°C. (ii) H_2O; 50% from **52**.[62]

Scheme 41

2.2.6. Identification of the Structure of β-Hydroxysilane 50

It is well known that β-hydroxysilanes undergo stereospecific elimination reactions in the presence of a base (the Peterson reaction).[56d,60] It was therefore expected that characterisation of the diene produced in such an elimination would enable us to deduce the relative stereochemistry in the parent β-hydroxysilane. Consequently **50** was treated with sodium hydride to generate the known *E*-diene[73] **53** as a single product. Additionally, the reaction of β-hydroxysilane **50** with tosyl chloride led to a 2:1 mixture of the *Z*-diene[73] **54** to the *E*-diene **53**, for comparison purposes. This allowed us to assign the stereochemistry of **50**, as that shown in Scheme 42.



Conditions: (i) NaH, THF, RT, 1.5h; quant.[71] (ii) TsCl, py, DCM, RT, 15h; quant.[73]

Scheme 42

With the relative stereochemistry of β-hydroxysilane **50** clarified the question of the selectivity of its formation arose. Obviously addition of a nucleophile to the aldehyde **48** could result in the production of two diastereomers. Only one diastereomer was isolated and characterised though, from ^{1}H NMR, our confidence only resides in confirming that the selectivity is greater than 12:1. Formation of **50** might be a result of preferred addition of the nucleophile along a trajectory that eclipses the flattened alkene as opposed to the sterically more demanding β,γ-CH_2- groups of the cyclohexyl ring. Such a Felkin-Ahn analysis is presented in Figure 2.

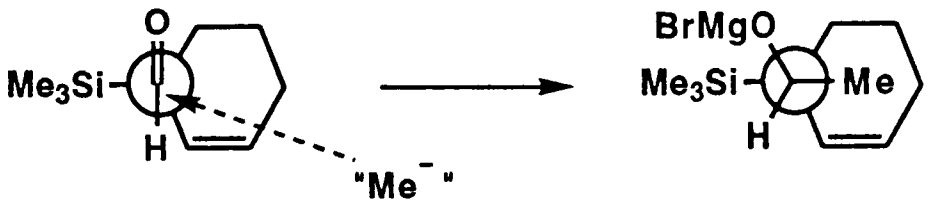
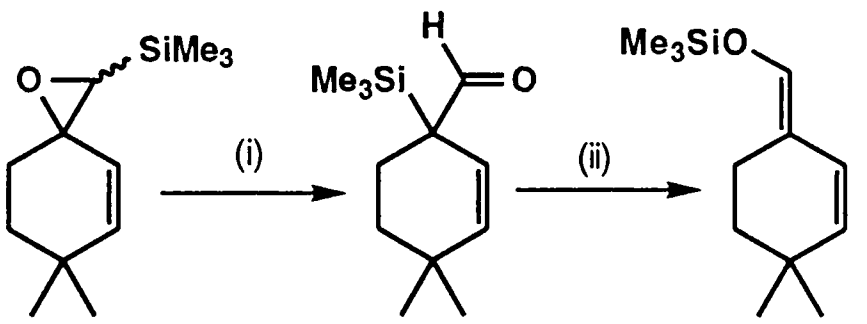


Figure 2

Interestingly, products obtained in such a manner are regioisomers of the products that would result from organometallic addition to an epoxysilane.

2.3. Studies on the Epoxysilane 44

Analogous isomerisation conditions were applied to epoxysilane **44**. An identical reaction sequence was expected, with the only difference lying in the rate of isomerisation. It was predicted that the sterically demanding methyl groups would influence the reactivity of the substrate. This was observed; the analogous aldehyde **55** *was* formed, though only after heating overnight. This α-trimethylsilylaldehyde was also shown to undergo slow thermal conversion to the dienol ether **56** in an identical sequence to that described earlier. These findings are depicted in Scheme 43.



Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ, 14h. (ii) PhH, Δ, 15h.

Scheme 43

2.4. Further Examination of the Isomerisation

Having established the identity of the trimethylsilylaldehydes, it was decided to investigate the isomerisation in more detail.

2.4.1. Isomerisation of Epoxysilane 42

^{1}H NMR studies showed that this isomerisation was complete within 1h at reflux but could also be cleanly performed at RT overnight. In all cases complete conversion of starting material occurred (by ^{1}H NMR) but the inability to purify the product meant that assignment of a yield was impossible. It was decided prudent to quantify the formation by comparing the integral of the protons associated with the trimethylsilyl group of the product with those trimethylsilyl-protons remaining. Thus the yield was estimated to be 60%.

2.4.2. Isomerisation of Epoxysilane 44

This isomerisation could not be encouraged at RT; since a greater reaction time at reflux was required to complete isomerisation this suggested that the rate limiting step was addition of the thiyl radical to the β-position of the alkene, in this case hindered by the *gem*-dimethyl grouping. Again, although the starting material was completely consumed in the reaction, the yield was estimated to be 55% (by ^{1}H NMR).

2.4.3. Acid-Catalysed, Anionic or Homolytic?

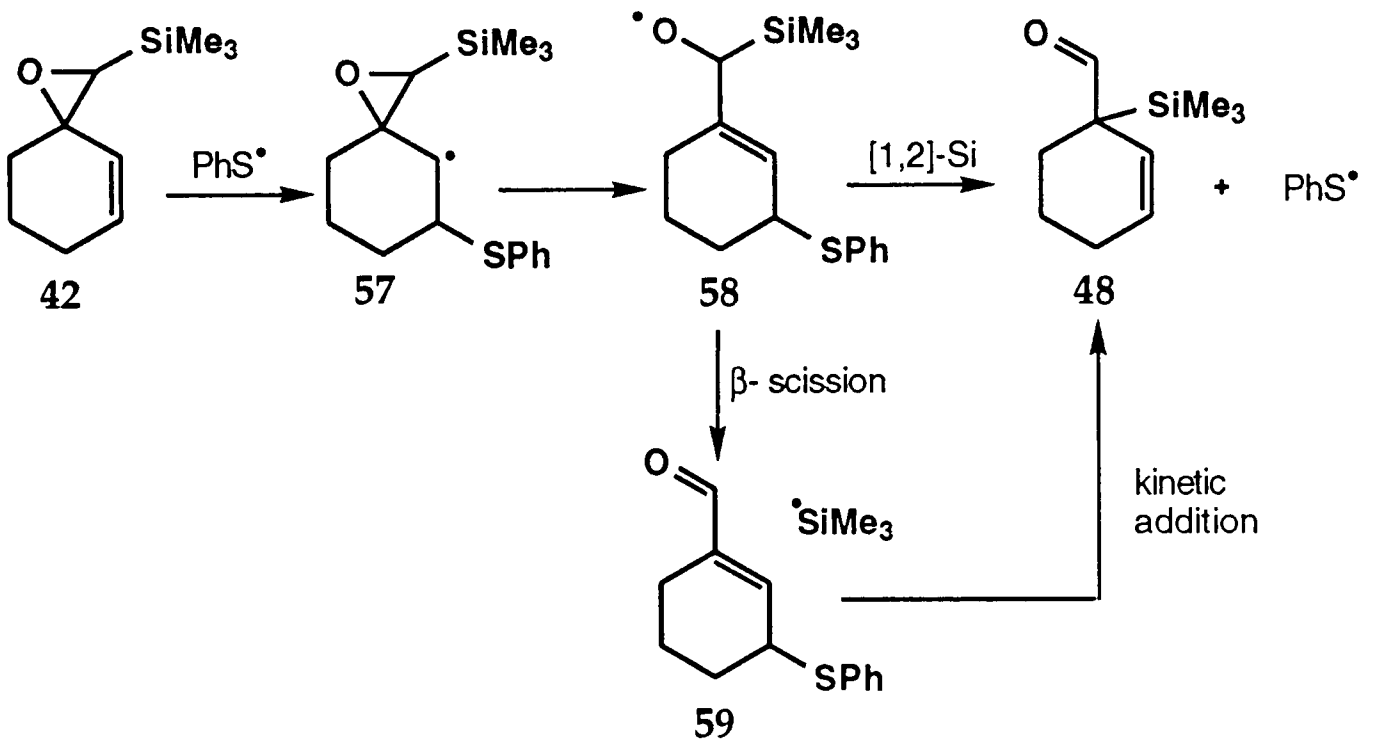
To clarify the nature of the isomerisation a number of test reactions were performed on the epoxysilane **42**. ^{1}H NMR spectra associated with this study are collected in Appendix B.

- Addition of tributyltin hydride and AIBN led to the expected rearrangement but the reaction was not as clean. Additionally a mixture of diphenyldisulphide and AIBN in benzene at reflux was found to induce isomerisation in an identical fashion to the conditions used earlier (**2.2.1.**).
- Isomerisation did not occur at RT without additives however the reaction did proceed slowly at RT with thiophenol alone (0.1 eq.) but was accelerated by a factor of at least five on addition of AIBN (0.1 eq.).

- Isomerisation did not occur using NaSPh (0.1 eq., benzene, RT).

These findings, in conjunction with the implied rate determining addition of a catalytic initiating species were only consistent with a homolytic process.

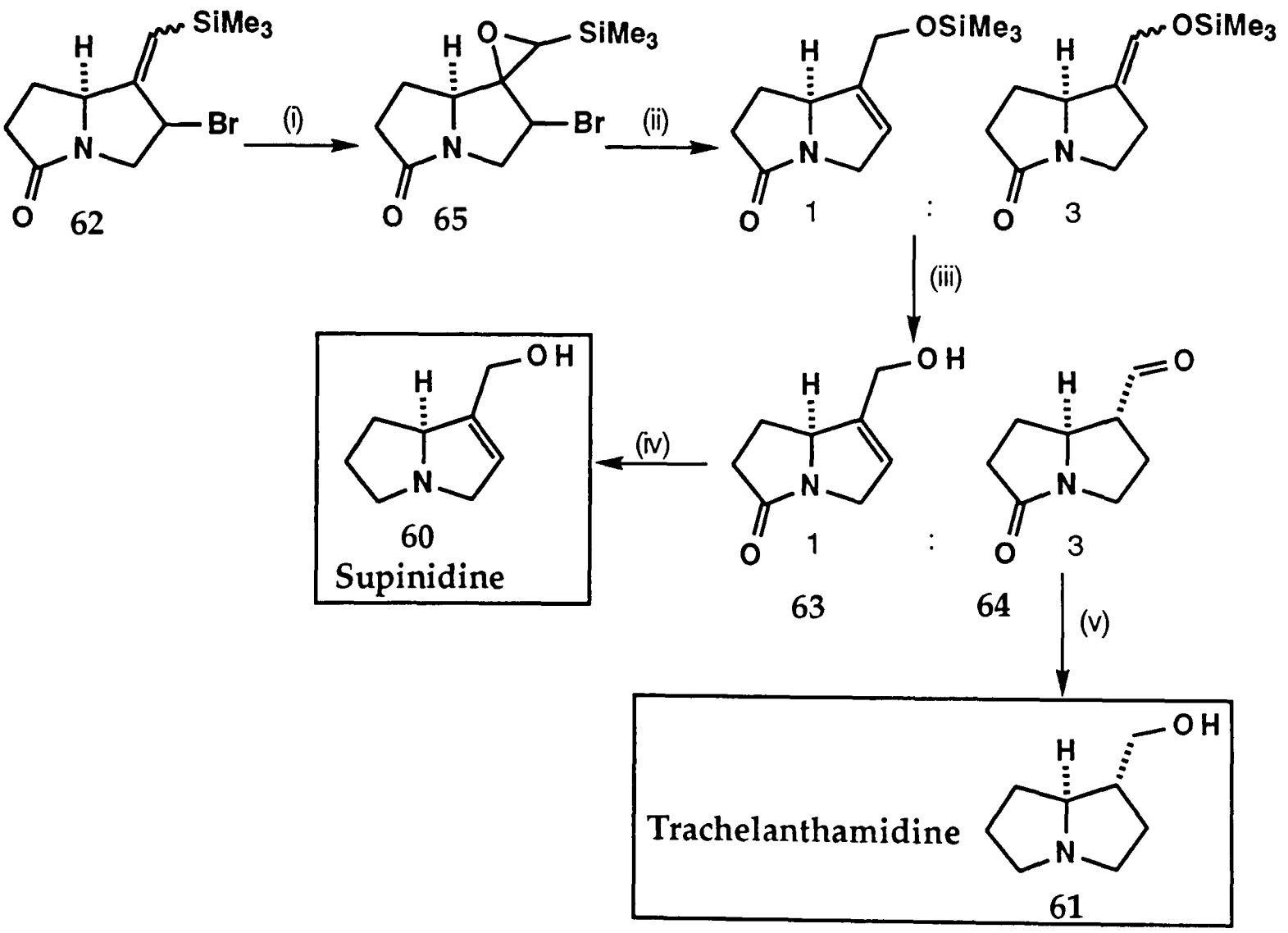
A plausible mechanism that leads by way of the desired homolytic C-O bond cleavage of **57**, to intermediate **58** is shown in Scheme 44. It was hoped that this α-siloxy radical would undergo a homolytic Brook rearrangement, but instead either a concerted 1,2-shift of the silyl group or a stepwise process involving the ejection of the silyl radical[74] must be operating.



Scheme 44

The concerted pathway seems less likely in light of the fact that authentic homolytic 1,2-shifts are scarce.[75] The case for the alternative is strengthened by knowledge that silyl radicals kinetically add to the alkene function of α, β-unsaturated carbonyls.[76] Attack by the silyl radical at the β-position of the enone **59** might be preferred on steric and electronic grounds, but is likely to be reversible; only addition at the α-position with subsequent ejection of the thiyl radical can lead to a chain process. It is suggested that the overall process is thermodynamically driven by formation of the carbonyl.

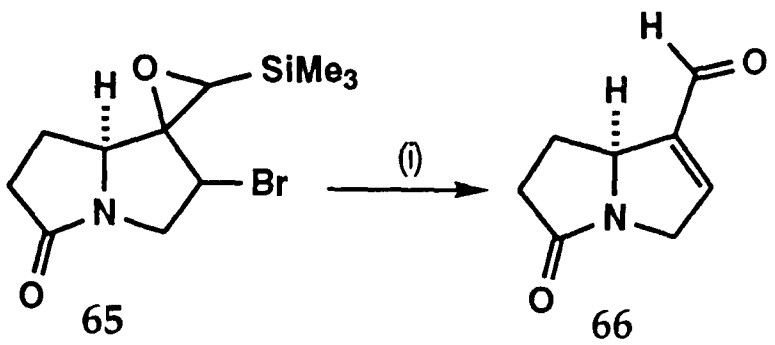
2.4.4. In response to the publication of these findings[66] we were delighted to receive a letter from Tsai expressing great interest in our work. He brought to our attention a recent study of his that had dwelt on a similar concept, but which had generated rather different results.[16] Tsai was working on a synthesis of Supinidine **60** and Trachelanthamidine **61**, and suggested that the vital transformation of α-bromo-vinylsilane[77] **62** to the Supinidine and Trachelanthamidine precursors **63** and **64** could be achieved *via* homolytic cleavage of epoxysilane **65** followed by subsequent radical Brook rearrangement. This efficient and elegant process was shown to operate (Scheme 45).



Conditions: (i) *m*CPBA, DCM, 60°C, 18h; 62%. (ii) $^{n}Bu_3SnH$ (1.5 eq.), AIBN (0.1 eq.), PhH, Δ, 4h. (iii) TBAF (3 eq.), THF; 66% from **65**. (iv) $LiAlH_4$, THF, 60°C, 15h.[16]

Scheme 45

In addition to these results Tsai also reported[16] a modification of the above radical reaction, which he hoped would increase the selectivity of formation of the Supinidine precursor **63**. However, treatment of epoxysilane **65** with tributyltin hydride and triethylborane at low temperature, gave the α,β-unsaturated aldehyde **66** (Scheme 46).

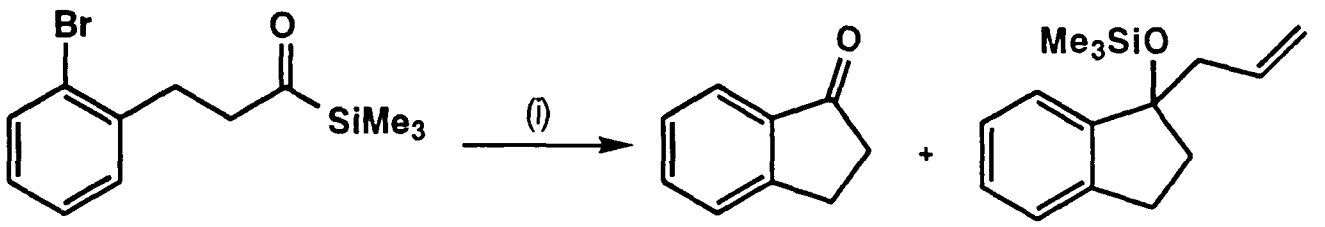


65 66

Conditions: (i) $^{n}Bu_3SnH$ (1.5 eq.), Et_3B (0.8 eq.), O_2, PhMe, 0°C, 4h; 70%.[16]

Scheme 46

In work on acylsilane systems, Tsai also had some intriguing results[78] leading to the formation of carbonyl compounds. For instance cyclisation of the aryl radical formed from bromide **67** led to the indanone **68** as a major product (Scheme 47).

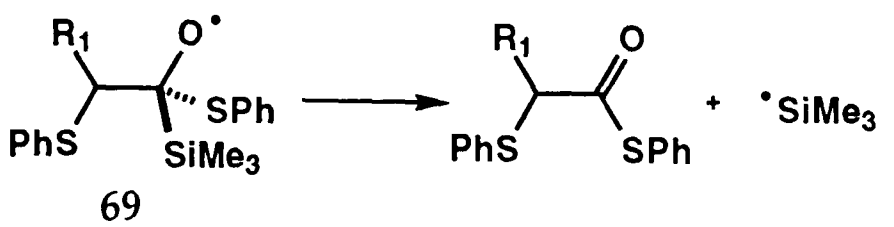


67 68

Conditions: (i) Allyl tributylstannane (2 eq.), AIBN (0.1 eq.), PhH, Δ.[78]

Scheme 47

A further example[79] of an α-siloxyradical **69** fragmentation is given in Scheme 48 in which the silyl radical is ejected even though the C-Si bond (76 kcal/mol) is stronger than the C-S bond (57 kcal/mol).



69

Scheme 48

2.4.5. These observations and our findings provide an insight into the complex chemistry associated with the homolytic cleavage of epoxysilanes and mechanism of the radical Brook rearrangement. In the work on epoxysilanes, a significant difference between the substrates that we and Tsai worked with lay in the method used for α-radical formation. Tsai proposed that an answer to the observed discrepancies lay in the difference between halogen abstraction and radical addition. Indeed when commenting on why he observed fragmentation in Scheme 47 rather than rearrangement, he wrote:

> "We attribute the easiness of fragmentation in this system [Scheme 47] to the conjugative stabilization of the resulting aryl ketone. This result is in accord with your finding."[78]

In response to our alternative explanation, that the mechanism of the radical Brook rearrangement could actually *always* follow an elimination, addition pathway, he wrote:

> "..., it may be true that fragmentation always occurs in the Brook rearrangement. However, if the silyl radical has the chance to escape out of the solvent cage, I think it has a very high probability to be trapped by tin hydride. This would leave behind the carbonyl part. In fact, in the cyclisation of $Br(CH)_4COSiMe_3$, we have checked by GC without seeing the presence of cyclopetanone (*sic.*). When we used allyl stannane instead of tributyltin hydride, we did not observe the formation of cyclopentanone either. Thus, we tend to believe that without conjugation effect, as I mentioned to you earlier, it is difficult to kick out the TMS radical. As for the radical Brook rearrangement, we tend to propose a pentacoordinated silicon intermediate. However, it would be difficult to deny the possibility of the formation of silyl radical within the solvent cage followed by a very fast readdition of silyl radical to the carbonyl oxygen in the cage."[80]

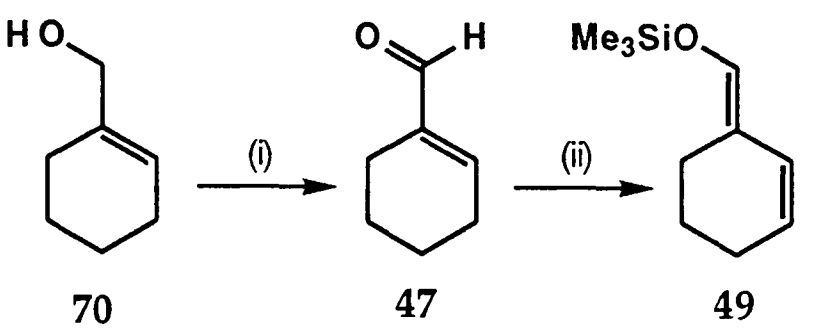
Nevertheless a model fitting both the radical Brook and our rearrangement that is in agreement with all the experimental findings to date

could involve ejection of a silyl radical and its re-addition, within the solvent cage, to the kinetic site of the enone.

2.5. Silyl-dienolether Formation

2.5.1. Isomerisation of Cyclohexene-Epoxysilane 42

To confirm the structure of the known silyl enolether[71] **49**, we prepared it *via* a different route, in order to compare spectra. The thermodynamic product **49** from silylation of aldehyde[69] **47**, formed by oxidation[81] of alcohol **70**, was performed as shown in Scheme 49.



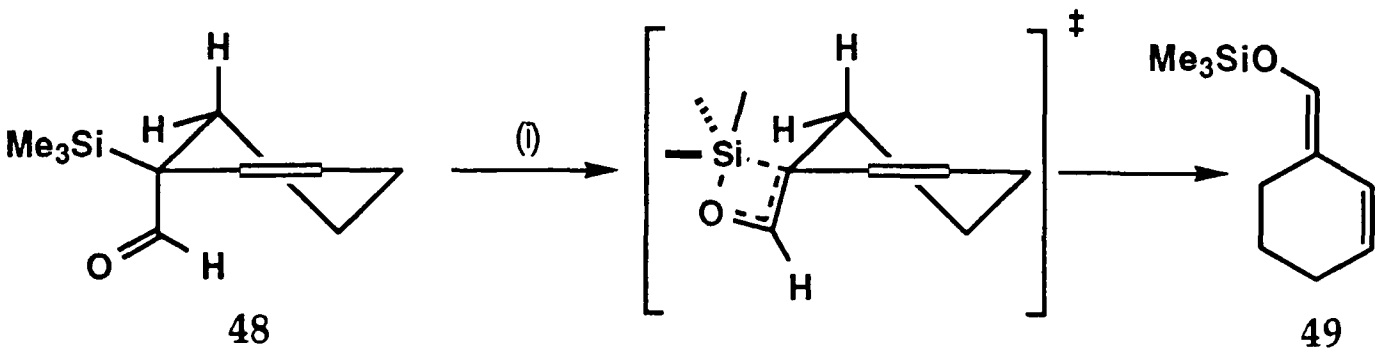
70 **47** **49**

Conditions: (i) PDC, 4Å Mol.S., DCM, 3h; 90%.[69]

(ii) TMSCl, Et_3N, PhH, $ZnCl_2$, 40°C, 15h; 50%.[71]

Scheme 49

The thermodynamic *E*-silyl dienol ether **49** was shown to be identical to the product derived from thermal isomerisation of the silylaldehyde **48**. This result is consistent with a four co-ordinate transition state[8,70] (Scheme 50).



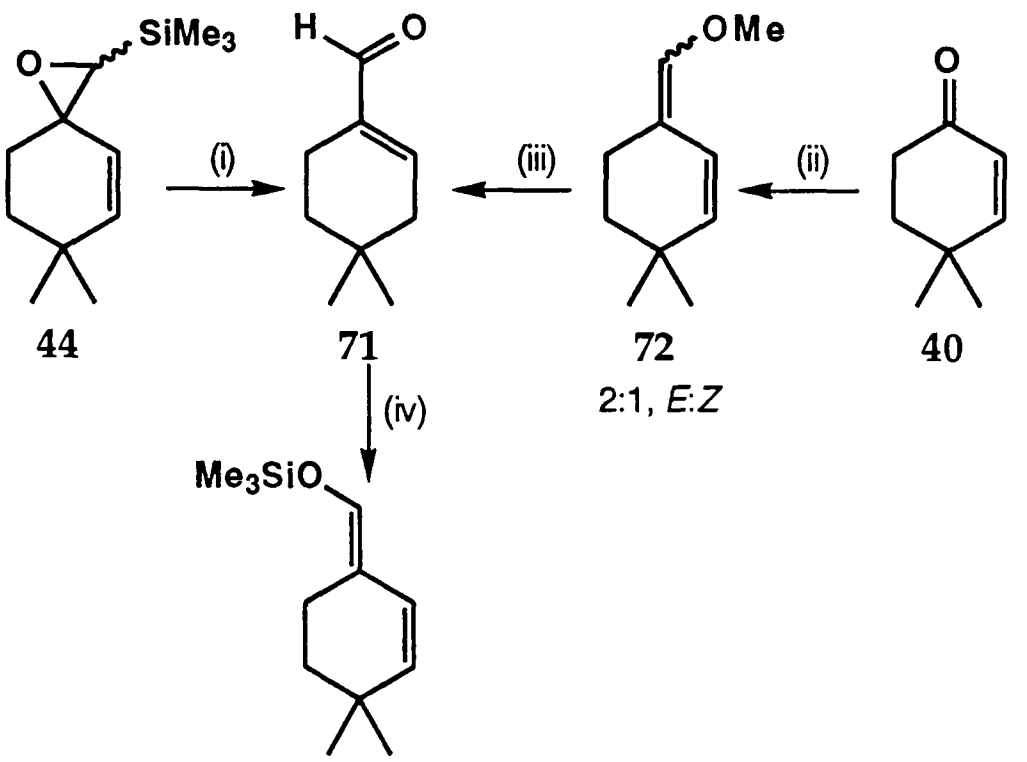
48 **49**

Conditions: (i) Δ, 24h.

Scheme 50

2.5.2. Isomerisation of Epoxysilane 44

The dimethyl silyl enol-ether **56** was also synthesised for comparison purposes. Aldehyde[82] **71** was generated either by hydrolysis[53] of epoxysilane **44** or through a Lewis-acid mediated Wittig reaction-hydrolysis procedure on 4,4-dimethyl-cyclohexenone **40** (Scheme 51).

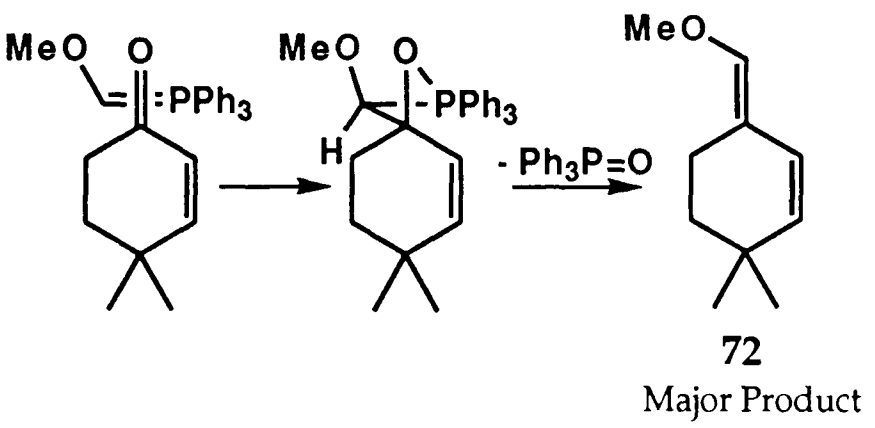


56

Conditions: (i) 10% aq. H_2SO_4, THF, RT, 15h; 40%.[53,82] (ii) $[Ph_3PCH_2OMe]^+Cl^-$, ^nBuLi, THF, $ZnBr_2$, 0°C; 19%. (iii) aq. H_2SO_4, THF, RT, 24h; 74%.[82] (iv) TMSCl, Et_3N, DMF, 40°C, 15h; 61%.

Scheme 51

The Lewis-acid induced Wittig reaction gave a majority of the *E*-isomer (Scheme 52) which might arise by a kinetic approach of the ylid prior to [2+2] cycloaddition.



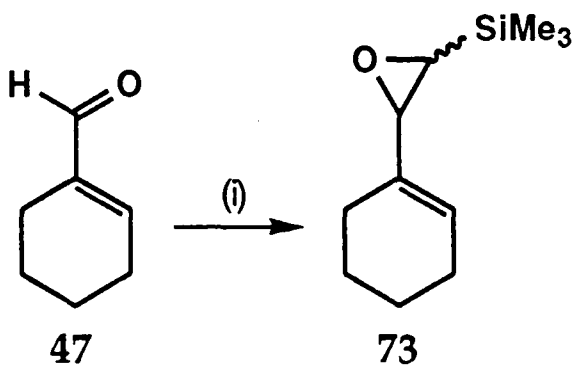
Scheme 52

Again the thermodynamic *E*-isomer of the silyl dienolether **56** proved to be identical to the major product formed from the thermal isomerisation of α-silylaldehyde **55**. This was also in agreement with a concerted mechanism involving a four co-ordinate transition state. This reaction was observed to be cleaner, although again due to the inability to purify the product, a precise yield could not be reported. The slightly shorter time required for isomerisation could reflect the increased desire for release in steric strain across the cyclohexenyl ring between one methyl group and the trimethylsilyl moiety.

2.6. Scope of the Isomerisation

It was decided to synthesise several other substrates for the radical isomerisation to observe whether the rearrangement was a general process.

2.6.1. Accordingly the more conformationally mobile epoxysilane **73** was prepared as a mixture (4:1) of diastereomers (Scheme 53).



47 **73**

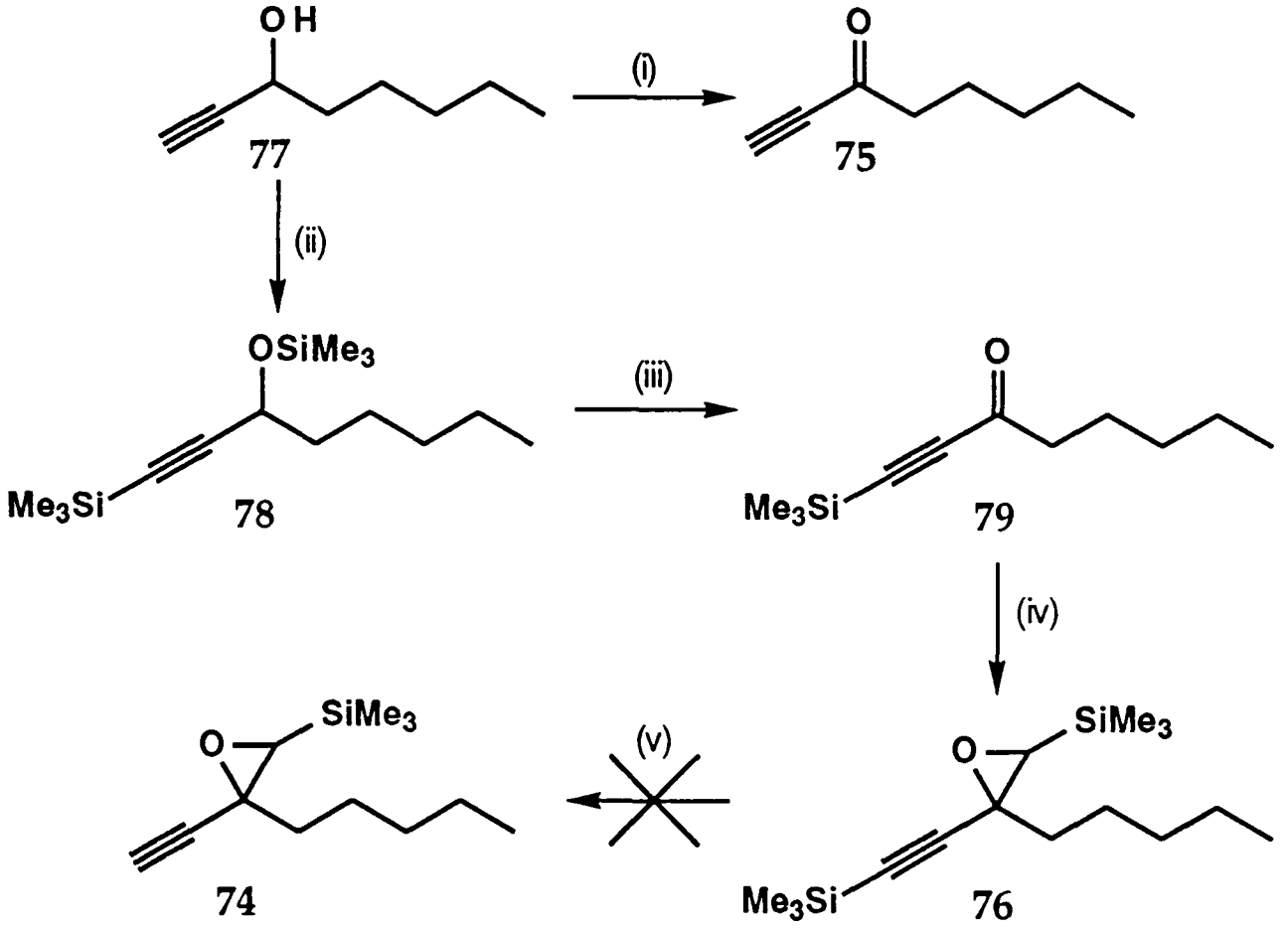
Conditions: (i) Me_3SiCH_2Cl, *sec*-BuLi, TMEDA, THF, -78°C to RT, 2h; 63%.

Scheme 53

Treating epoxysilane **73** to the radical conditions used previously to instigate isomerisation resulted only in recovered starting material. This was found to be the case even on increasing the temperature to 120°C. We have no explanation for this complete lack of reactivity.

2.6.2. An Alkynyl Substrate

The alkynyl epoxysilane **74** (Scheme 54) could not be formed directly from octynone[83] **75** and protection of the alkyne was necessary to form the substrate. However, since subsequent deprotection of the alkynyl trimethylsilyl group[84] could not be achieved without destruction of the epoxysilane, the isomerisation of the silylated alkynyl epoxysilane **76** (4:3 mixture of diastereomers) itself was investigated.



Conditions: (i) Jones' reagent, H_2O, 10°C to RT, 15h; 91%. (ii) ^{n}BuLi, TMSCl, THF, -78°C to RT, 1h; 77%. (iii) Jones' reagent, H_2O, 10°C to RT, 15h; 66%. [85] (iv) Me_3SiCH_2Cl, *sec*-BuLi, TMEDA, THF, -78°C to RT, 2h; 59%. (v) TBAF; $AgNO_3$, KCN; MeLi.[84]

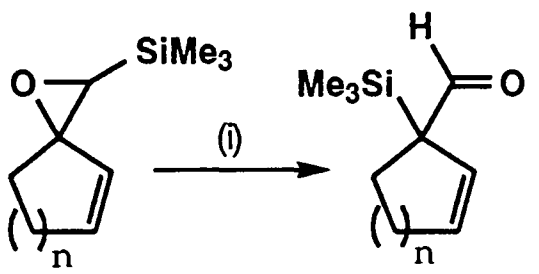
Scheme 54

Reaction of epoxysilane **76** with the thiophenol, AIBN mix previously used resulted in complete recovery of starting material. Steric hindrance around the β-position of the alkene probably precludes desired thiyl radical addition.

Because of these unfavourable results further investigations in this area were ceased.

2.7. Future Work

2.7.1. Research in this area has revealed a wealth of potential chemistry to explore more deeply. It would be interesting to observe whether this rearrangement occurred on alkenyl epoxysilanes of different ring sizes, Scheme 55.

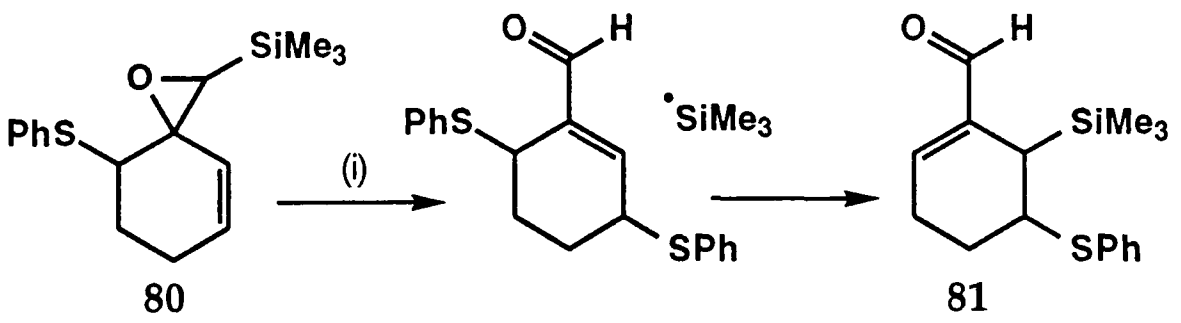


n=1, 3, 4 for example

Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ.

Scheme 55

2.7.2. It would be of value to investigate a substrate which might allow confirmation of the proposal that the rearrangement occurs *via* ejection and re-addition of a silyl radical (Scheme 56). A substrate such as **80** would give enable the possibility of forming a β-silyl-aldehyde[86] **81** to support the mechanism.

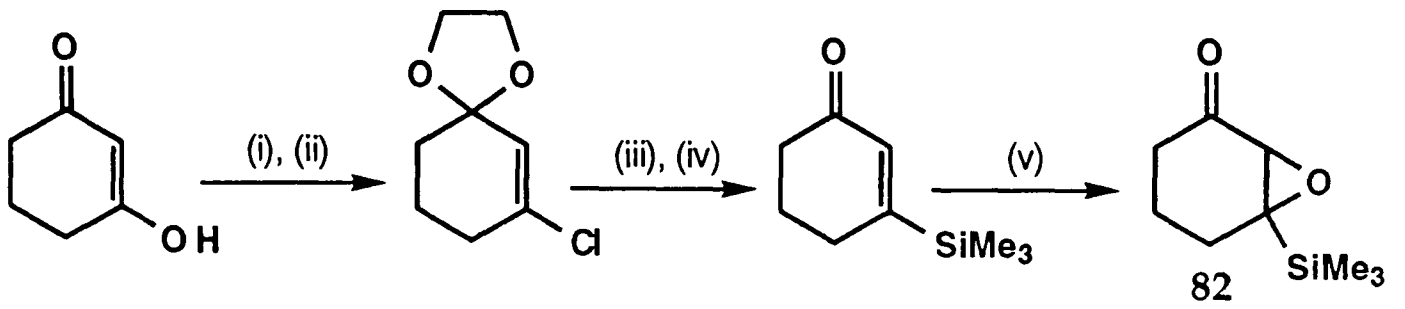


Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ.

Scheme 56

2.7.3. Rawal,[38] Kim[37] and Shimizu[43] have all demonstrated the feasibility of homolytic C-O homolytic bond cleavage in keto epoxides. It would thus be fascinating to investigate whether the Brook or our rearrangement occurred in an analogous keto-epoxysilane. A substrate such as **82** would need to be

synthesised as shown in Scheme 57 and treated with a catalytic quantity of tributyltin hydride and AIBN.

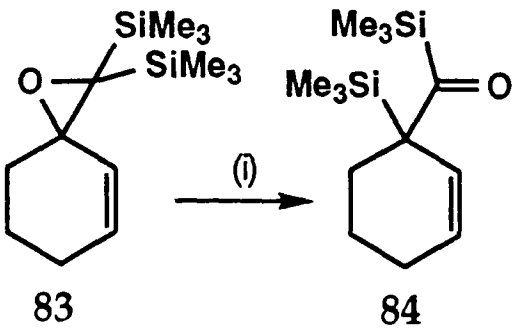


Conditions: (i) $(COCl)_2$, DMF. (ii) Ethanediol, H^+.
(iii) ^nBuLi, TMSCl. (iv) aq. H^+. (v) NaOH, H_2O_2.

Scheme 57

2.7.4. It would be interesting to examine *irreversible* addition of a radical to the β-position of the alkenyl epoxysilanes studied in this project in order to generate a system analogous to that studied by Tsai. Under such circumstances it would be expected for the radical Brook rearrangement to occur.

2.7.5. Hodgson's synthesis of disilylepoxides[87] would allow the synthesis of substrate **83** that on rearrangement might lead to unusually functionalised acyl silanes **84** (Scheme 58).

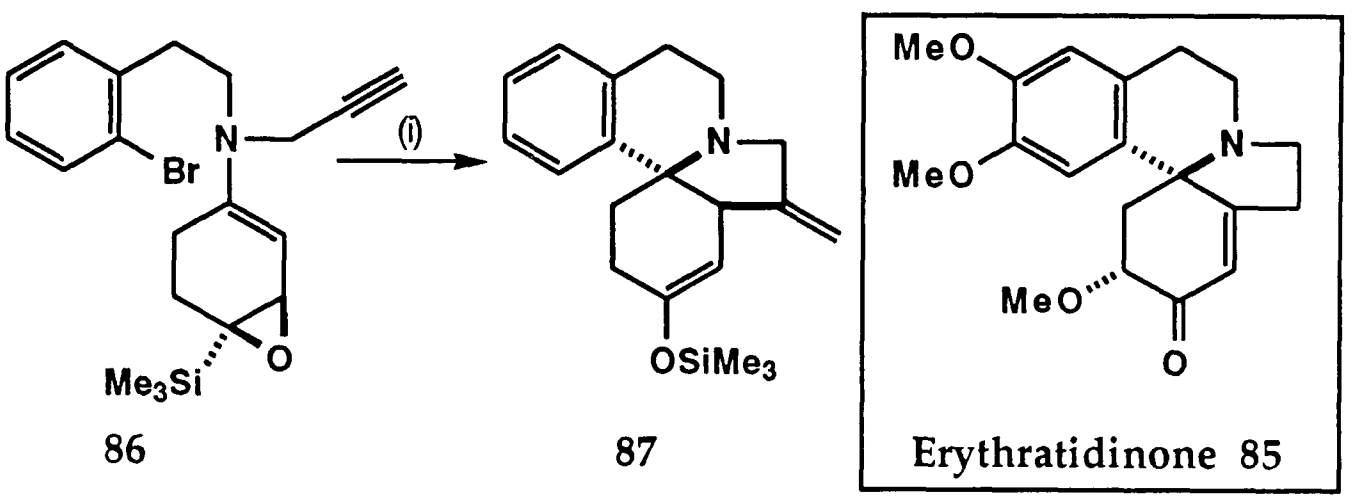


Conditions: (i) 0.1 eq. PhSH, 0.1 eq. AIBN, PhH, Δ.

Scheme 58

2.7.6. It would be interesting to note the effect of changing the groups attached to silicon. For instance *tris*(trimethylsilyl)epoxysilanes would be expected to fragment with greater ease.

2.7.7. Application of the methodology in a synthesis would be the ultimate goal. A system that lends itself for exploration is the compound Erythratidinone[88] **85**, an *Erythrina* alkaloid.[88] At the time of proposing this approach[89] there were no precedents for the specific synthetic scheme, however, examination of the area now would suggest that the following sequence (Scheme 59) *via* tandem radical cyclisation-rearrangement of **86** would be possible to give the related tetracycle **87** rather efficiently.



Conditions: (i) $^{n}Bu_3SnH$, AIBN, PhH, Δ.

Scheme 59

2.7.7. Chemistry of the Allyl-α-Trimethylsilyl Aldehydes

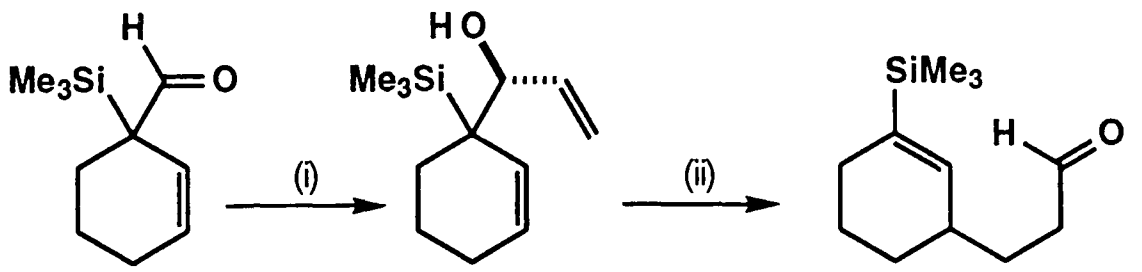
In addition to the work on the use, limitations and mechanism of the radical Brook and our rearrangements, there is a vast amount of chemistry that could be explored on the isomerisation products themselves. They are intriguing ambiphilic compounds being both allylsilanes and α-silylaldehydes thus bringing together two useful synthetic silyl-functional groups.

2.7.7.1. Allylsilanes are outstandingly useful in organic synthesis reacting as carbon nucleophiles with a wide variety of electrophiles in a highly regio- and stereoselective manner.[1a,1b,90] Trapping of the β-hydroxysilanes formed *in situ* from organometallic addition to the α-trimethylsilyl aldehydes with a silyl

protecting group would give rapid access to such allylsilanes. It would then be possible to explore their C-C bond forming chemistry.

2.7.7.2. Enders and co-workers[90c] have shown that α-silylaldehydes are valuable precursors to allylsilanes through Wittig olefination. This methodology applied to the isomerisation products would give rise to a doubly allylic silicon species; the chemistry of such a compound could then be further investigated.

2.7.7.3. α-Silylaldehydes are extremely valuable vinyl cation sources[56] and thus the isomerisation products give the potential for selective formation of a wide variety of dienes dependent purely on the organometallic species added. Addition of vinylmagnesium bromide to the allyl-α-trimethylsilylaldehyde would generate a 1,5-diene **88** which could feasibly undergo a [3,3]-sigmatropic shift to give a vinylsilane **89**, Scheme 60.



48 88 89

Conditions: (i) Vinylmagnesium bromide, THF. (ii) Δ.

Scheme 60

Conclusion

We have demonstrated an unprecedented free-radical isomerisation of alkenyl epoxysilanes to hitherto unknown allyl-α-trimethylsilylaldehydes. This work not only provides a fascinating route towards a wide variety of functional groups in a highly selective manner but also sheds important light on the mechanism of the related homolytic Brook rearrangement.

EXPERIMENTAL

3.1. General Experimental

Boiling points (b.p.) were measured using a Kugelrohr distillation unit. 'High vacuum' refers to the pressure obtained on using a Lexbold Vacuum-pump and lies within the range 0.5mbar to 2mbar.

Proton (^{1}H) NMR spectra were run on either a Varian Gemini 200 (200MHz), a Bruker AC 200 (200MHz) or a Bruker AM 500 (500MHz) spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm) downfield of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shift and coupling data.[91] Abbreviations used in the descriptions of multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J) are quoted to the nearest 0.5Hz (200MHz spectrometers) and 0.1Hz (500MHz spectrometers).

Carbon-13 (^{13}C) NMR spectra were recorded on either a Varian Gemini 200 (50.3MHz), a Bruker AC 200 (50.3MHz) or a Bruker AM 500 (125MHz) spectrometer. Chemical shifts (δ_C) are quoted in parts per million (ppm) downfield of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shift using the DEPT sequence, where appropriate, and by comparison with data from similar structures.

Infrared spectra were recorded on either a Perkin-Elmer 1750 or a Perkin-Elmer Paragon 1000 Fourier transform spectrometer, absorption maxima ($\nu_{max.}$) being recorded in wavenumbers (cm^{-1}) and classified as strong (s), medium (m), weak (w), broad (br) or a shoulder (sh).

Mass spectra were recorded on VG Micromass ZAB 1F and Masslab 20-250 spectrometers using direct chemical ionisation (C.I., NH_3). GC mass

spectra (GCMS) were recorded by the author on a VG TRIO-1 (DB-5 column) system under chemical ionisation (C.I., NH_3) conditions. *m/z* values are reported in Daltons and are followed by their percentage abundancies in parentheses; only peaks with a signal greater than 10% are reported. High resolution mass spectra (HRMS) were recorded at the EPSRC Mass Spectrometry Service Centre at the University of Swansea and are calculated from the molecular formula corresponding to the observed signal using the most abundant isotopes of each element, to 4 decimal places.

Thin layer chromatography (t.l.c.) was performed on Merck DC-Alufolien Kieselgel $60F_{254}$ 0.2mm precoated plates. Product spots were visualised by the quenching of u.v. fluorescence ($\lambda_{max.}$=254nm) then stained and heated with 5% (w/v) *dodeca*-molybdophosphoric acid in ethanol. Where retention factors (R_f) are reported, the solvent system used follows in parentheses. Only in cases where the product formed a streak on t.l.c. or where a product spot could not be obtained under a variety of staining solutions is an R_f not quoted.

Flash column chromatography was performed by the method of Still *et al.*[92] on silica gel (Sorbsil C60 40/60 or Merck silica gel 60 (230-400 mesh ASTM)). The solvent system used follows in parentheses.

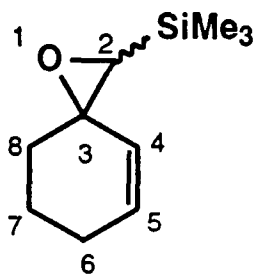
Solvents and commercially available reagents were dried and purified before use, where appropriate, using standard procedures; DCM, TMEDA, benzene, triethylamine and toluene were heated at reflux over and distilled from calcium hydride; DMF was obtained by reduced pressure distillation from calcium hydride. THF was obtained dry and oxygen-free by distillation from sodium benzophenone ketyl under nitrogen.[93] 'Petrol' refers to that fraction of light petroleum ether boiling in the range 30-40°C, and was distilled before use to remove involatile impurities.

Jones' reagent[94] was prepared according to the literature procedure. $ZnCl_2$ and $ZnBr_2$ were heated on a Kugelrohr apparatus (150°C, high vacuum) for 1h before use.

All non-aqueous experiments were carried out under an Ar or N_2 atmosphere unless specified and in each experimental procedure the work was performed at RT unless reported otherwise.

3.2. Main Experimental

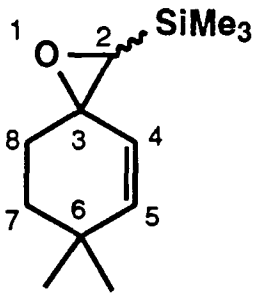
1-Oxa-2-trimethylsilylspiro[2,5]oct-4-ene 42[51a]



The procedure described by Magnus *et al.*,[51a] was repeated using chloromethyltrimethylsilane (2.1ml, 15.0mmol), THF (20ml), *sec*-butyllithium (12.1ml, 1.3M in hexanes, 15.8mmol), TMEDA (2.4ml, 15.8mmol) and 2-cyclohexen-1-one **39** (0.80ml, 8.25mmol) to give the title compounds **42**. Distillation on a Kugelrohr apparatus (RT, high vacuum) gave the epoxysilanes **42** (0.93g, 71%) as an inseparable mixture of colourless oils (ratio 3:1). R_f (1:1, petrol:ether) 0.80; $\nu_{max.}$ (thin film) 2928 (s), 1710 (m), 1456 (w), 1410 (w), 1250 (s), 900 (m), 883 (m), 841 (s) cm^{-1}; major isomer, δ_H (500MHz, C_6D_6) 0.06 (9H, s, $Si(CH_3)_3$), 1.52-1.59 (2H, m), 1.64-1.88 (4H, m), 2.13 (1H, s, **H**(2)), 5.31 (1H, dt, *J* 6.0, 2.0, **H**(4)), 5.81-5.87 (1H, m, **H**(5)); δ_C (125MHz, C_6D_6) -1.8 ($Si(CH_3)_3$), 21.8, 24.9, 30.4 ($3xCH_2$), 58.9 (**C**(2)), 59.7 (**C**(3)), 133.0, 133.0 (**C**(4), **C**(5)); minor isomer, δ_H (500MHz, C_6D_6) 0.08 (9H, s, $Si(CH_3)_3$), 1.52-1.59 (2H, m), 1.64-1.88 (4H, m), 2.15 (1H, s, **H**(2)), 5.48 (1H, dt, *J* 6.0, 2.1, **H**(4)), 5.81-5.87 (1H, m, **H**(5)); δ_C (125MHz, C_6D_6) -1.8 ($Si(CH_3)_3$), 22.1, 25.2, 34.0 ($3xCH_2$), 59.8 (**C**(2)), 59.0

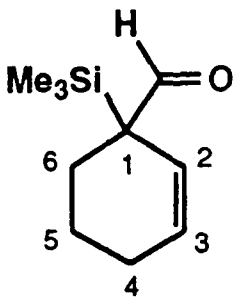
(**C**(3)), 129.5, 134.0 (**C**(4), **C**(5)); *m/z* (C.I., NH_3) 184 (M(^{29}Si)H$^+$, 12), 183 (M(^{28}Si)H$^+$, 100), 90 (14%).

6,6-Dimethyl-1-oxa-2-trimethylsilylspiro[2,5]oct-4-ene 44



Magnus' procedure[51a] was repeated using chloromethyltrimethylsilane (0.70ml, 5.00mmol), THF (8ml), *sec*-butyllithium (4.0ml, 1.3M in hexanes, 5.25mmol), TMEDA (0.79ml, 5.25mmol) and 4,4-dimethyl-2-cyclohexen-1-one **40** (0.35ml, 2.50mmol) to give the title compounds **44**. Distillation on a Kugelrohr apparatus (75°C, high vacuum) gave the dimethylepoxysilanes **44** (0.42g, 80%) as an inseparable mixture (ratio 3:1) of colourless oils. $\nu_{max.}$ (thin film) 2957 (s), 1454 (m), 1412 (w), 1379 (m), 1361 (m), 1250 (s), 1027 (w), 921 (m), 841 (s), 778 (m) cm^{-1}; major isomer, δ_H (500MHz, C_6D_6) 0.06 (9H, s, Si(C**H**$_3$)$_3$), 0.90 (3H, s, C**H**$_3$), 0.92 (3H, s, C**H**$_3$), 1.47-1.65 (2H, m), 1.76-1.83 (2H, m), 2.14 (1H, s, **H**(2)), 5.19 (1H, d, *J* 10.0, **H**(4)), 5.61 (1H, d, *J* 10.0, **H**(5)); δ_C (125MHz, C_6D_6) -1.8 (Si(**C**H$_3$)$_3$), 27.1, 36.0 (2x**C**H$_2$), 28.5, 29.2 (2x**C**H$_3$), 31.2 (**C**(6)), 58.5 (**C**(2)), 59.1 (**C**(3)), 128.3, 144.0 (**C**(4), **C**(5)); minor isomer, δ_H (500MHz, C_6D_6) 0.07 (9H, s, Si(C**H**$_3$)$_3$), 0.89 (3H, s, C**H**$_3$), 0.91 (3H, s, C**H**$_3$), 1.47-1.65 (2H, m), 1.76-1.83 (2H, m), 2.17 (1H, s, **H**(2)), 5.36 (1H, d, *J* 10.0, **H**(4)), 5.59 (1H, d, *J* 10.0, **H**(5)); δ_C (125MHz, C_6D_6) -1.9 (Si(**C**H$_3$)$_3$), 28.9, 29.0 (**C**H$_3$), 31.6, 36.3 (2x**C**H$_2$), 32.0 (**C**(6)), 59.5 (**C**(2)), 59.9 (**C**(3)), 130.1, 143.3 (**C**(4), **C**(5)); *m/z* (C.I., NH_3) 212 (M(^{29}Si)H$^+$, 12), 211 (M(^{28}Si)H$^+$, 100), 195 (18), 90 (22%).

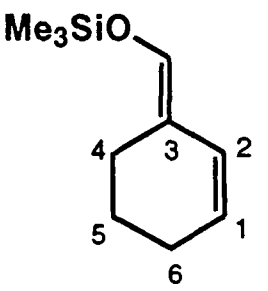
1-Trimethylsilylcyclohex-2-ene-1-carboxaldehyde 48



To a solution of the epoxysilane **42** (40mg, 0.22mmol) and AIBN (4mg, 0.02mmol) in degassed benzene (2ml) was added PhSH (3μl, 0.02mmol) and the solution either stirred for 15h at RT or heated at reflux for 1h. The solvent was removed *in vacuo* to afford the trimethylsilylaldehyde **48** (60% by ^{1}H NMR) as a yellow oil. $\nu_{max.}$ (thin film) 2954 (s), 2933 (s), 2702 (w), 1697 (s), 1640 (w), 1440 (m), 1252 (s), 1163 (w), 1129 (w), 944 (m), 900 (m), 843 (s) cm^{-1}; δ_H (200MHz, C_6D_6) -0.14 (9H, s, Si(C**H**$_3$)$_3$), 1.10-1.25 (2H, m), 1.55-1.75 (3H, m), 2.30-2.45 (1H, m), 5.60-5.69 (1H, m, **H**(3)), 5.73-5.79 (1H, m, **H**(2)), 9.46 (1H, s, C**H**O); δ_C (50.3MHz, C_6D_6) -4.7 (Si(**C**H$_3$)$_3$), 20.4, 23.9, 24.6 (3x**C**H$_2$), 51.4 (**C**(1)), 124.0, 128.3 (**C**(2), **C**(3)), 200.3 (**C**HO); *m/z* (C.I., NH_3) 184 (M(^{29}Si)H$^+$, 11), 183 (M(^{28}Si)H$^+$, 100%).

(*E*)-3(Trimethylsilyloxymethylene)cyclohexene 49[71]

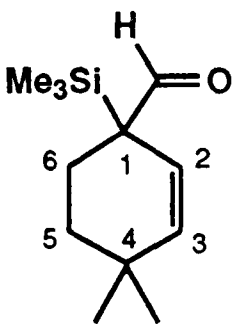
Method 1



A stirred solution of the trimethylsilyl-aldehyde **48** (40mg, 0.21mmol) in degassed benzene (2ml) was heated at reflux. After 24h the solvent was removed *in vacuo* to give the title compound **49** as an oil. R_f (1:1, petrol:ether) 0.70 (uv active); $\nu_{max.}$ (thin film) 1643 (s), 1609 (m) cm^{-1}; δ_H (200MHz, C_6D_6) 0.10 (9H, s, Si(C**H**$_3$)$_3$), 1.54-1.64 (2H, m), 1.93-1.99 (2H, m), 2.48-2.56 (2H, m),

5.55-5.60 (1H, dt, *J* 10.0, 6.0, **H**(1)), 6.07 (1H, dt, *J* 10.0, 2.0, **H**(2)), 6.22 (1H, br s, **H**COSi); *m/z* (C.I., NH_3) 184 ($M(^{29}Si)H^+$, 10), 183 ($M(^{28}Si)H^+$, 100), 90 (19%).

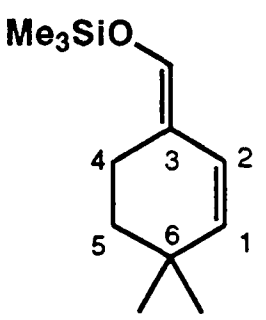
4,4-Dimethyl-1-trimethylsilylcyclohex-2-ene-1-carboxaldehyde 55



To a solution of the dimethyl-epoxysilane **44** (79mg, 0.37mmol) and AIBN (6mg, 0.03mmol) in degassed benzene (2ml) was added PhSH (4µl, 0.04mmol) and the solution stirred under argon at reflux. After 14h the solvent was removed *in vacuo* to afford the title compound **55** (55% by NMR) as an oil. $\nu_{max.}$ (thin film) 2957 (s), 2867 (m), 1690 (s), 1646 (w), 1471 (w), 1376 (w), 1251 (s), 1174 (m), 1156 (m), 1025 (m), 845 (s) cm^{-1}; δ_H (200MHz, C_6D_6) -0.15 (9H, s, $Si(CH_3)_3$), 0.79 (3H, s, CH_3), 0.81 (3H, s, CH_3), 1.10-1.60 (3H, m), 2.30 (1H, dt, *J* 13.0, 4.0, $H(6)_a$), 5.43 (1H, d, *J* 11.0, **H**(3)), 5.63 (1H, d, *J* 11.0, **H**(2)), 9.45 (1H, s, CHO); δ_C (50.3MHz, C_6D_6) -4.6 ($Si(CH_3)_3$), 20.8, 27.0 ($2xCH_2$), 27.6, 30.9 ($2xCH_3$), 32.0 (**C**(4)), 51.5 (**C**(1)), 121.5, 129.1 (**C**(2), **C**(3)), 200.6 (**C**HO); *m/z* (C.I., NH_3) 212 ($M(^{29}Si)H^+$, 11), 211 ($M(^{28}Si)H^+$, 100), 195 (12), 90 (17%).

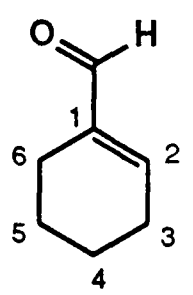
(*E*)-6,6-Dimethyl-3(trimethylsilyloxymethylene)cyclohexene 56

Method 1



A solution of the dimethyl-trimethylsilyl-aldehyde **55** (79mg, 0.37mmol) in degassed benzene (2ml) was heated at reflux. After 15h the solvent was removed *in vacuo* to afford the title compound **56** as an oil. $\nu_{max.}$ (thin film) 2962 (s), 2926 (s), 2855 (m), 1731 (w), 1645 (m), 1467 (w), 1261 (s), 1097 (s), 1024 (s), 801 (m) cm^{-1}; δ_H (200MHz, C_6D_6) 0.09 (9H, s, $Si(CH_3)_3$), 0.92 (6H, s, 2xCH_3), 1.50 (2H, t, *J* 6.0, **H**$(5)_2$), 2.60 (2H, td, *J* 6.0, 0.5, **H**$(4)_2$), 5.35 (1H, d, *J* 10.0, **H**(1)), 5.95 (1H, d, *J* 10.0, **H**(2)), 6.22 (1H, br s, **H**COSi); *m/z* (C.I., NH_3) 212 ($M(^{29}Si)H^+$, 20), 211 ($M(^{28}Si)H^+$, 100), 195 (40), 90 (20), 73 (14%).

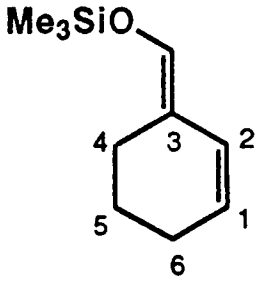
Cyclohexene-1-carboxaldehyde 47[69]



To a stirred suspension of activated molecular sieves (1g, 4Å powdered) and PDC (1.4g, 4.00mmol) in DCM (20ml) was added 1-hydroxymethylcyclohexene **70** (0.3g, 2.68mmol). After 3h the solution was concentrated to half of its original volume, ether (20ml) was added, and the solution passed through Celite®. The organic solution was washed with sat. aq. $CuSO_4$ (15ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the aldehyde **47** (0.264 g, 90%) as a yellow oil. R_f (1:1, petrol:ether) 0.55 (uv active); $\nu_{max.}$ (thin film) 1690 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.58-1.75 (4H, m), 2.10-2.22 (2H, m), 2.22-2.40 (2H, m), 6.75-6.85 (1H, m, **H**(2)), 9.37 (1H, s, C**H**O); *m/z* (C.I., NH_3) 128 (MNH_4^+, 22), 111 (MH^+, 100%).

(*E*)-3-(Trimethylsilyloxymethylene)cyclohexene 49[71]

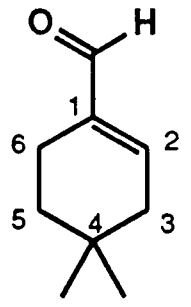
Method 2



The method of Wenkert *et al.*[71] was repeated using anhydrous $ZnCl_2$ (20mg, 0.15mmol), benzene (10ml), aldehyde **47** (0.28g, 2.50mmol), triethylamine (700µl, 5.00mmol) and chlorotrimethylsilane (0.64ml, 5.00mmol) to give the silyl enol ether **49** (0.23g, 50%) as an orange oil. This compound proved to be identical to that described above.

4,4-Dimethylcyclohexene-1-carboxaldehyde 71[82]

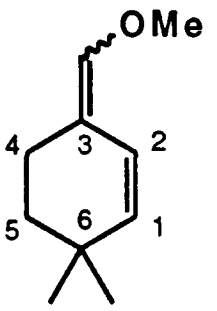
Method 1



To a stirred solution of the dimethyl-epoxysilane **44** (91mg, 0.43mmol) in THF (4ml) was added 10% aq. H_2SO_4 (500µl). After 15h the solution was diluted with 10% aq. NaOH (2ml) and extracted with ether (2x10ml). The combined organic layers were washed successively with water (10ml) and brine (10ml), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (2:1, petrol:ether) gave the title compound **71** (23mg, 40%) as a yellow, sweet-smelling oil. R_f (1:1, petrol:ether) 0.51 (uv active); $\nu_{max.}$ (thin film) 2956 (s), 2927 (s), 1685 (s), 1644 (m), 1456 (m), 1418 (w), 1395 (w), 1379 (w), 1248 (w), 1203 (w), 1156 (m), 869 (m), 840 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.11 (6H, s, 2xCH_3), 1.55-1.70 (2H, m), 2.10-2.20 (2H, m), 2.20-2.32 (2H, m), 6.70-6.80 (1H, m,

H(2)), 9.39 (1H, s, C**H**O); *m/z* (C.I., NH_3) 156 (MNH_4^+, 45), 139 (MH^+, 70), 138 (MNH_4^+-H_2O, 60), 123 (35), 109 (25), 95 (100), 81(19), 67(20), 56 (16%).

(*E*)- and (*Z*)-6,6-Dimethyl(methoxymethylene)cyclohexene 72

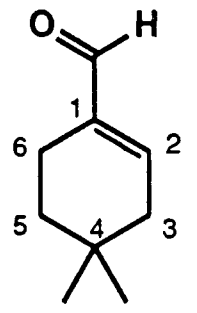


To a stirred solution of anhydrous $ZnBr_2$ (0.64g, 2.84mmol) in THF (4ml) was added 4,4-dimethyl-2-cyclohexen-1-one **40** (0.2ml, 1.40mmol). Meanwhile, to a cooled (0°C) solution of (methoxymethyl)triphenylphosphonium chloride (0.72g, 2.10mmol) in THF (8ml) was added *n*-butyllithium (1.3ml, 1.6M in hexanes, 2.10mmol) dropwise resulting in a deep red solution. After 30mins the dimethylcyclohexenone solution was added to the solution of the ylid *via* cannula, decolourising the mixture. After 14h ether (30ml) was added and the reaction mixture filtered and diluted with water (20ml). The organic portion was separated, washed successively with 1M aq. HCl (10ml) and brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (20:1, petrol:ether) to afford the methyl enol ethers **72** (40mg, 19%) as an inseparable mixture (ratio (*E*):(*Z*), 2:1) of fruity smelling oils. R_f (1:1, petrol:ether) 0.69 (uv active); $\nu_{max.}$ (thin film) 2954 (s), 2928 (s), 2863 (m), 1662 (m), 1654 (m), 1603 (w), 1452 (w), 1373 (w), 1359 (w), 1250 (w), 1240 (w), 1221 (m), 1205 (m), 1169 (w), 1134 (s), 990 (w) cm^{-1}; major isomer (*E*), δ_H (200MHz, $CDCl_3$) 1.01 (6H, s, 2xC**H**$_3$), 1.45-1.53 (2H, m), 2.39 (2H, td, *J* 7.0, 2.0, **H**(4)$_2$), 3.64 (3H, s, OC**H**$_3$), 5.34 (1H, d, *J* 9.5, **H**(1)), 5.79 (1H, s, **H**COCH$_3$), 5.81 (1H, d, *J* 9.5, **H**(2)); δ_C (50.3MHz, $CDCl_3$) 19.0 (**C**H$_2$), 29.2 (2x**C**H$_3$), 31.9 (**C**H$_2$), 36.0 (**C**(6)), 59.8 (O**C**H$_3$), 115.4 (**C**(3)), 119.4 (**C**(1)), 135.4 (**C**(2)), 144.28 (H**C**OCH$_3$); minor isomer (*Z*), δ_H (200MHz, $CDCl_3$) 1.02 (6H, s, 2xC**H**$_3$), 1.45-1.53 (2H, m), 2.19

(2H, td, *J* 6.0, 1.0, **H**(4)$_2$), 3.60 (3H, s, OC**H**$_3$), 5.46 (1H, d, *J* 10.0, **H**(1)), 5.98 (1H, s, **H**COCH$_3$), 6.36 (1H, d, *J* 10.0, **H**(2)); δ_C (50.3MHz, $CDCl_3$) 22.8 (**C**H$_2$), 29.3 (2x**C**H$_3$), 32.5 (**C**H$_2$), 37.3 (**C**(6)), 59.6 (O**C**H$_3$), 113.5 (**C**(3)), 119.4 (**C**(1)), 137.7 (**C**(2)), 141.7 (H**C**OCH$_3$); *m/z* (C.I., NH_3) 153 (MH^+, 12), 152 (MNH_4^+-H_2O, 80), 138 (MNH_4^+-MeOH, 10), 137 (100) 105 (40) 91 (20) 77 (15%); Accurate Mass: Found 153.1279, $C_{10}H_{17}O$ (MH^+) requires 153.127940.

4,4-Dimethylcyclohexene-1-carboxaldehyde 71[82]

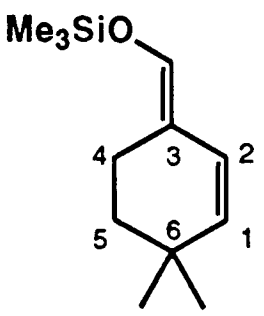
Method 2



To a vigorously stirred solution of the methoxyenol ether **72** (30mg, 0.20mmol) in 1:2, H_2O: THF (2ml) was added conc. H_2SO_4 (2 drops). After 24h the solution was diluted with 10% aq. NaOH (2ml) and extracted with ether (2x10ml). The combined organic layers were washed successively with water (10ml) and brine (10ml), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (2:1, petrol:ether) gave the title compound **71** (20mg, 74%) as a yellow, sweet-smelling oil. This compound was identical to that described above.

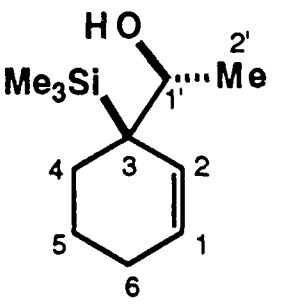
(*E*)-6,6-Dimethyl-3-(trimethylsilyloxymethylene)cyclohexene 56

Method 2



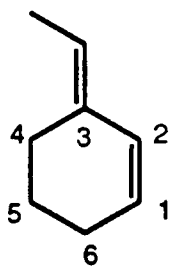
The method of Wenkert *et al.*[79] was repeated using anhydrous $ZnCl_2$ (1.2mg, 9μmol), benzene (2ml), aldehyde **71** (40mg, 0.29mmol), triethylamine (80μl, 0.58mmol) and chlorotrimethylsilane (73μl, 0.58mmol) to give the title silyl enol ether **56** (37mg, 61%) as an oil. This compound proved to be identical to that described above.

***rel*-(1'*R*, 3*R*)-3-(1'-Hydroxyethyl)-3-trimethylsilylcyclohexene 50**



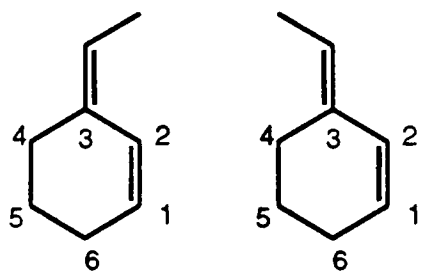
To a cooled (-78°C) solution of the crude silyl aldehyde **48** (191mg, 1.08mmol) in THF (3ml) was added dropwise methylmagnesium bromide (0.4ml, 3M solution in THF, 1.20mmol). The reaction mixture was warmed to 0°C over 1.5h, CH_3CO_2H (74μl, 1.30mmol) was added and the solution left to warm to RT. After 1.5h 1M aq. NaOH (5ml) was added and the solution extracted with ether (2x10ml). The combined organic portions were washed with water (10ml) and brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (10:1, petrol:ether) to afford the hydroxysilane **50** (128mg, 60% from **42**) as a colourless oil. R_f (1:1, petrol:ether) 0.70; $\nu_{max.}$ (thin film) 3436 (br s), 2945 (s), 2836 (m), 1455 (w), 1246 (s), 1094 (m), 838 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.05 (9H, 3xs, $Si(C\mathbf{H}_3)_3$), 1.18 (3H, d, *J* 6.5, $\mathbf{H}(2')_3$), 1.40-1.70 (4H, m), 1.70-2.00 (2H, m), 3.92 (1H, q, *J* 6.5, **H**(1')), 5.39 (1H, br d, *J* 10.5, **H**(2)), 5.73-5.80 (1H, m, **H**(1)); δ_C (50.3MHz, $CDCl_3$) -2.3 ($Si(\mathbf{C}H_3)_3$), 20.1 (**C**(2')), 20.2, 23.7, 24.6 ($3x\mathbf{C}H_2$), 35.2 (**C**(3)), 73.1 (**C**(1')), 126.8, 129.8 (**C**(1), **C**(2)); *m/z* (C.I., NH_3) 182 ($M(^{29}Si)H^+$-H_2O, 15), 181 ($M(^{28}Si)H^+$-H_2O, 100), 109 (MH^+-Me_3SiOH, 15), 90 (55%); Accurate Mass: Found 181.1413, $C_{11}H_{21}Si$ (MH^+-H_2O) requires 181.141252.

(*E*)-3-Ethylidenecyclohexene 53[73]



To a stirred solution of *n*-pentane washed sodium hydride (11mg, 60% dispersion in oil, 0.28mmol) in THF (2ml) was added hydroxy silane **50** (27mg, 0.14mmol) in THF (1ml). After 1.5h 1M aq. NaOH (1ml) was added and the reaction mixture diluted with water (10ml) and ether (10ml). The organic portion was separated, washed with brine (10ml), dried ($MgSO_4$) and concentrated to give the title diene **53** (quant. by NMR) as a volatile oil. R_f (1:1, petrol:ether) 0.80 (uv active); $\nu_{max.}$ (thin film) 2953 (s), 2924 (s), 2854 (m), 1458 (w), 1249 (w), 843 (w), 667 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.64 (3H, d, *J* 7.0, C**H**$_3$), 1.60-1.90 (4H, m), 2.10-2.20 (2H, m), 5.27 (1H, q, *J* 7.0, C**H**Me), 5.65 (1H, dt, *J* 10.0, 4.0, **H**(1)), 6.00 (1H, d, *J* 10.0, **H**(2)); *m/z* (C.I., NH_3) 109 (MH^+, 100%).

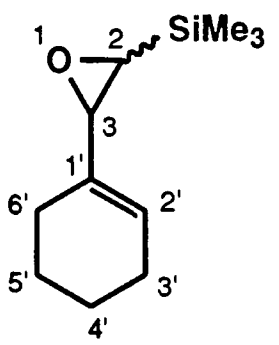
(*Z*)-3-Ethylidenecyclohexene 54 and (*E*)-3-Ethylidenecyclohexene 53[73]



To a cooled (0°C) solution of hydroxy silane **50** (50mg, 0.25mmol) in DCM (2ml) was added successively a solution of TsCl (100mg, 0.50mmol) in DCM (1ml) and pyridine (61µl, 0.76mmol). After 15h the reaction mixture was diluted with DCM (20ml), washed with 1M aq. HCl (2x10ml) and brine (10ml), dried ($MgSO_4$) and concentrated to give the title dienes **53** and **54** (quant. by NMR) as an inseparable mixture (ratio (*Z*):(*E*), 2:1) of volatile oils. *Z*-isomer: R_f (1:1,

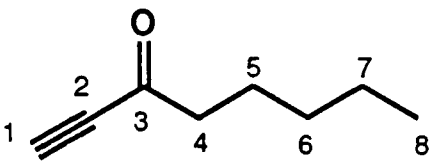
petrol:ether) 0.80 (uv active); $\nu_{max.}$ (thin film) 2930 (s), 2870 (m), 1450 (w), 1249 (w), 843 (w), 667 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.67 (3H, d, *J* 6.0, C**H**$_3$), 1.60-1.80 (2H, m), 2.10-2.35 (4H, m), 5.17 (1H, q, *J* 6.0, C**H**Me), 5.82 (1H, m, **H**(1)), 6.43 (1H, br d, *J* 10.0, **H**(2)); *m/z* (C.I., NH_3) 109 (MH^+, 100%).

3-Cyclohexen-1-yl-2-trimethylsilyloxirane 73



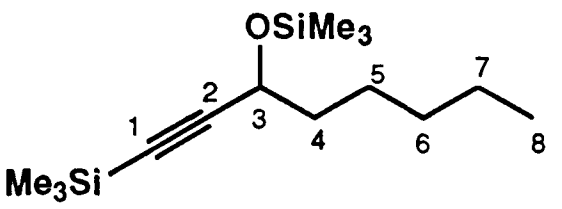
The procedure described by Magnus *et al.*,[51a] was repeated using chloromethyltrimethylsilane (700µl, 5.00mmol), THF (8ml), *sec*-butyllithium (4.0ml, 1.3M in hexanes, 5.30mmol), TMEDA (790µl, 5.30mmol) and cyclohexene-1-carboxaldehyde **47** (280µl, 2.50mmol) to give the title compounds **73**. Distillation on a Kugelrohr apparatus (50°C, high vacuum) gave the epoxysilanes **73** (310mg, 63%) as an inseparable mixture of colourless oils (ratio 4:1). $\nu_{max.}$ (thin film) 2932 (s), 1439 (m), 1249 (s), 841 (s), 754 (w) cm^{-1}; major isomer, δ_H (200MHz, C_6D_6) 0.02 (9H, s, Si(C**H**$_3$)$_3$), 1.30-1.60 (4H, m), 1.70-1.90 (4H, m), 2.12 (1H, d, *J* 5.0, **H**(2)), 3.25 (1H, d, *J* 5.0, **H**(3)), 5.75-5.82 (1H, m, **H**(2')); δ_C (50.3MHz, C_6D_6) -2.2 (Si(**C**H$_3$)$_3$), 22.2, 22.6, 24.2, 25.8 (4x**C**H$_2$), 51.8 (**C**(2)), 58.0 (**C**(3)), 121.8 (**C**(2')), 134.0 (**C**(1')); minor isomer, δ_H (200MHz, C_6D_6) 0.10 (9H, s, Si(C**H**$_3$)$_3$), 1.30-1.60 (4H, m), 1.70-1.90 (4H, m), 2.23 (1H, d, *J* 4.0, **H**(2)), 4.50 (1H, d, *J* 4.0, **H**(3)), 5.40-5.60 (1H, m, **H**(2')); δ_C (50.3MHz, C_6D_6) -1.3 (Si(**C**H$_3$)$_3$), 22.3, 22.5, 24.8, 25.2 (4x**C**H$_2$), 74.3 (**C**(2)), 79.8 (**C**(3)), 128.1 (**C**(2')), 148.4 (**C**(1')); *m/z* (C.I., NH_3) 198 (M(^{29}Si)H$^+$, 12), 197 (M(^{28}Si)H$^+$, 100) 125 (12), 90 (18%).

1-Octyn-3-one 75[83]



The method described by Colas *et. al.*[83] was repeated using 1-octyn-3-ol **77** (1g, 7.90mmol), water (3ml) and Jones' reagent (5.9ml, 2M solution in aq. H_2SO_4, 11.90mmol) to give the ketone **75** (0.89g, 91%) as a colourless oil. R_f (1:1, petrol:ether) 0.55 (uv active); $\nu_{max.}$ (thin film) 2957 (s), 2933 (s), 2862 (m), 2094 (m), 1683 (s), 1467 (m), 1132 (w), 1059 (m), 1028 (m), 654 (m), 629 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.80 (3H, t, *J* 6.5, **H**$(8)_3$), 1.10-1.30 (6H, m), 2.50 (2H, t, *J* 6.0, **H**$(4)_2$), 3.27 (1H, s, **H**(1)); *m/z* (C.I., NH_3) 125 (MH^+, 30), 99 (35), 98 (55), 85 (24) 83 (100) 71 (14) 55 (30%).

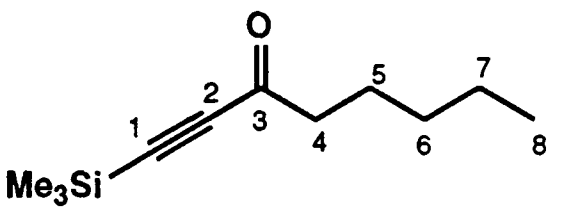
1-Trimethylsilyl-3-trimethylsilyloxyoct-1-yne 78



To a cooled (-78°C) solution of 1-octyn-3-ol **77** (0.86g, 6.85mmol) in THF (8ml) was added successively *n*-butyllithium (9.4ml, 1.6M in hexanes, 15.10mmol) and, after 20mins, chlorotrimethylsilane (2.2ml, 17.10mmol) dropwise. The reaction mixture was warmed to RT over 1h and diluted with 1M aq. HCl (10ml) and ether (20ml). The separated organic layer was washed with brine (15ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the disilyl alkyne **78** (1.42g, 77%) as a colourless oil. $\nu_{max.}$ (thin film) 2959 (s), 2862 (m), 2172 (w), 1450 (w), 1340 (w), 1251 (s), 1090 (m), 843 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.15 (9H, s, Si(C**H**$_3)_3$), 0.16 (9H, s, Si(C**H**$_3)_3$), 0.86 (3H, t, *J* 6.5, **H**$(8)_3$), 1.20-1.45 (6H, m), 1.58-1.68 (2H, m), 4.30 (1H, t, *J* 7.5, **H**(3)); δ_C (50.3MHz, $CDCl_3$) -0.4 (C(1)Si(**C**H$_3)_3$), 0.0 (C(3)OSi(**C**H$_3)_3$), 13.8 (**C**(8)), 22.4, 24.7, 31.3, 38.3 (4x**C**H$_2$),

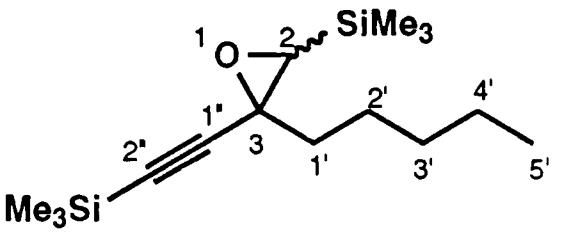
63.1 (**C**(3)), 88.6, 107.7 (**C**(1), **C**(2)); *m/z* (C.I., NH_3) 200 (10), 199 (MH^+-Me_3Si, 52), 182 (11), 181 (MH^+-Me_3Si-H_2O, 55), 91 (10), 90 (Me_3SiOH^+, 100) 73 (26%).

1-Trimethylsilyl-1-octyn-3-one 79[85]



The procedure reported by Colas[83] was repeated using the protected alcohol **78** (1.32g, 4.84mmol), water (5ml) and Jones' reagent (4.0ml, 2M solution in aq. H_2SO_4, 7.25mmol) to give the title compound **79**. Distillation on a Kugelrohr apparatus (125°C, high vacuum) gave the silyl ketone **79** (0.81g, 66%) as an oil. R_f (1:1, petrol:ether) 0.55 (uv active); $\nu_{max.}$ (thin film) 2960 (s), 2933 (s), 2874 (m), 2151 (w), 1681 (s), 1467 (w), 1409 (w), 1253 (s), 1134 (m), 1084 (m), 864 (s), 847 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.24 (9H, s, $Si(CH_3)_3$) 0.90 (3H, t, *J* 6.0, **H**$(8)_3$), 1.20-1.40 (4H, m), 1.60-1.80 (2H, m), 2.55 (2H, t, *J* 7.0, **H**$(4)_2$); δ_C (50.3MHz, $CDCl_3$) -1.0 ($Si(CH_3)_3$), 13.6 (**C**(8)), 22.2, 23.5, 30.9, ($3x$**C**H_2), 45.1 (**C**(4)), 97.4, 102.1 (**C**(1), **C**(2)), 188.3 (**C**(3)); *m/z* (C.I., NH_3) 215 ($M(^{29}Si)NH_4^+$, 15), 214 ($M(^{28}Si)NH_4^+$, 100), 198 ($M(^{29}Si)H^+$, 18), 197 ($M(^{28}Si)H^+$, 92), 181 (15), 125 (45%).

3-Pentyl-3-(trimethylsilylethynyl)-2-trimethylsilyloxirane 76



The procedure described by Magnus *et al.*,[51a] was repeated using chloromethyltrimethylsilane (700µl, 5.00mmol), THF (8ml), *sec*-butyllithium (4.0ml, 1.3M in hexanes, 5.30mmol), TMEDA (790µl, 5.30mmol) and the silyl alkynone **79** (0.49ml, 2.50mmol) to give the title compounds **76**. Distillation on

a Kugelrohr apparatus (100°C, high vacuum) gave the epoxysilanes **76** (416mg, 59%) as a mixture (ratio 5:4) of inseparable colourless oils. $\nu_{max.}$ (thin film) 2958 (s), 2862 (m), 2170 (s), 1681 (w), 1466 (m), 1251 (s), 1034 (w), 844 (s) cm^{-1}; major isomer, δ_H (200MHz, C_6D_6) 0.09 (9H, s, C(2)Si(C**H**$_3$)$_3$), 0.12 (9H, s, C(2")Si(C**H**$_3$)$_3$), 0.82 (3H, t, *J* 5.0, **H**(5')$_3$), 1.15-1.30 (4H, m), 1.50-1.80 (4H, m), 2.59 (1H, s, **H**(2)); δ_C (50.3MHz, C_6D_6) -2.9 (C(2)Si(**C**H$_3$)$_3$), -0.6 (C(2")Si(**C**H$_3$)$_3$), 13.6 (**C**(5')), 22.4, 25.9, 31.4, 35.0 (4x**C**H$_2$), 54.8 (**C**(3), 59.0 (**C**(2)), 86.0, 107.4 (**C**(1"), **C**(2")); minor isomer, δ_H (200MHz, C_6D_6) 0.09 (9H, s, C(2)Si(C**H**$_3$)$_3$), 0.12 (9H, s, C(2")Si(C**H**$_3$)$_3$), 0.82 (3H, t, *J* 5.0, **H**(5')$_3$), 1.15-1.30 (4H, m), 1.50-1.80 (4H, m), 2.04 (1H, s, **H**(2)); δ_C (50.3MHz, C_6D_6) -2.5 (C(2)Si(**C**H$_3$)$_3$), -0.8 (C(2")Si(**C**H$_3$)$_3$), 15.0 (**C**(5')), 22.1, 25.4, 31.2, 38.6 (4x**C**H$_2$), 53.5 (**C**(3), 58.2 (**C**(2)), 89.2, 105.7 (**C**(1"), **C**(2")); *m/z* (C.I., NH_3) 284 (M(^{29}Si)H$^+$, 12), 283 (M(^{28}Si)H$^+$, 100) 225 (12) 211 (16) 147 (10%).

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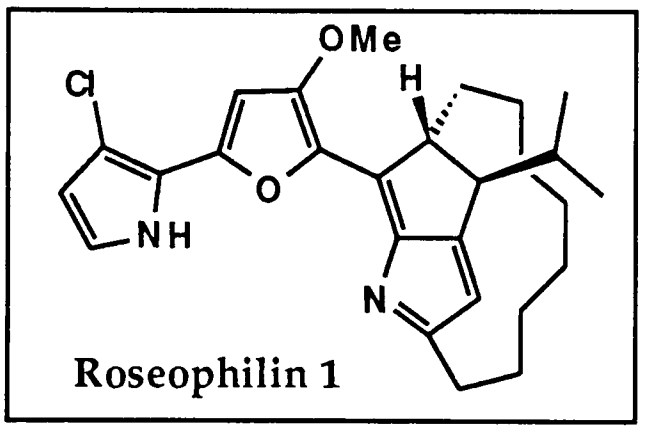
INTRODUCTION

4.1. Background

In 1992 Seto and co-workers,[1] whilst engaged in screening for new antitumour antibiotics, isolated a novel active substance, Roseophilin **1**, from the culture broth of an actinomycete identified as *Streptomyces griseoviridis*. Column chromatography ($CHCl_3$:MeOH, 20:1) of the active organic fraction extracted from the organism gave a reddish purple powder of Roseophilin hydrochloride which was found to exhibit cytotoxicity against K562 human erythroid leukaemia cells (IC_{50}, 0.34μM) and KB human epidermoid carcinoma cells (IC_{50}, 0.88μM).



Roseophilin 1

Detailed NMR studies were instrumental in elucidating the structure. All one-bond ^1H-^{13}C connectivities were ascertained by a series of ^1H-^{13}C COSY experiments and further ^1H-^1H COSY, HMBC[2] long-range ^1H-^{13}C correlation and n.O.e. experiments confirmed the relative stereochemistry of the two stereogenic centres to be as depicted. No crystals suitable for X-ray diffraction could be grown and, as yet, the absolute stereochemistry is unknown.

Roseophilin **1** possesses an alluring pentacyclic structure with intriguing heterocyclic and macrocyclic regions. The pyrrole-furan moiety is connected directly to a bicyclic azafulvene core in a planar arrangement instilling contiguous π-orbital overlap over 16 atoms. The novel and distinctive alkyl

chain enveloping the bicyclic core appears, from modelling, to be normal to the heterocyclic plane providing a fascinating structure (shown in Appendix E).

This synthetically demanding target was of great interest to us not only because of its potent cytotoxicity (making it an interesting lead compound for antitumour agents), but also because of the challenge in devising and applying methodology towards the construction of such a structurally complex molecule. A total synthesis would also confirm the structure, help establish the absolute stereochemistry of the molecule and provide a useful method for the formation of structurally related analogues; with such a collection to hand, the existence of structure activity relationships (SAR) could be investigated in the hope of devising the optimal structure for use as a drug.

4.2. Related Natural Products

4.2.1. Metacycloprodigiosin 2

In 1969 Wasserman and co-workers isolated an orange-brown crystal from strain M-3 of *Streptomyces longisporus ruber*.[3] The structure was elucidated and found to be a C-25 prodigiosin analogue[4] containing a bipyrrole in conjugation with a novel macrocyclic *meta*-bridged pyrrole.

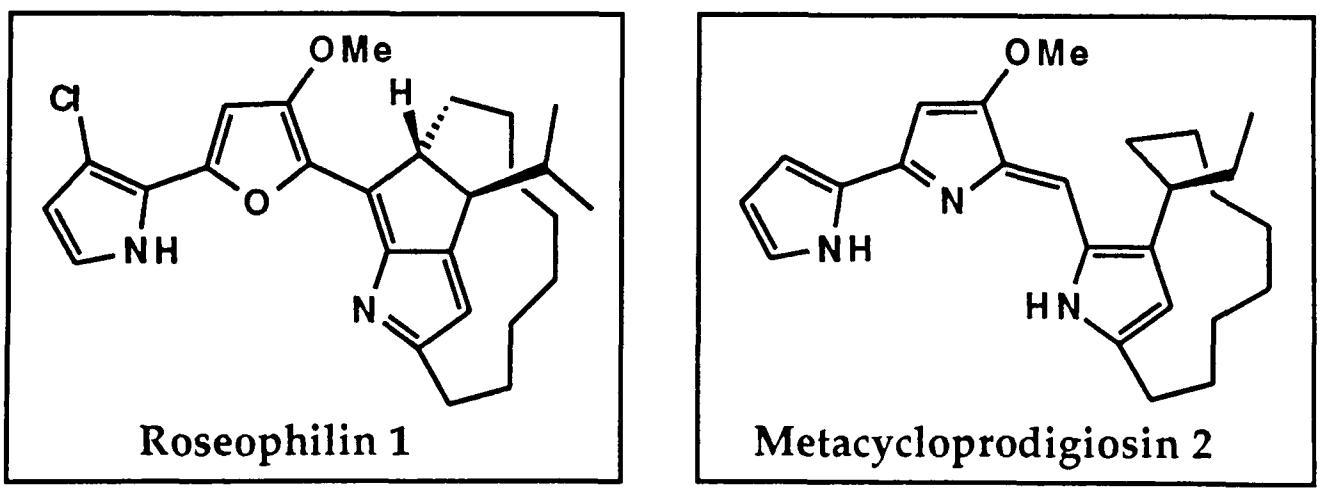


Figure 1

Figure 1 shows a comparison of this structure, Metacycloprodigiosin **2**, and Roseophilin **1**. They bear a striking resemblance, in particular the almost

identical tricyclic conjugated heterocyclic core, the macrocycle which differs only by one carbon and finally an alkyl substituent in both structures.

Metacycloprodigiosin **2** was then synthesised by Wasserman[5] in order to confirm the assignment; his retrosynthetic analysis relied on the coupling of pyrrole-macrocycle **3** to the known bipyrrole aldehyde[4] **4** shown in Figure 2.

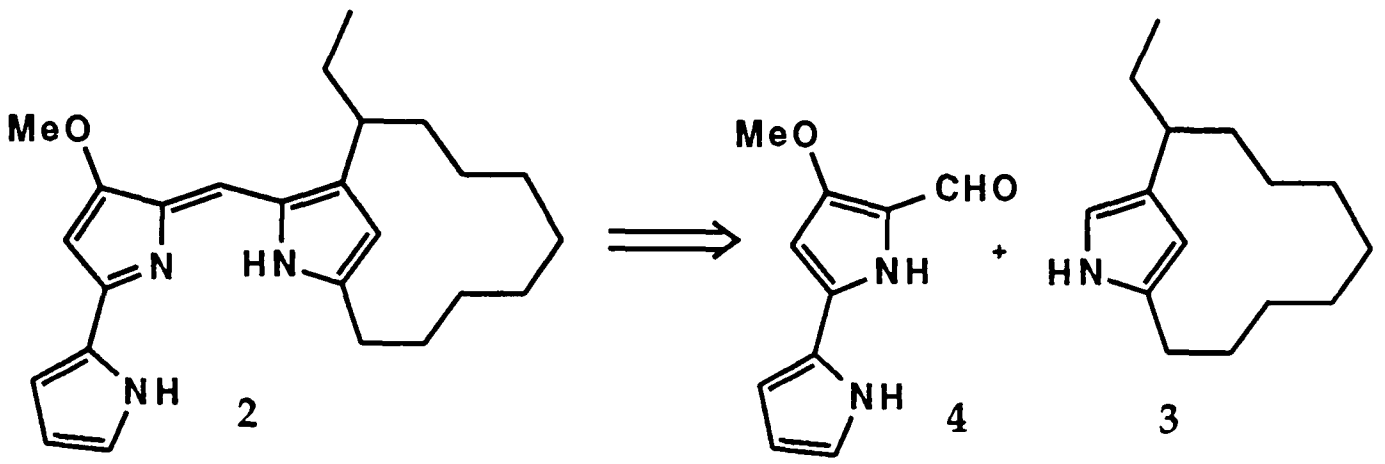
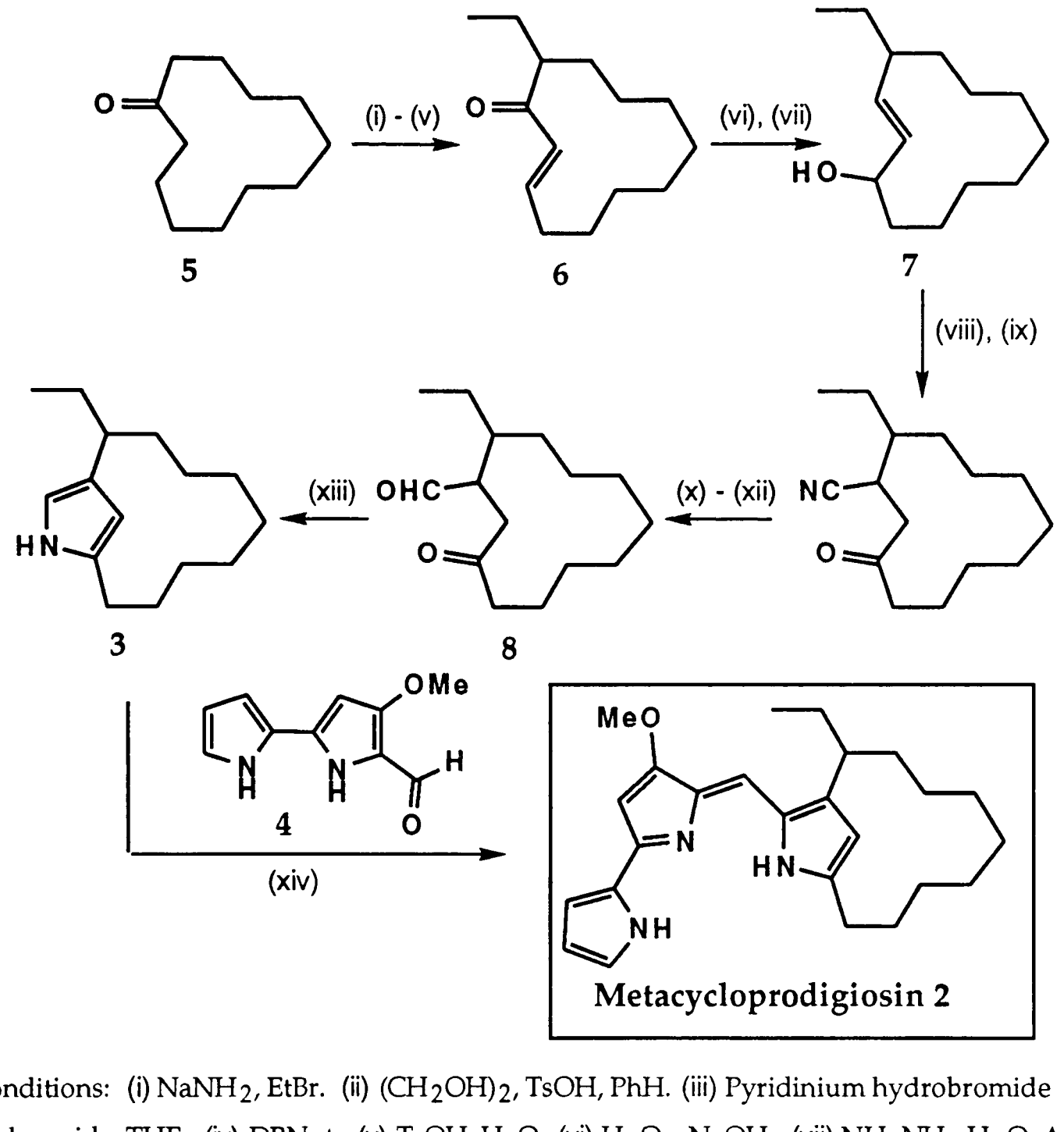


Figure 2

The synthesis started with cyclododecanone **5** to provide the carbocyclic fragment and then the Wharton transposition[6] to interconvert enone **6** to allylic alcohol **7**. Formation of the 1,4-dicarbonyl **8** then led, *via* the Paal-Knorr condensation[7] with ammonia, to the macrocyclic pyrrole **3**. The known methoxybipyrrole aldehyde **4** was then coupled to the macrocycle to generate racemic Metacycloprodigiosin **2** as a brilliant red pigment in 14 steps and 1.1% overall yield (Scheme 1).



Conditions: (i) $NaNH_2$, EtBr. (ii) $(CH_2OH)_2$, TsOH, PhH. (iii) Pyridinium hydrobromide perbromide, THF. (iv) DBN, Δ. (v) TsOH, H_2O. (vi) H_2O_2, NaOH. (vii) $NH_2NH_2.H_2O$, AcOH, EtOH. (viii) $Na_2Cr_2O_7$, H_2SO_4, H_2O. (ix) KCN, NH_4Cl, H_2O, DMF. (x) $(CH_2OH)_2$, TsOH, PhH. (xi) DIBALH, Et_2O. (xii) TsOH, H_2O. (xiii) $(NH_4)_2CO_3$, H_2O, DMF. (xiv) EtOH, HCl.

Scheme 1

The similarity between the uv and visible spectra of Roseophilin **1** and Metacycloprodigiosin **2** helped Seto to identify the conjugated ring system in Roseophilin **1**.

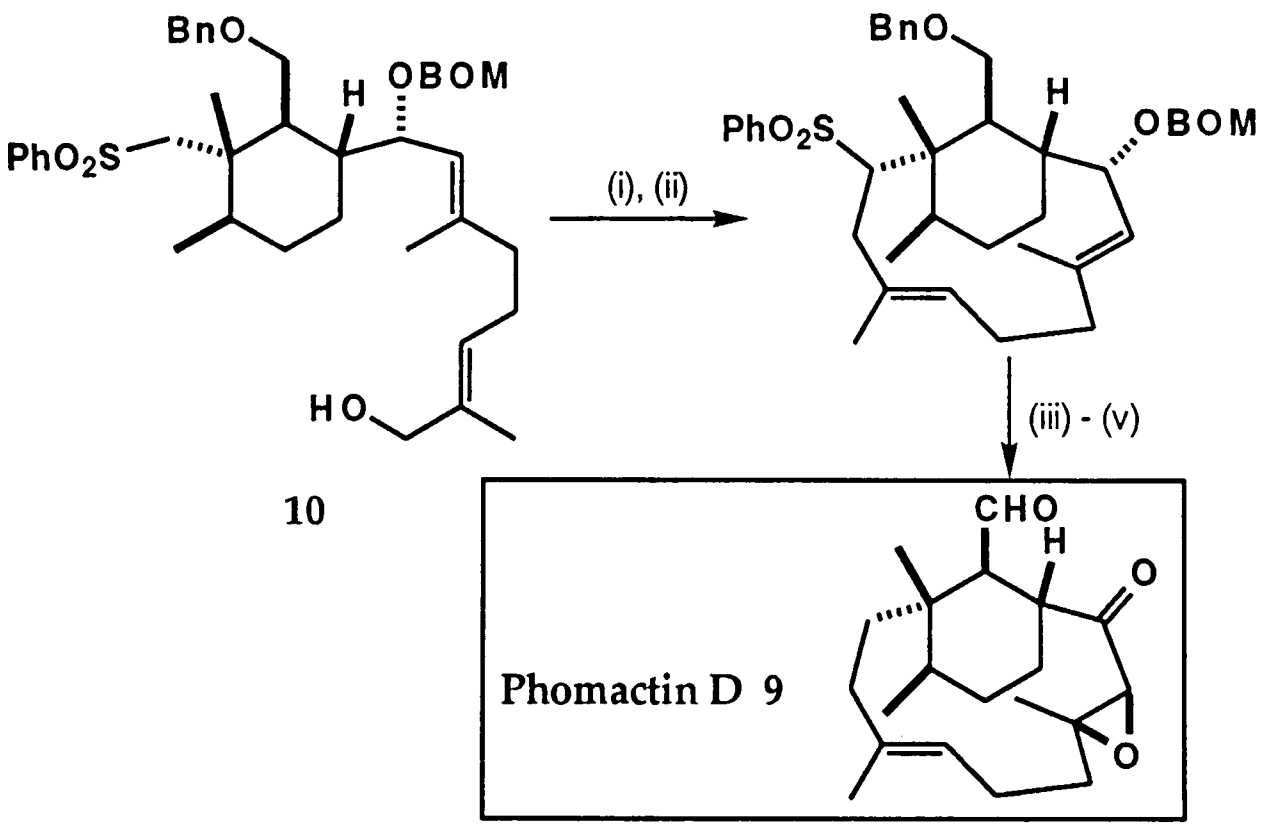
4.2.2. Biological Studies on Metacycloprodigiosin 2

Recent biological studies by Shearer and co-workers[8] have shown that Metacycloprodigiosin suppresses T-cell proliferation induced by concavalin A *in vitro*. In addition it suppresses anti-graft cytotoxic T-cell activity of BALB/c

spleen grafted with C57B1/6 skin but has only partial effects on antibody production. The study was limited due to the high toxicity of Metacycloprodigiosin but Shearer suggested that chemical modification of the antibiotic might improve the bioavailability and toxicity, and thus the efficacy for suppression of graft rejection.

4.2.3. The Phomactins

Another family of structures which resemble Roseophilin, in part, are the Phomactins. Isolated from the culture filtrate of the marine fungus, *Phoma* sp. (SANK 11486) they have proven to be novel platelet activating factor antagonists.[9] Their similarity to Roseophilin lies solely in the macrocyclic strap of the bi- or tri-cyclic ring systems. Synthetic studies have been instigated[10] and Yamada *et al.*[11] reported the first total synthesis of Phomactin D **9**, forming the macrocycle by an intramolecular S_N2 process on the chloride generated from **10** (Scheme 2).



Conditions: (i) MsCl, DMAP, DCM. (ii) KHMDS, THF; 39% (2 steps). (iii) Na, liq. NH_3, THF, -34°C; 98%. (iv) $VO(acac)_2$, ^tBuOOH, PhH. (v) PDC, 4ÅMol.S., DCM; 60% (2 steps).

Scheme 2

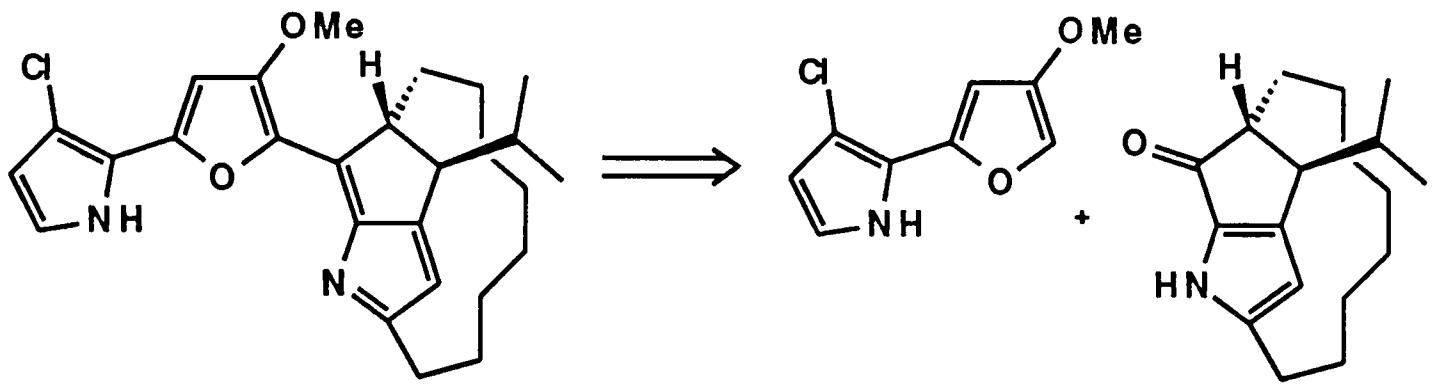
4.3. Biological Activity of Roseophilin

There have been few reports concerned with Roseophilin subsequent to its structure elucidation. Indeed, despite Seto's enthusiastic approbation, further results pertaining to its biological testing have not been forthcoming and as yet its mode of action is unknown. However, personal correspondence with Seto recently revealed that detailed studies had in fact been instigated though ultimately terminated on the discovery that Roseophilin was highly toxic to normal cells.[12]

4.4. Previous Synthetic Approaches to Roseophilin Fragments

4.4.1. The Synthesis of Model Heterocyclic Ring Systems

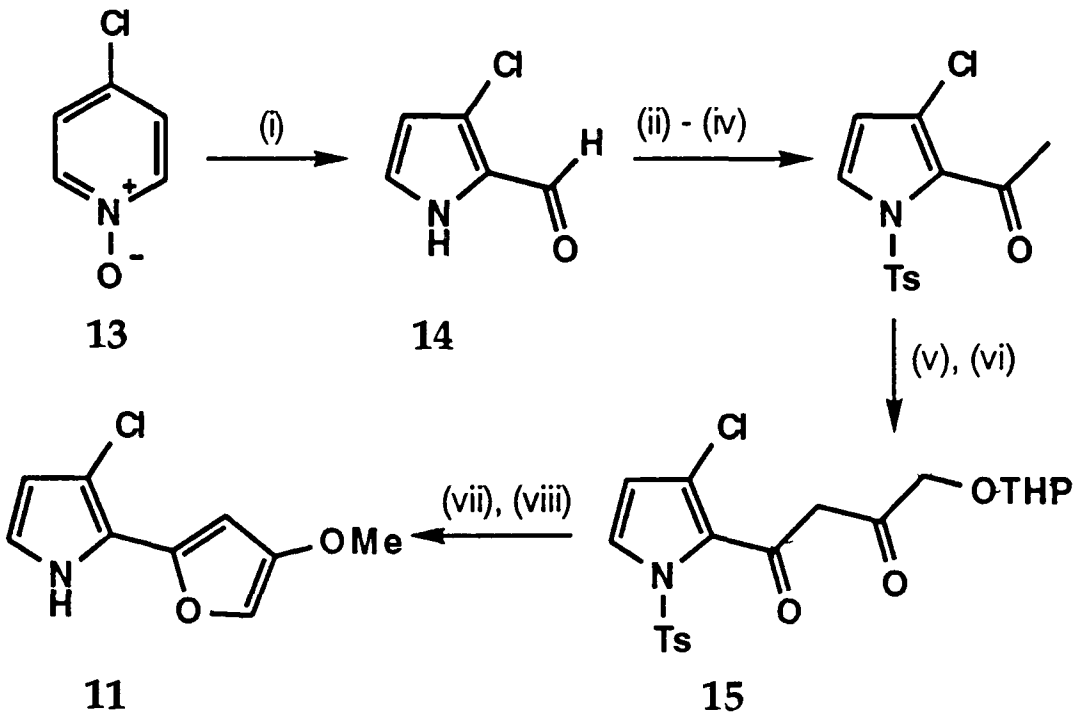
Terashima was the first to publish work that tackled the synthetic issue.[13] He and his co-workers suggested that the cytotoxicity of Roseophilin could originate from the conjugated heterocyclic ring system, which they imagined might interact with DNA. They envisaged a retrosynthetic analysis based on the coupling of bis-heterocycle **11** with a macrocyclic keto-pyrrole fragment **12** shown in Figure 3.



1 **11** **12**

Figure 3

In accordance with this analysis they set out on an elegant synthesis of the pyrrole-furan fragment **11** starting from readily available 4-chloro-pyridine-*N*-oxide **13** as shown in Scheme 3.

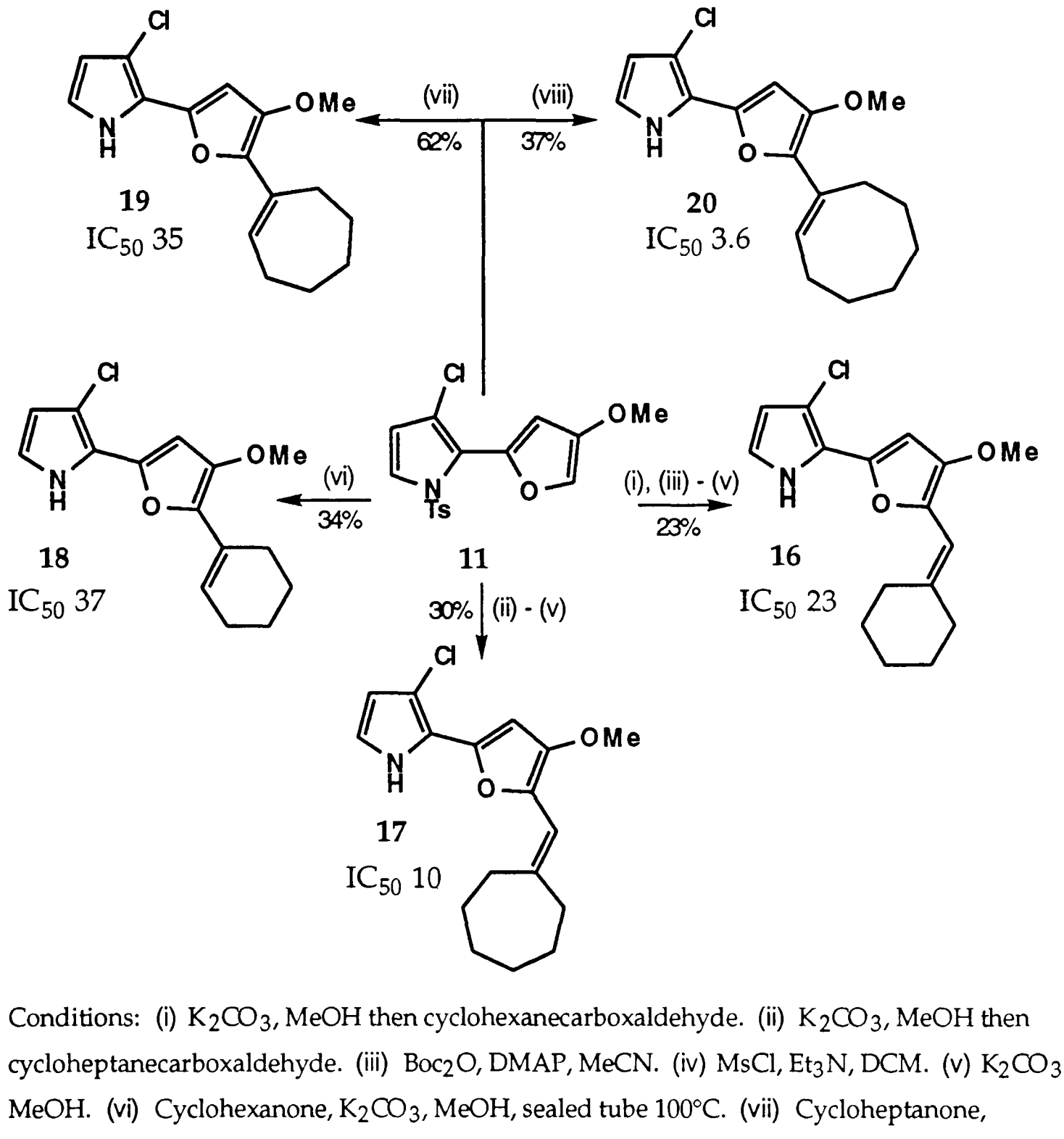


Conditions: (i) $CuSO_4$, *hv*; 35%. (ii) TsCl, Et_3N, MeCN; 98%. (iii) MeMgBr, THF; 84%. (iv) Dess-Martin periodinane, DCM; 95%. (v) LDA, $THPOCH_2CHO$, THF, -78°C; 54%. (vi) Dess-Martin periodinane, DCM; 60%. (vii) CSA, MeOH; 76%. (viii) K_2CO_3, MeOH; 71%.

Scheme 3

The first step made use of a known photochemical rearrangement, developed by Streith, to generate the required 3-chloropyrrole carboxaldehyde **14**.[14] Subsequent elaboration around the carbonyl allowed the construction of the methoxy-furan *via* the 1,3-dicarbonyl **15**.

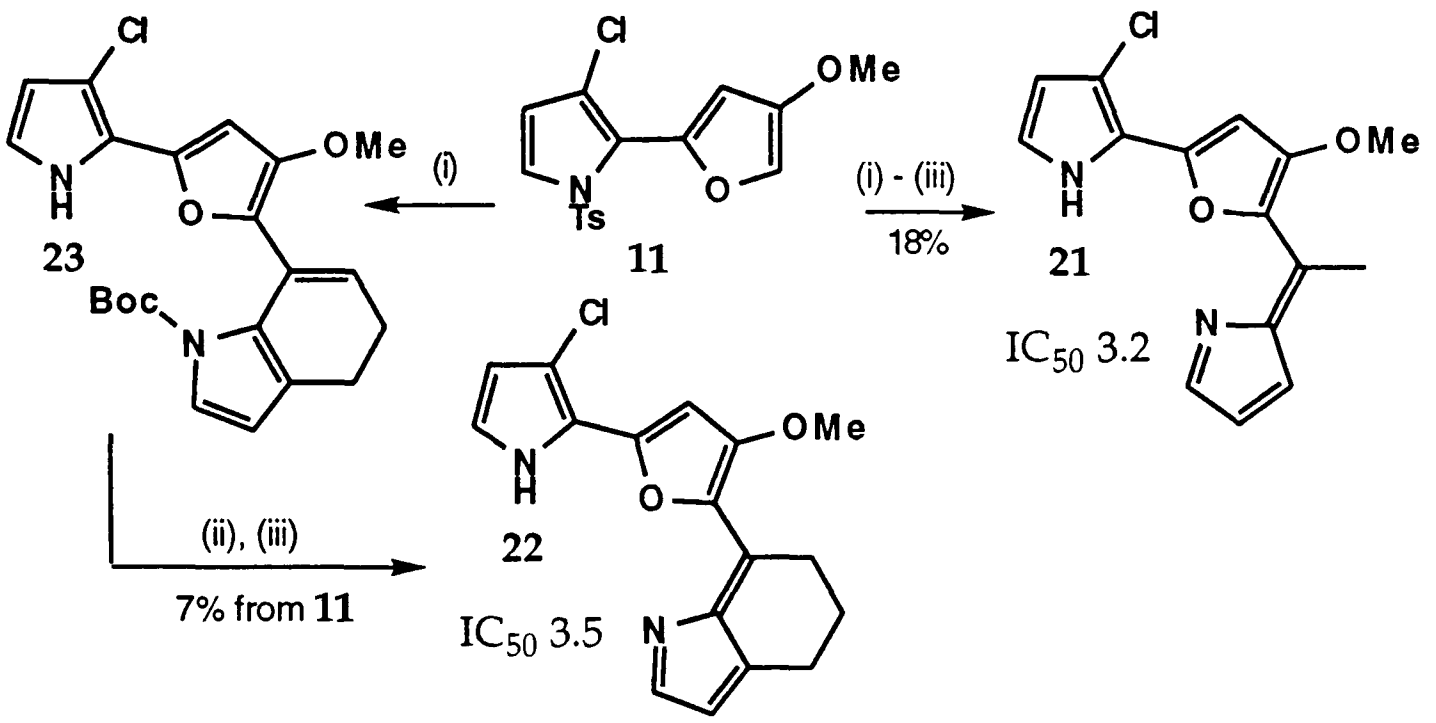
Terashima sought to couple the bis-heterocycle **11** with a variety of aldehydes and ketones in order to prepare a series of Roseophilin model compounds and thus investigate both his hypothesis and the possibility of a SAR. Accordingly the tricycles **16-20** were prepared and tested against P388 *Murine Leukaemia* cells. The *in vitro* activities (IC_{50} μg/ml) are reported in Scheme 4.



Conditions: (i) K_2CO_3, MeOH then cyclohexanecarboxaldehyde. (ii) K_2CO_3, MeOH then cycloheptanecarboxaldehyde. (iii) Boc_2O, DMAP, MeCN. (iv) MsCl, Et_3N, DCM. (v) K_2CO_3, MeOH. (vi) Cyclohexanone, K_2CO_3, MeOH, sealed tube 100°C. (vii) Cycloheptanone, K_2CO_3, MeOH, sealed tube 100°C. (viii) Cyclooctanone, K_2CO_3, MeOH, sealed tube 120°C.

Scheme 4

The observed cytotoxicities, against P388 *Murine Leukaemia* cells, did not approach those reported for Roseophilin against other cell lines (IC_{50} 0.15 μg/ml for K562 cells; IC_{50} 0.40 μg/ml for KB cells) and the bis-heterocycle **11** alone was even less active (>100μg/ml). Terashima reasoned that an azafulvene conjugated bis-heterocycle should be more active and thus the two dark-red TFA salts **21** and **22** (Scheme 5) were prepared by coupling the furan with a keto-pyrrole in acid.



Conditions: (i) $CH(OMe)_3$, CSA, MeOH, Boc-protected-2-acylpyrrole. (ii) K_2CO_3, MeOH. (iii) TFA, $CHCl_3$.

Scheme 5

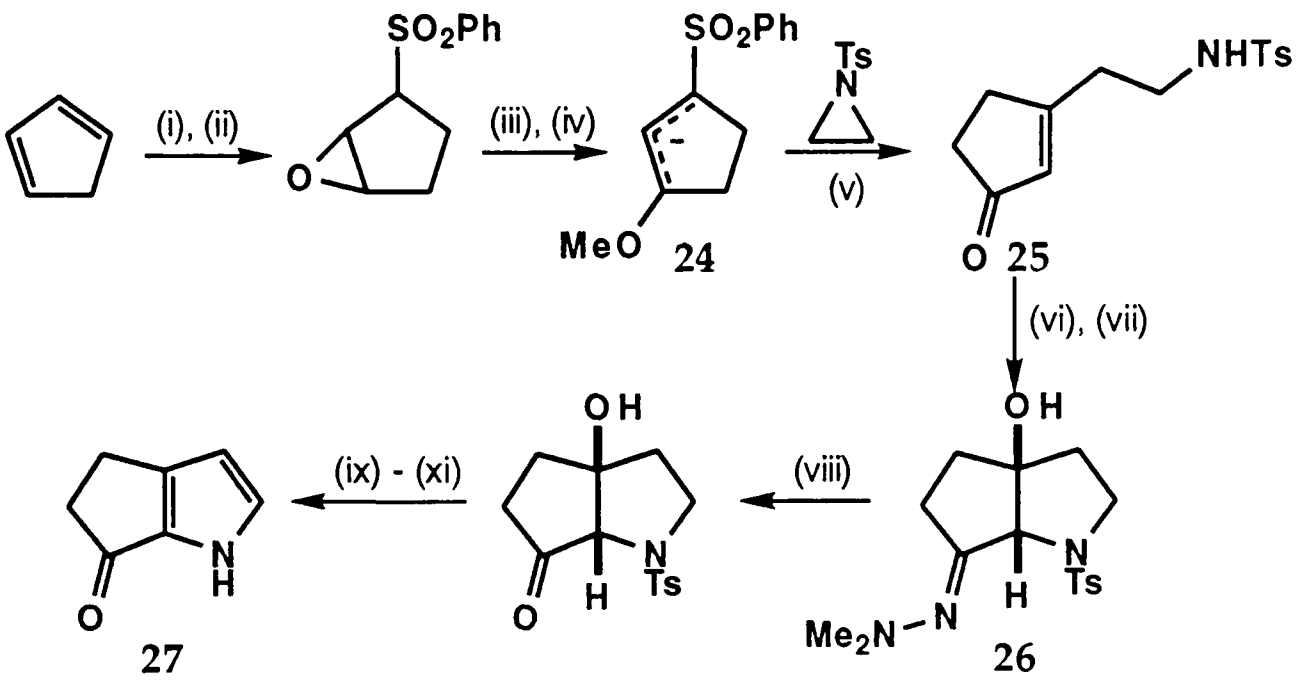
Interestingly acidic deprotection of the alkenyl-pyrrole **23** generated the required azafulvene directly. The *in vitro* activities (μg/ml) observed were still 10 times lower than that observed for Roseophilin, albeit on different cell lines, suggesting Terashima's hypothesis to be incomplete, i.e. the macrocycle must also play an important role in the high cytotoxicity. The *in vivo* activities have not yet been reported but are currently under investigation.

Despite the low yields for the coupling reactions Terashima has successfully demonstrated the desirability of a [3.3.0]ketopyrrole core in the synthesis of further model core-fragments and Roseophilin itself.

4.4.2. Synthesis of a Keto-pyrrole Roseophilin Model

Fuchs and co-workers turned their attention to the synthesis of a [3.3.0]keto-pyrrole Roseophilin model, making use of their recent annulation methodology for the formation of β-substituted enones.[15a] Accordingly tosylaziridine was treated with allysulphonyl anion **24** to generate enone **25**. Subsequent epoxidation and hydrazone formation led to the [3.3.0]bicycle **26** *via* an ingenious fragmentation, cyclisation sequence. Hydrolysis of the

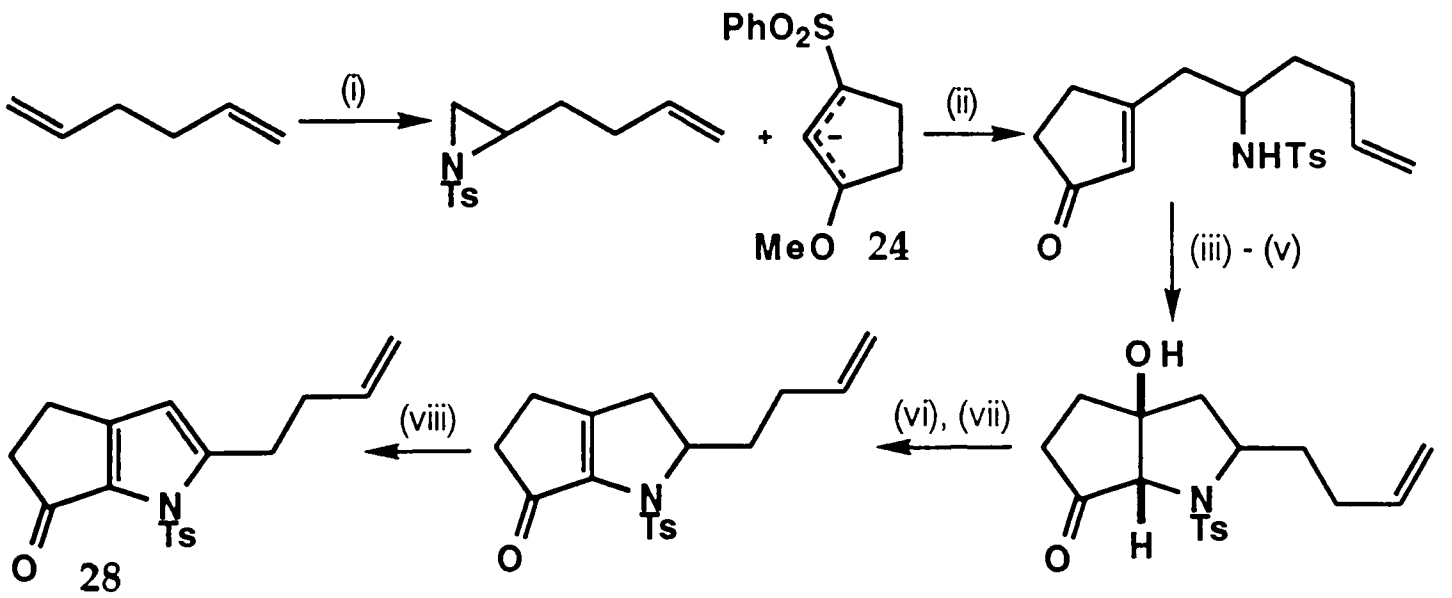
hydrazone **26** followed by double elimination provided the desired keto-pyrrole[15b] **27** in a rather lengthy but efficient process (Scheme 6).



Conditions: (i) $HCl_{(g)}$. (ii) NaSPh followed by AcOOH (3 equiv.). (iii) NaOH, MeI, PTC, P_2-Et phosphazene base,[16] THF, Δ; 66% over 3 steps. (iv) ^nBuLi, -78°C. (v) SiO_2, H_2O. (vi) H_2O_2, NaOH. (vii) Me_2NNH_2, cat. $EtCO_2H$, EtOAc, -40°C. (viii) SiO_2, THF-H_2O; 62% over 5 steps. (ix) MsCl, Et_3N, THF. (x) Al_2O_3, DCM; 98% over 2 steps. (xi) DBU, MeCN, 50°C; 80%.

Scheme 6

Further application of this strategy to the synthesis of a substituted ketopyrrole proved effective as shown in the formation of **28** in Scheme 7.[15b]

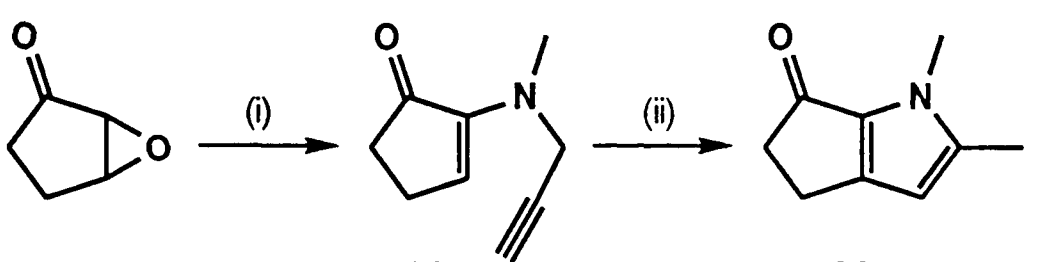


Conditions: (i) TsN=IPh; 45%. (ii) SiO_2, H_2O; 73%. (iii) H_2O_2, NaOH. (iv) Me_2NNH_2, cat. $EtCO_2H$, EtOAc, -40°C. (v) SiO_2, THF-H_2O; 58% over 3 steps. (vi) MsCl, Et_3N, THF. (vii) Al_2O_3, DCM; 81% over 2 steps. (viii) NIS, CCl_4; 93%.

Scheme 7

4.4.3. Further Model Systems

The synthesis of oxotetrahydroindole fragments, such as those used by Terashima,[13] is most commonly achieved using the direct electrophilic substitution of pyrroles[17] or lithiation of pyrroles followed by condensation of a Grignard reagent with 2-pyridylthiol esters.[18] Reports concerned with the syntheses of bicyclic five-membered keto-pyrroles, such as that required for the core of Roseophilin, are rarer. A recent example, making use of the thermal rearrangement of vinylpropargylamines[19] **29**, is shown in Scheme 8. Although **30** is a model structure for the Roseophilin core, Cossy *et al.* have not reported that they intend to adapt the methodology to a synthesis.



29 **30**

Conditions: (i) *N*-Methyl-propargylamine, MeOH, H_2O. (ii) PhMe, Δ; 30% (2 steps).

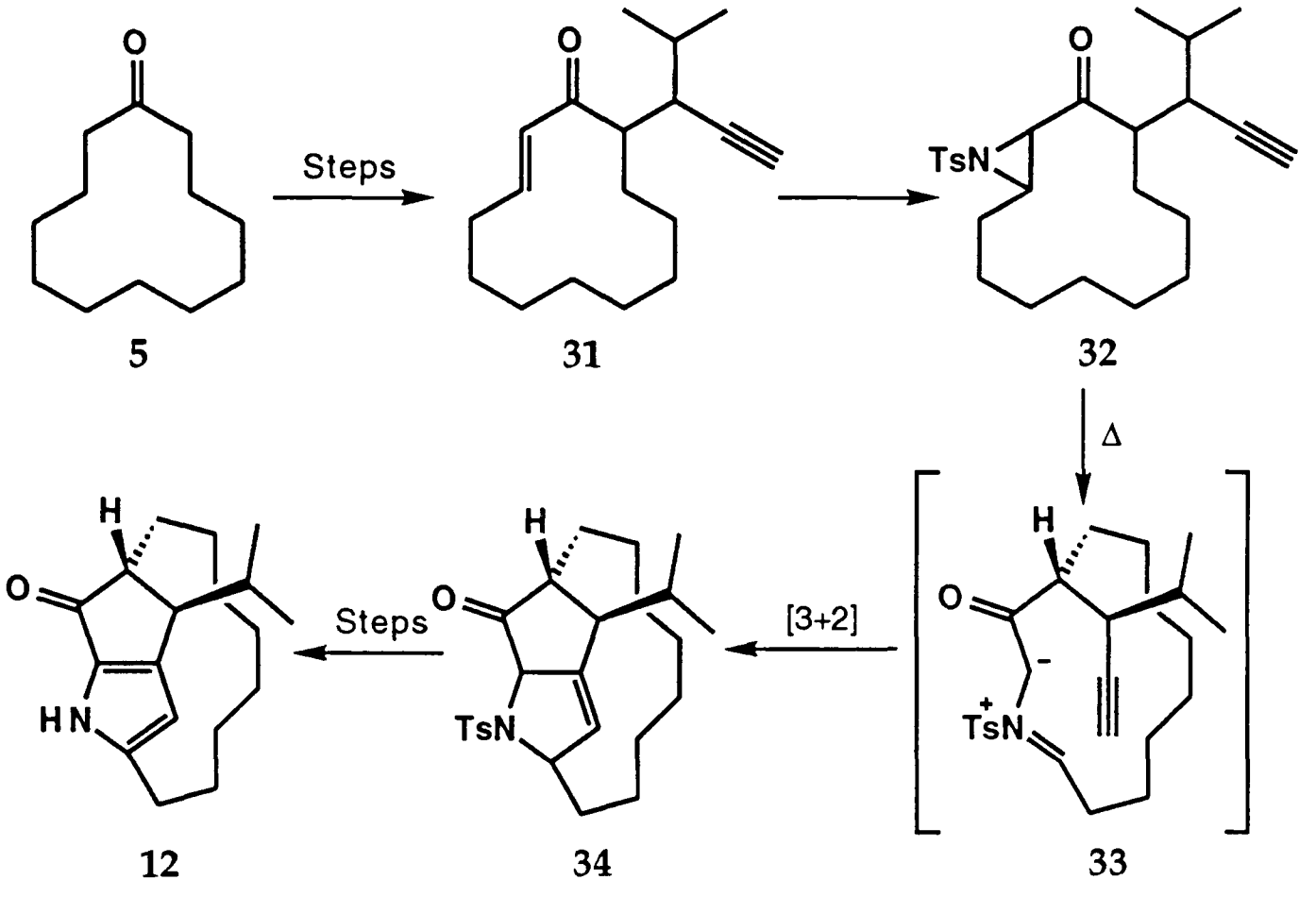
Scheme 8

4.4.3. Studies toward the Total Synthesis

The above approaches have dealt only with the heterocyclic or unsubstituted bicyclic-ketopyrrole fragments. An ingenious, though to our knowledge unsuccessful, approach to the rapid synthesis of the macrocyclic keto-pyrrole **12** was proposed by Kocienski.[20]

The elegant sequence made use of cyclododecanone **5**, thus avoiding macrocycle formation altogether. The α,β-unsaturated ketone **31** was converted to an aziridine[21] **32** which, it was hoped, would undergo thermal isomerisation to the stabilised azomethine ylid[22] **33**, thus effecting a one atom ring expansion. It was envisaged that this ylid would react in an intramolecular [3+2] cycloaddition with the terminal alkyne producing the tricyclic framework **34** in

one step. All attempts so far to effect this transformation, to our knowledge, have been unsuccessful. The general strategy is shown in Scheme 9.



Scheme 9

4.5. Retrosynthetic Analysis

4.5.1. We identified the importance of the tricyclic-ketopyrrole **12** and envisaged it's derivation from the γ,δ-unsaturated-macrocyclic ketone[23] **35** (Figure 4).

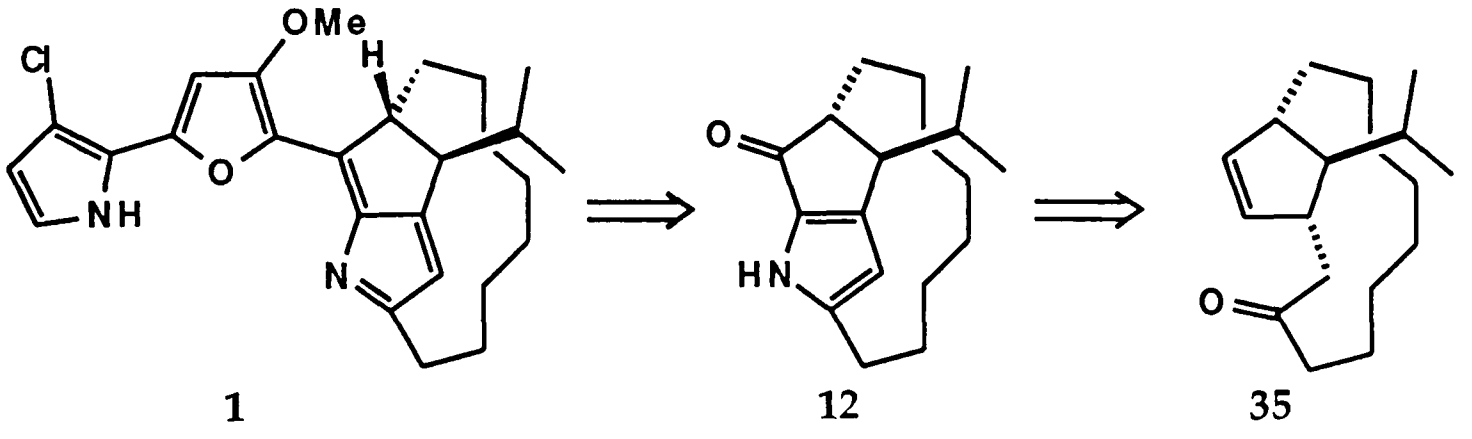


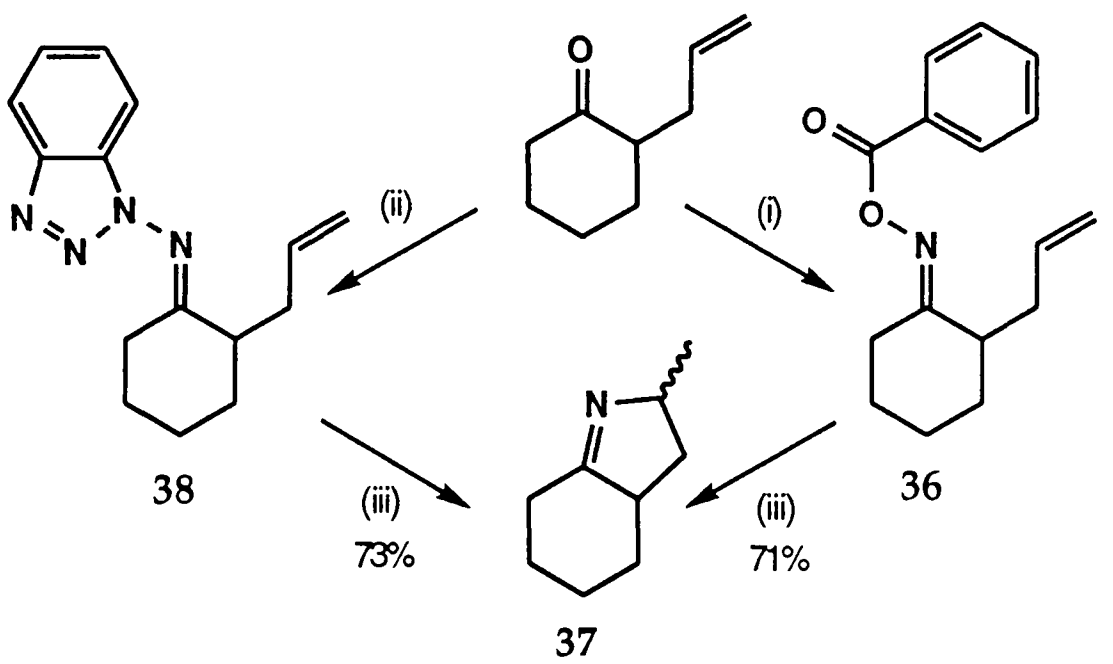
Figure 4

Our work was therefore *solely* to be involved in attempts to construct the tricyclic-ketopyrrole **12**; no investigations into the bis-heterocyclic fragment were envisaged. Chapters **5** and **6** discuss our investigations in detail.

We proposed that transformation of the ketone **35** to the ketopyrrole **12** could be achieved using either an iminyl radical cyclisation onto the *exo* alkene followed by oxidative transformation (**4.5.2.**), or through the electrophilic induced cyclisation of an oxime to form a nitrone with subsequent functional group manipulation (**4.5.3.**).

4.5.2. Iminyl Radical Cyclisations

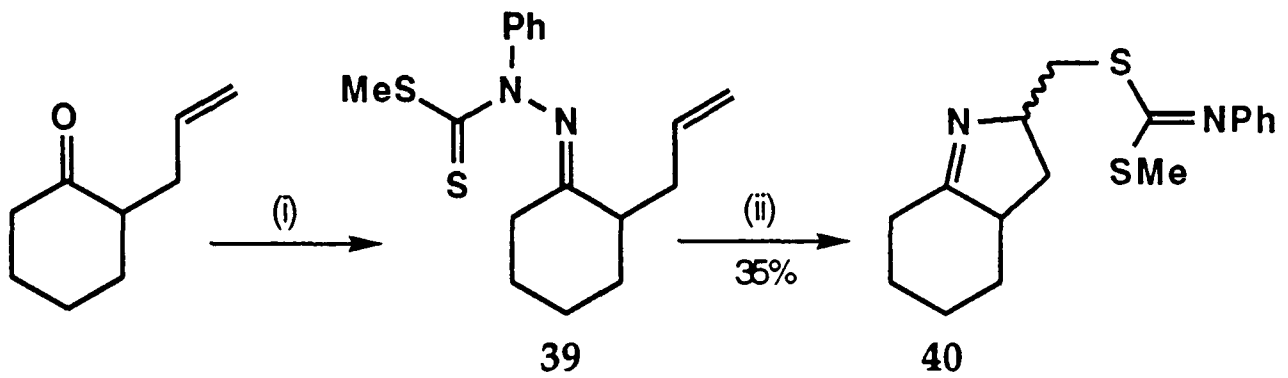
Zard and co-workers have been instrumental in identifying the ease of synthesis and potential of iminyl radicals.[24] He has also demonstrated the effectiveness of stannyl radical attack on the carbonyl oxygen of an *O*-acyloxime **36** resulting in an iminyl radical that can cyclise on to an alkene to form a bicyclic heterocycle **37**. More recently El Kaim and co-workers[25] have shown that an analogous sequence can be achieved using a benzotriazole derivative **38** to form the iminyl radical as shown in Scheme 10.



Conditions: (i) $NH_2OH.HCl$, NaOAc, MeOH. PhCOCl, py.
(ii) *N*-Aminobenzotriazole, TsOH. (iii) $^nBu_3SnH$, AIBN, Δ

Scheme 10

Zard has also identified the possibility of using atom transfer conditions in order to promote a non-reductive cyclisation.[26] Using a novel dithioesterphenylhydrazone **39** he has affected a transformation that results in the sulphur substituted-heterocycle **40** shown in Scheme 11.



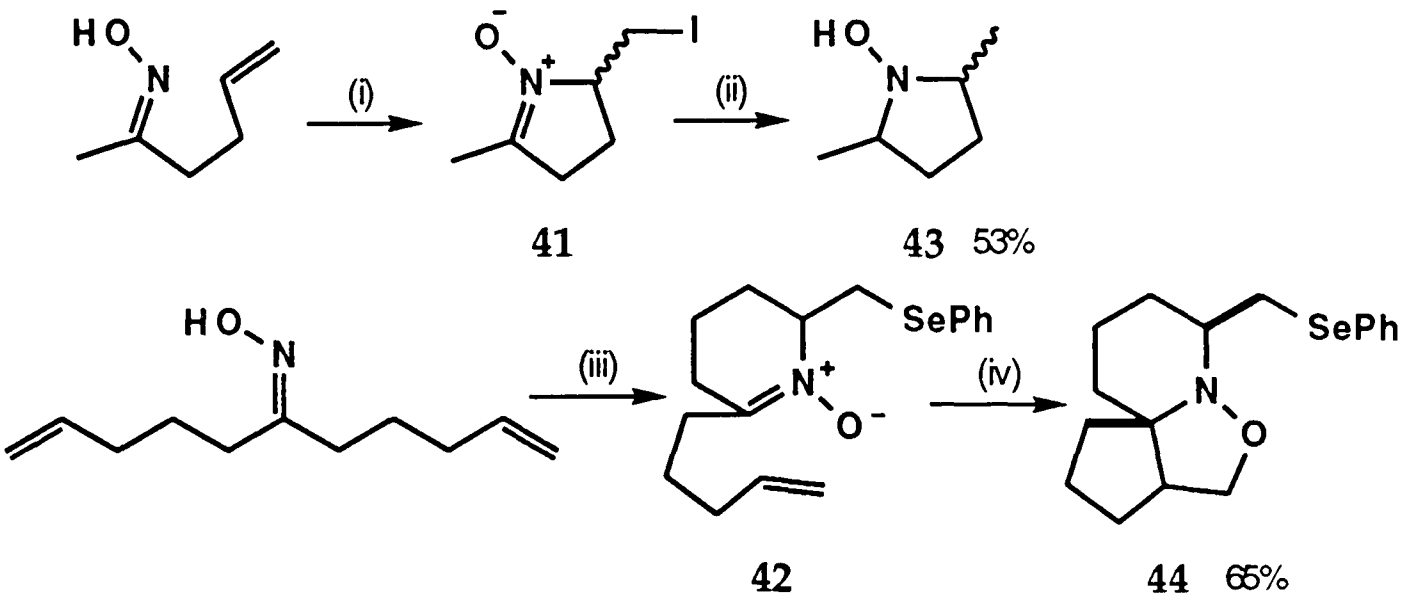
39 **40**

Conditions: (i) 1-(Methylthio-thiocarbonyl)-1-phenylhydrazine. (ii) 0.1 eq. $(^{n}Bu_3Sn)_2$, cyclohexane, *hν*.[26]

Scheme 11

4.5.3. Electrophile Induced Cyclisations of Oximes

Grigg and co-workers[27] reported an electrophile induced cyclisation of oximes onto carbon-carbon π-bonds[28] resulting in nitrones. Further work by Tiecco *et al.*[29] has developed this methodology. Scheme 12 shows the potential of such a sequence, since the resultant nitrones **41** and **42** can be reduced to pyrrolidines, e.g. **43**, or further cyclised to tricycles, e.g. **44**.



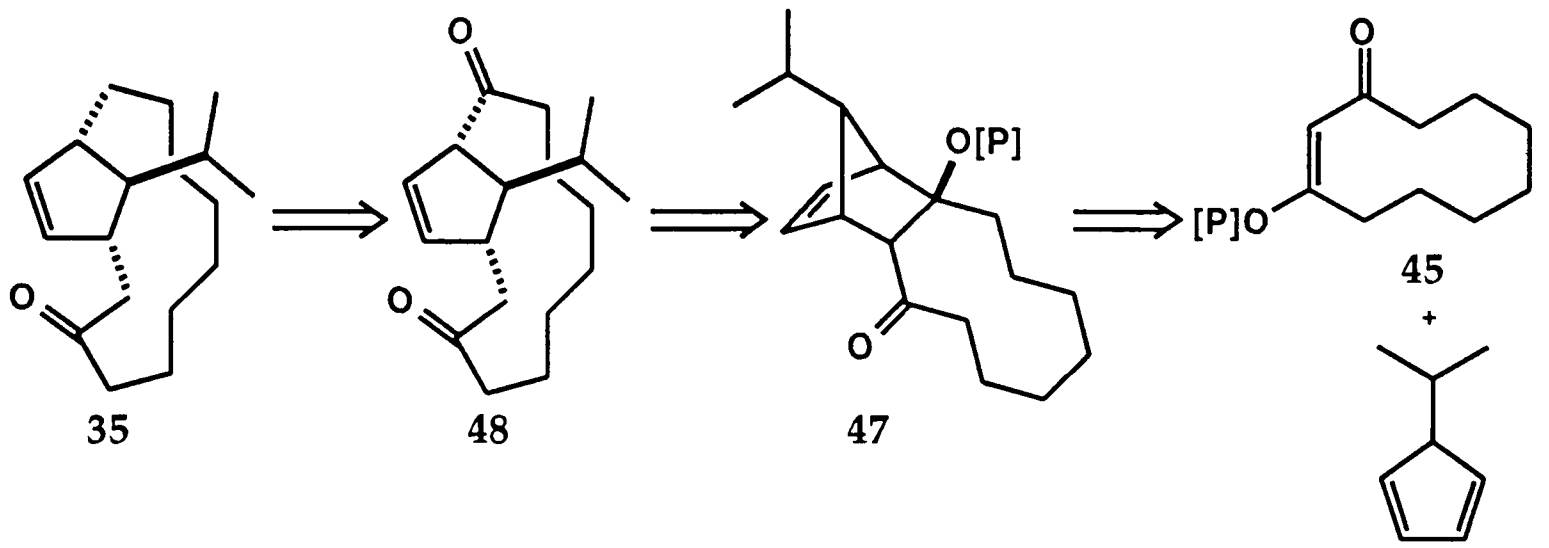
Conditions: (i) I_2, DCM, K_2CO_3; quant. (ii) $LiAlH_4$. (iii) PhSeBr, MeCN, K_2CO_3; quant. (iv) Δ

Scheme 12

RESULTS & DISCUSSION I‡

5.1. Retrosynthetic Analysis

We proposed that the Diels-Alder reaction between a protected β-hydroxycyclodecenone **45** and isopropyl-cyclopentadiene[30] **46** would give an *endo*-adduct **47** with the isopropyl group in the desired orientation shown in Figure 5 despite possible complications arising from [1,5]-hydrogen shifts.



46

Figure 5

Such selectivity, initially reported by Corey and co-workers,[31] has been observed in a wide variety of Diels-Alder reactions.[31,32] One recent example of this, in an asymmetric fashion towards the synthesis of a Corey prostaglandin intermediate **49** by Kagan,[32b] is given in Scheme 13.

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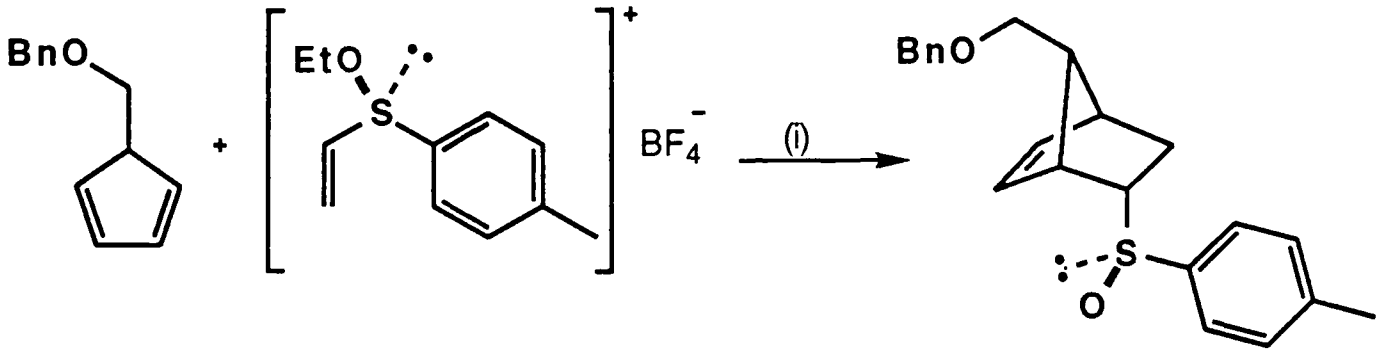
‡ This work was presented as a poster at the Pre-doctoral Symposium to the Autumn meeting of the Royal Society of Chemistry at Sheffield University, September 1995. In addition the majority of this work was presented orally at the 211th Meeting of the American Chemical Society in New Orleans, Louisiana, USA in March 1996[87] and at the Oxford University Graduate Symposium, Dyson Perrins Laboratory, September 1996.



49

Conditions: (i) NaOH; endo/exo> 98:2; d.e. > 96%.

Scheme 13

Furthermore such an isopropyl substituted adduct **47** would, in theory, be able to fragment directly *via* a retro-aldol reaction[33] to give the ring-opened bicycle **48**. Selective reduction of the most hindered ketone would give the unsaturated macrocyclic ketone **35**. A review of similar cycloaddition, fragmentation approaches to medium and large rings is given in Section **5.2.**.

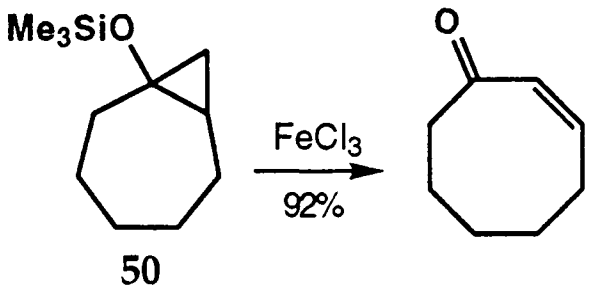
5.2. Cycloaddition-Fragmentation Approaches to Ring Systems

In order to form a medium or large ring through fragmentation[34] of a cycloadduct, the cycloaddition precursors need to be carefully chosen so that the relationship of functional groups in the cycloadduct, combined with the intermediate ring strain, create a system whose stability is increased once fragmentation has occurred; thus there are numerous examples of ring-expansions *via* fragmentations of 3- and 4-membered rings. The following section provides a brief insight into the types of strategies adopted.

5.2.1. [2+1] Cycloaddition-Radical Fragmentation

There are numerous reports of fragmentations of radicals α- to cyclopropane ring systems[35] and such cyclopropyl systems tend to be readily available from alkenes using either the Simmons-Smith reaction[36] or related carbenoid addition processes. One example, from the work of Saegusa *et al.*,[35b]

of a medium ring synthesis *via* a one carbon ring-expansion of **50** is shown in Scheme 14.

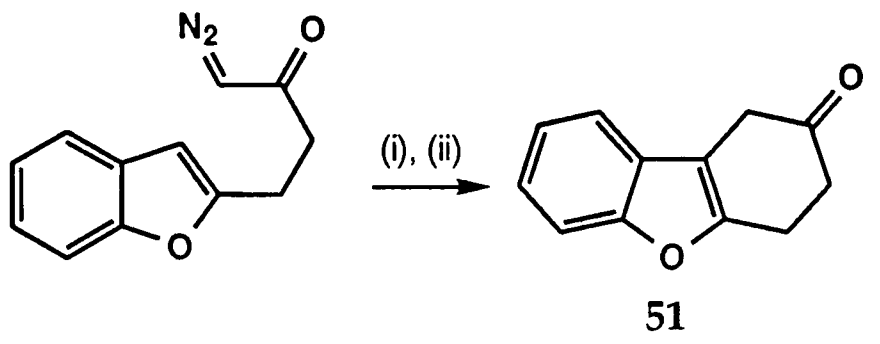


50

Scheme 14

5.2.2. [2+1] Cycloaddition-Retro-Aldol Fragmentation

There are many examples of heterolytic fragmentations of hydroxycyclopropyl ketones.[37] One example, reported by Padwa and co-workers,[37b] of a ring expansion promoted by the retro-aldol type reaction[33] of an intermediate oxycyclopropyl ketone (Scheme 15) led to generation of the tricycle **51**.



51

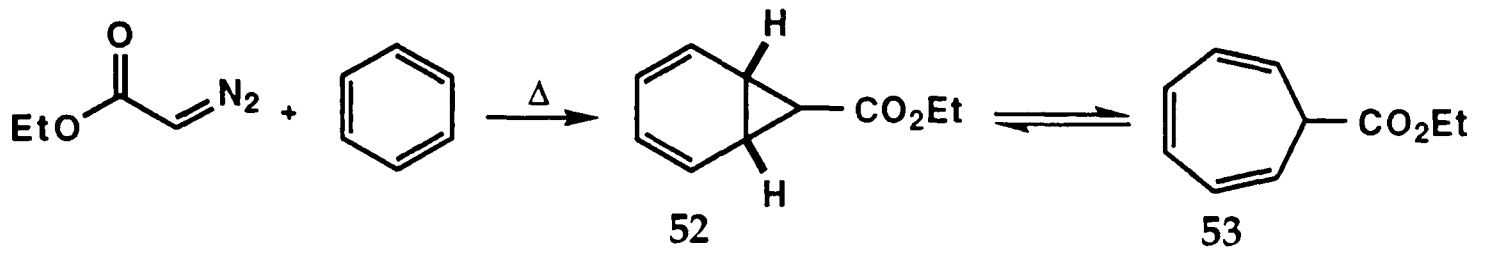
Conditions: (i) $Rh_2(OAc)_4$. (ii) H^+.[37b]

Scheme 15

Stork and Macdonald[38] reported the formation of 2-chloro-2-cyclopentadecenone, a precursor for their synthesis of Muscone, *via* a Grob-type fragmentation[34a,b] of a siloxydichlorocyclopropane system.

5.2.3. [2+1] Cycloaddition-Electrocyclic fragmentation

Carbene additions to aromatic compounds give 1,3-diene products which are in thermal equilibrium with cycloheptatrienes by virtue of a *disrotatory* ring-opening reaction. An example of the rearrangement of the 1,3-diene **52** to **53**, reported by Baldwin and Smith,[39] is shown in Scheme 16.



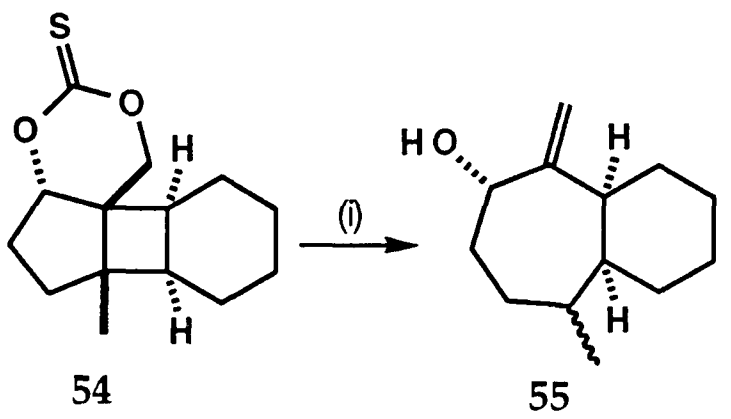
52 53

Scheme 16

The sigmatropic rearrangement of vinylcyclopropanes to cyclopentenes is also well documented.[40]

5.2.4. [2+2] Cycloaddition-Radical Fragmentation

Ziegler reported an elegant sequence based on the ring opening of a cyclobutylcarbinyl radical[41] **54,** derived from a [2+2] cycloadduct, fragmented to generate the medium ring bicycle **55** (Scheme 17).

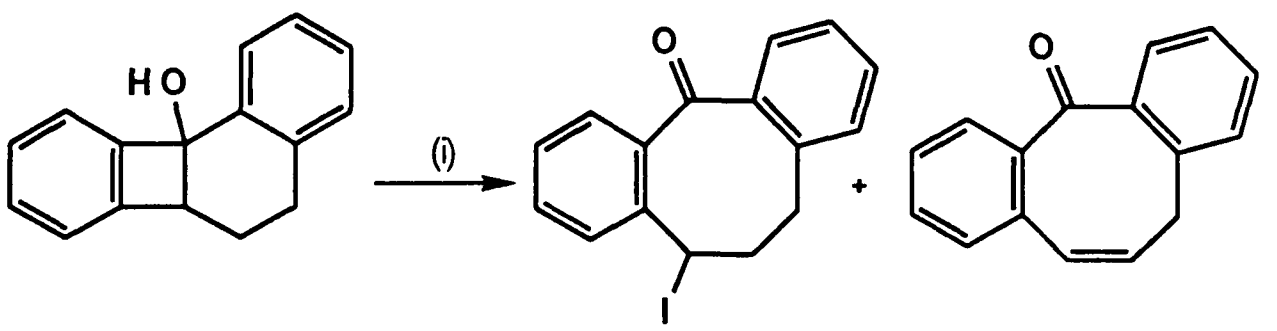


54 55

Conditions: (i) $^{n}Bu_3SnH$, AIBN, PhH; (1:1 mixture of diastereomers).[41]

Scheme 17

A similar process has been achieved by Suginome,[42] involving an alkoxy radical fragmentation of cycloadduct **56,** shown in Scheme 18.



56 59% 19%

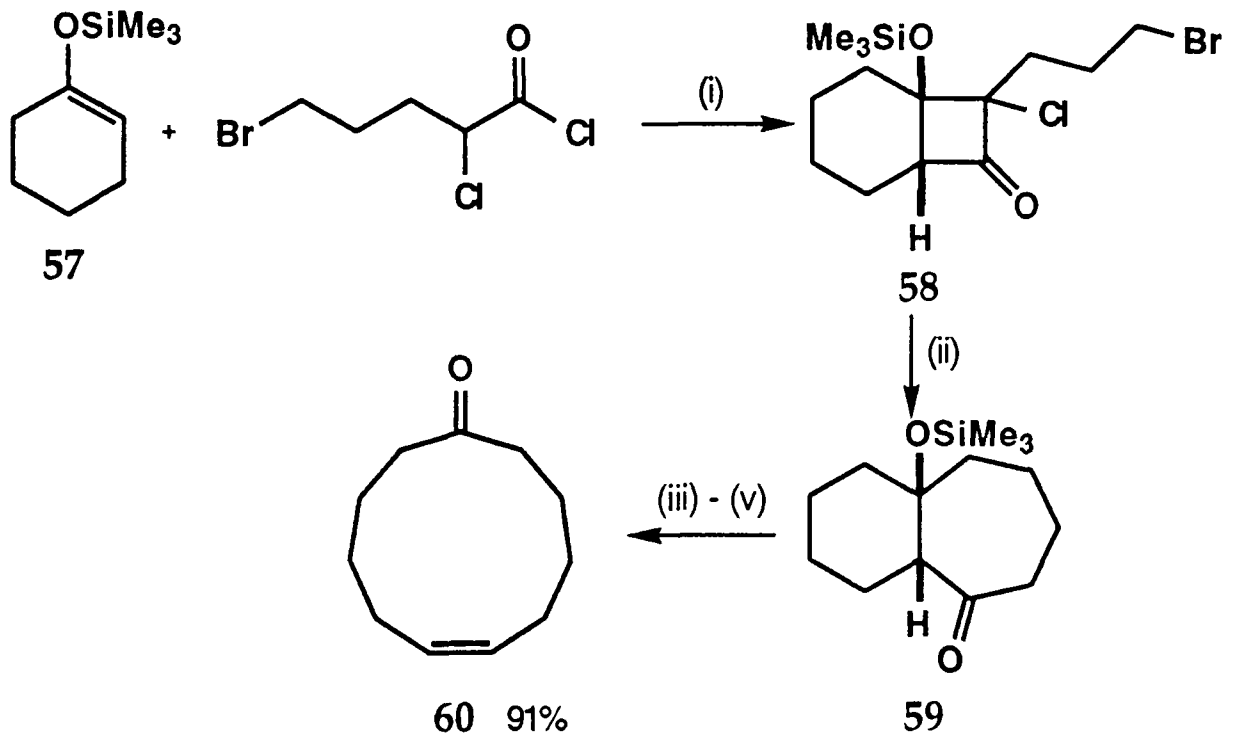
Conditions: (i) I_2-I_2O, *hv*.[42]

Scheme 18

Lange and Gottardo[43] have also reported syntheses based on similar strategies.

5.2.5. [2+2] Cycloaddition-Radical Ring Expansion-Grob Fragmentation

Dowd and Zhang have reported the synthesis of bicyclo[5.4.0]undecanes and decalins[44] *via* radical ring expansion of bicyclo[4.2.0]cycloadducts and have extended this approach to an ingenious synthesis of 11-membered rings[45] based on the initial cycloaddition of a ketene to a silyl enol ether **57**, rather than an unfunctionalised alkene. The cycloadduct **58** in Scheme 19 undergoes a free-radical 3-carbon ring expansion to yield bicyclic β-hydroxyketone **59**. Rather than submitting this to retro-aldol conditions, Dowd *et al.* further manipulated the functional groups to promote a Grob fragmentation[34a,b] and generation of the cycloalkenone **60**.



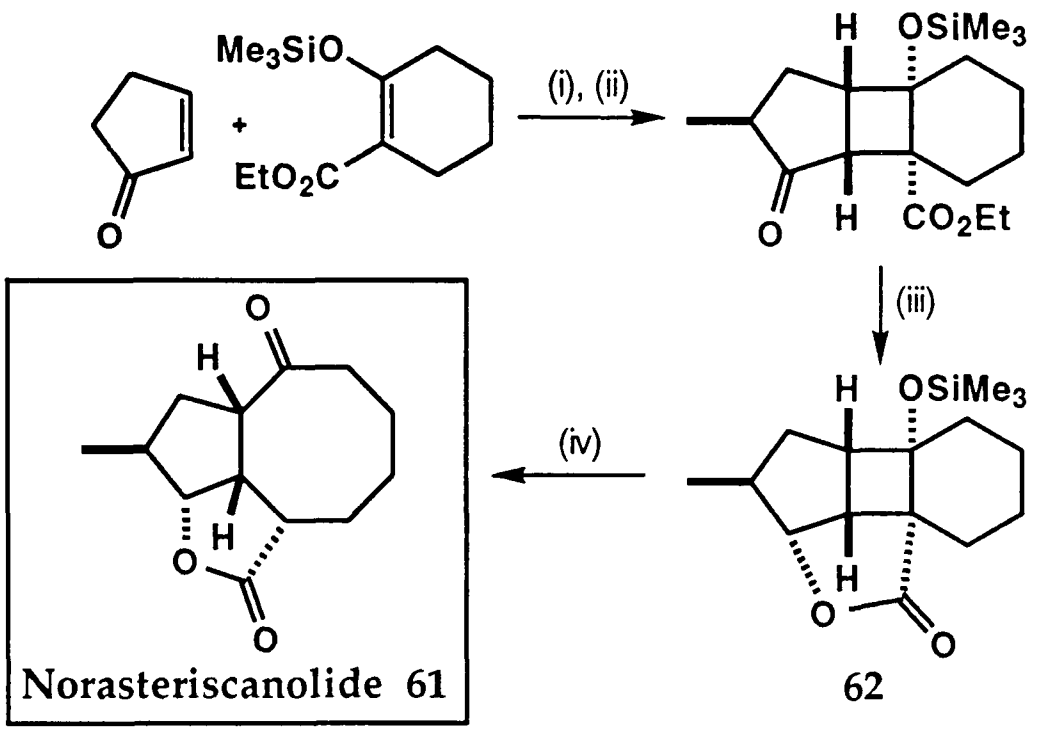
Conditions: (i) Et_3N. (ii) *n*-Bu_3SnH, AIBN, PhH. (iii) $LiAlH_4$. (iv) MsCl, Et_3N. (v) ^tBuOK.[45]

Scheme 19

5.2.6. [2+2] Cycloaddition-Retro-aldol Fragmentation

Lange and co-workers[46] have reported a number of such cycloaddition, fragmentation sequences. In their recent synthesis of Norasteriscanolide **61**,

Lange[46a] made use of the de Mayo reaction[47] in the construction of the carbon framework. The de Mayo reaction involves the [2+2] photoaddition of β-diketones with alkenes to give adducts which fragment in a retro-aldol reaction[33] to give ring enlarged products. Lange's impressive four step synthesis of Norasteriscanolide **61** *via* retro-aldolisation of the β-hydroxylactone **62** is shown in Scheme 20.



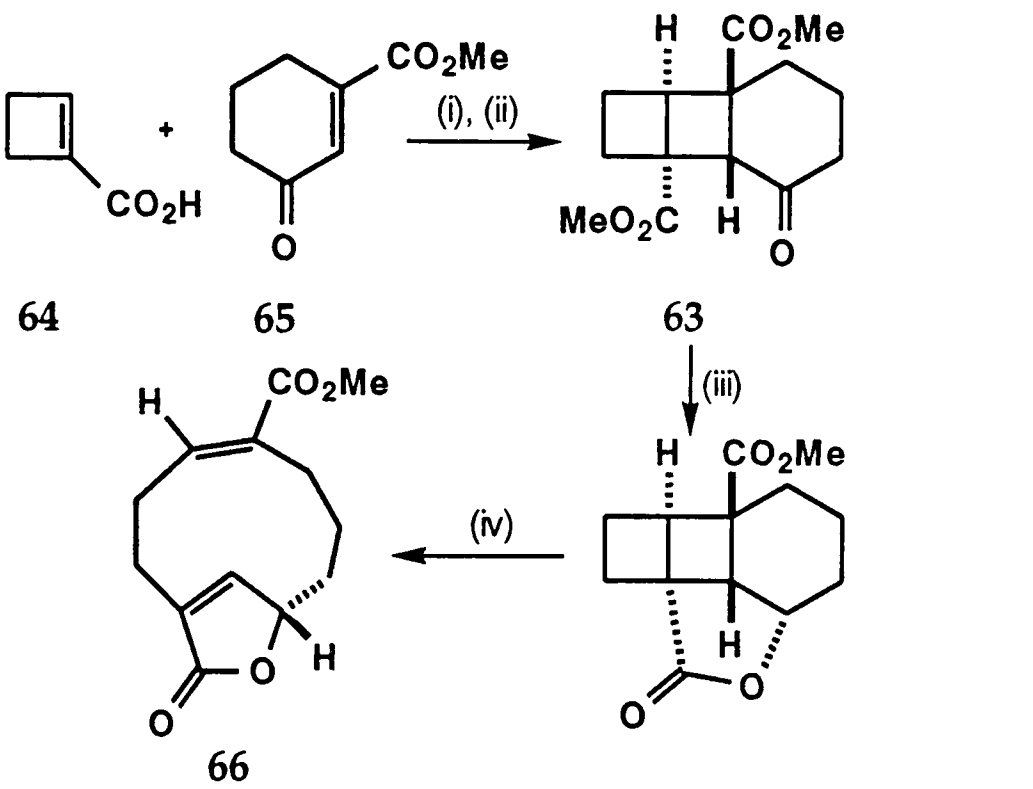
Conditions: (i) *hν*, DCM; 35%. (ii) LDA, MeI; 95%. (iii) $NaBH_4$; 83%. (iv) TBAF; 97%.[46a]

Scheme 20

Several other interesting examples employing this strategy include work by Naito *et al.*[48] and Wiesner and co-workers[49] in their synthesis of a Julolidine derivative.

5.2.7. [2+2] Cycloaddition-Retro [2+2] Fragmentation

Lange *et al.* have also employed retro [2+2] fragmentations as a method of ring expansion.[50] They showed that the tricycle **63** formed from [2+2] cycloaddition of the enones **64** and **65** could ultimately be ring opened on heating to a ten-membered ring **66** (Scheme 21).

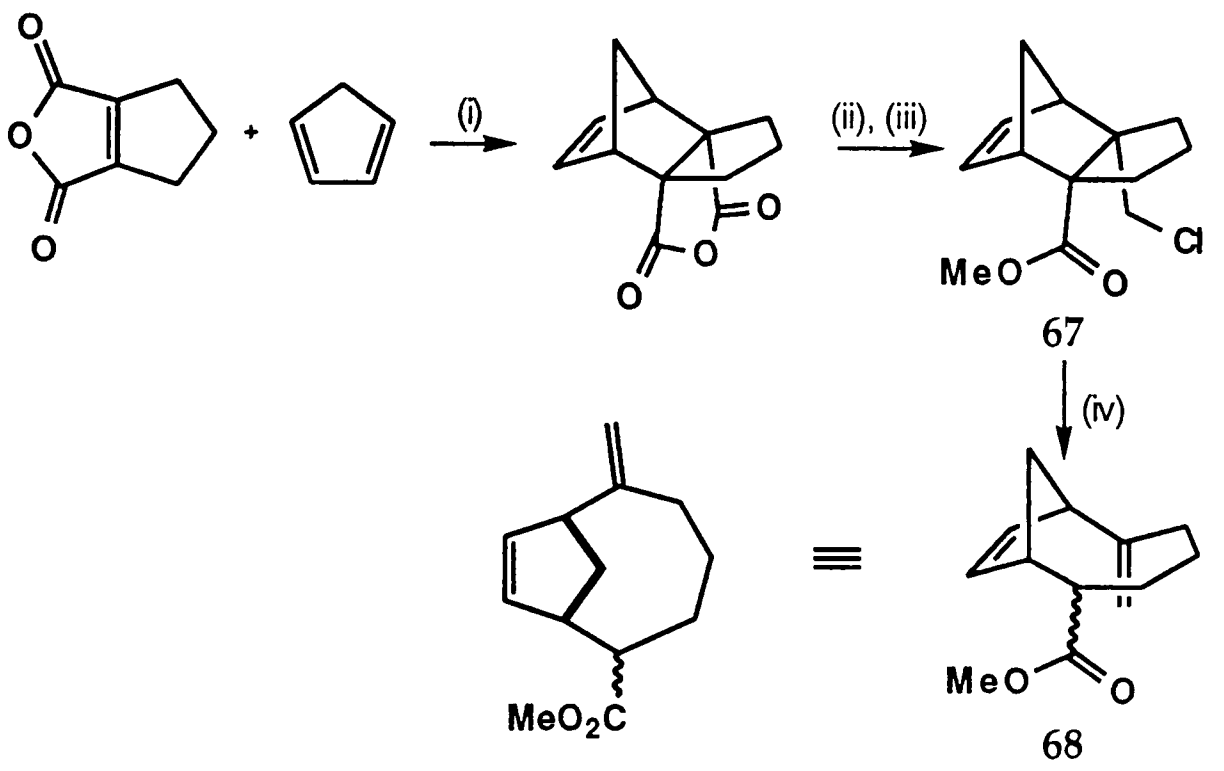


Conditions: (i) *hν*, PhH. (ii) CH_2N_2; 53% (2 steps). (iii) $NaBH_3CN$; 51%. (iv) Δ; 85%.[50a]

Scheme 21

5.2.8. [4+2] Cycloaddition-Radical Fragmentation

Recent work by Ghosh and co-workers[51] has demonstrated the feasibility of radical fragmentations of carefully constructed Diels-Alder adducts **67** to give cyclooctanes **68** (Scheme 22).



Conditions: (i) $AlCl_3$, THF, 0°C. (ii) $NaBH_4$; 81%.
(iii) $SOCl_2$, MeOH. (iv) $^nBu_3SnH$, AIBN, Δ; 87%.[51]

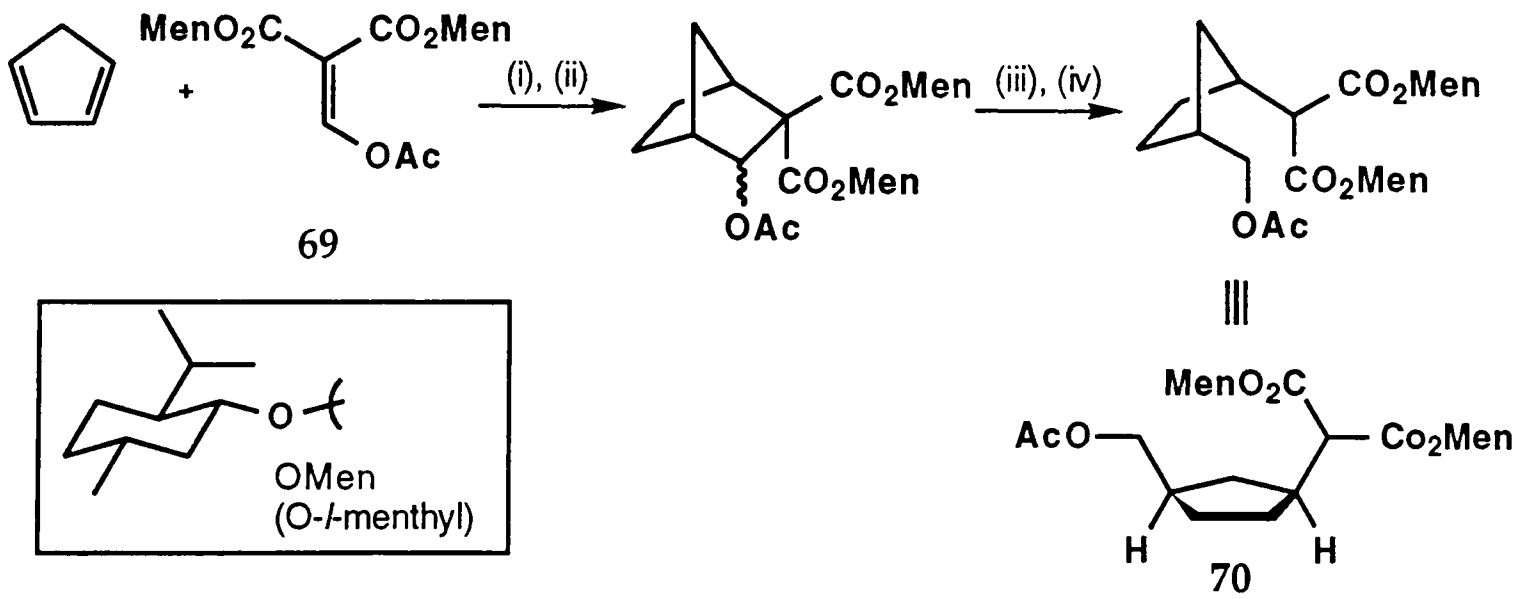
Scheme 22

Ring cleavage *via* a carbon-centred radical has mainly been observed in strained rings such as cyclopropanes[35] and cyclobutanes[43,52] and Ghosh attributes the fragmentation observed in his system to both the release of the strain associated with the norbornene and with the non-bonded interactions between protons in the cycloadduct.

5.2.9. [4+2] Cycloaddition-Retro-Aldol Fragmentation

In order for an intermolecular Diels-Alder reaction to generate a β-hydroxyketone capable of forming cyclic products on retro-aldol fragmentation,[33] the precursors to the pericyclic reaction need to be a β-hydroxycycloalkenone dienophile and a diene.

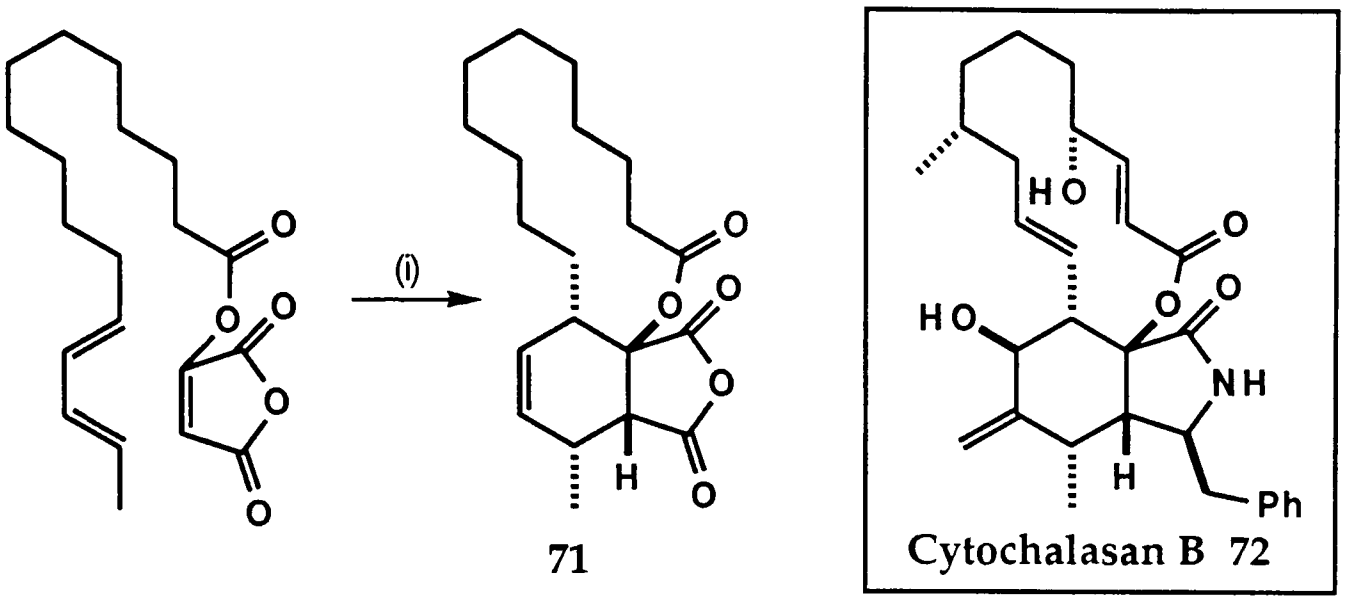
Katagiri and Kaneko have demonstrated the effectiveness of this Diels-Alder, retro-aldol methodology, albeit in an acyclic case, in their syntheses of carbocyclic analogues of C-nucleosides.[53] Scheme 23 shows such a sequence involving the [4+2] cycloaddition reaction of the chiral dienophile **69** with cyclopentadiene generating enantiomerically pure carbocycle **70** after the retro-aldol reaction.[53a]



Conditions: (i) $TiCl_4$, PhMe, -78°C; 83% (endo: exo, 3:1). (ii) 10% Pd-C, EtOH: Et_2O (2:1). (iii) $NaBH_4$, NaOMe-MeOH; 81%. (iv) Ac_2O, py, PhH (e.e. >90%).[53a]

Scheme 23

There have been other reports of Diels-Alder reactions utilising protected β-hydroxyenones,[54-57] for example Thomas' formation of the tricycle[57] **71**, containing the skeleton of Cytochalasan B **72**, in Scheme 24.



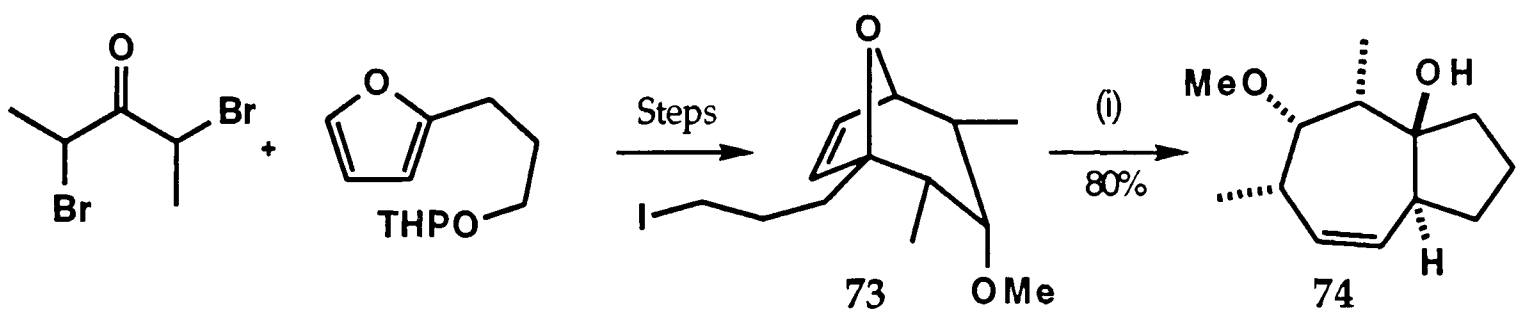
Conditions: (i) Δ, 6h; 70%.[57]

Scheme 24

However, although there have been many reports of Diels-Alder reactions involving cycloalkenones,[58] and acyclic protected β-hydroxyalkenones[53-57] as dienophiles, reports of β-hydroxycycloalkenone derivatives in [4+2] cycloadditions are rare.

5.2.10. [4+3] Cycloaddition-Fragmentation

The [4+3] cycloaddition[59] between a furan and an oxyallylic cation generates an adduct which is capable of fragmenting to give a medium ring.[60,61] One strategy reported by Lautens *et al.*,[61] employing an anionic ring fragmentation of **73** to give the bicycle **74**, is described in Scheme 25.



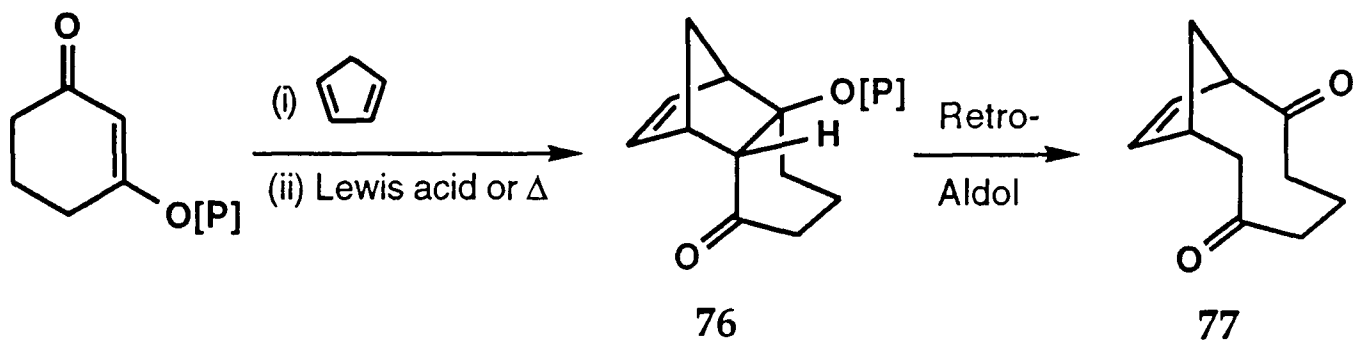
Conditions: (i) ^{t}BuLi, Et_2O.[61]

Scheme 25

5.3. Model Studies Part I

5.3.1. Diels-Alder Reactions with 3-Hydroxycyclohexenone Dienophiles

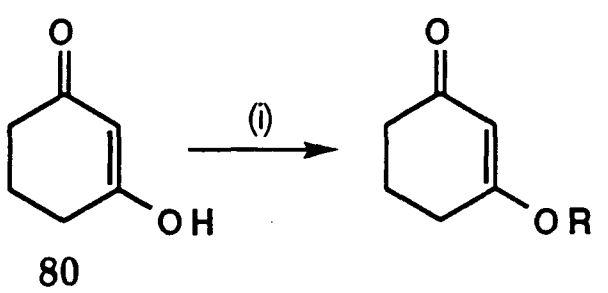
It was decided to test the feasibility of our approach by investigating the Diels-Alder reaction between cyclopentadiene[62] **75** and a variety of protected 3-hydroxy-2-cyclohexenones. It was hoped that the cycloadducts **76** would then undergo retro-aldol reaction to give ring expanded products **77**. This test cycloaddition, fragmentation approach is shown in Scheme 26.



76 **77**

Scheme 26

Accordingly the two known precursors **78** and **79** were prepared[63,64] (Scheme 27).



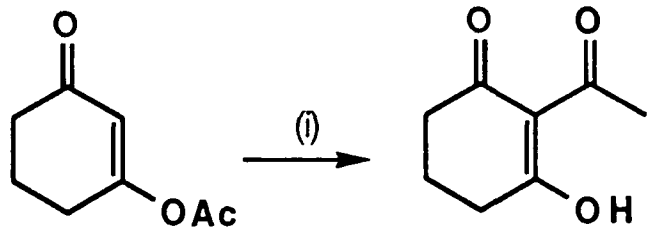
80

Conditions: (i) For **78**: R = -$SiMe_3$; $Me_3SiNHSiMe_3$, Im, Δ, 2h; 87%.[63] (i) For **79**: R = -Ac; Ac_2O, Im, RT, 15h; 81%.[64]

Scheme 27

Attempts to effect the Diels-Alder reaction between cyclopentadiene[62] **75** and these substrates under a variety of conditions (Δ, reflux; Δ, sealed tube; $AlCl_3$; $SnCl_4$; $TiCl_4$; $BF_3.OEt_2$) proved unsuccessful. The reactions involving Lewis acids were all performed at temperatures ranging from -78°C to RT.

It was decided to prepare a more electron-deficient dienophile; therefore **81** was synthesised (Scheme 28) by a Fries-type rearrangement of the acetate[64] **79**. Attempts to prepare a protected form of this tetrasubstituted alkenone failed.



79 81

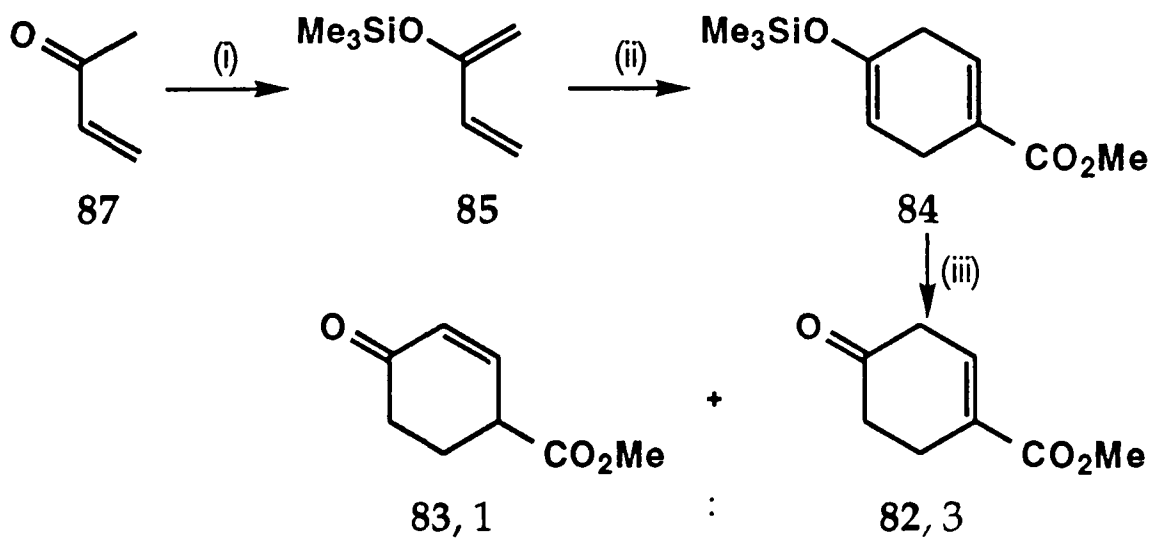
Conditions: (i) $AlCl_3$, DCM, 0°C to RT, 1h; 92%.[64]

Scheme 28

No cycloaddition products were observed on treatment of **81** with cyclopentadiene[62] **75** under the conditions mentioned previously.

5.3.2. Diels-Alder Reactions with 1,5-Ketoester Dienophiles

It was suggested that the electronic and steric effects, resulting from direct attachment of an electron-donating group to a substituted alkene terminus, were responsible for the lack of reactivity of the dienophiles. Thus we proposed to synthesise a theoretically more reactive di-substituted cyclohexenone which, after cycloaddition, could conceivably fragment in a decarboxylation process.[65] Accordingly the known cyclohexenones[66] **82** and **83** (ratio **82**:**83**, 3:1) were prepared *via* hydrolysis of the cycloadduct **84**, derived in turn from the Diels-Alder reaction between diene **85** and methyl propiolate **86** (Scheme 29).[67,68]



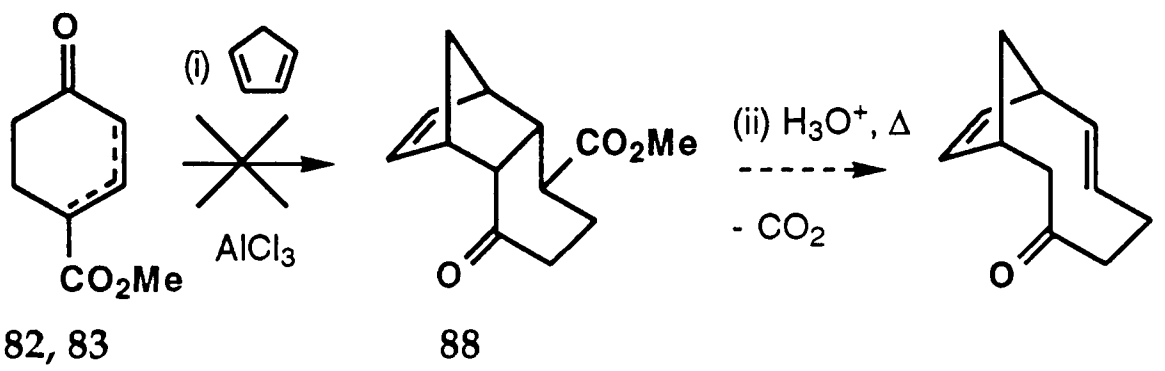
87 85 84 83, 1 : 82, 3

Conditions: (i) TMSCl, NaI, Et_3N, MeCN, 15h, Δ; 60%.[68] (ii) Methyl propiolate **86**, sealed tube, 140°C, 87h; 30%.[67] (iii) H_2SO_4, (1:1, THF:H_2O), 1h; 63%.[66,67]

Scheme 29

Despite the mixture of isomers, the Diels-Alder reaction with cyclopentadiene **75** was attempted using $SnCl_4$ and $AlCl_3$. It was thought that under such Lewis acidic conditions interconversion of the alkenes would occur to allow the cycloaddition to proceed through the presumably more reactive dienophile **83**.

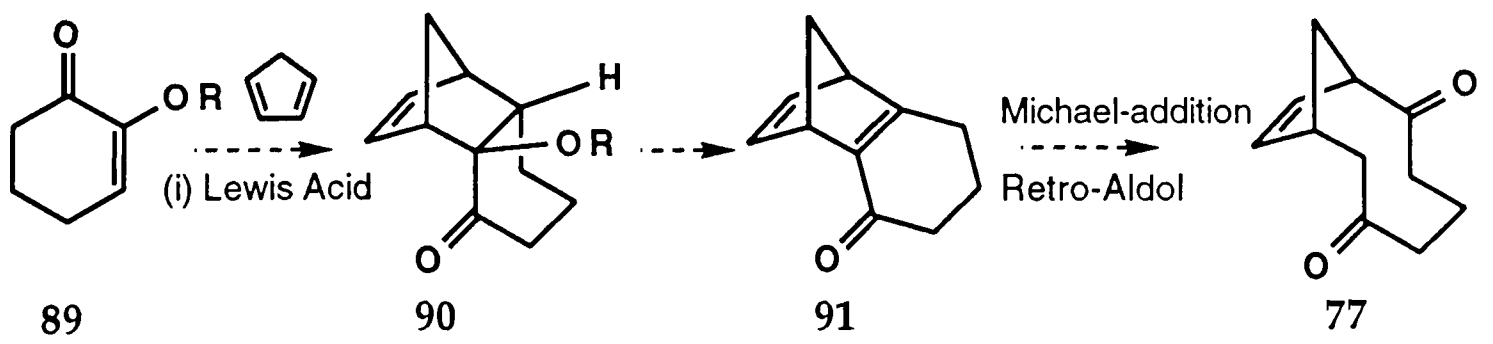
However, under these conditions, no cyclised products were observed. Scheme 30 summarises this overall, unsuccessful strategy to form the 1,5 dicarbonyl adduct **88** with subsequent fragmentation.



Scheme 30

5.3.3. Diels-Alder Reactions with 2-Hydroxycylohexenone Dienophiles

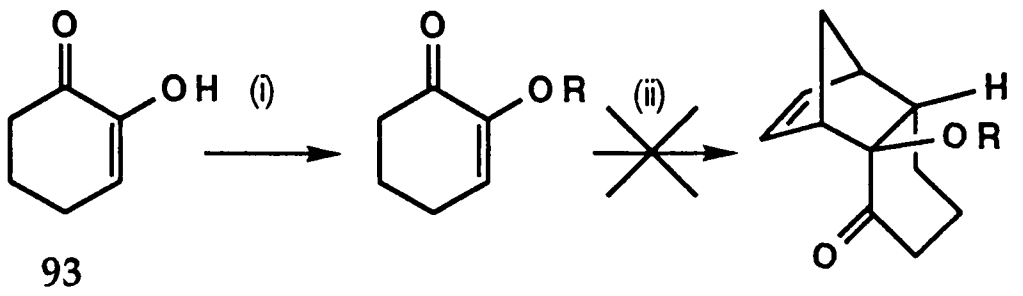
We then turned our attention to investigating the cycloaddition between cyclopentadiene **75** and a 2- substituted cyclohexenone **89**. We hoped that the cycloadduct **90** thus formed, might eliminate to give an enone **91**, which could be induced to undergo Michael addition and retro-aldol type fragmentation giving **77**. This strategy is illustrated in Scheme 31.



Scheme 31

Although there are several known medium-ring cycloalkynone equivalents[69,70] for the formation of adducts similar to **91**, we were attracted to the above route due to the reported ease with which readily available 2-hydroxycyclohexenones undergo such cycloadditions[71] although we were also wary of complications that could arise from α-ketol rearrangements.[72]

The acetate[73] **92** was synthesised, but treatment of this or the unprotected 2-hydroxycyclohexenone **93** with cyclopentadiene **75** and Lewis acids[71] did not generate identifiable cycloadducts (Scheme 32).



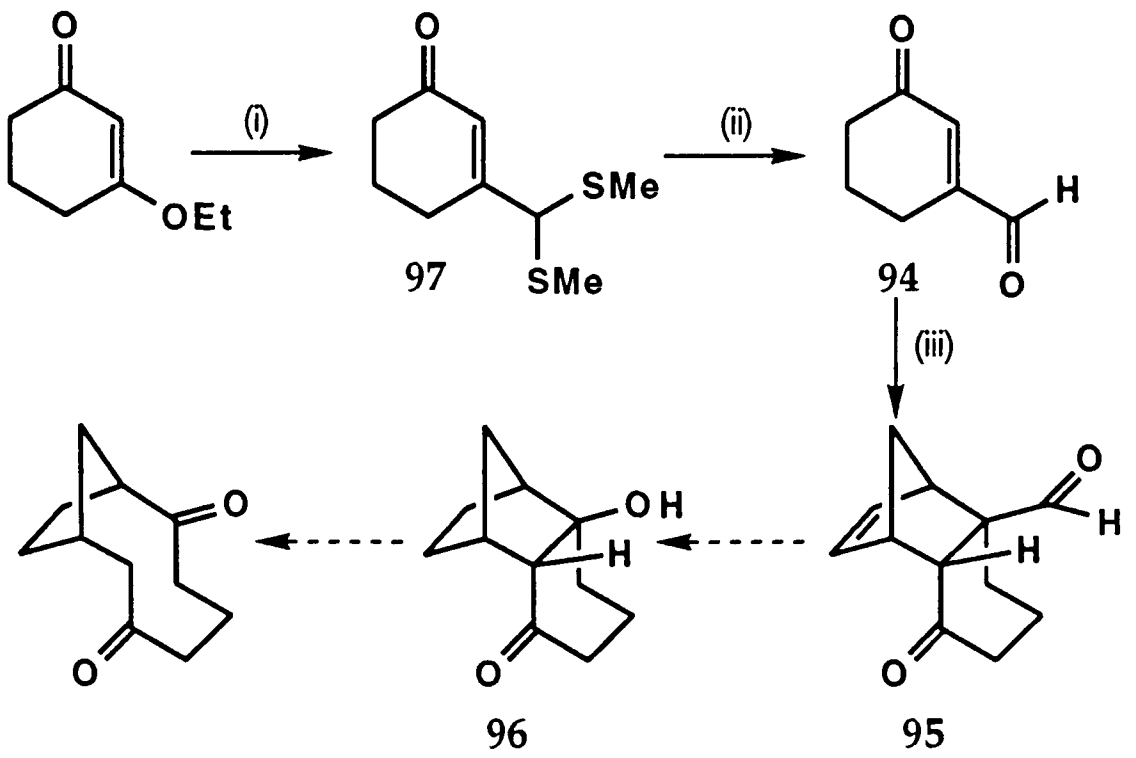
93

Conditions: (i) For **92**, R= OAc: Ac_2O, Im, RT, 15h; 77%.
(ii) **92**, R= OAc or **93**, R= OH; $TiCl_4$, MeCN, -78°C.[71]

Scheme 32

5.3.4. Diels-Alder Reactions with 3-Formylcyclohexenone Dienophiles

We decided to use a doubly activated dienophile **94** in order to achieve a cycloaddition reaction. Conceivably the cycloadduct **95** (once reduced) could undergo selective Baeyer-Villiger reaction[74] to give the β-hydroxyketone precursor **96** to the retro-aldol reaction. Thus the known aldehyde[75] **94** was prepared *via* hydrolysis of the thioketal[75] **97** and submitted to the conditions required for Diels-Alder reaction (Scheme 33).



Conditions: (i) $(MeS)_2CH_2$, ^nBuLi, THF, 0°C, 4h; aq. HCl, 15h, RT, 75%.[75] (ii) $BF_3.OEt_2$, HgO, (THF:H_2O, 1:1), 0°C, 1.5h; 79%.[75] (iii) $AlCl_3$, DCM, Cyclopentadiene, -78°C, 1.5h; RT, 6h; 50%.

Scheme 33

The cycloadduct **95** did form (Appendix C), though the reaction could not be driven to completion resulting in a mixture of starting material and product.

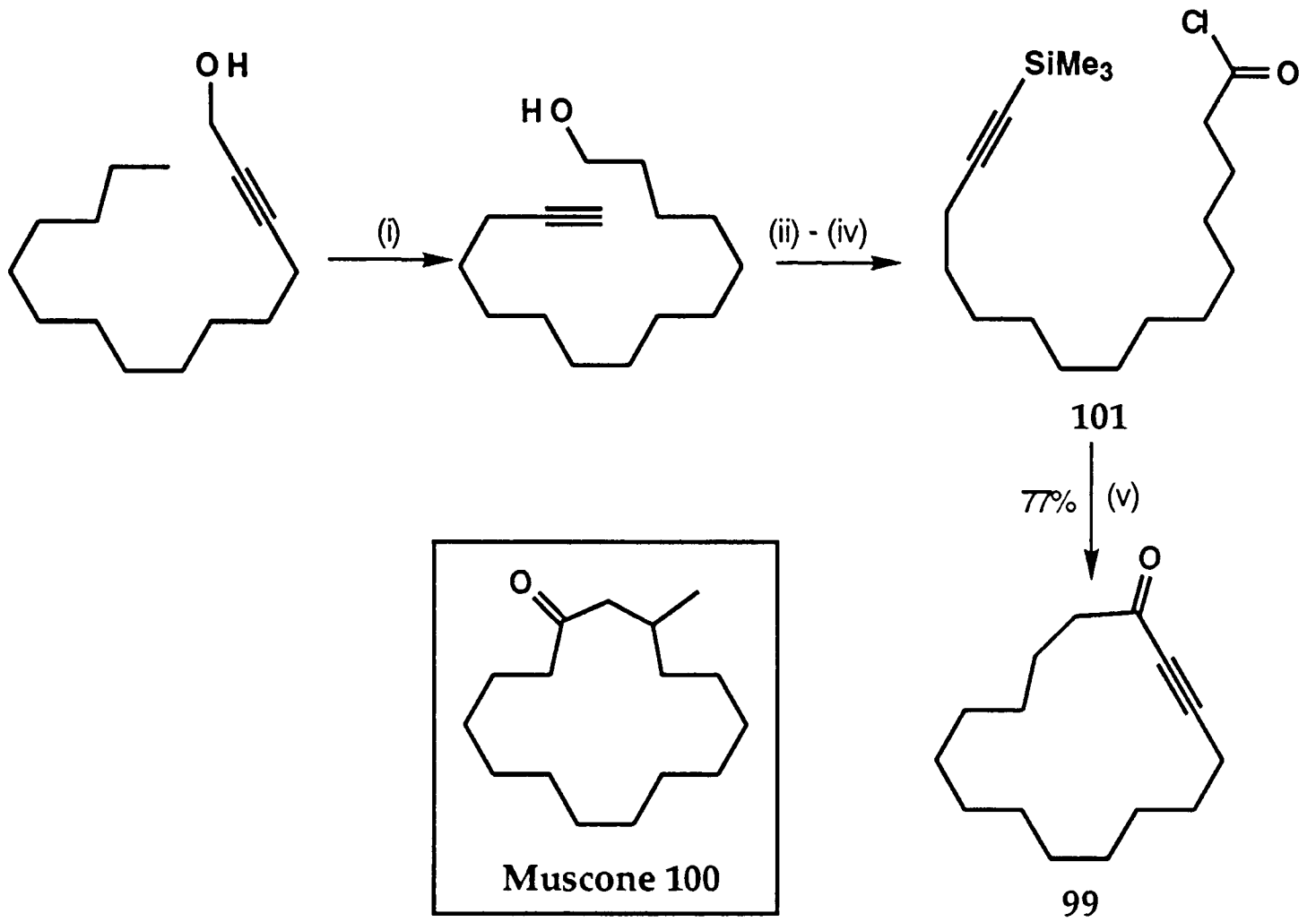
5.4. Model Studies Part II

5.4.1. Previously we investigated the possibility of generating a cycloadduct which could undergo a Michael, retro-aldol type fission process (**5.3.3.**). In the 6-membered model system we proposed to generate such adducts from substituted cycloalkenones followed by elimination, however, if a larger ring cycloalkynone was used, the enone cycloadduct would be available directly.

Work run concurrently with the 3-formylcyclohexenone investigation (**5.3.4.**) was concerned with the synthesis and subsequent Diels-Alder reaction of the unreported cyclodec-2-yn-1-one **98**. The latter work (**5.3.4.**) was suspended in favour of this new approach.

We were attracted to this approach because it would lead to the correct ring-size for Roseophilin. Although the required cycloalkynone **98** was unknown, Utimoto had reported an approach to similar ring systems based on

a silicon accelerated intramolecular Friedel-Crafts acylation between a silylalkyne and an acid chloride.[76] This is illustrated by formation of **99** (an intermediate towards racemic Muscone **100**) from the acid chloride **101** (Scheme 34).



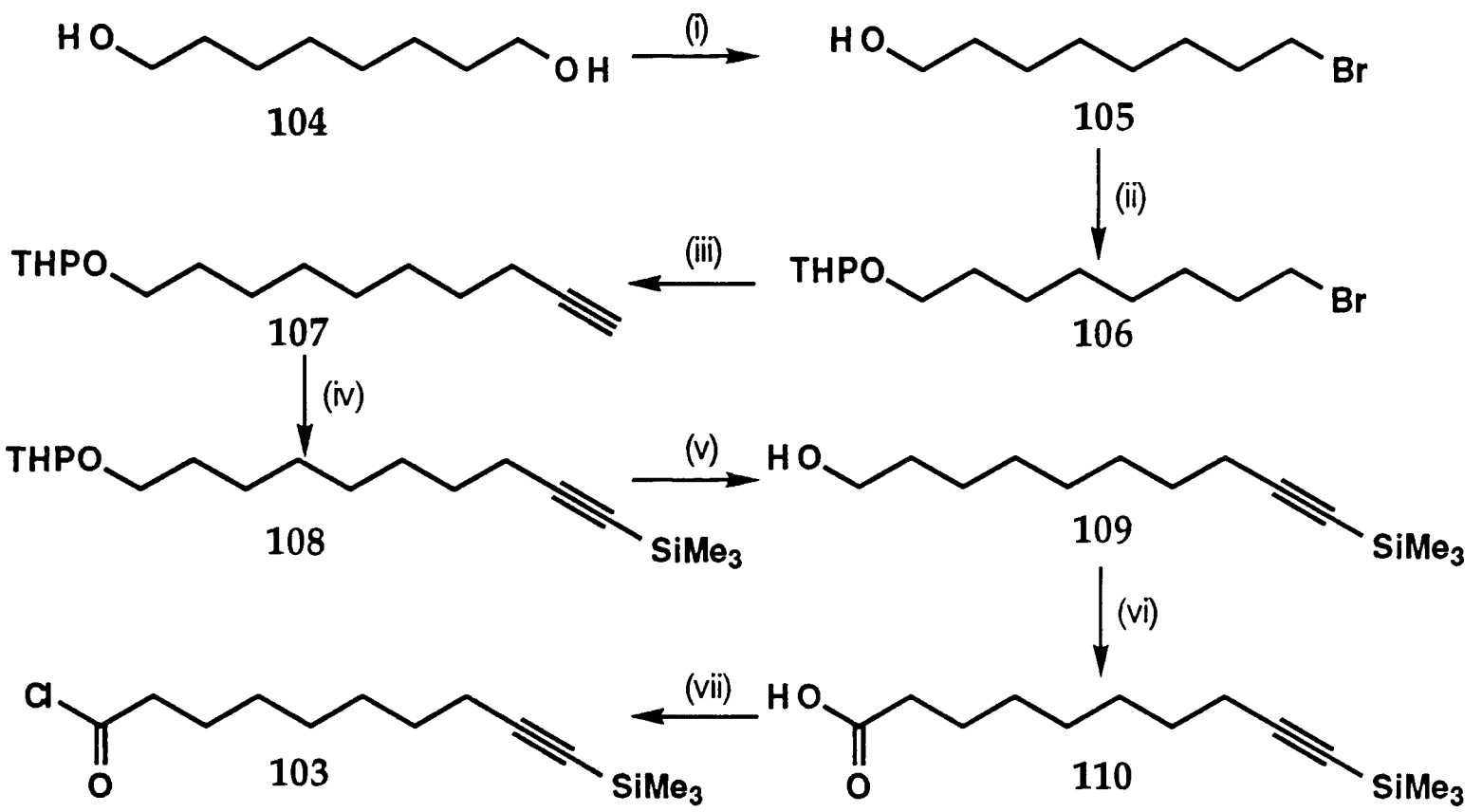
Conditions: (i) Excess KAPA. (ii) ^{n}BuLi, TMSCl. (iii) Jones' reagent.[77]
(iv) $(COCl)_2$, PhH. (v) $AlCl_3$, DCM, Δ, slow addition of acid chloride, 3h.

Scheme 34

Using this methodology Utimoto *et al.* successfully synthesised cycloalkynones with ring sizes 11, 13 and 15.[76] They even attempted the same cyclisation on small ring analogues (sizes 5, 6, 7 and 8) and isolated the corresponding 3-chloro-2-silyl-2-cycloalkenones suggesting that the mechanism proceeds through a vinyl cation β-to silicon.[78]

Gleiter and Merger recently reported the isolation of the highly strained cyclonon-2-yn-1-one **102** from hydrolysis of the addition product derived from dichlorocarbene and cyclooctyne,[79] and the existence of the smallest ring cycloalkynone: cyclooct-2-yn-1-one has been postulated from the results of trapping experiments.[80]

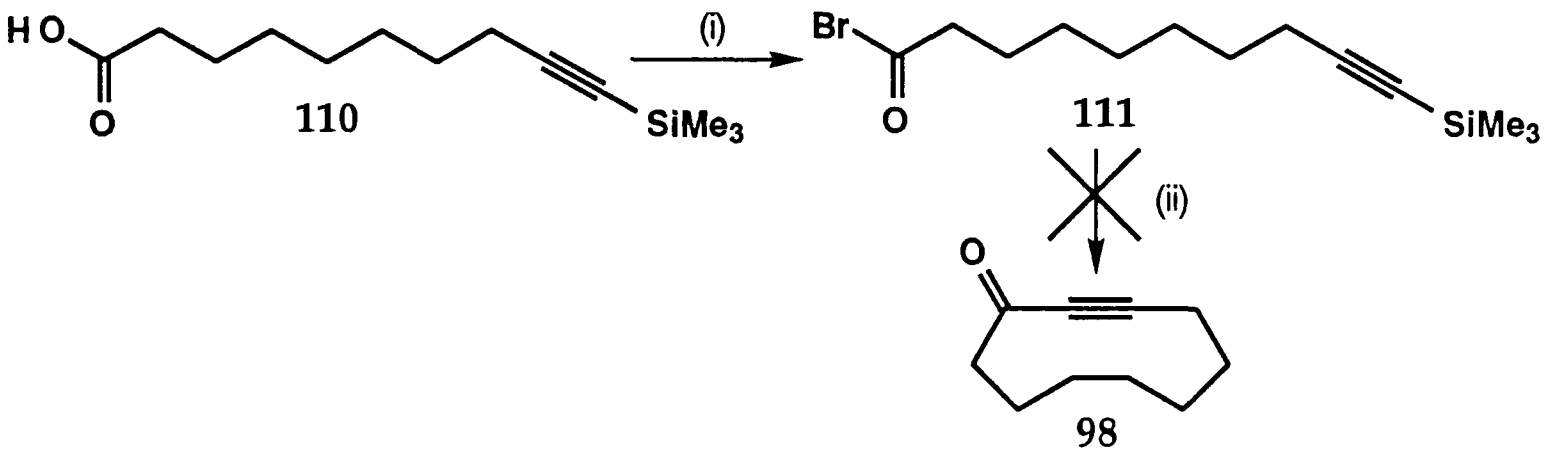
Thus the required cyclisation precursor **103** was synthesised in 7 steps and 60% overall yield from octan-1,8-diol **104** (Scheme 35).



Conditions: (i) 48% aq. HBr, PhH, Dean Stark (-H_2O), Δ, 18h; 85%.[81] (ii) DHP, HCl, 15mins; 95%.[82,83,84] (iii) Li acetylide-EDA complex, DMPU, NaI, THF, 15h; 95%.[83,84] (iv) ^{n}BuLi, TMSCl, -78°C, 1h; 96%. (v) TsOH, MeOH, 15h; 96%.[85] (vi) Jones' reagent, acetone, 0°C, 30mins; 90%.[77] (vii) $(COCl)_2$, PhH, 3h; 95%.[76]

Scheme 35

Initial attempts to effect the cyclisation by slow addition of the acid chloride to a refluxing solution of DCM and $AlCl_3$ at high dilution, as reported by Utimoto,[76] proved unsuccessful. Subsequently the acid bromide **111** was synthesised and treated to the identical conditions described above. Again, no product was isolated; further attempts to cyclise the acid bromide using either $AgNO_3$ or CsF also failed (Scheme 36).

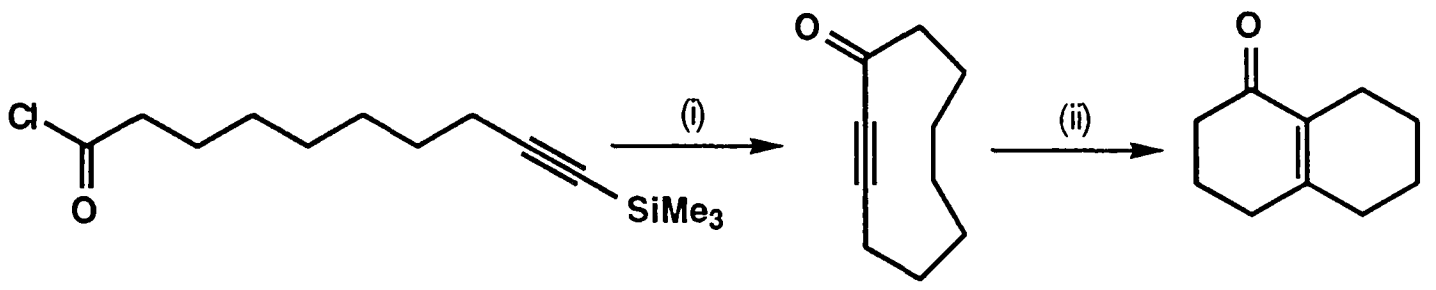


Conditions: (i) $(COBr)_2$, PhH, 3h; 90%. (ii) $AgNO_3$, THF or CsF, 18-crown-6, MeCN[86] or $AlCl_3$, DCM.

Scheme 36

Further work led to the discovery that the cyclisation of the acid chloride **103** could be achieved to give **98**[87] when working at higher concentrations and at temperatures between 0°C and RT. From examining the work-up procedure under a variety of conditions, it was found that sodium sulphate or sodium bicarbonate effectively removed the aluminium salts.

The unreported cyclodec-2-yn-1-one **98** proved to be volatile and rather labile, forming the known bicyclic ketone[88] **112** on silica gel column chromatography (Scheme 37).



103 **98** **112**

Conditions: (i) $AlCl_3$, DCM, 0°C to RT, 75mins; 81%. (ii) SiO_2; 71%.[88]

Scheme 37

A model of cyclodec-2-yn-1-one **98** is shown in Appendix E. It can be seen that the linking methylene chain cannot avoid close contact with the β-position of the alkyne. Conceivably, under acidic conditions, a transannular hydride Michael attack on the alkynone is feasible. The resultant enolate could

then conceivably attack the latent cation forming the [4.4.0] skeleton. Subsequent isomerisation would lead to the product.

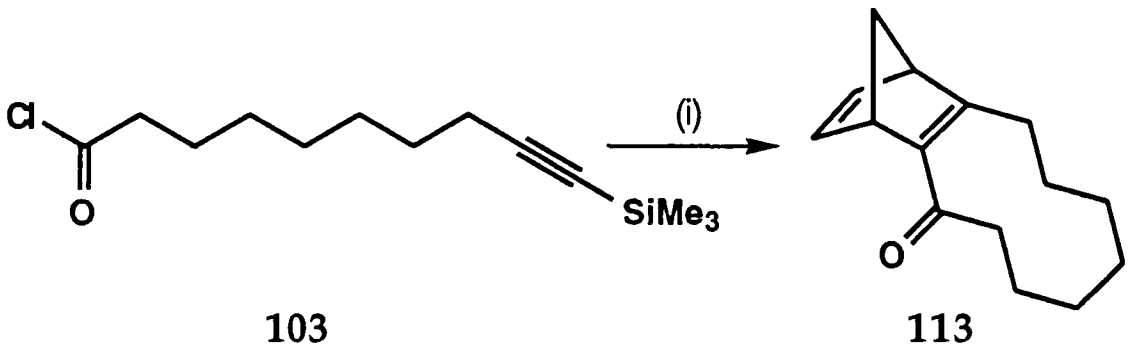
The considerable strain in the molecule causes a downfield shift of the β-triple bond carbon by 9ppm in the ^{13}C NMR spectrum compared to undec-6-yn-5-one, though cyclonon-2-yn-1-one **102**, as expected, shows a greater difference;[79] Table 1 shows a comparison:

Ynone	δ_C α-carbon (ppm)	δ_C β-carbon (ppm)
Cyclonon-2-yn-1-one **102**[79]	84.9	113.7
Cyclodec-2-yn-1-one **98**[87]	82.5	102.9
Undec-6-yn-5-one[79]	80.9	94.1

Table 1

Due to the instability of **98** we proposed to perform the Diels-Alder reaction in one-pot with the alkynone formed *in situ*.

The acid chloride **103** was treated with $AlCl_3$ and cyclopentadiene at a range of temperatures to give the desired cycloadduct **113** in a one-pot cyclisation, Diels-Alder reaction process (Scheme 38).[87]



103 **113**

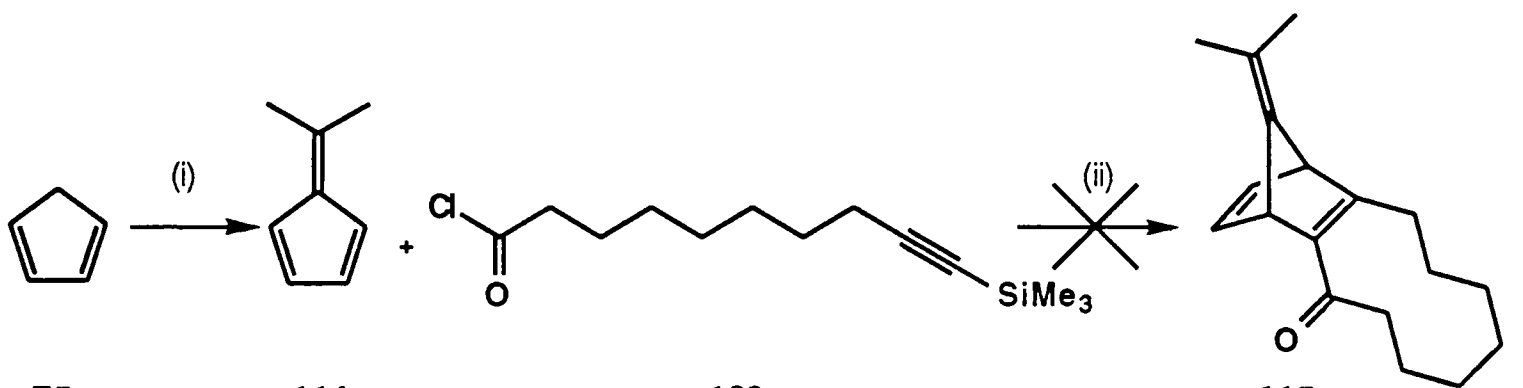
Conditions: (i) Cyclopentadiene, $AlCl_3$, DCM, either 0°C to RT, 3h; 48% or -78°C to RT, 15h; 79%.

Scheme 38

The effectiveness of the sequence was extremely sensitive to the scale of the process, the reaction conditions and work-up procedure, however, good

crude yields of the cycloadduct were readily obtainable. Unfortunately it was discovered that, on silica gel column chromatography, only a low recovery of pure material could be obtained (~10% overall yield at best) and even on neutral alumina the overall yield was ~15%. A pure sample could not be obtained even after distillation.

For comparison purposes the one-pot reaction was attempted with 6,6-dimethylfulvene[89] **114** in place of cyclopentadiene **75**, to see whether the cycloadduct **115** thus formed could be reduced selectively at the apex position. However, the sequence did not yield any of the cycloadduct **115** (Scheme 39).



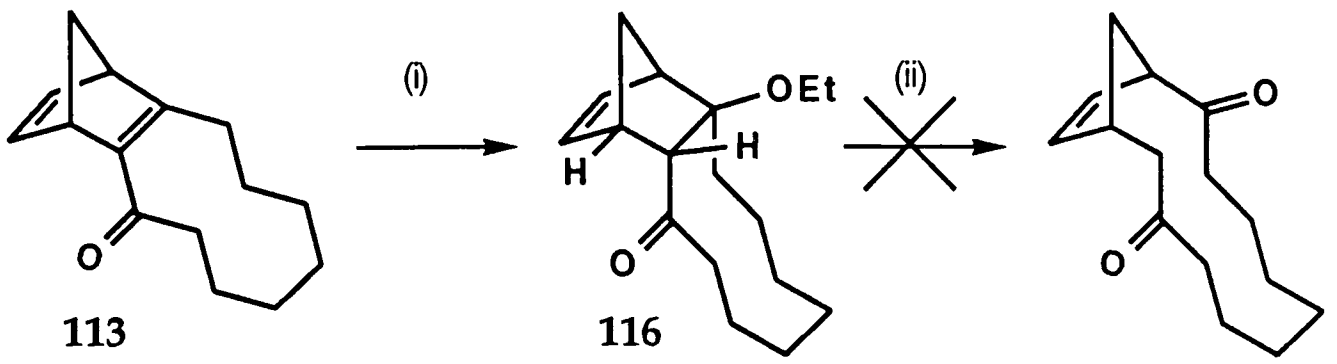
75 114 103 115

Conditions: (i) Acetone, EtOH, Pyrrolidine, AcOH, 20mins; 81%.[89] (ii) $AlCl_3$, DCM.

Scheme 39

Despite the problems associated with obtaining large quantities of pure cycloadduct **113**, we were keen to investigate the proposed Michael attack, retro-aldol ring expansion reaction.

Treatment of **113** with NaOH in EtOH resulted in the formation of addition product **116** (the relative stereochemistry was assumed to be that shown on the basis of the coupling constant between the bridgehead proton and that next to the carbonyl group).[87] Attempts to induce fragmentation using Lewis acids failed (Scheme 40).



113 116

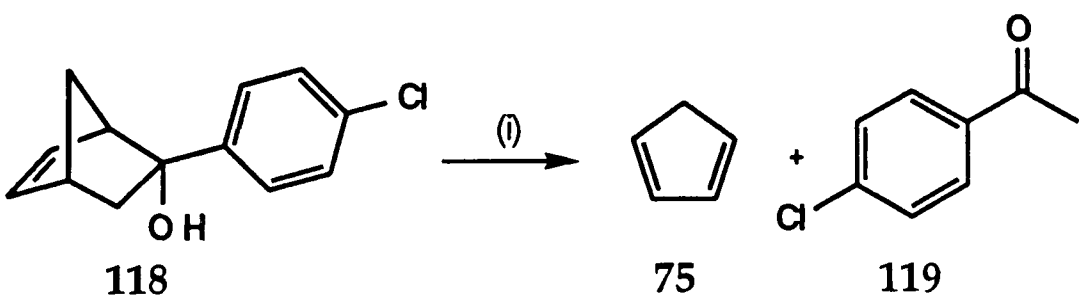
Conditions: (i) NaOH, EtOH; 74%. (ii) $BF_3.OEt_2$.

Scheme 40

Again, although the crude yield was high, on column chromatography only a small amount (22%) was recovered.

Further examination of this reaction with NaOH in EtOH, with lithium trimethylsilanolate[90] and with NaOMe in MeOH, led to the observation that the same complex mixture of unidentified products was formed in each case. Also, attempts to epoxidise the α,β-unsaturated ketone with H_2O_2 and NaOH led to the isolation of a compound that seemed to be a β,γ-unsaturated ketone **117** (Appendix C).

We were unsure why such problems were occurring. One possibility could be that the β-hydroxy ketone, once formed, undergoes an oxyanion-assisted retro-Diels-Alder reaction;[91,92] a relevant precedent was reported by Miyashi and co-workers [92] in the fragmentation of **118** to cyclopentadiene **75** and **119** (Scheme 41).



118 75 119

Conditions: (i) KH, 18-crown-6, THF, RT; quant.

Scheme 41

In order to rule out this possibility attempts were made to hydrogenate the cycloadduct **113**. Despite a variety of catalysts: $(Ph_3P)_3RhCl$,[93] Pd-C and Pd Black under 1 atm of hydrogen, the non-conjugated alkene remained intact.

Subsequent attempts to use the crude cycloadduct **113** in further reactions (in order to minimise loss of material in the purification stage) proved unsuccessful. A variety of reactions were performed on crude **113**, including dihydroxylation[94] of the isolated alkene followed by its protection as an acetonide. The crude ^{1}H NMR spectra were promising, but there was always a low recovery after column chromatography; in short, all the reactions performed on crude material proved inconclusive.

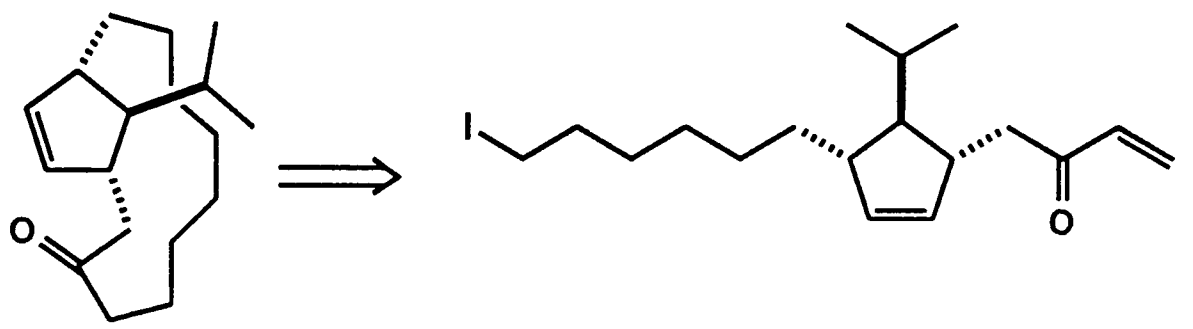
Additionally the cycloadduct **113** was observed to undergo a polymerisation process on storage to give material that was insoluble in all available solvents.

Due to these complications work on this approach was discontinued and a new route devised (Chapter 6).

RESULTS & DISCUSSION II‡

6.1. Retrosynthetic Analysis

We proposed an alternative route to the macrocyclic ketone **35** based on the free-radical cyclisation of the iodoenone **120** (Figure 6).



35 **120**

Figure 6

The following Section (**6.2.**) briefly reviews the area of free-radical macrocyclisations.

6.2. Free Radical Macrocyclisations

6.2.1. There has been a resurgence of interest in free radical chemistry over the last 15 years resulting in a rediscovery of the importance and potential of homolytic bond forming processes.[95,96]

6.2.2. Background

6.2.2.1. The use of free-radical chemistry in the construction of carbocycles has received a vast amount of attention[95,97] and has traditionally been applied to

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‡ This work was presented as a poster at the Pre-doctoral Symposium to the Autumn meeting of the Royal Society of Chemistry at Brunel University, September 1996. In addition the majority of this work was presented orally at the 211th Meeting of the American Chemical Society in New Orleans, Louisiana, USA in March 1996[87] and at the Oxford University Graduate Symposium, Dyson Perrins Laboratory, September 1996.

the ready preparation of 5- and 6-membered rings as can be seen from the comparison of rate constants[98] shown in Table 2.

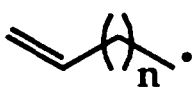
	k_{exo} (s^{-1}) at 25°C	k_{-exo} (s^{-1}) at 25°C	k_{endo} (s^{-1}) at 25°C
n=1	1.8×10^4	2.0×10^8	-
n=2	1.0	4.7×10^3	-
n=3	2.3×10^5	-	4.1×10^3
n=4	5.2×10^3	-	8.3×10^2
n=5	<70	-	1.2×10^2

Table 2

6.2.2.2. Carbon radicals are mildly nucleophilic in character and thus their addition to an alkene is affected by electronic factors.[97c,99] Table 3 shows a comparison of the relative rates of addition of the cyclohexyl radical to the β-position of a variety of functionalised alkenes.[96c]

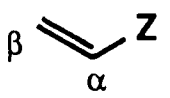
	k_{rel}
Z = Me	0.004
Z = Ph	1
Z = CO_2Et	6.7
Z = COMe	13
Z = CN	24
Z = CHO	34

Table 3

Thus electron-withdrawing groups increase the rate significantly with respect to an isolated carbon-carbon double bond.

6.2.2.3. A second critical factor in assessing the ease of carbon radical additions is the steric environment at the β-position of such an α-substituted alkene.[97c,98] From Table 4 it is seen that substitution at the β-position retards the addition of a cyclohexyl radical.[96c]

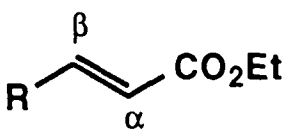
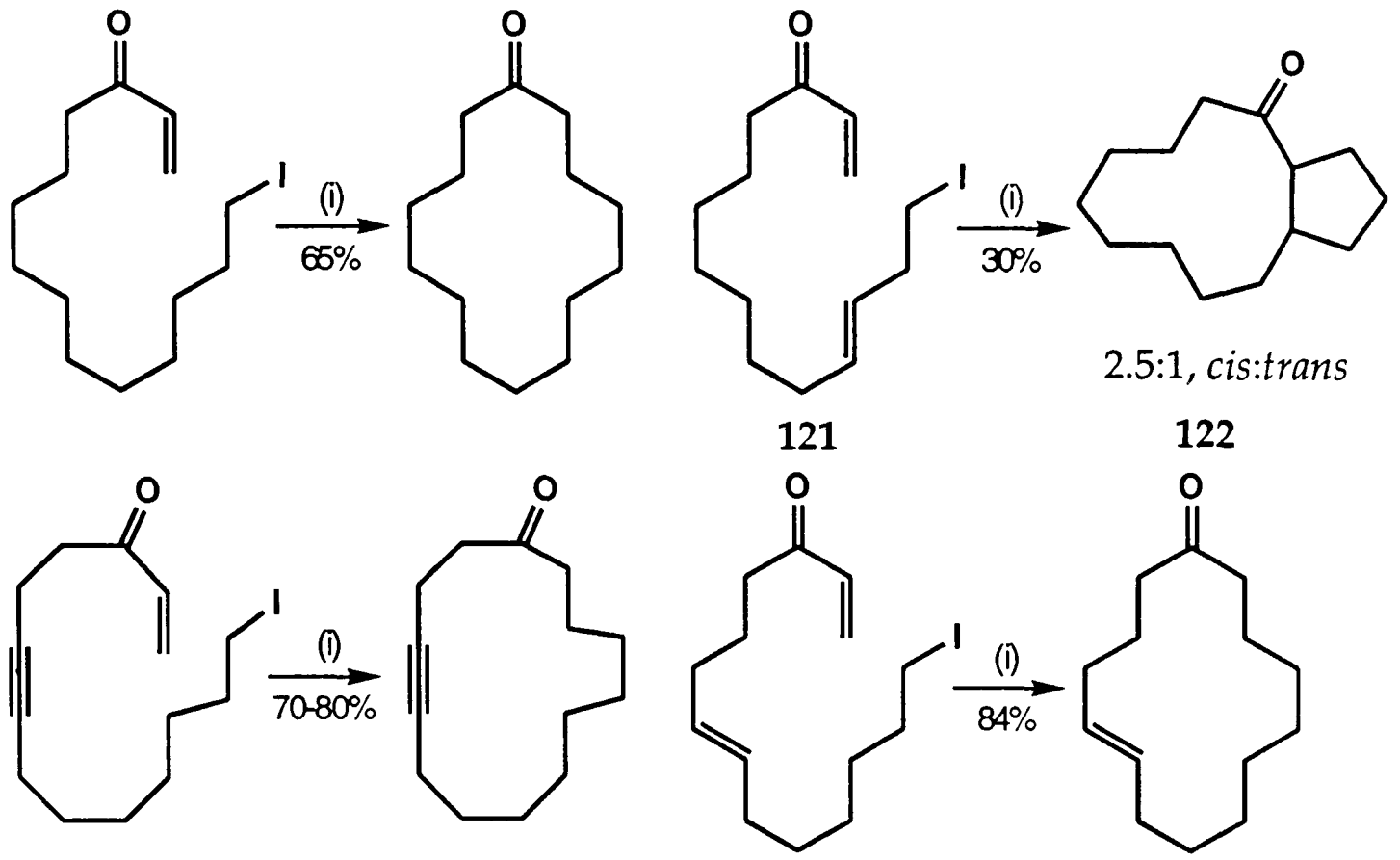
	k_{rel}
R = H	1
R = Me	~0.01

Table 4

6.2.3. Macrocyclisation

6.2.3.1. Porter and co-workers suggested that free-radical cyclisations to form large rings could be feasible.[96] Their reasoning built on the fact that $k_{intramolecular}/k_{intermolecular}$ values for large ring formation are typically between 10^{-1} and 10^{-2}M.[100] That is, the effective molarity of an ω-functional group in a chain greater then 12 atoms would lie in the range 0.1M to 0.01M. Porter postulated that a radical reaction that propagated at such low concentrations (~10mM) could react in an intra- as well as an intermolecular fashion and that such competition could be influenced by electronic and steric factors at the site of radical attack (*viz.* **6.2.2.2.** & **6.2.2.3.**).

6.2.3.2. The hypothesis was tested by the preparation of a wide variety of macrocyclisation precursors consisting of an unsubstituted enone and terminal halide functionality. A number of examples of the subsequent macrocyclisations are given in Scheme 42.



Conditions: (i) $^{n}Bu_3SnH$, AIBN, Δ.

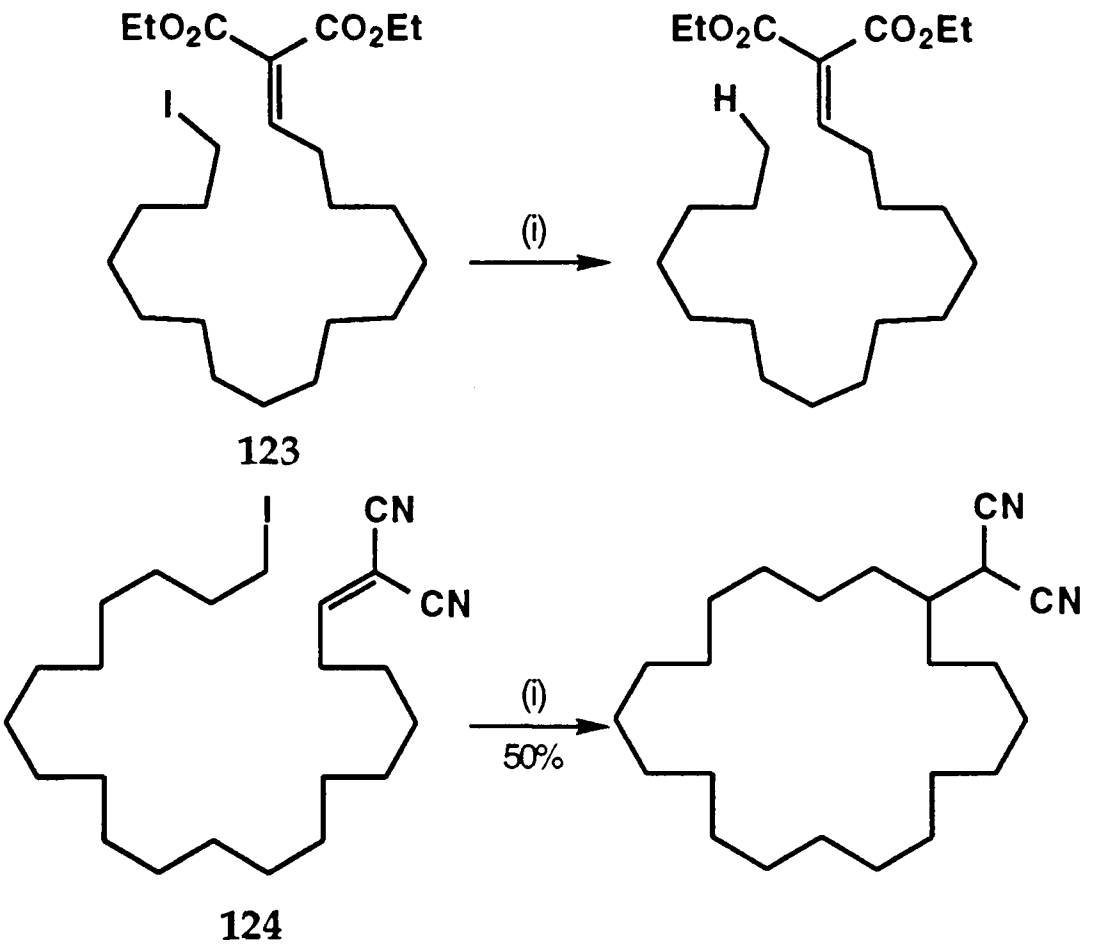
Scheme 42

The reactions were carried out at concentrations between 2-10mM with the optimum concentrations around 3-6mM; under these conditions the cyclisations proved to be extremely efficient. As expected the carbon radical formed from halogen abstraction preferentially attacked the β-position of the enone rather than the alkyne or alkene within the chain. Interestingly in the case of **121**, where the first-formed radical after macrocyclisation could attain a favourable conformation for transannular reaction, only the bicyclic system **122** was isolated.[96c] The calculated rate constant for such a transannular 5*exo* cyclisation is significantly less than that in an acyclic system (Table 5).

Cyclisation	k (s^{-1}) at 80°C
Acyclic 5-*exo*	1.4×10^6
Transannular 5-*exo*	$0.5\text{-}1.5 \times 10^5$

Table 5

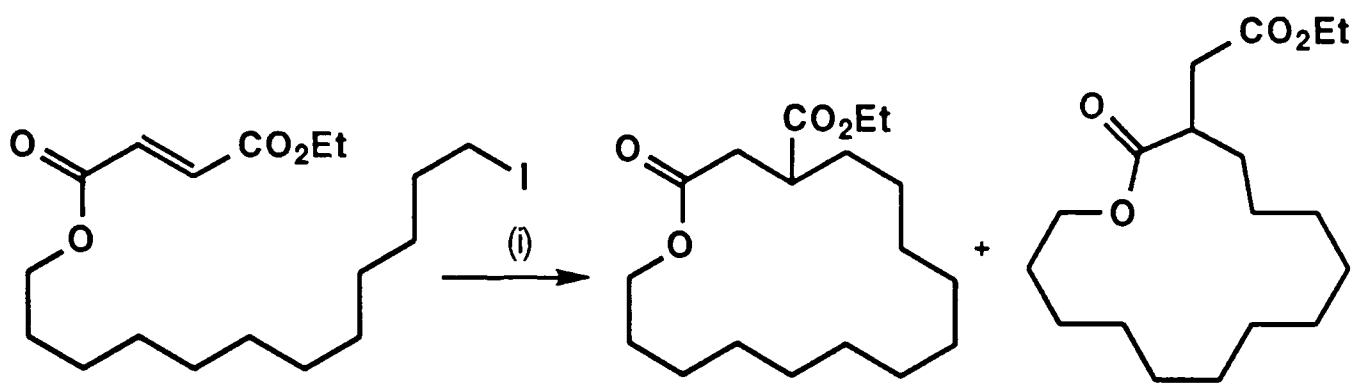
6.2.3.3. Porter observed that the *endo*-cyclisation mode dominated over the *exo*-process. He suggested that this is due to both the electronic effect associated with the carbonyl group and the increase in steric compression that would result from radical attack at a substituted carbon. Even systems which favour *exo*-cyclisation strongly on electronic grounds[96b] (e.g. **123**) are not effective (Scheme 43) unless the alkene is activated by two nitrile groups[96c] (**124**).



Conditions: (i) $^{n}Bu_3SnH$, AIBN, Δ.

Scheme 43

Another interesting study involved the cyclisations of ω-iodoalkylfumarates (e.g. **125**) where both *exo*- and *endo*-cyclisations were electronically favourable and sterically unbiased.[96b] In each case the *endo*-mode was the preferred pathway (Scheme 44) suggesting that unfavourable transannular interactions associated with smaller ring sizes contribute to the regioselectivity. These observations have led to the general guideline for radical macrocyclisations that "*endocyclisation modes are favoured.*"



125 ***Endo*:*Exo*, 2.5:1**

Conditions: (i) $^{n}Bu_3SnH$, AIBN, Δ.[96b]

Scheme 44

6.2.3.4. Porter noted that the best results were obtained in systems which had a degree of rigidity due to unsaturation in the tether, possibly due to reduced transannular interactions and a more favourable conformation of the substrate for cyclisation.[96c] Higher yields were also obtained with iodides rather than bromides and tertiary iodides were preferred to primary iodides with propagation occurring in concentrations as low as 0.07mM. Furthermore, in a study on the cyclisation of a tertiary iodide acrylate, the product distribution depended directly on the concentration of tributyltin hydride; the yield of cyclic product increased at the expense of the reduction product as the tributyltin hydride concentration was reduced.[96b]

6.2.3.5. These findings are consistent with a mechanism involving rate determining abstraction of the halogen, subsequent cyclisation and final hydrogen abstraction from the tributyltin hydride with stannyl and carbon radicals carrying the chain. The increase in acyclic to cyclic products at higher concentrations results from a faster rate of hydrogen abstraction from tributyltin hydride compared to cyclisation. No evidence for atom transfer has been observed.[102]

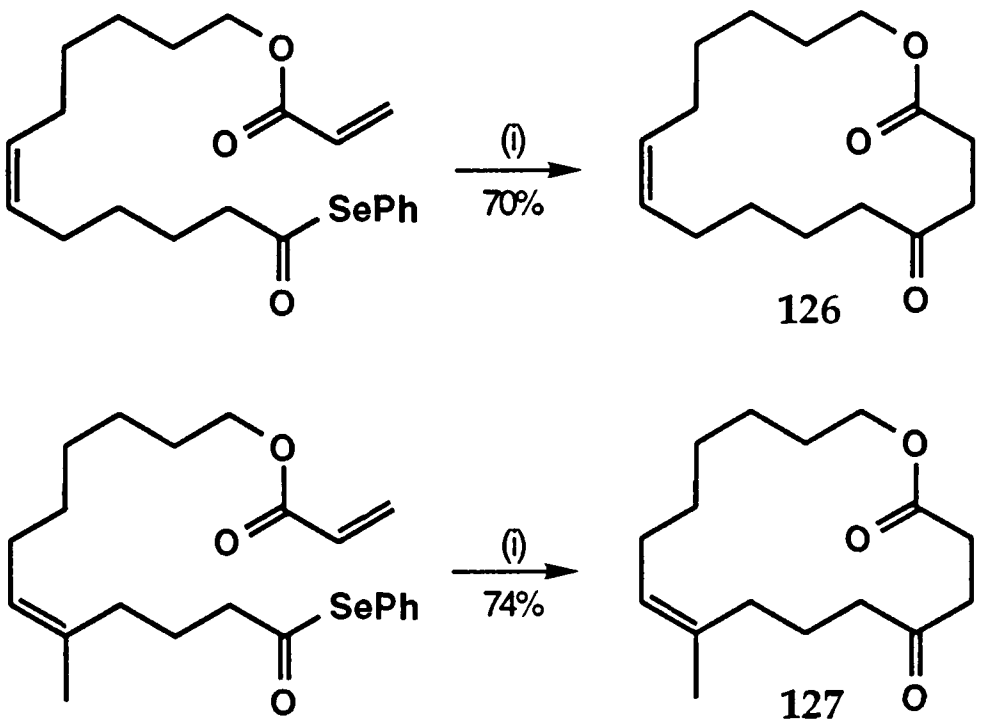
6.2.3.6. On the basis of data accumulated in a number of studies Porter has suggested rate constants for the radical cyclisations leading to 14-membered rings.[96b] These values (Table 6), in dilute conditions, approach the limit for useful free-radical reactions and Porter has demonstrated that macrocyclisation can even compete with 6-*exo* processes.[96c]

Cyclisation	k (s^{-1}) at 80°C
5-*exo*	1.4×10^6
6-*exo*	$3.4\text{-}4.3 \times 10^4$
7-*exo*	3×10^2
14-*endo*	$1\text{-}8 \times 10^4$

Table 6

6.2.4. Further Free-Radical Macrocyclisation Studies

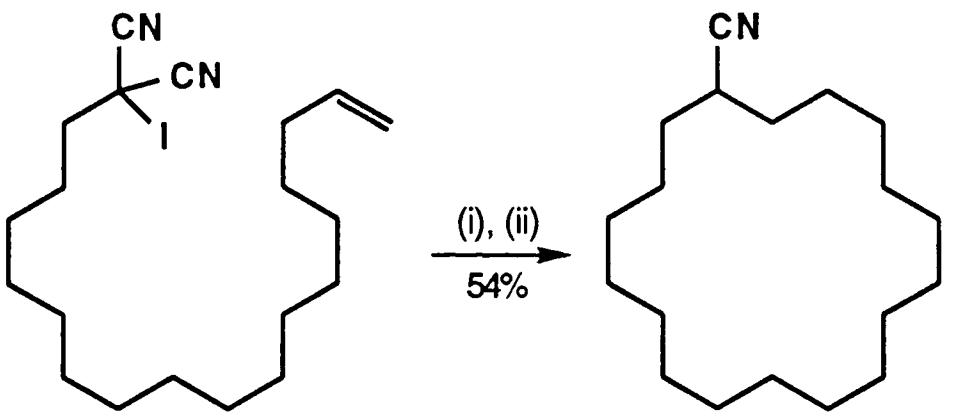
6.2.4.1. Acyl radicals exhibit nucleophilic character and reactivity comparable to that of alkyl radicals[101] and Boger and Mathvink have demonstrated their effective macrocyclisation using the Porter conditions; several examples of 1,4-dicarbonyl products **126** and **127** are given in Scheme 45. Interestingly the macrocyclisation competes efficiently with both 5-*exo* and 6-*exo* cyclisations suggesting that the rate of macrolide formation by intramolecular acyl radical addition to an acrylate exceeds that of the comparable alkyl radical addition.[101c]



Conditions: (i) ^{n}Bu$_3$SnH, AIBN, Δ.[101c]

Scheme 45

6.2.4.2. Curran and co-workers reported a novel macrocyclisation of an electrophilic radical in their recent studies on atom-transfer reactions.[102] Heating the iodomalononitrile **128** in low concentration resulted in atom-transfer macrocyclisation; subsequent reduction with tributyltin hydride gave the unprecedented *mono*-nitrile macrocycle **129** (Scheme 46).



128 **129**

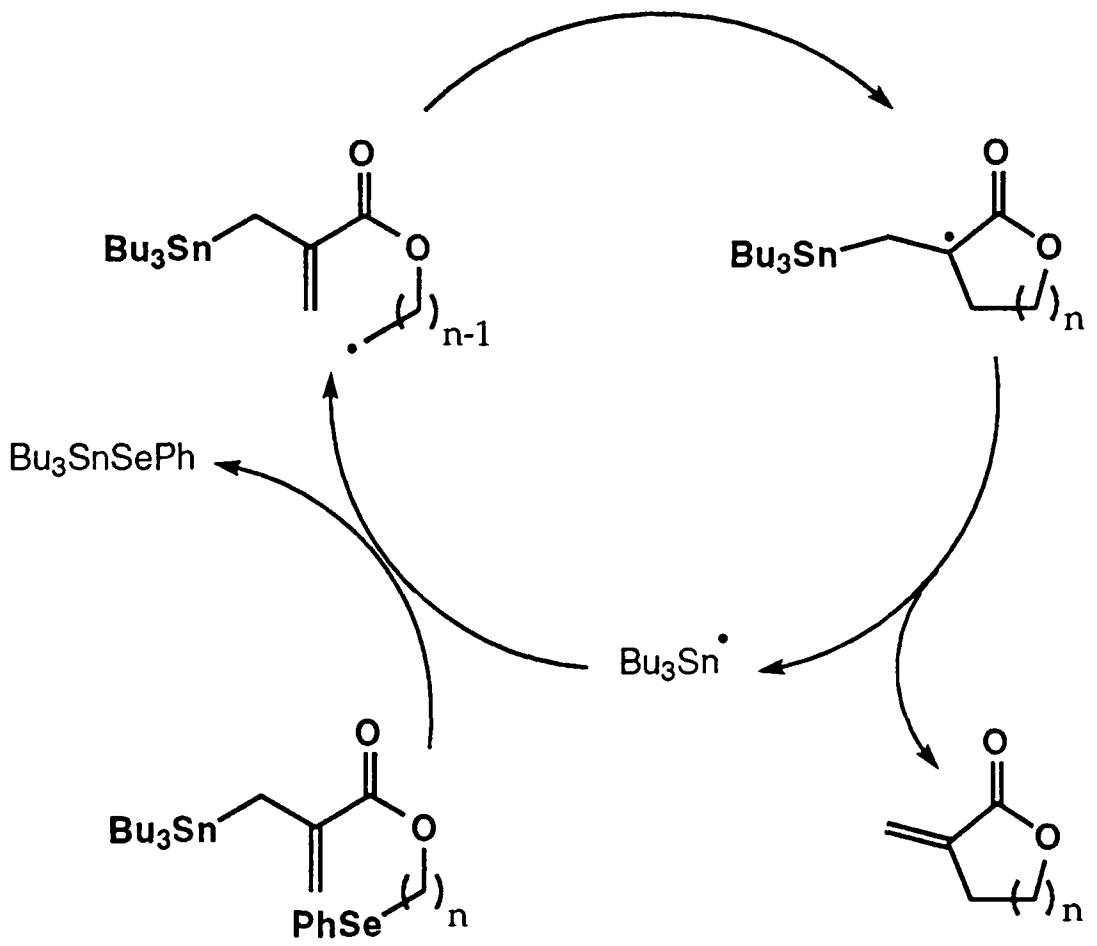
Conditions: (i) PhH, 3mM, Δ. (ii) excess ^{n}Bu$_3$SnH.[102]

Scheme 46

6.2.4.3. Porter and others have demonstrated the structural requirements and experimental conditions (e.g. low concentration, slow addition of tributyltin hydride) for successful macrocyclisations,[95b,96,97d,103] nevertheless a persistent

problem has been associated with the competing direct reduction process of the initially formed carbon radical resulting in acyclic products.

Baldwin and co-workers proposed a sequence involving radical attack on to allylic stannyl acrylates to generate enones *via* a fragmentation reaction which ejects a stannyl radical.[104] Since the chain carrier is released as a product of the reaction, only a catalytic quantity of tributyltin hydride is required to effect initiation of the process thus eliminating the competing reduction pathway (Scheme 47).



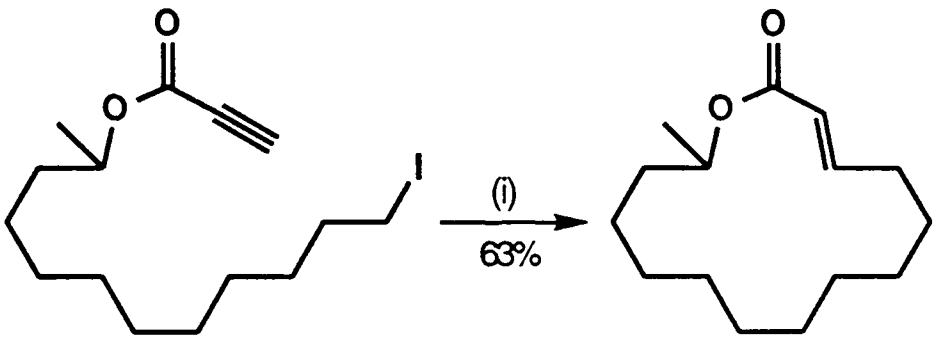
Scheme 47

The proposal proved successful and a variety of rings (of size n+4) were synthesised as shown in Table 7.

n	Yield (%)	n	Yield (%)
6	54	9	50
7	46	10	80
8	61	11	72

Table 7

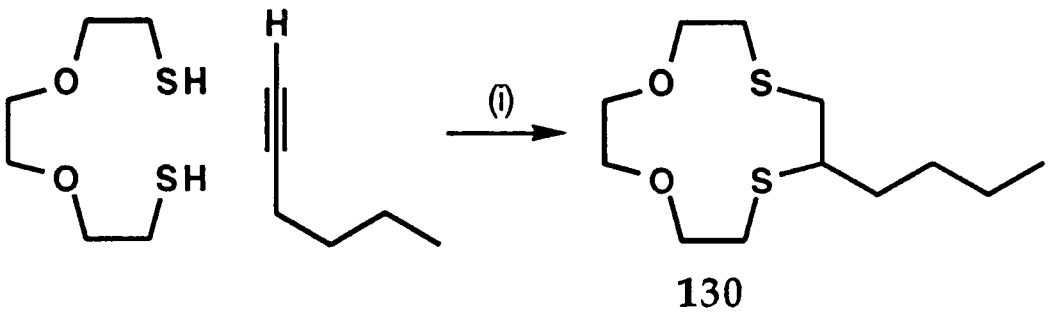
6.2.4.4. Baldwin *et al.*[105] proposed that the propiolate functionality would be a good radicalphile under the macrocyclisation conditions pioneered by Porter; moreover, such methodology would provide rapid access to large ring α,β-unsaturated lactones (Scheme 48). Interestingly cyclisation only occurred to form lactones with ring sizes greater than 13 atoms and of the possible cyclisation products only the *trans*-α,β-unsaturated lactones were observed.



Conditions: (i) Ph_3SnH, AIBN, slow addition, 4mM, Δ.[105]

Scheme 48

6.2.4.5. Troyansky and co-workers[106] have reported a novel, one-step, free-radical intermolecular macrocyclisation process towards the construction of thiacrown ethers **130**. Although the initial radical attack is intermolecular, a subsequent radical cyclisation occurs (Scheme 49).



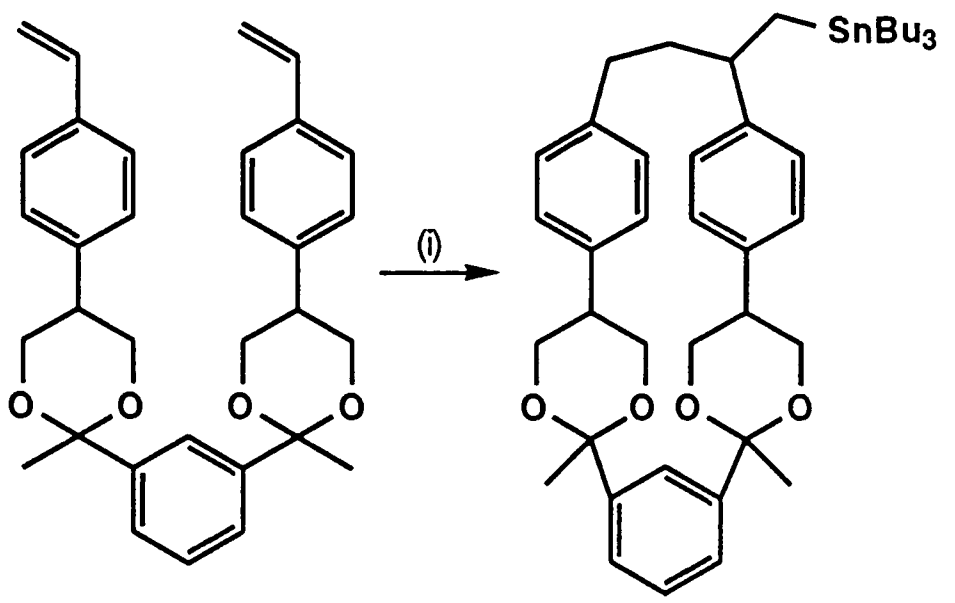
130

Conditions: (i) Pr_3B, O_2, slow addition of 1-hexyne, 25mM, RT, 4h; 30%.[106]

Scheme 49

6.2.4.6. Shea *et al.*[107] have studied the macrocyclisations of *bis*-styrene ketals **131** with tributyltin hydride to form 22-membered rings **132** (Scheme 50).

Interestingly they determined the rate constant for macrocyclisation to be $k_{cyclisation}$ 5.2 x 10^3 s^{-1} (60°C).

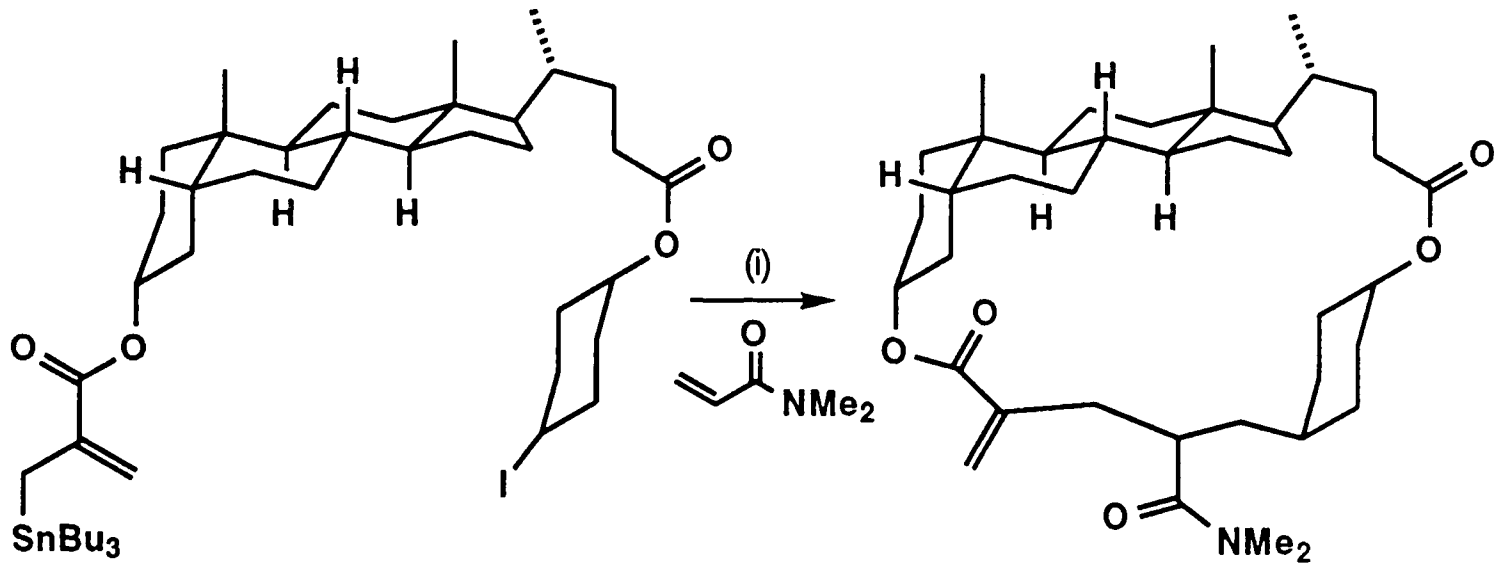


131 **132**

Conditions: (i) $^{n}Bu_3SnH$, AIBN, 0.62mM, Δ, 5h; 54%.[107]

Scheme 50

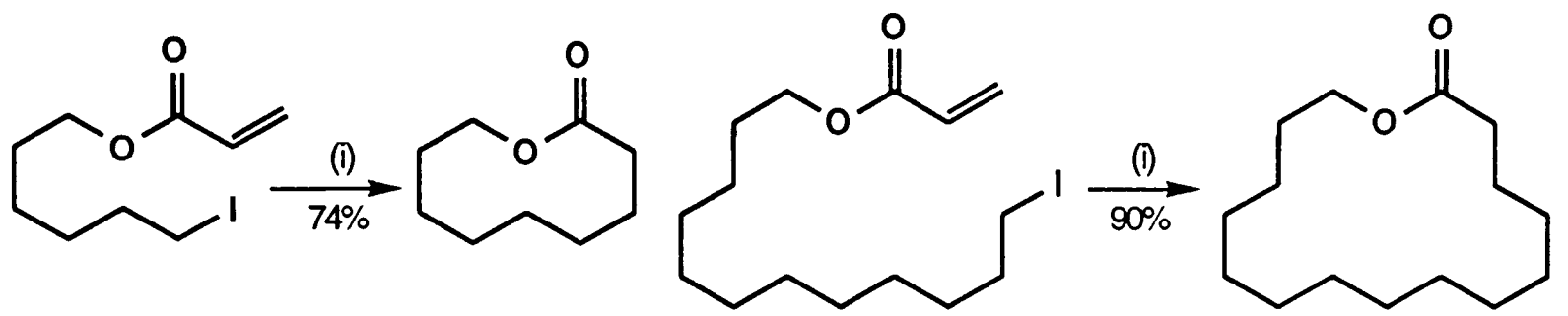
6.2.4.7. Recent work from Porter's group has investigated a radical addition, cyclisation, chain transfer (ACT) strategy for the formation of telomers derived from steroids.[108] The approach makes use of Baldwin's allylic stannyl acrylate model, but also involves an initial intermolecular attack on to an activated alkene prior to cyclisation (Scheme 51).



Conditions: (i) $(^{n}Bu_3Sn)_2$, $h\nu$, RT; 51%.[108]

Scheme 51

6.2.4.8. Recent studies by Kurata and co-workers have demonstrated the photostimulated cyclisation reaction of ω-iodoalkylacrylates using metal hydride complexes.[109] Two examples of this highly efficient process, involving photolysis of the iodides **133** and **134** in the presence of $NaBH_3CN$, are given in Scheme 52. Even the yield for formation of the 10-membered ring **135** is extremely good.

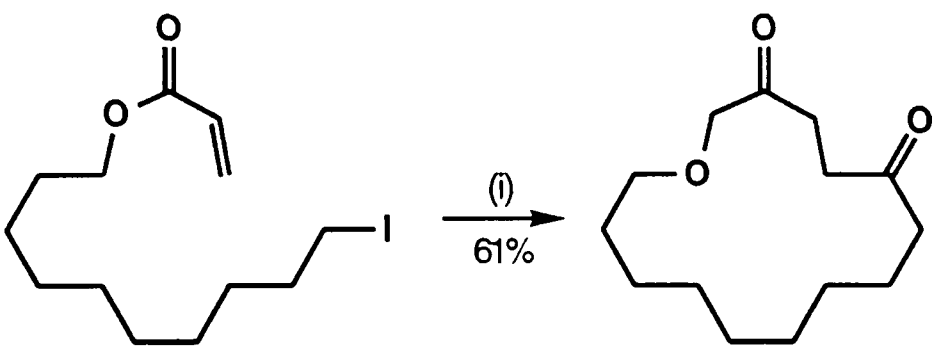


133 **135** **134**

Conditions: (i) $NaBH_3CN$ (1mmol), MeOH, *hν*, 3h, RT, 5mM.[109]

Scheme 52

6.2.4.9. Sonoda *et al.* have reported a strategy for macrocyclisation based on free-radical carbonylation.[110] The use of carbon monoxide as a radical acceptor is not well established[111] but Sonoda has used it to great effect in such cyclisations. Thus reaction of the iodoalkylacrylate **136** with *tris*(trimethylsilyl) silane gave the alkyl radical which added intermolecularly to carbon monoxide generating an acyl radical; this subsequently cyclised to give the γ-ketolactone **137** (Scheme 53).

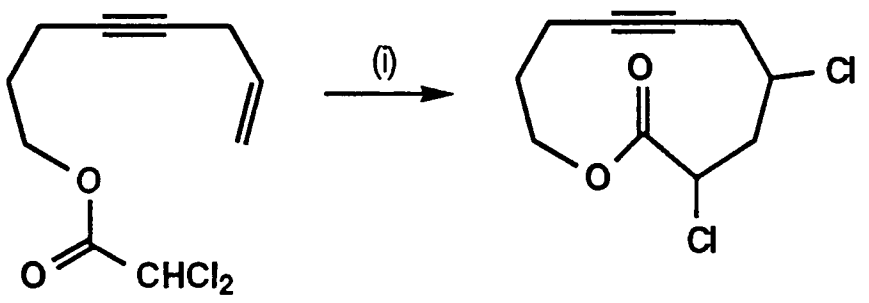


136 **137**

Conditions: (i) $(Me_3Si)_3SiH$, AIBN, 5mM, CO 30 atm, Δ.[110]

Scheme 53

6.2.4.10. The generation of 11-membered rings *via* an atom transfer process involving radical intermediates has been described by Speckamp and co-workers.[112] Scheme 54 shows the copper catalysed *endo*-cyclisation of a rigid 11-membered chain **138** to form the lactone **139**.



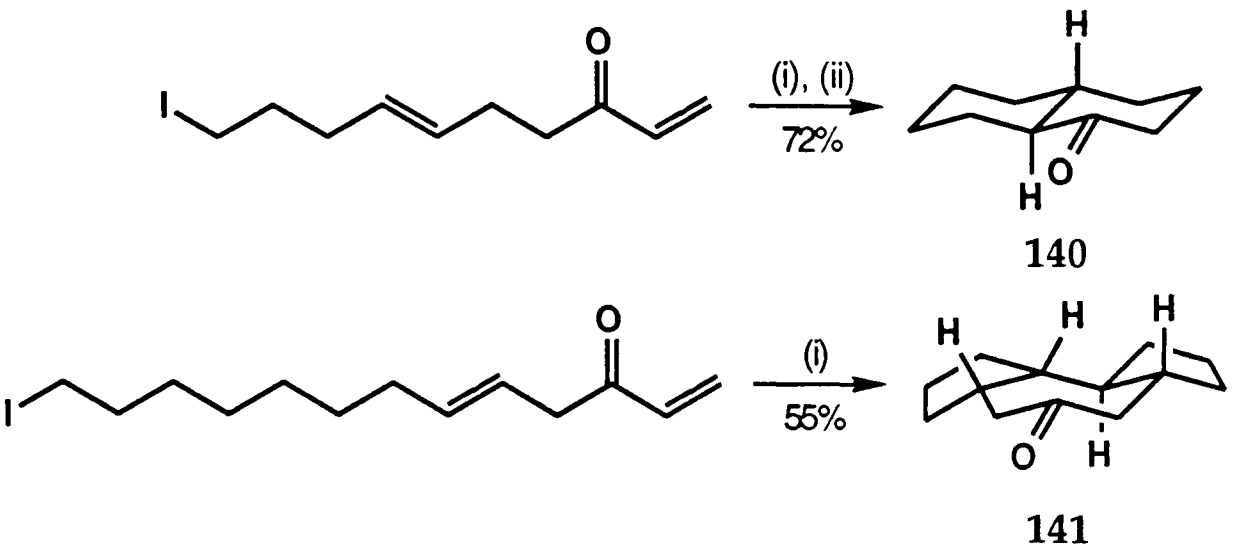
138 **139**

Conditions: (i) Cu(2,2'-bipyridine)Cl, 18h; 51% (2:1 mixture of isomers).[112]

Scheme 54

6.2.4.11. Pattenden and co-workers have investigated polycycle construction using free-radical chemistry.[113-115] Pattenden proposed that analogous cyclisations exhibited in Nature, involving cationic species, could be mimicked in a carefully preorganised system using tandem radical cyclisation methodology. Two general approaches were conceived, the first involving a macrocyclisation-transannulation strategy,[113,114] which will be briefly discussed, and the second a series of *endo*-cyclisations.[115]

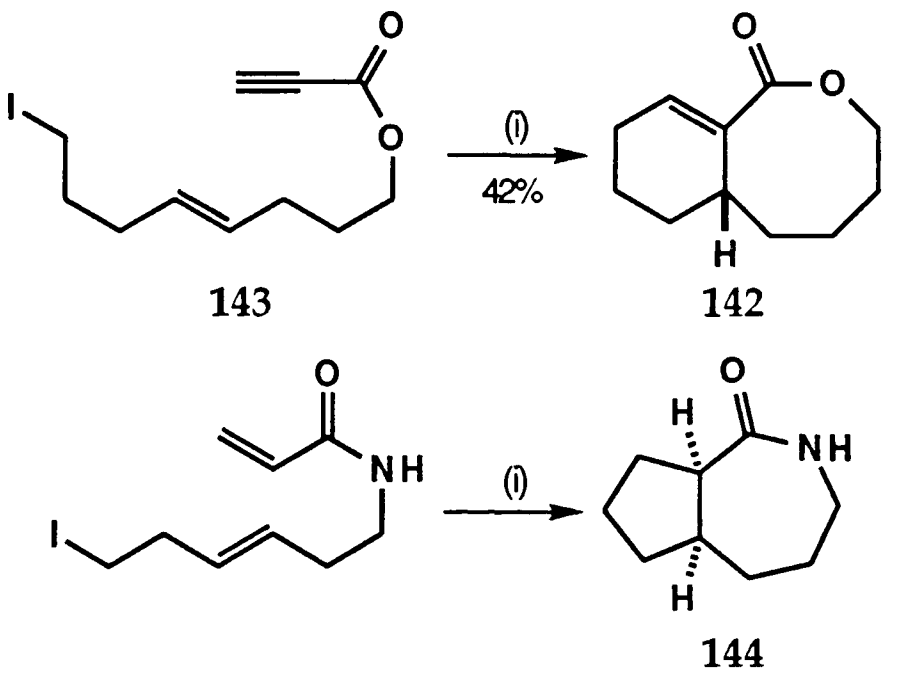
Pattenden *et al.* built upon Porter's earlier work and in an elegant study showed that both approaches were feasible in systems with the correct structural features. Interestingly they reported the rapid formation of bi- (**140**) and tri-cyclic ketones (**141**) from simple starting materials (Scheme 55). In the first example the 10-*endo* process is proceeded by a 6-*endo/exo* cyclisation, however, in the second case the penultimate carbon-centred radical undergoes a 5-*exo* (7-*endo*) process in preference to the 6-*endo* thus generating the angular 5,7,5-ring fused tricycle **141**; the relative stereochemistry was confirmed by an X-ray crystal structure on the DNP derivative.



Conditions: (i) $^{n}Bu_3SnH$, AIBN, 0.5h, 3mM, Δ. (ii) DBU.

Scheme 55

6.2.4.12. Recent application of this methodology to the synthesis of ring-fused lactones and lactams has also been reported by Pattenden and co-workers.[114] Interestingly the bicyclic lactone **142** was formed, presumably *via* transannular cyclisation of the carbon-centred radical generated after 12-*endo* cyclisation of the iodopropiolate **143**. Some examples are shown in Scheme 56; the relative stereochemistry of both **142** and **144** was confirmed by X-ray crystallography.

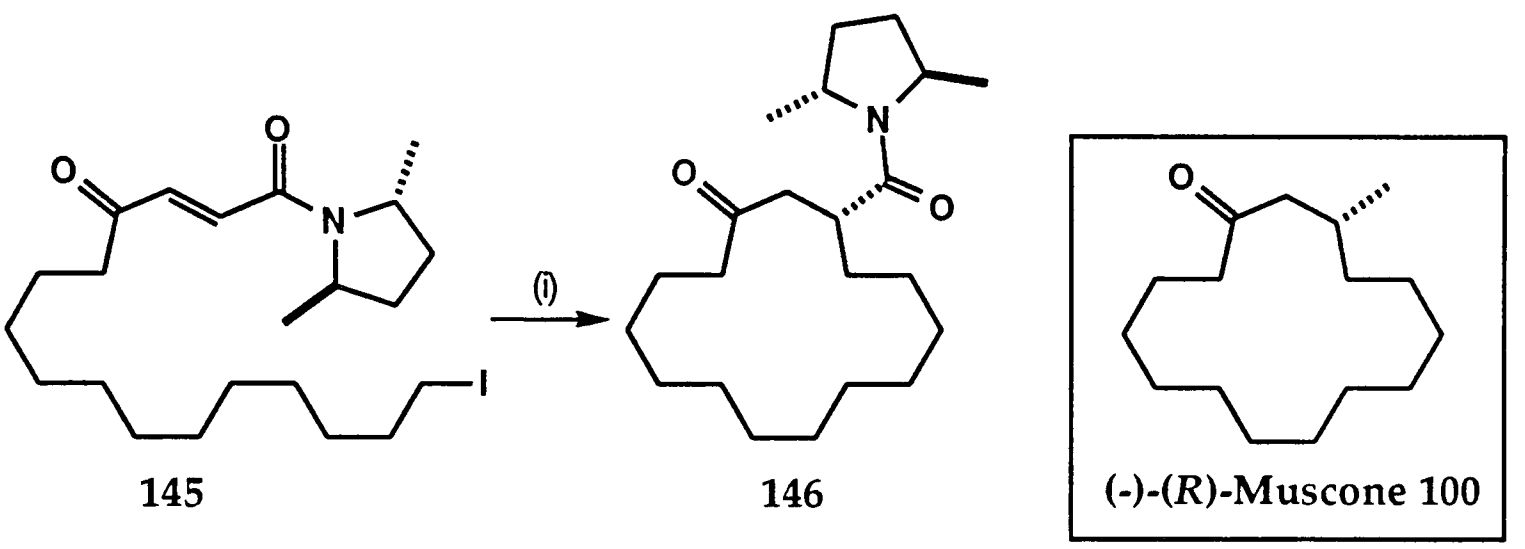


Conditions: (i) $^{n}Bu_3SnH$, AIBN, slow addition 3-4h, 5mM, Δ.

Scheme 56

6.2.5. Free-Radical Macrocyclisations in the Synthesis of Natural Products

6.2.5.1. Porter and co-workers described the diastereoselective intramolecular addition of a radical in their synthesis of (-)-(*R*)-Muscone **100**.[96d] Their strategy involved predominantly *endo* addition on to an alkene bearing a chiral amide unit **145** to generate the macrocycle **146**, which was converted to Muscone **100** (Scheme 57).

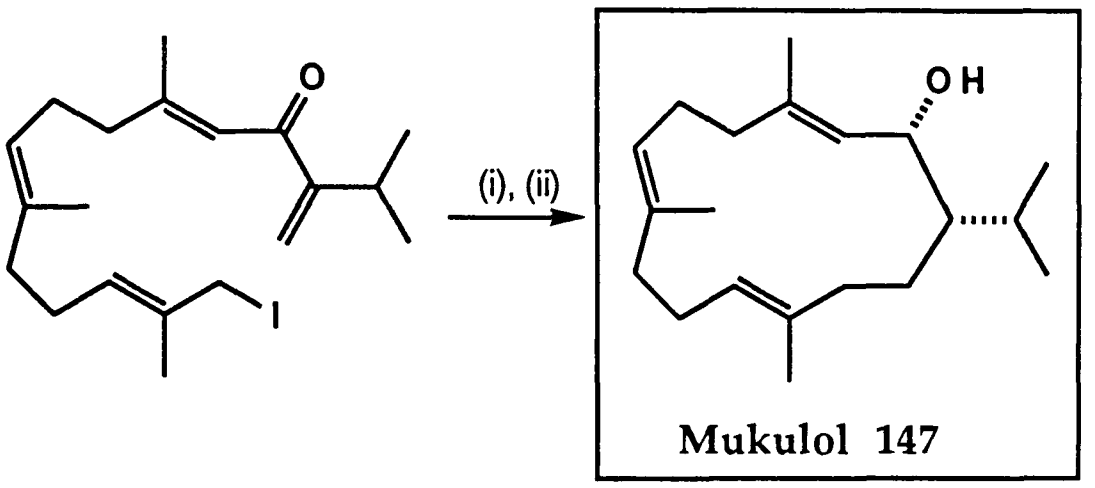


145 **146**

Conditions: (i) $^{n}Bu_3SnH$, AIBN, 3h, 4.5mM, Δ; 40-45%. (*endo R*:*endo S*:*exo R*:*exo S*, 13:1:1:1).

Scheme 57

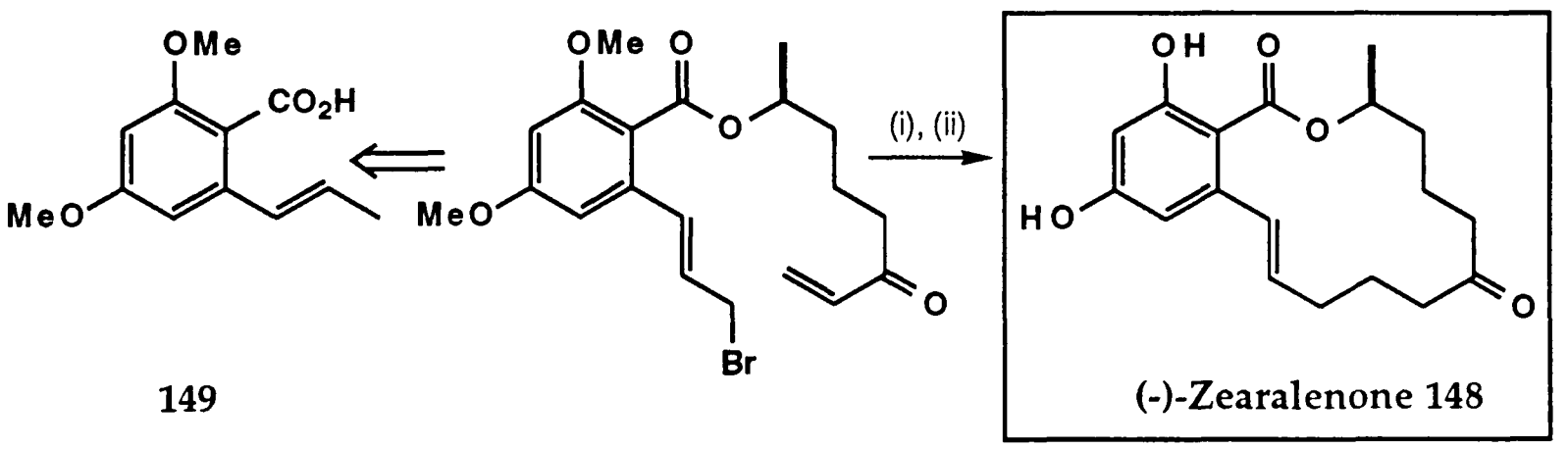
6.2.5.2. Pattenden and co-workers have been instrumental in the demonstration of free-radical macrocyclisation methodology in the total synthesis of natural products.[113-117,120,123,127] Their pioneering work began with studies on the construction of the cembrene skeleton[117] and the synthesis of Mukulol **147**, a 14-ring carbocyclic metabolite isolated from the gum resin of the Indian tree *Comiphora mukul*.[118] The key step involved a 14-*endo*-trig cyclisation of an allylic radical (Scheme 58) generating two cyclic products of which the minor *cis*- isomer was separated out.



Conditions: (i) $^{n}Bu_3SnH$, AIBN, Δ; 40% (4:1, *trans*: *cis* alkenes). (ii) $LiAlH_4$.

Scheme 58

6.2.5.3. Zearalenone **148** is an oestrogenic mycotoxin which was first isolated from the mycelium of the fungus *Gibberella zeae (Fusarim graminearum).*[119] Again Pattenden proposed a strategy based upon the 14-*endo*-trig cyclisation of an allylic radical ultimately derived from the resorcinol derivative **149**. Scheme 59 shows the key steps in this first synthesis of enantiomerically pure Zearalenone **148.**[120]

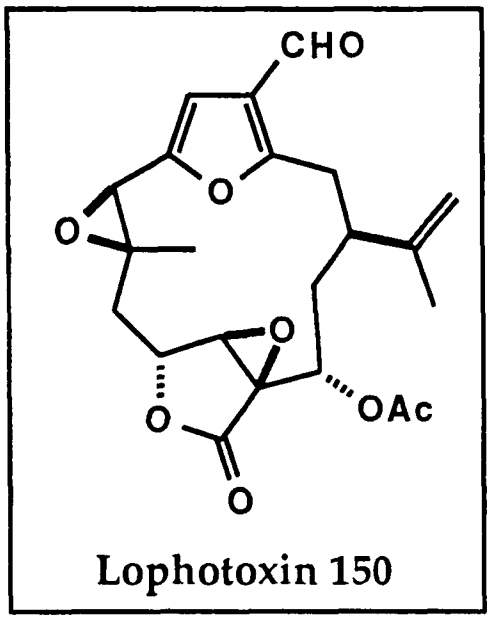


Conditions: (i) $(Me_3Si)_3SiH$, AIBN, Δ; 55%. (ii) BBr_3.

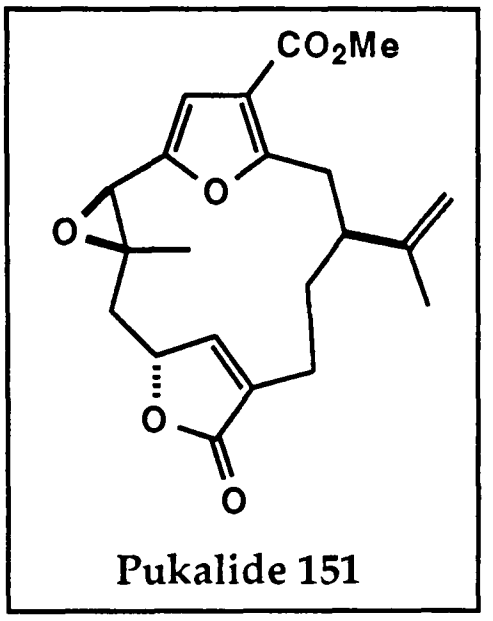
Scheme 59

6.2.5.4. Pattenden returned to his studies on the cembranoid family of marine diterpines, in particular the potent neurotoxin Lophotoxin[121] **150** and related Pukalide **151**, and demonstrated that the furanocembrane unit **152** was readily

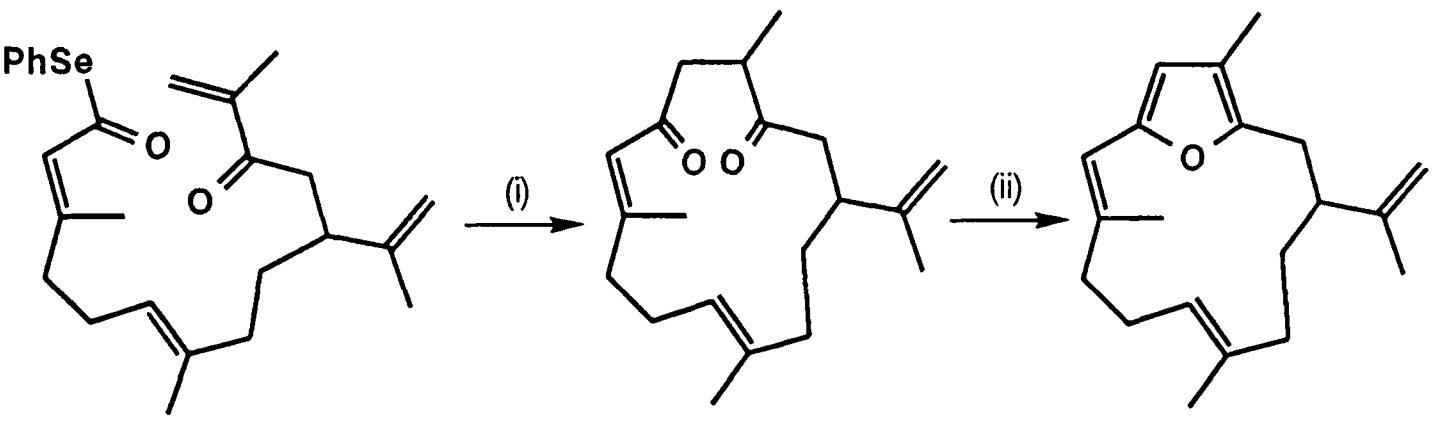
accessible *via* the 1,4-diketone **153** formed from an allylic acyl radical[122] macrocyclisation on to an enone.[123] This is illustrated in Scheme 60.



Lophotoxin 150



Pukalide 151

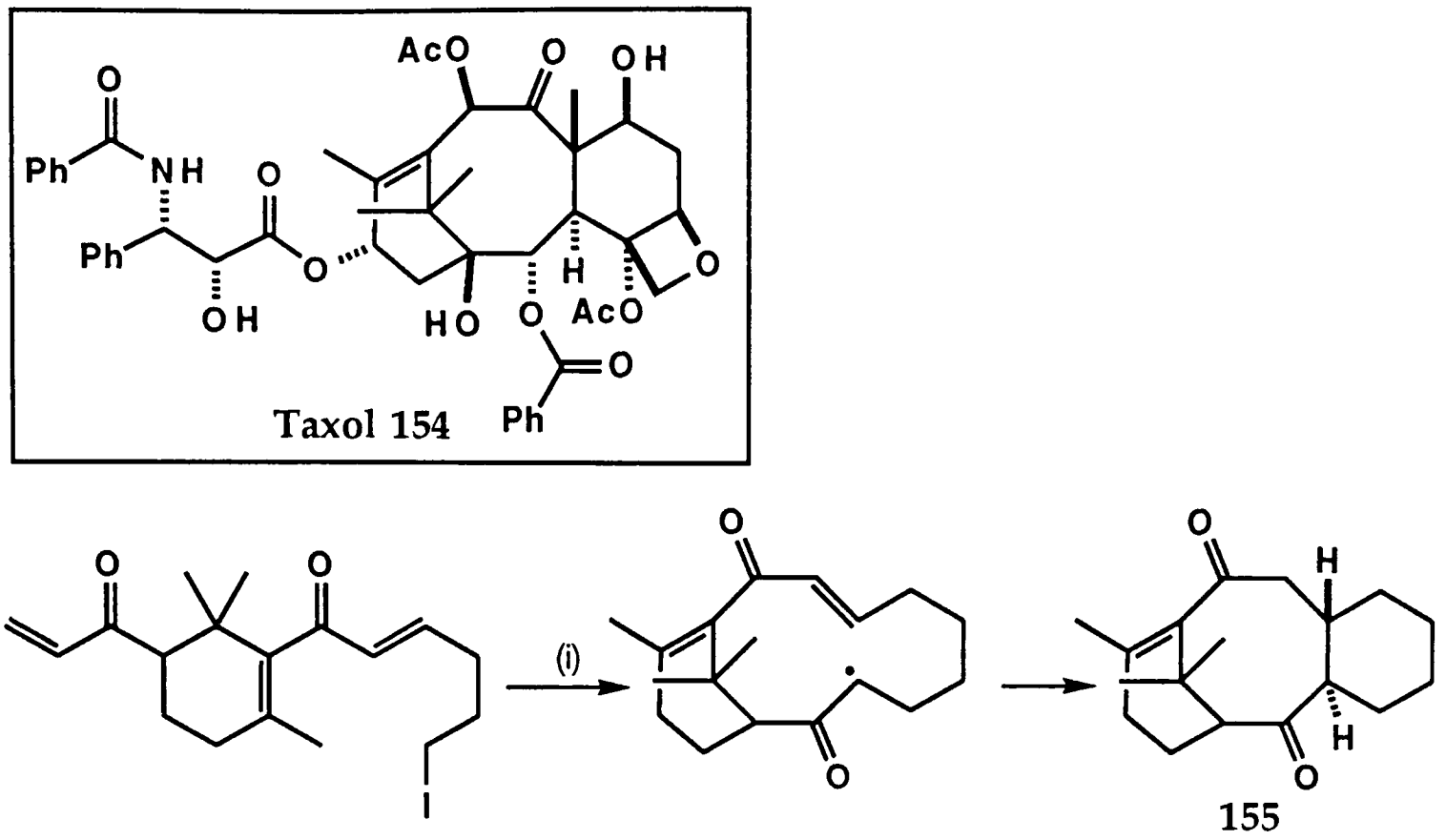


153 **152**

Conditions: (i) $^{n}Bu_3SnH$, AIBN, Δ; 40%. (ii) TsOH, $CHCl_3$; 50%.

Scheme 60

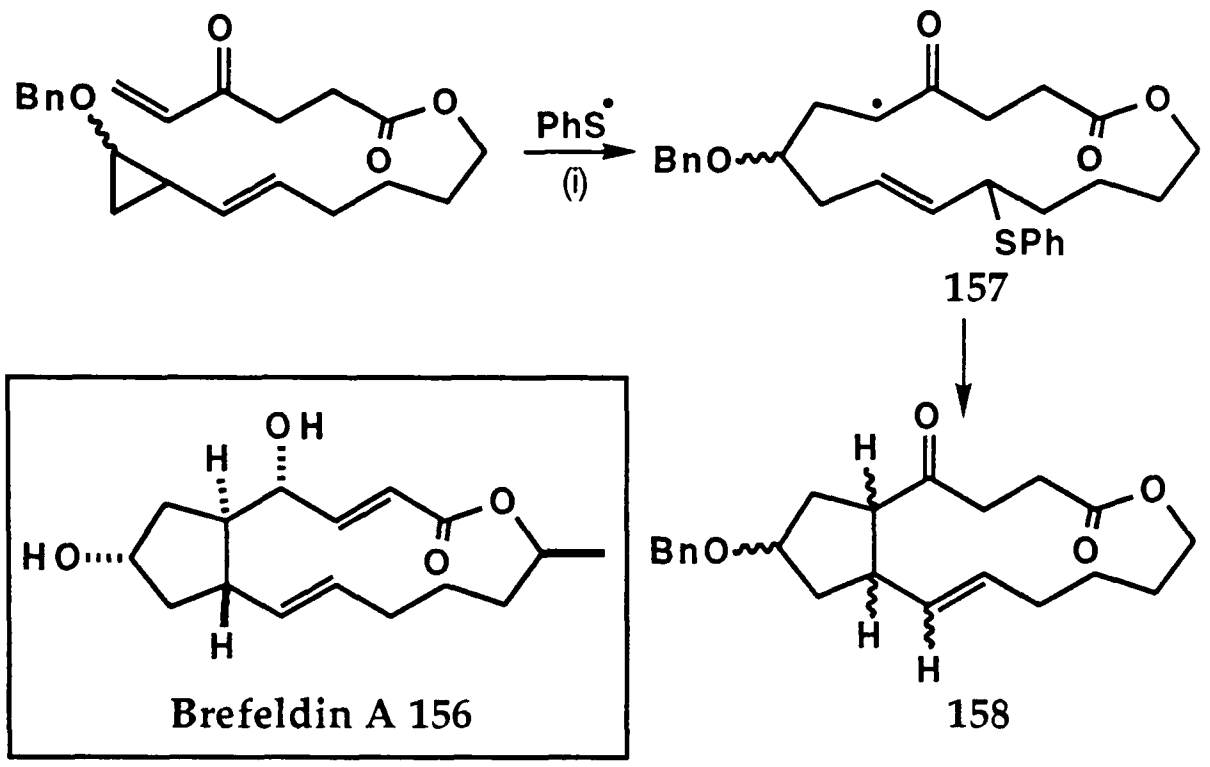
6.2.5.5. The taxane diterpenes, in particular Taxol **154**, have become a major focus of attention over the last 20 years because of their activities against leukaemia and breast and ovary cancers.[124] Taxol was isolated from the bark of the yew tree *Taxus brevifolia*[125] and for many years remained an unconquered synthetic target.[126] Pattenden *et al.* proposed a remarkable radical macrocyclisation, transannulation approach to the taxane skeleton **155** which is shown in Scheme 61.[127] Further studies using an ynone radicalphile boosted the yield of the corresponding tricycle to >60% demonstrating an astonishingly efficient sequence.[113d]



Conditions: (i) $^{n}Bu_3SnH$, AIBN, Δ; 25%.

Scheme 61

6.2.5.6. Feldman *et al.* envisaged that a tandem radical process could lead to an entry into the Brefeldin ring system. Brefeldin A **156** has recently been shown to be a valuable probe of metabolism and subcellular structure by virtue of its effective alteration of proton traffic between the endoplasmic reticulum and the Golgi complex.[128] This elegant stratagem, building upon their work on thiyl radical induced ring opening of alkenyl cyclopropanes,[129] involved macrocyclisation of the carbon radical formed from the initial cyclopropyl fragmentation. The radical **157** thus formed would, they reasoned, be perfectly set up to cyclise across the ring and re-eject the thiyl radical, thus necessitating only catalytic quantities of the radical progenitor.[128] The hypothesis proved correct and a variety of such cyclisations were achieved resulting in a mixture of products **158**; one example is given in Scheme 62.



Conditions: (i) PhSSPh (0.1eq.), AIBN, *hν*, RT; 43% (mixture of isomers).

Scheme 62

6.3. Model Studies Part III

6.3.1. Strategies for the Synthesis of Bicyclic Systems *via* Macrocyclisations

Whilst examining the feasibility of forming a bicyclo[10.2.1]pentadecane skeleton (such as that required for the macrocyclic ketone **35**) we identified three general strategies that could be adopted using free-radical macrocyclisation chemistry.

- Strategy **A** involves the cyclisation of a radical at the terminus of a carbon chain onto an activated alkene within a ring system (Figure 7).

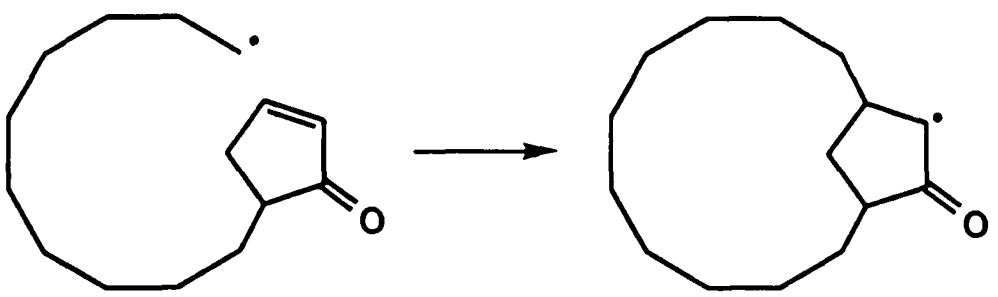


Figure 7

- In strategy **B** (Figure 8) the ring system simply acts as a tether between the donor and acceptor radical groups, which are situated at the chain termini. In

such a system, depending on the functional groups present in the ring, the possibility exists of a *cis-*, *trans-* or *pseudo-planar* relationship across the ring between the donor and the acceptor groups.

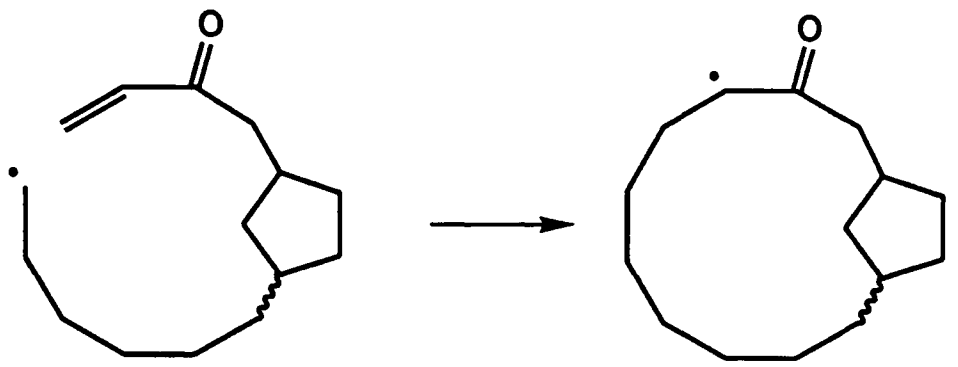


Figure 8

- Strategy **C** is the reverse of strategy **A**, i.e. a secondary cycloalkyl radical cyclises onto an activated alkene positioned at the terminus of an alkyl chain (Figure 9).

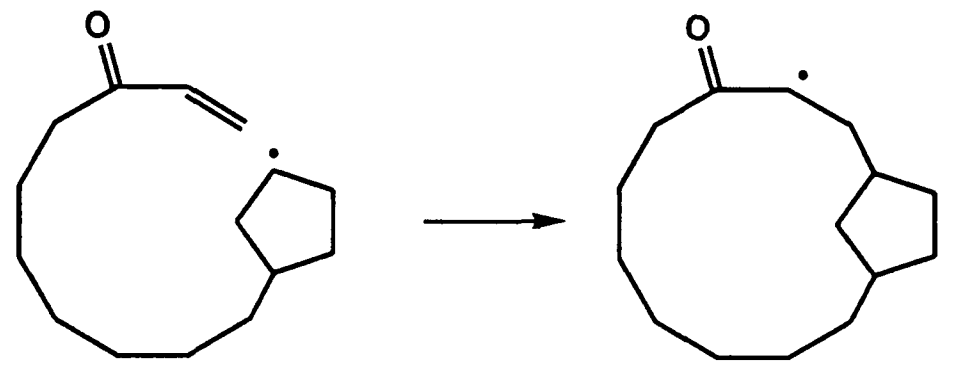


Figure 9

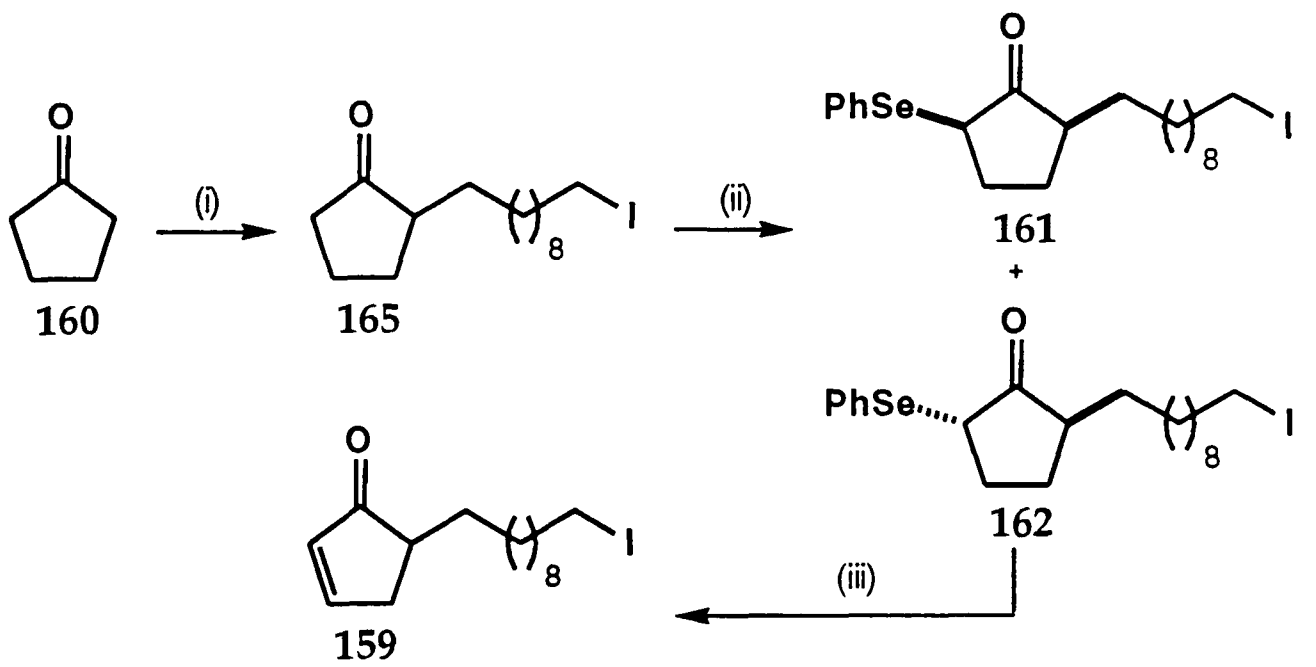
We decided to investigate each of these strategies on systems which could be readily synthesised. Initially we were not concerned with ensuring that the functionality was compatible with our target macrocyclic ketone **35**, rather we concentrated only on the construction of the required bicyclo[10.2.1] framework, i.e. a system which would involve a 13/14[†]-*endo*-trig radical cyclisation.

[†] Classification of the ring size formed in the macrocyclisation step depends on which route around the cyclopentane ring is followed.

6.3.2. Strategy A: Macrocyclisation onto a Cycloalkenone Acceptor

The major advantage of this route would be the rapidity with which the precursors for both model and real systems could be constructed. As mentioned earlier (**6.2.2.3.**) steric effects are critical in determining the ability of a radical to add to an activated alkene and we thought it may be difficult for cyclisation to occur in this case. Nevertheless we wished to investigate the possibility of promoting this type of cyclisation using a Lewis acid.[130]

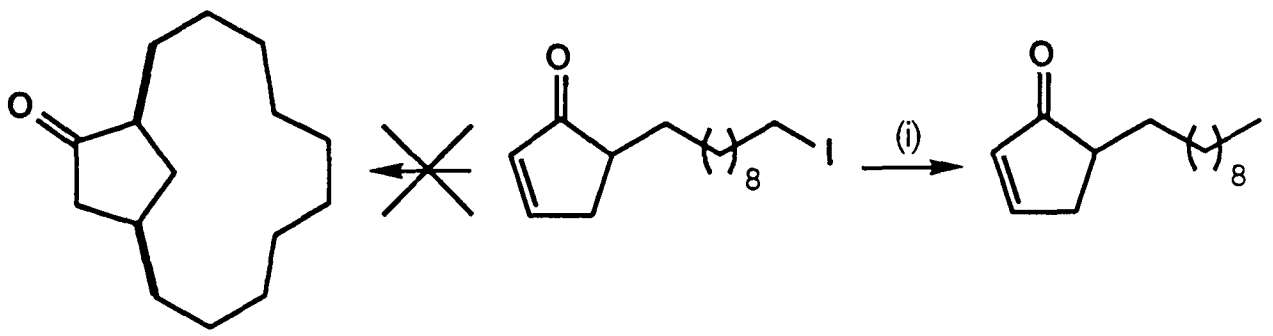
The radical precursor **159** was prepared in three steps from cyclopentanone **160** (Scheme 63). Alkylation of cyclopentanone **160** required addition of DMPU, and the subsequent selenation[131] products **161** and **162** were identified by the coupling constants of the α- proton to the phenylseleno-substituent in the ^{1}H NMR spectrum: *trans*-, δ_H 3.68 (1H, t, *J* 8.3 Hz); *cis*-, δ_H 3.87 (1H, d, *J* 6.7 Hz). In the *trans*- isomer the α- proton is able to couple to both adjacent methylene protons whereas in the *cis*- isomer, the α- proton is orthogonal to one of the adjacent protons. (The data for the uncharacterised diselenide **163** side-product obtained on one occasion and the corresponding selenoenone **164** are reported in Appendix C).



Conditions: (i) LDA, DMPU, 1,10-diiododecane, THF, -78°C to RT, 15h; 63%. (ii) LDA, PhSeBr, THF, -78°C to RT, 3h; 42% (*trans* **162**); 29% (*cis* **161**).[131] (iii) H_2O_2, DCM, 0°C to RT, 15h; 86%.[132]

Scheme 63

Subjecting iodoenone **159** to the conditions described by Porter[96c] (1.1 eq. $^{n}Bu_3SnH$, 0.1 eq. AIBN, 5mM, Δ, 3h) resulted, as predicted, in a quantitative conversion (by ^1H NMR) to the direct reduction product **166** rather than the cyclised product **167**. Attempts to effect the cyclisation using slow addition and higher dilution led to identical results. The use of *tris*(trimethylsilyl)silane[133] ($(Me_3Si)_3SiH$) also resulted in the formation of **166**. Even though complexation of the enone **159** with $ZnBr_2$ (0.5 eq. to 1.0 eq.) caused a significant downfield shift (0.1-0.2 ppm) of the β-alkene proton (hinting at increased electrophilicity at that centre) the effect was insufficient to induce addition (Scheme 64).[130]



167 **159** **166**

Conditions: (i) $^{n}Bu_3SnH$, AIBN, $ZnBr_2$, slow addition (6h), 3mM, Δ; 50%.

Scheme 64

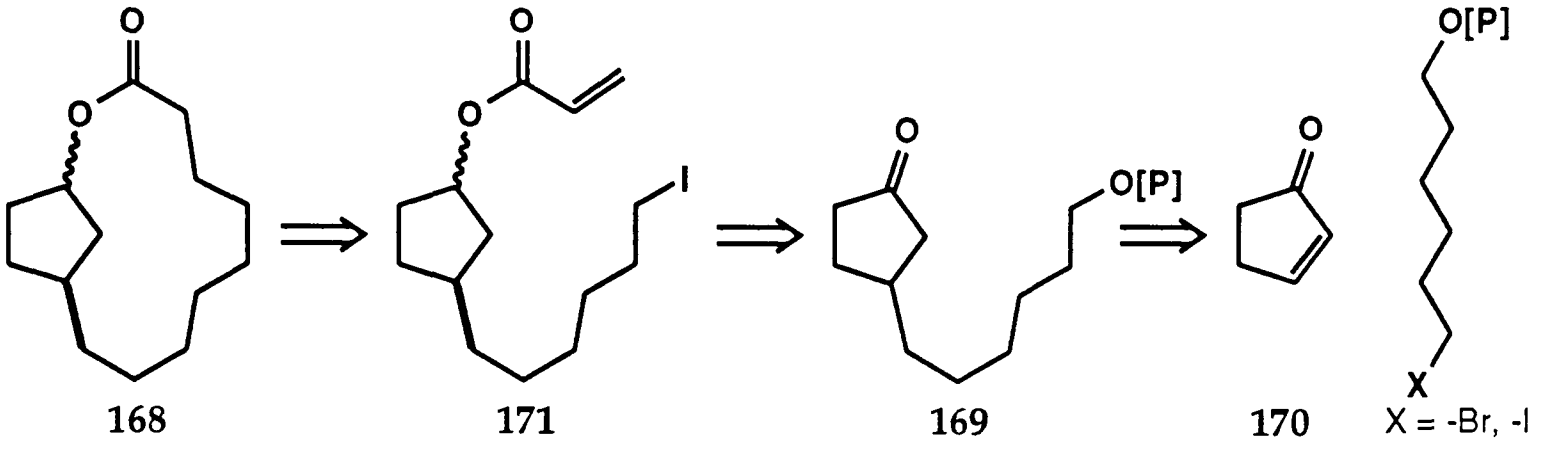
Work-up of the reaction with tributyltin hydride was facilitated by the addition of thiophenol. The predominant tin sulphide species that formed proved to be hydrolytically stable and could be easily removed by column chromatography.[134]

Thus strategy **A** failed because the enone was unreactive. The cyclisation may be feasible if a more nucleophilic radical, such as an acyl radical, were used, however, these conditions were not attempted and work on this approach ceased.

6.3.3. Strategy B: Macrocyclisation Involving a Cycloalkane Tether

6.3.3.1. We chose the lactone **168** as a readily prepared target in a test of this strategy. Our retrosynthetic approach towards the radical precursors for such a

system involved functionalisation of the cuprate addition product **169** (Figure 10).



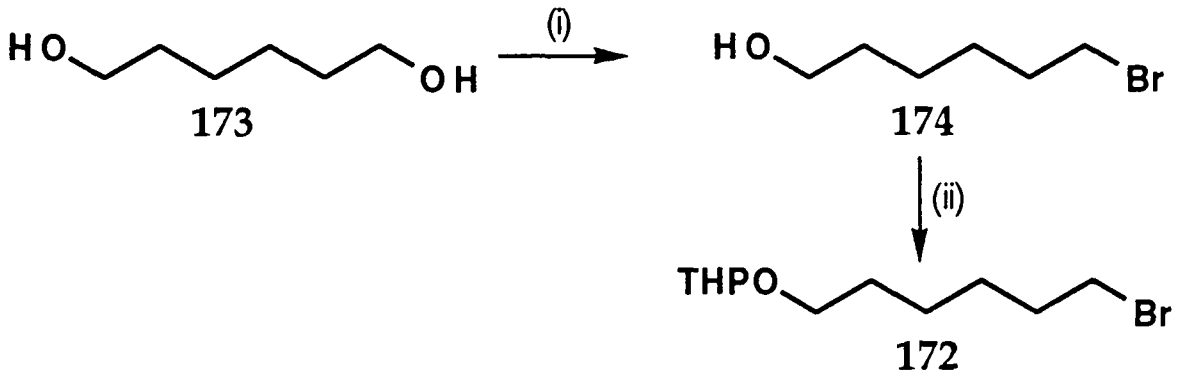
168 **171** **169** **170**

Figure 10

In this system the iodoacrylates **171** can have a *cis*- or *trans*- relationship. We intended to synthesise both isomers and test the macrocyclisation on each of these independently.

6.3.3.2. Synthesis of a Functionalised Hexyl Copper Reagent

Our initial work was concerned with developing a suitably functionalised cuprate to generate the Michael adduct **169**. Thus the protected bromide[135,136] **172** was prepared by standard methods (Scheme 65).



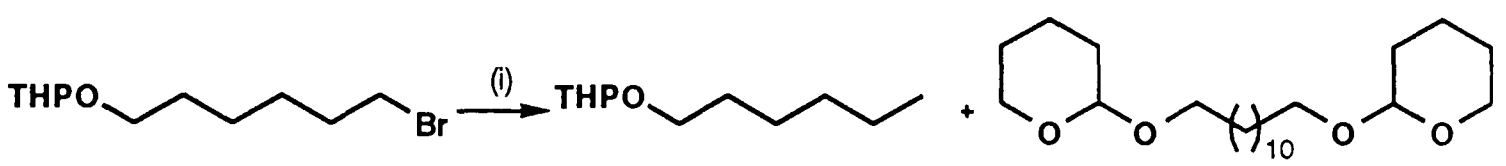
173 **174** **172**

Conditions: (i) 48% aq. HBr, PhH, Δ, 18h; 87%.[81] (ii) DHP, conc. HCl, 20mins; 98%.[82]

Scheme 65

It was hoped that the Grignard reagent[137] derived from **172** would add in a Michael fashion to cyclopentenone **170** in the presence of a copper catalyst. Attempts to form the corresponding Grignard reagent[135,136] and, as a test, add it to benzaldehyde **175**, resulted in the isolation of the reduced bromide **176** and the corresponding Wurtz coupled[138] dimer **177** (Scheme 66). Although the

Grignard reagent apparently formed (Mg dissolved) under no circumstances (such as solvent change,[138] or through activation of the magnesium,[139]) could any addition products be isolated in the tests with simple aldehydes and ketones. Interestingly the dimer **177** proved to be a single diastereomer, suggesting a significant degree of chelation between the magnesium and the THP oxygens, however, it is unknown whether the dimer was *meso-* (σ_V plane) or *dl-* (C_2 symmetric).

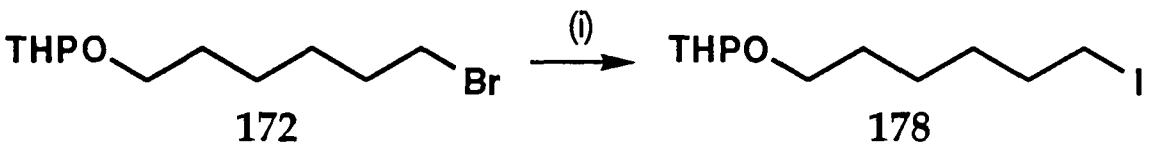


172 **176** **177**

Conditions: (i) Mg, I_2, THF, Δ to RT, 3h; Work-up; 41% monomer[140] **176**, 45% dimer **177**.

Scheme 66

Next, the iodide[141] **178** was synthesised (Scheme 67) in the hope that lithium-halogen exchange with ^{t}BuLi would give the corresponding functionalised organolithium species.



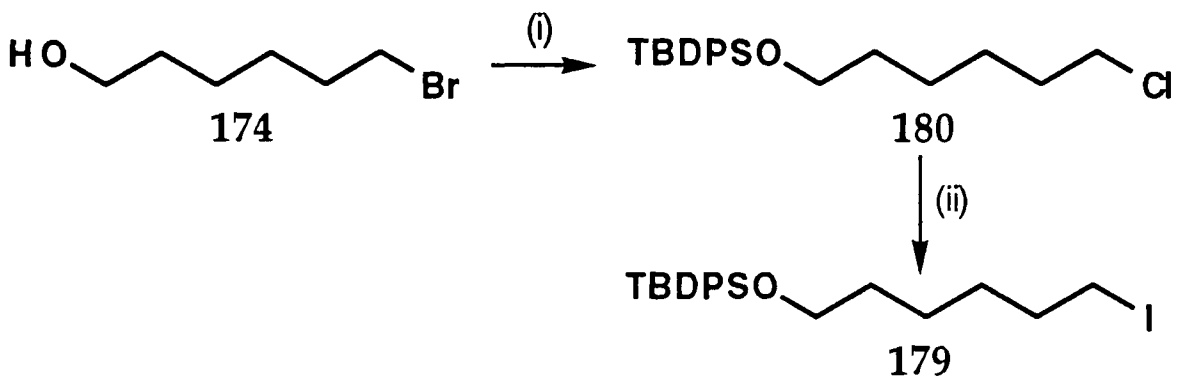
172 **178**

Conditions: (i) NaI, acetone, 15h; 96%.[141]

Scheme 67

Metallation of **178** with ^{t}BuLi or with lithium naphthalene[142] again gave exclusively reduced and coupled products on addition of test carbonyl electrophiles.

Consequently the *t*-butyldiphenylsilyl[143] protected alcohol **179** was prepared (Scheme 68); however, metallation and subsequent addition of benzaldehyde **175** resulted in no observed addition products; instead complex mixtures, including elimination of the -O[Si] functionality, were generated.

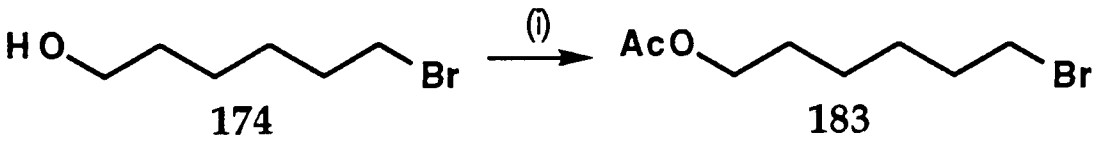


Conditions: (i) TBDPSCl, Im, DMF, 15h; 96%.[143] (ii) NaI, acetone, Δ, 15h; 87%.

Scheme 68

It was decided therefore to make use of a system which is known to transmetallate effectively, namely, bromo- **181** or iodohexene **182**. We envisaged functionalising the terminal alkene to an alcohol, by means of a hydroboration reaction, once Michael addition to cyclopentenone **170** had occurred.

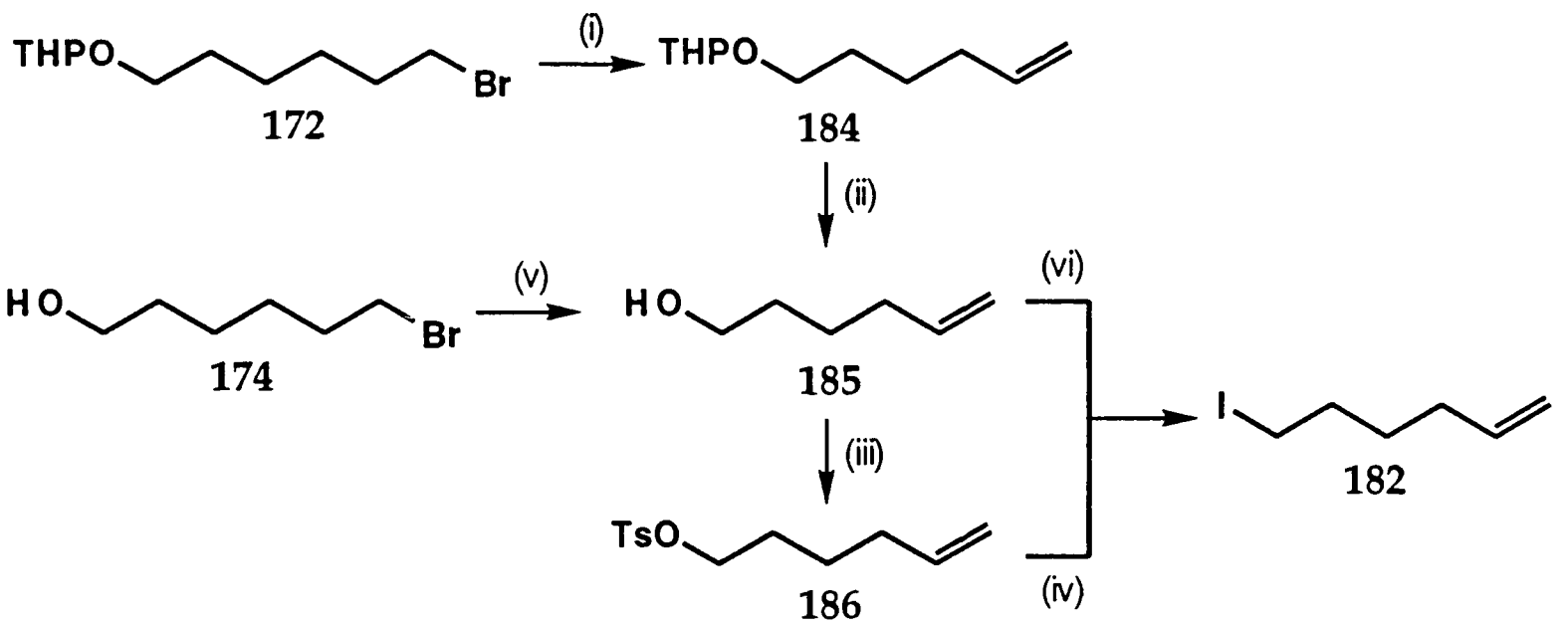
A rapid route towards bromohexene **181**, involving *mono*-elimination of HBr from 1,6-dibromohexane using DMPU rather than the reported use of HMPA,[144a] proved unsuccessful. Pyrolysis[144b] of the acetate[145] **183** (Scheme 69) was hoped to lead to bromohexene **181**, however, the temperature required for elimination could not be achieved and starting material was recovered; the corresponding xanthate was not investigated.



Conditions: (i) Ac_2O, Im, 15h; 82%.[145]

Scheme 69

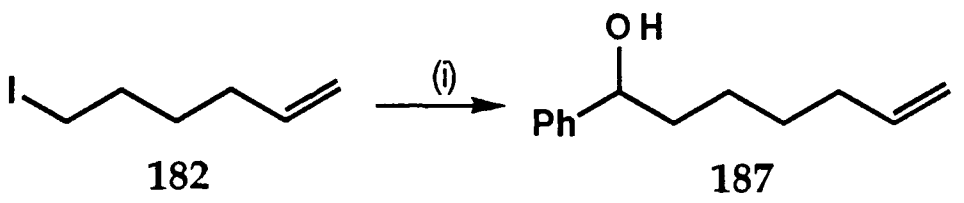
Consequently a more lengthy synthesis of iodohexene **182** from the protected bromide **172** was completed; subsequent improvement gave **182** in two steps from bromohexanol **174** (Scheme 70).



Conditions: (i) $KOBu^t$, DMSO, 15h; 96%.[146] (ii) TsOH, MeOH, 15h; 55%.[85,147] (iii) TsCl, py, DCM, 15h; 85%.[147] (iv) NaI, acetone, 15h; 91%.[147] (v) $KOBu^t$, DMSO, 20h; 65%[95% based on recovered **174**].[147] (vi) Ph_3P, I_2, Im, (3:1, MeCN:Et_2O), 0°C to RT, 15h; 56%.[147,148]

Scheme 70

A test reaction was carried out with benzaldehyde **175** (depicted in Scheme 71). The choice of solvent was crucial to the lithium-iodine exchange;[149] reactions in THF proved unsuccessful, however, the use of ether led to a clean reaction. The optimum solvent system required for formation of alkyllithiums was noted to be (3:2, *n*-pentane:ether).[149]

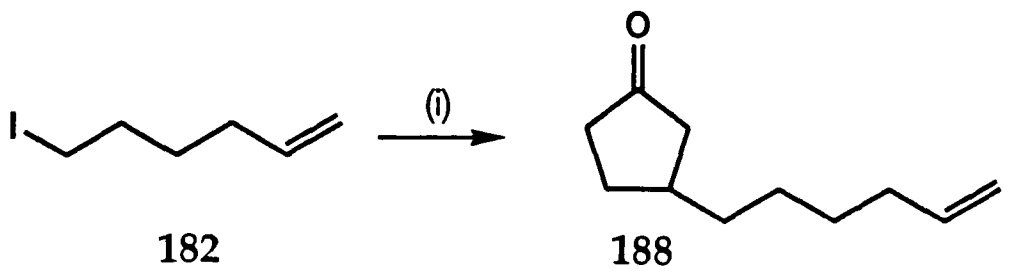


Conditions: (i) ^{t}BuLi, Et_2O, PhCHO, -78°C to RT, 4h; 85%.

Scheme 71

6.3.3.3. Application to the Synthesis of the Free-radical Precursors

Having identified an appropriate organometallic reagent we attempted to generate the Michael adduct from cyclopentenone **170**. Initial attempts gave no product, however, the use of iodotrimethylsilane to activate the enone[150,151] in combination with dimethylsulphide as a co-solvent[152] allowed the synthesis of the desired adduct **188** in excellent yield (Scheme 72).

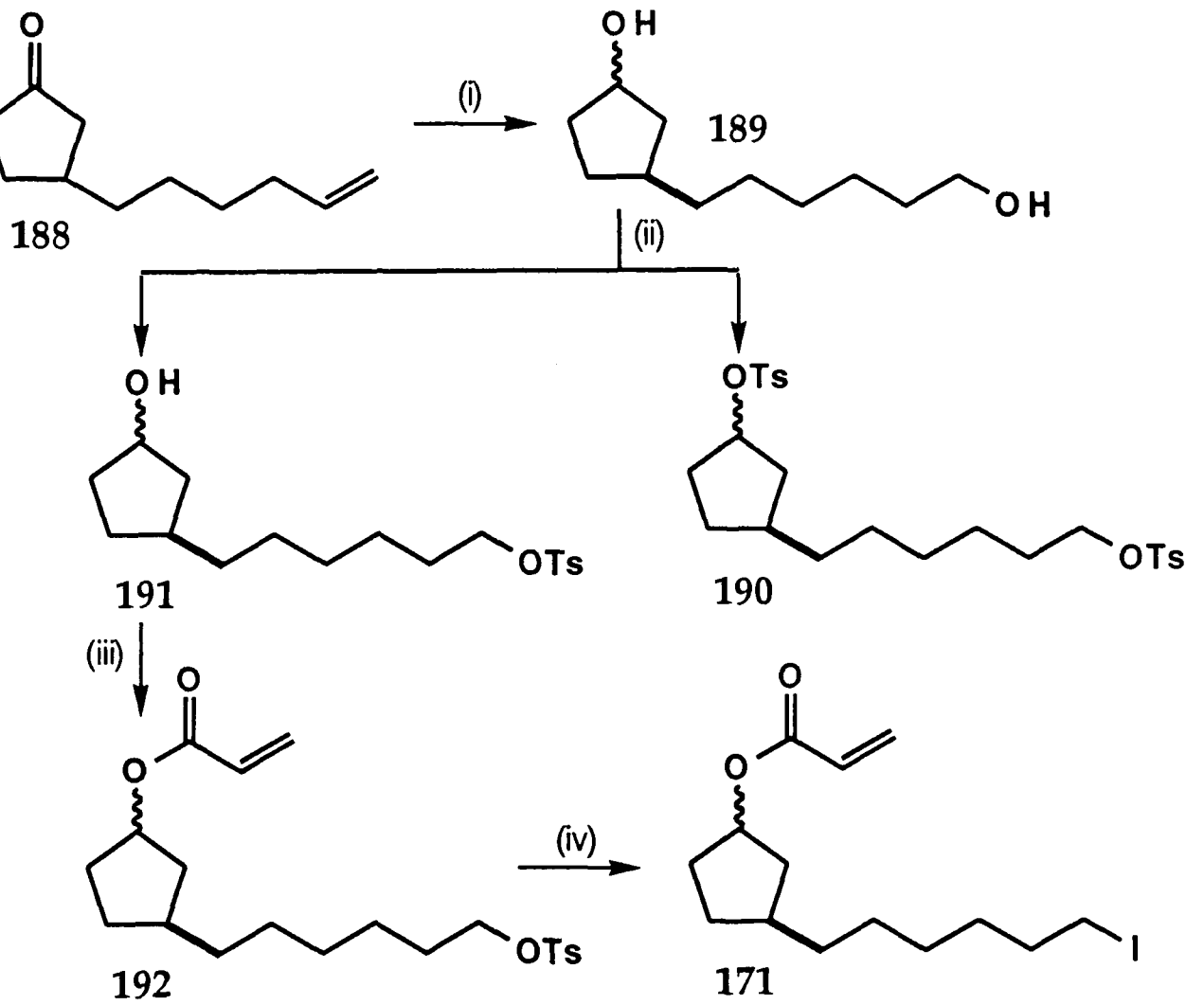


182 188

Conditions: (i) ^{t}BuLi, Et_2O, Me_2S, $CuBr.SMe_2$, [153] -78°C, to -30°C, 30mins; re-cool to -78°C to RT, TMSI, cyclopentenone **170**, 15h; acid work-up; 97%.

Scheme 72

The Michael adduct **188** was then converted to the desired iodo-acrylate radical precursors **171** over 4 steps (Scheme 73). Unfortunately the diastereomers **189**, generated on reduction with BH_3.THF,[154] co-ran on t.l.c. and could not be separated. All subsequent reactions were performed on a mixture of isomers. Formation of the undesired di-tosylate **190** (Appendix C) could not be prevented, even at low temperature.



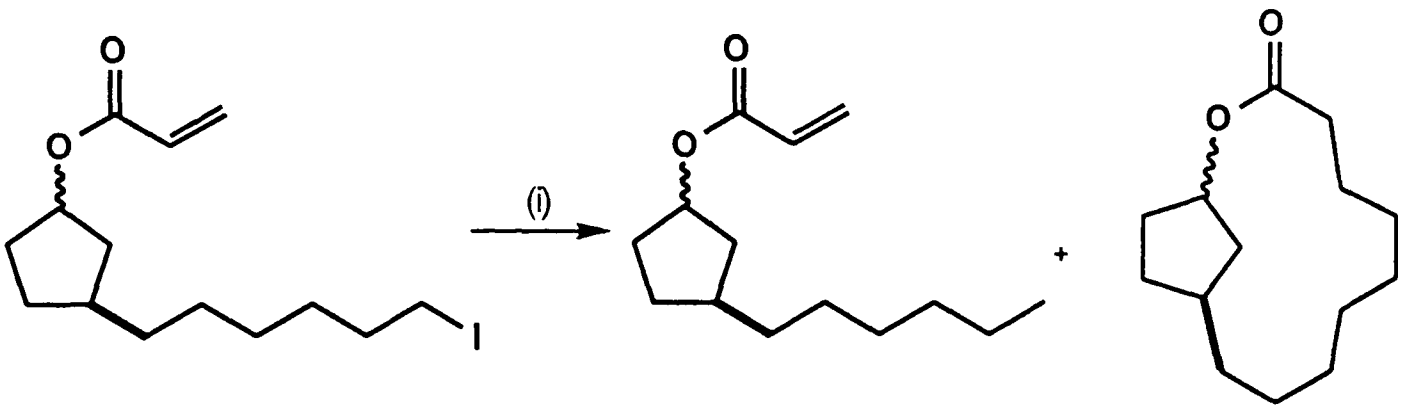
Conditions: (i) BH_3.THF, THF, 0°C to RT, 15h, then H_2O_2, NaOH, EtOH, 5h; 77% (1:1 mixture of diastereomers).[154] (ii) TsCl, py, 15h; (Di-tosylates **190**: 10%, mono-tosylates **191**: 60%). (iii) Et_3N, Acryloyl chloride, PhH, 10°C to RT, 15h; 71%. (iv) NaI, acetone, 15h; 89%.

Scheme 73

6.3.3.4. Free-Radical Macrocyclisations of Iodo-Acrylates 171

Initially the macrocyclisation was performed with tributyltin hydride (1.1 eq.) added in one portion at 5mM concentration. This predominantly led to the directly reduced compound. Subsequent studies involved the slow addition of tributyltin hydride (1.1 eq. over 6 to 10h) at 2-3mM concentrations. Studies with $(Me_3Si)_3SiH$ led to results which were identical to those obtained with tributyltin hydride, thus further studies made use of tributyltin hydride only.

Using the optimised conditions, the major products isolated from the reaction (using thiophenol[134]), were tentatively identified to be the acrylates **193** (with the iodide directly reduced) and the cyclised material **168**. We have no knowledge of the relative stereochemistry of each of these products and have assigned them as a mixture; however, the *cis*- acrylate would be more likely to cyclise than the *trans*- and thus a greater proportion of the cyclised material is likely to be of *cis*- stereochemistry; equally the acyclic product is likely to have predominantly *trans*- stereochemistry across the ring junction (Scheme 74).



171 **193** **168**

Conditions: (i) $^{n}Bu_3SnH$, AIBN, PhH, slow addition (10h), 2.5mM, Δ, 3h; 78% (**193**:**168**, 1.3:1).

Scheme 74

In summary, this strategy, when applied to a system which has a *cis*-relationship between groups across the ring, seems to be feasible.

6.3.4. Strategy C: Macrocyclisation Involving a Cycloalkyl Radical

6.3.4.1. The retrosynthetic analysis of our target lactone **194** (Figure 11) was similar to that described in Section **6.3.3.** except the acrylate would be connected to the primary alcohol and the secondary alcohol would become the cycloalkyl radical progenitor.

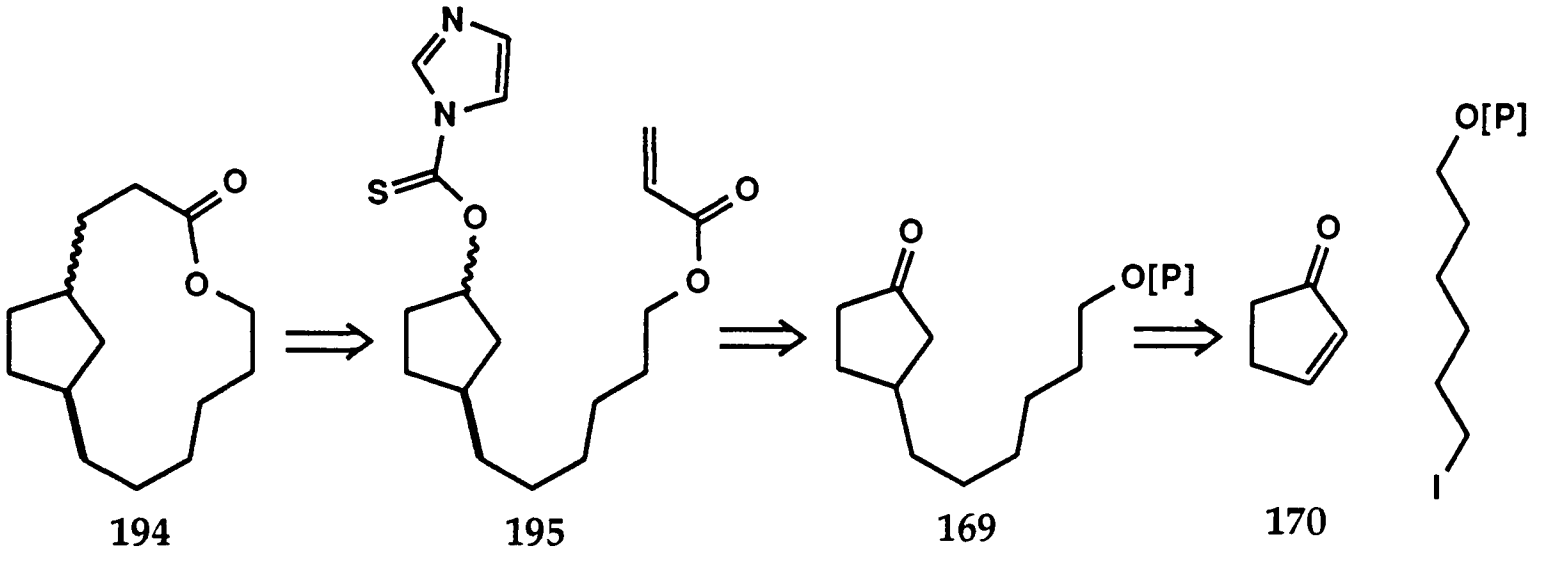
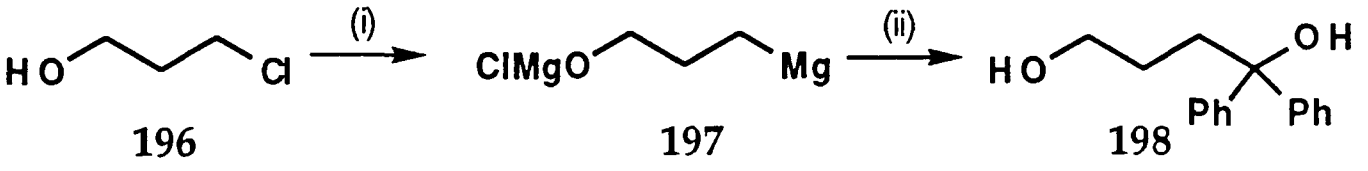


Figure 11

6.3.4.2. Synthesis of a Hydroxylated Hexyl Copper Reagent

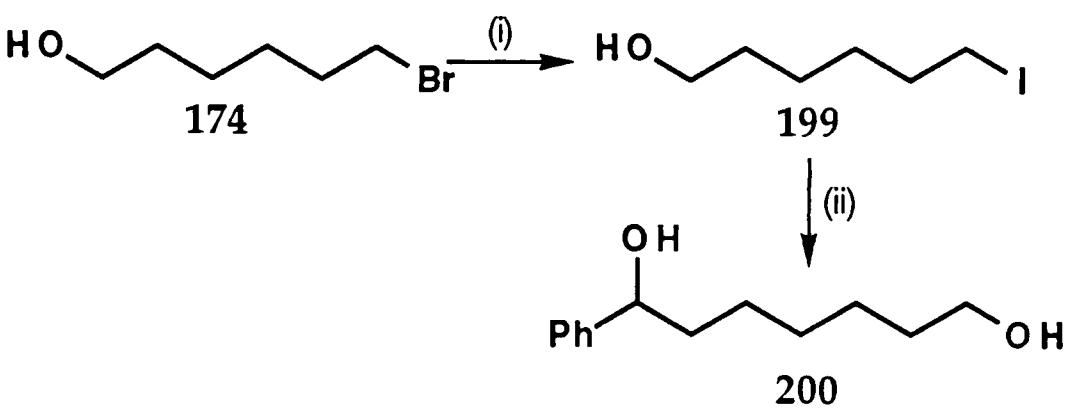
We wished to improve upon the strategy involving formation of the organolithium species from iodohexene (**6.3.3.2.**). Alexakis and co-workers[155,156] had been concerned with the same problem; one solution they identified employed a *t*-Bu- protecting group for the alcohol,[156] a second involved deriving a Grignard reagent directly from a chloro-alcohol.[155] Alexakis found that deprotonation of the alcohol **196** with methylmagnesium chloride generated a magnesium salt that could be effectively transformed into Grignard reagent **197**, as illustrated by formation of **198** (Scheme 75).



Conditions: (i) MeMgCl, -30°C, THF, 20mins; Mg, Δ, 1,2-dibromoethane, 2-3h. (ii) Benzophenone; 79%.[155]

Scheme 75

We considered that an analogous organolithium species could be generated. Thus iodo-hexanol[156] **199** was deprotonated (^{n}BuLi) and transmetallated (^{t}BuLi) to generate an organolithium species[157] that added to benzaldehyde **175**, in a test reaction, to generate the unreported diol **200** (Scheme 76).

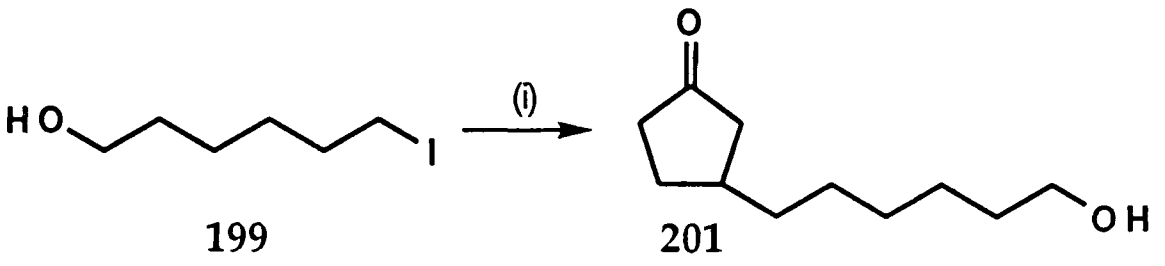


Conditions: (i) NaI, acetone, 15h; 93%.[156] (ii) ^{n}BuLi, Et_2O, 15mins, -78°C; ^{t}BuLi, 15mins; PhCHO **175**, -78°C to RT, 3h; 53%.

Scheme 76

6.3.4.3. Application to the Synthesis of the Free-Radical Precursors

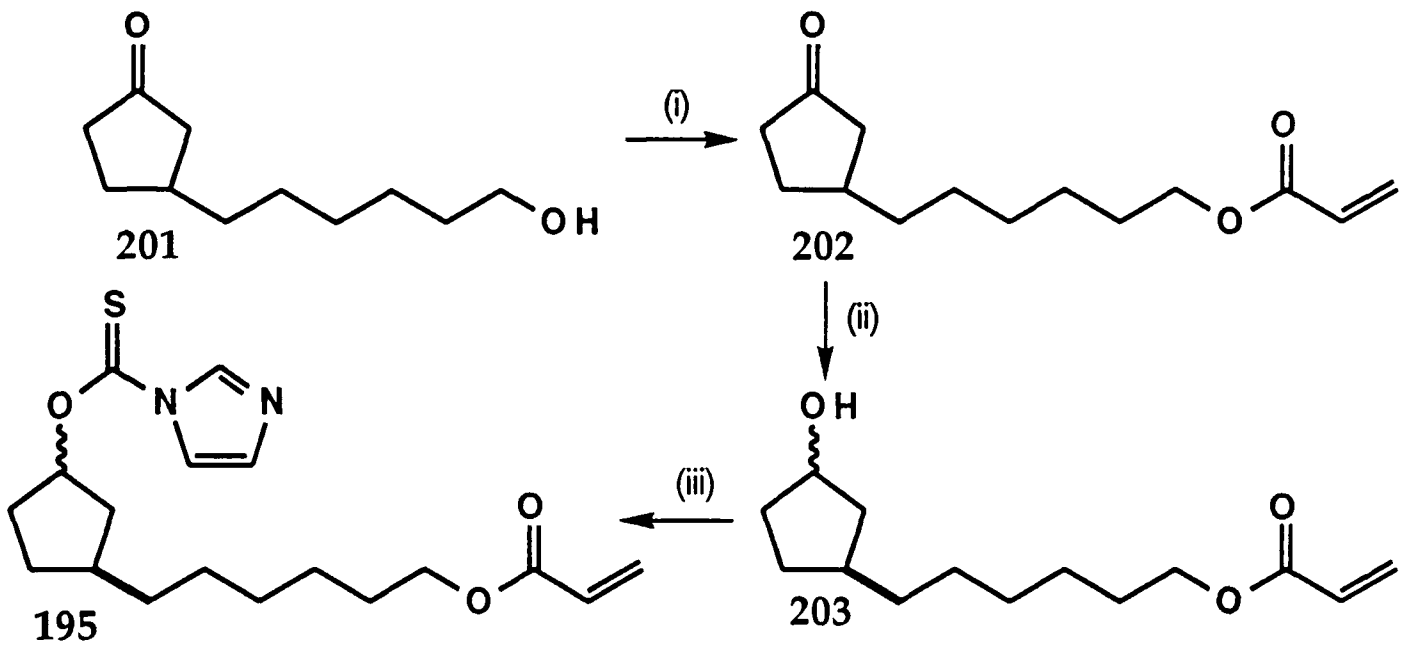
Using the *cuprate* version of this new methodology, the hydroxyhexyl-cyclopentanone **201** was synthesised in one-step (Scheme 77).



Conditions: (i) ^{n}BuLi, Et_2O, 15mins, -78°C; ^{t}BuLi, 15mins; Me_2S, $CuBr.SMe_2$, -78°C to -20°C, 20mins; TMSI, -78°C, 10mins; cyclopentenone **170**, -78°C to RT, 15h; 40%.

Scheme 77

Further transformation to the thioimidazolyl acrylates **195** was achieved in three further steps (Scheme 78). Again, a diastereomeric mixture of alcohols **203** was formed on reduction of the ketone **202**, but this was of no consequence since the stereochemistry would be lost on generating the radical.

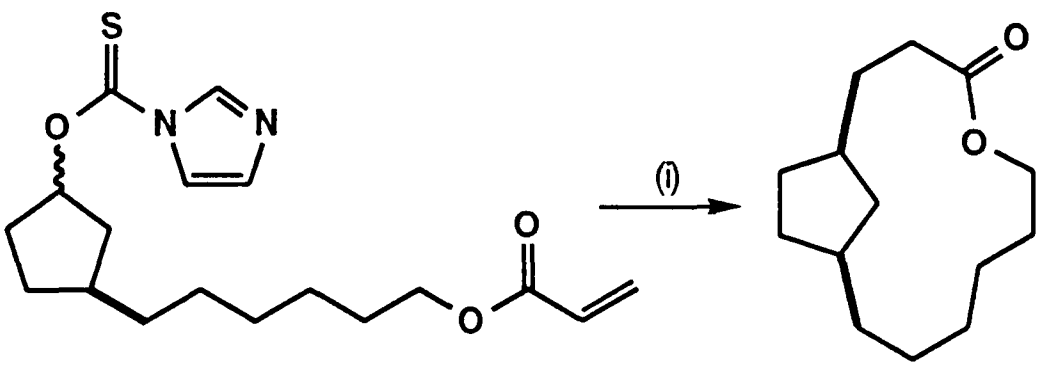


Conditions: (i) Et_3N, Acryloyl chloride, DCM, 0°C to RT, 7h; 82%.
(ii) $NaBH_4$, EtOH, 4h; 92%. (iii) Im_2CS, DCM, 15h; 93%.

Scheme 78

6.3.4.4. Free-Radical Macrocyclisations of Thio-Imidazolyl Acrylates

On subjecting **195** to the conditions required for macrocyclisation, a single major product was formed; ^1H NMR spectroscopy of the crude reaction mixture showed a total absence of olefinic peaks, and the mass from GCMS was consistent with that for the cyclised material **204**. Purification (using thiophenol[134]) led to a product which we have assigned as **204**. Again we have no evidence for the relative stereochemistry of the product; however, the *cis*-product is probably more likely to form than the *trans*- (Scheme 79).



195 **204**

Conditions: (i) $^nBu_3SnH$, AIBN, PhH, slow addition (10h), then further 3h, 2.5mM, Δ; 38%.

Scheme 79

In summary this strategy circumvents the problem of having *cis*- and *trans*- substituents across the ring.

6.4. Model Studies Part IV

6.4.1. Retrosynthetic Strategy for Model System

We decided to work on a carbocyclic model system that resembled the real system but lacked the isopropyl substituent. Hence our target macrocyclic ketone **205** was as shown in Figure 12. We were attracted to strategy **B** out of those described because it would be compatible with the functionality that would be required in Roseophilin itself.

We proposed that the free-radical precursor **206** could be derived from the product resulting from the reaction between a functionalised cuprate and the oxabicycle[158] **207** (Figure 12), *c.f.* Curran's work on Hirsutene.[159]

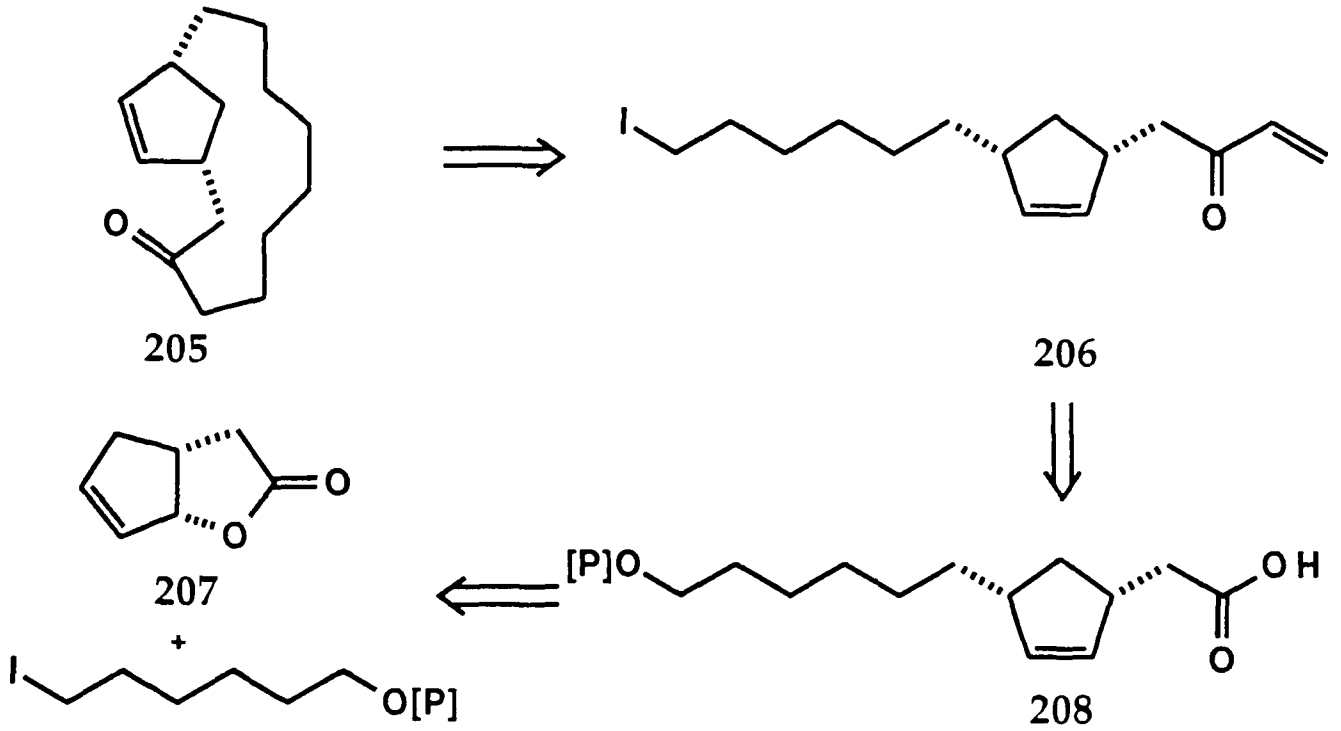


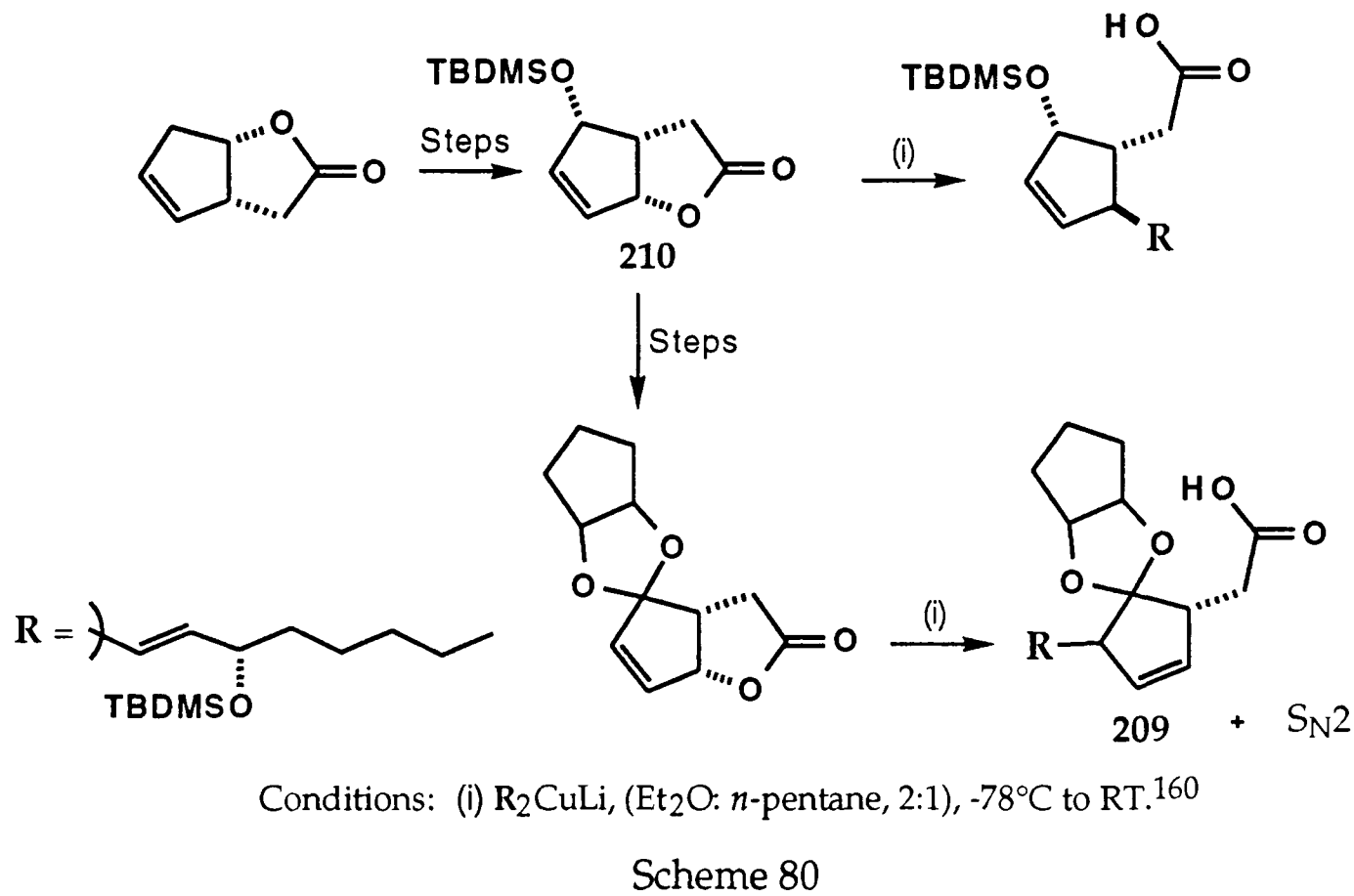
Figure 12

We were aware that a *cis*- relationship between the substituents on the cyclopentene ring would be desirable to promote the cyclisation and so were keen to develop stereoselective methods for the formation of **208**. A brief review of cuprate additions to vinyl lactones and vinyl epoxides follows.

6.4.2. Cuprate Additions to Vinyl Lactones and Vinyl Epoxides

6.4.2.1. Additions to Vinyl Lactones

Corey and Mann[160] reported the synthesis of prostaglandins employing cuprates. They observed that the regioselectivity, with a higher-order dialkyl cuprate, depended on the steric environment of the sites of attack, as shown in Scheme 80.

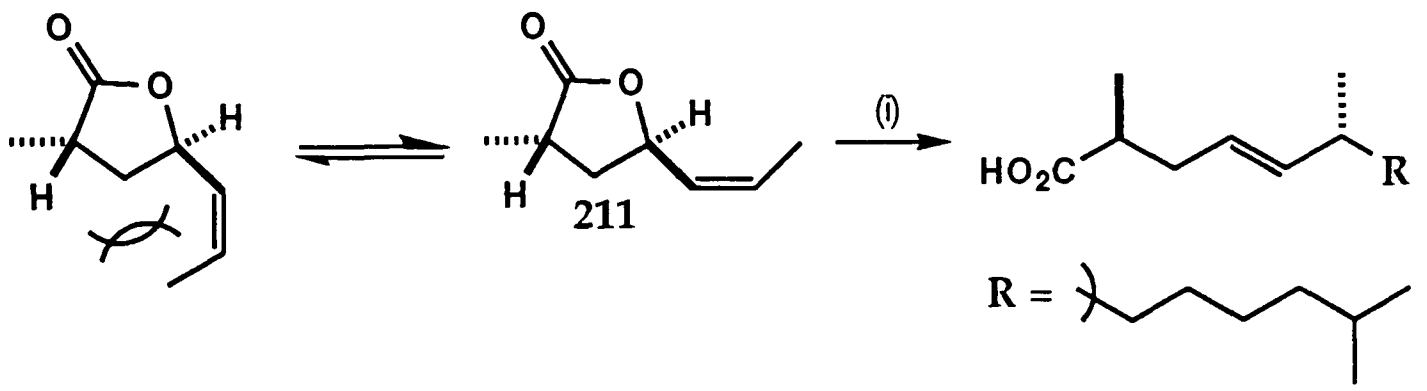


Conditions: (i) R_2CuLi, (Et_2O: *n*-pentane, 2:1), -78°C to RT.[160]

Scheme 80

Corey did not specify the stereochemistry in the 1,4- addition product **209**, however, he did suggest that solely 1,2- attack on **210** was a consequence of the bulk of the siloxy group and a preference for *syn*- attack in the S_N2' process,[161] implying that a *cis*- relationship across the cyclopentene ring resulted.

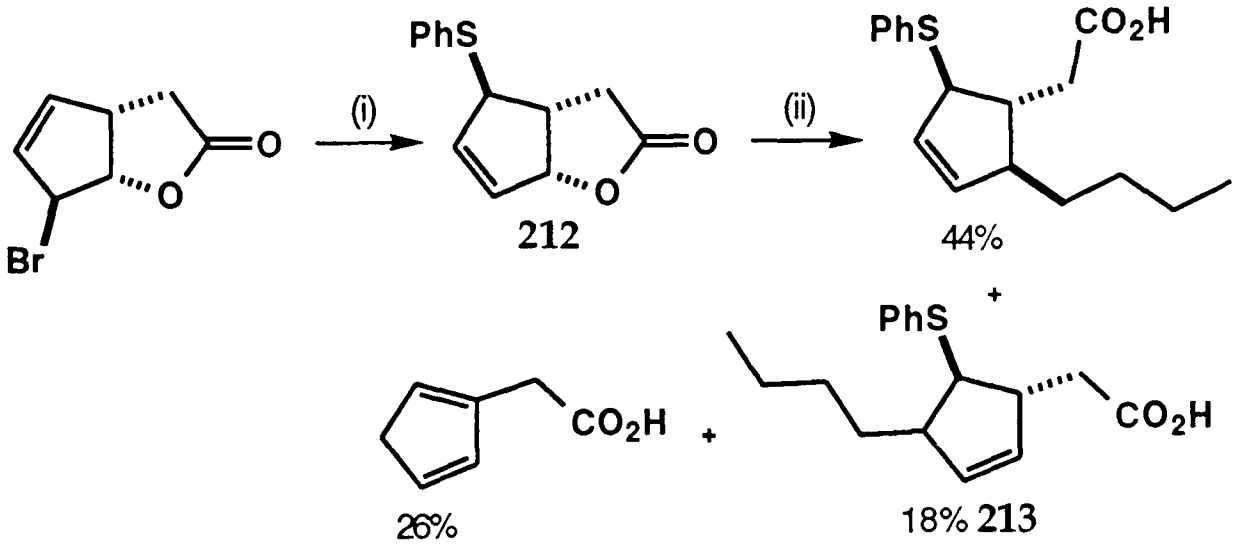
Trost *et al.*[162] noted that the addition of monoalkyl cuprates to acyclic vinyl lactones resulted in selective *anti*- S_N2' attack and hence was a useful approach to chirality transfer (Scheme 81). Non-bonded interactions are minimised in the alkene **211**, and it is this conformer through which the addition proceeds.



Conditions: (i) R(CuCN)Li, Et_2O, -20°C to 0°C; 94%.[162]

Scheme 81

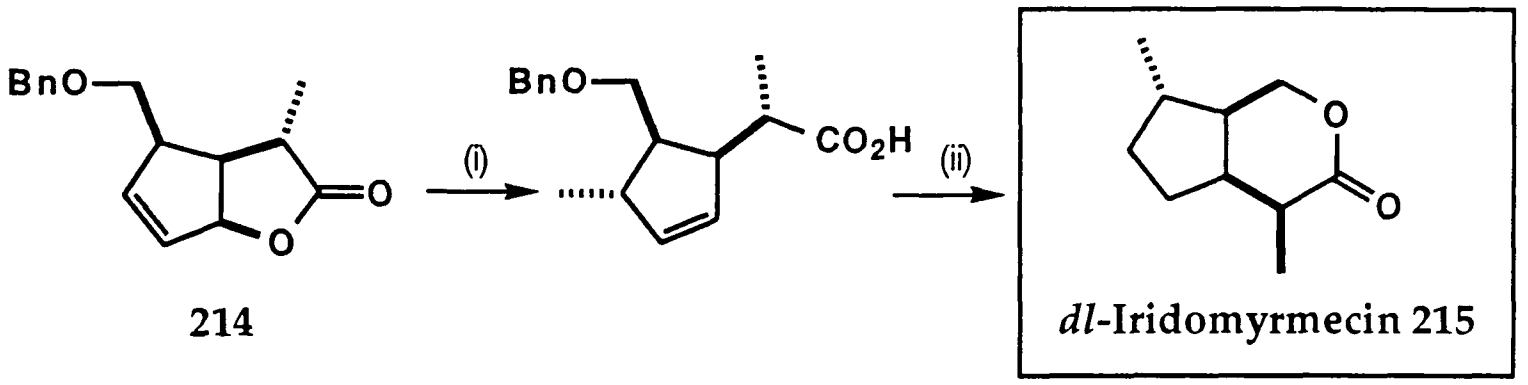
A study by Roberts and co-workers[163] highlighted that cuprate attack on cyclopentenyl vinyl lactones was not as straightforward as the analogous work on allylic acetates and acyclic vinyl lactones. Roberts showed that addition of a dialkyl cuprate to **212** resulted in three products - the stereochemistry of the 1,4- adduct **213** was again undefined (Scheme 82) though previous work in the group[164] suggested *anti-* attack.



Conditions: (i) NaSPh; 83%. (ii) ^{n}BuLi (2.4 eq.), CuBr.SMe_2 (1.2 eq.), Et_2O, Me_2S, -78°C to -40°C, 4h.[163]

Scheme 82

Concurrent work by Grieco and Srinivasan[165] succeeded in identifying the stereochemistry (*syn-* or *anti-*) associated with S_N2' attack of dimethyl cuprate. They were able to show conclusively that, in the system **214**, (Scheme 83) exclusive S_N2' attack had occurred, and also, by conversion to Iridomyrmecin **215**, that the reaction had proceeded with exclusive *anti-* attack.

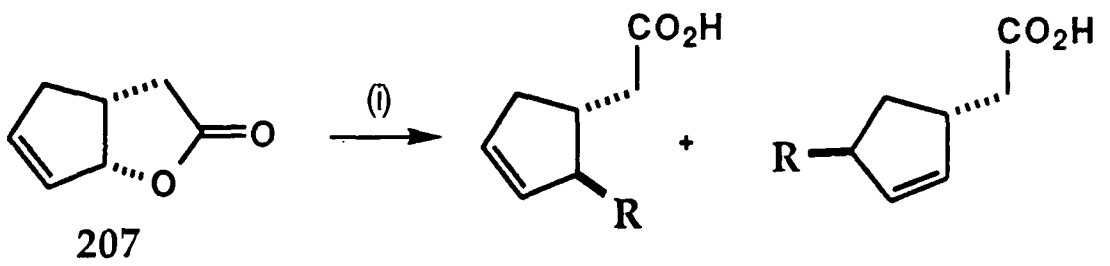


214 **dl-Iridomyrmecin 215**

Conditions: (i) $LiMe_2Cu$, Et_2O, -20°C to -40°C, 75mins; 84%. (ii) H_2, 10% Pd-C, 24h; 76%.[165]

Scheme 83

Curran, whilst working on the synthesis of Hirsutene[159] noted that "While the products of *anti-* opening are usually observed, regioselectivity has varied from complete S_N2' to complete S_N2 depending on the substituents on the vinyl lactone and the nature of the organocopper reagent."[166] His group showed that, in general, the opening of cyclic vinyl lactones with lithium dimethylcuprate was controlled by substitution. However, the opening with a monoalkyl cuprate derived from an alkylmagnesium bromide and copper bromide-dimethyl sulphide complex, formulated as "RCu", exhibited good to excellent S_N2' selectivity. Interestingly this selectivity was lost on the use of a catalytic amount of copper bromide-dimethyl sulphide complex. This is summarised in Scheme 84.[166]

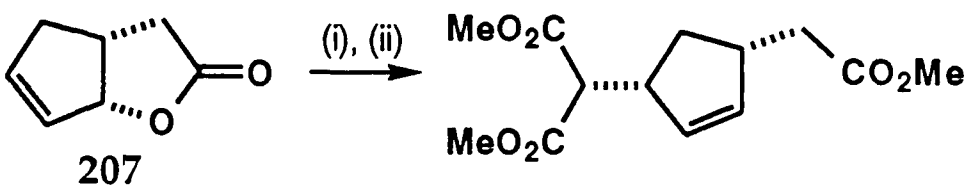


207

(i)	1,2-	1,4-	Yield (%)
$MeMgBr$/ 1 eq. $CuBr.SMe_2$	2	98	97
$MeMgBr$/ cat. $CuBr.SMe_2$	50	50	unreported
$MeLi$/ 1 eq. $CuBr.SMe_2$	14	86	91
$LiMe_2Cu$	38	62	91

Scheme 84

Although a cuprate tends to add 1,4- in an *anti-* fashion there are numerous reports of nucleophiles adding to cyclic vinyl lactone systems in a *syn-* mode, particularly when using palladium catalysis. Trost and co-workers[167] reported the overall *syn-* addition of dimethylmalonate to the oxabicycle **207** (Scheme 85) in the presence of *tetrakis*(triphenylphosphine)palladium(0).[168]



207

Conditions: (i) $(Ph_3P)_4Pd$, Ph_3P, dimethyl malonate, NaH, THF, Δ, 6h. (ii) CH_2N_2; 84%.[167]

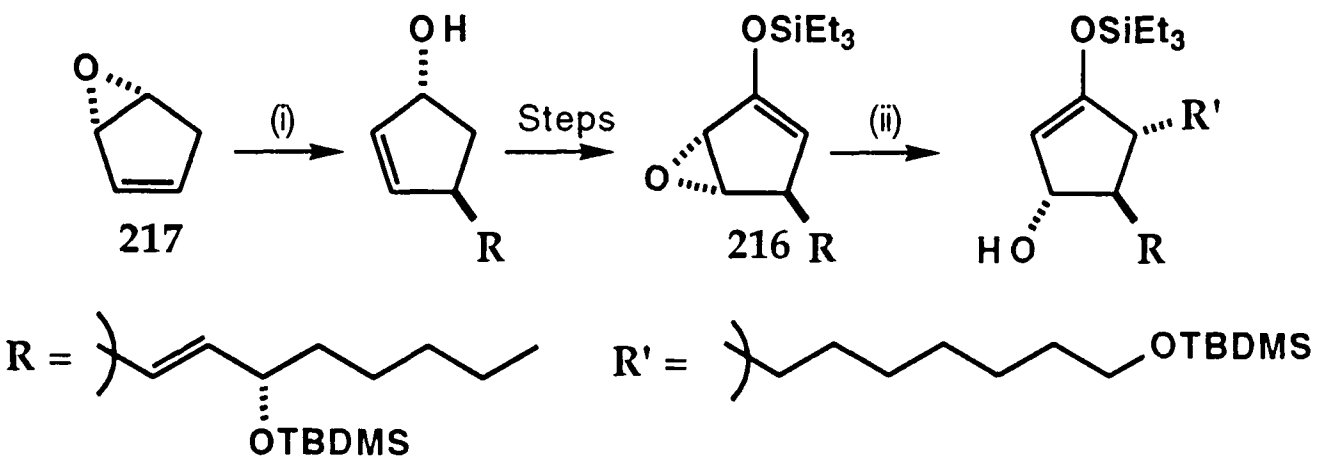
Scheme 85

In a more recent example, Aggarwal *et al.*[169] showed that this process was effective on similar substrates with a variety of heteroatom nucleophiles, e.g. azide, pyrrolidine, a silyl protected uracil and phenylsulphonyl.

6.4.2.2. Additions to Vinyl Epoxides

Initial studies of cuprate additions to cyclic 1,3-diene monoepoxides[170] (ring size: 5, 6 and 7) revealed a strong preference, in general, for *anti-* addition, in agreement with the addition to vinyl lactones (**6.4.2.1.**) though contrary to the previous dogma on S_N2' reactions.[161] The regiochemistry of attack depended on the nature of the cuprate and substitution around the site of attack although, in general, monoalkyl cuprates seemed to favour S_N2' attack and higher order cuprates, S_N2.

Marino's route towards PGE_1[171] illustrates some of these facets (Scheme 86).

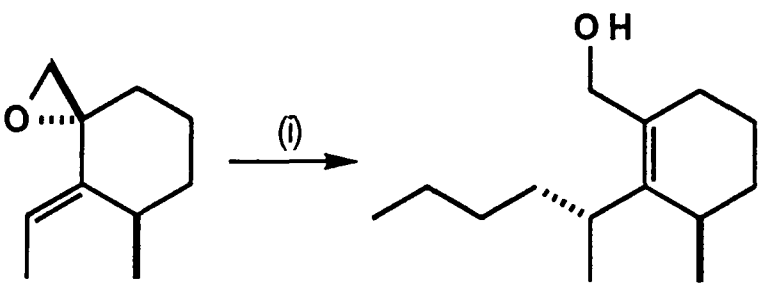


Conditions: (i) RCu(CN)Li, Et_2O; 80%. (ii) R'Cu(CN)Li; 88%.[171]

Scheme 86

Interestingly in step (ii) the cuprate added with overall *syn-* selectivity. Initially this was explained on steric grounds, however, further studies showed that it was likely that *anti-* 1,2- attack of LiI on **216** had occurred with subsequent *anti-* S_N2' attack of **R'**Cu(CN)Li (i.e. a double *anti-* attack).

One final example comes from work by Ziegler and Cady who were the first to employ exocyclic epoxides for the introduction of stereocentres in side chains by S_N2' alkylation.[172] They noted that additions were influenced strongly by steric effects to an extent where *syn-* addition could dominate over *anti-* with spectacular selectivity (Scheme 87).



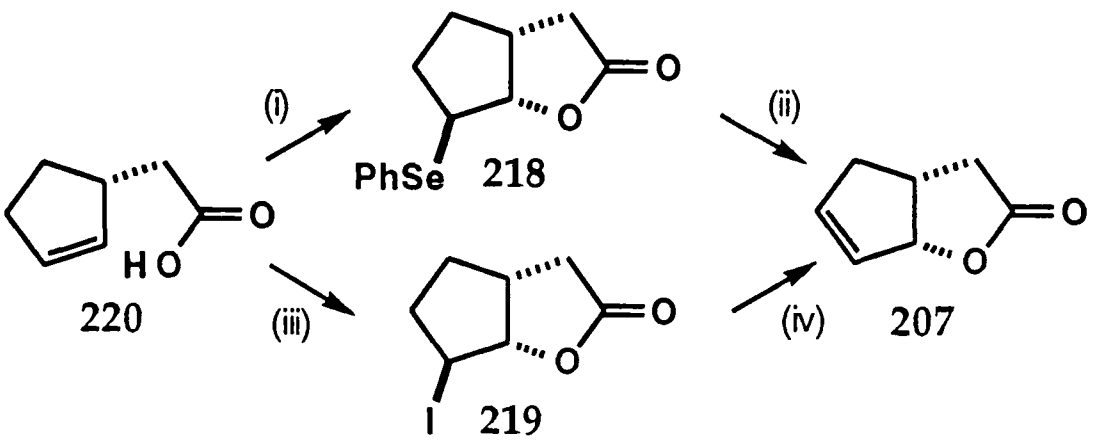
Conditions: (i) Bu_2CuLi, Et_2O; 95% (5% *anti-* addition).[172]

Scheme 87

6.4.3. Attempts to Promote *syn-* Addition of a Cuprate

We were keen to generate a product with *cis-* stereochemistry across the cyclopentene ring (**6.4.1.**) and thus sought to develop a method for encouraging overall *syn-* addition of a cuprate to the oxabicycle[158] **207**.

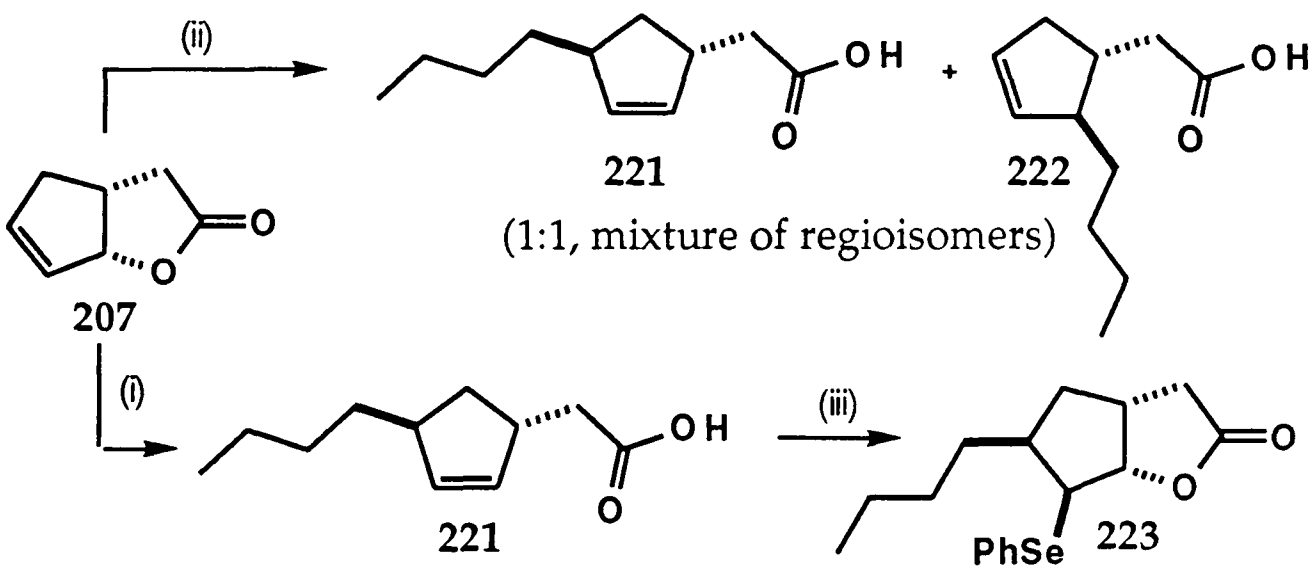
Accordingly **207** was generated, using either selenium chemistry **218**,[173] or *via* the iodo-lactone[174] **219** (Scheme 88).



Conditions: (i) PhSeCl, DCM, -78°C to RT, 3h; 85%.[173] (ii) H_2O_2, DCM, 0°C to RT, 15h; 92%.[173] (iii) $KHCO_3$, KI, I_2, H_2O, Et_2O, 13h; 94%.[174] (iv) DBU, PhH, Δ, 3h; 90%.[158]

Scheme 88

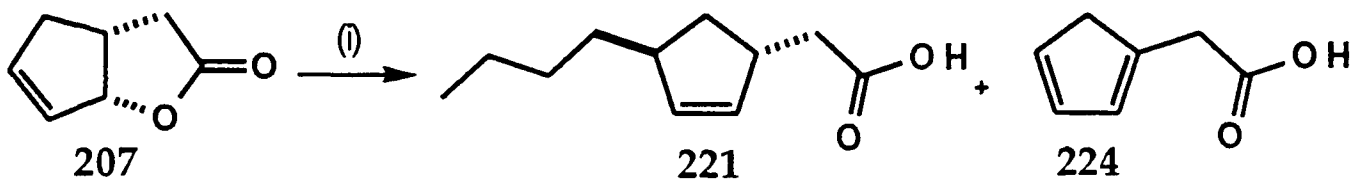
Several test reactions were then performed with monoalkyl cuprates derived from butylmagnesium chloride and butyllithium. The results were in accordance with the observations made by Curran;[159,166] a single product **221** formed with a monoalkyl cuprate derived from a Grignard reagent and $CuBr.SMe_2$, whereas a mixture of isomers **221** and **222** was obtained with the organocyanocuprate derived from butyllithium. **221** was identified as the *anti*-S_N2' addition product by conversion to the corresponding seleno-lactone **223** (Scheme 89).



Conditions: (i) ^{n}BuMgCl, $CuBr.SMe_2$, THF, SMe_2, -20°C to RT, 15h; 74%. (ii) ^{n}BuLi, CuCN, THF, -78°C to -20°C, then to RT, 15h; 69%. (iii) PhSeCl, DCM, -78°C to RT, 3h; 84%.

Scheme 89

We hoped to reverse the mode of addition of the cuprate, from *anti-* to *syn-*, by pre-co-ordinating the oxabicycle **207** to *tetrakis*(triphenylphosphine)-palladium(0),[168] in an analogous way to that demonstrated by Trost[167] and Aggarwal.[169] However, the products isolated from the reaction of a monoalkyl cuprate derived from butylmagnesium chloride and the palladium co-ordinated oxabicycle **207** were observed to be the *trans-* product **221** and the cyclopentadienyl acid[163] **224** (Appendix C) formed by elimination (Scheme 90).



207 **221** **224**

(1:1 mixture)

Conditions: (i) ^{n}BuMgCl, CuBr.SMe_2, THF, SMe_2, $Pd(PPh_3)_4$, PPh_3,-20°C to RT; 82%.

Scheme 90

6.4.4. The *Trans*-Cyclopentene Model Series

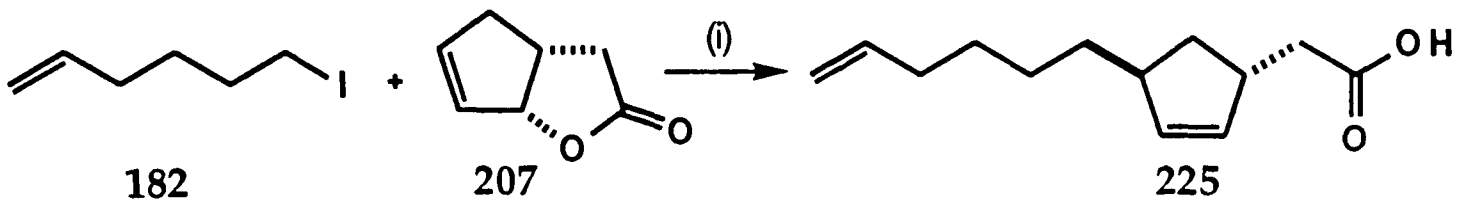
Due to problems associated with obtaining a *syn-* addition product we decided to pursue the readily available *trans-* series. Analysis of molecular models of the *trans-* free-radical macrocyclisation precursor suggested that cyclisation might occur as the alkyl radical could overlap, without obvious strain, with the enone π^* orbital. We thus concentrated on synthesising the *trans-* radical precursor and testing out the feasibility of this hypothesis.

6.4.4.1. The First Generation Series

Work initially began on this approach prior to the development of the methodology outlined in Section **6.3.4.2.** and relied on the hexenyl organolithium approach detailed in Section **6.3.3.2.**.

We were wary that the regioselectivity of attack of a cuprate, derived from an organolithium species, on the sterically unbiased oxabicycle **207** might

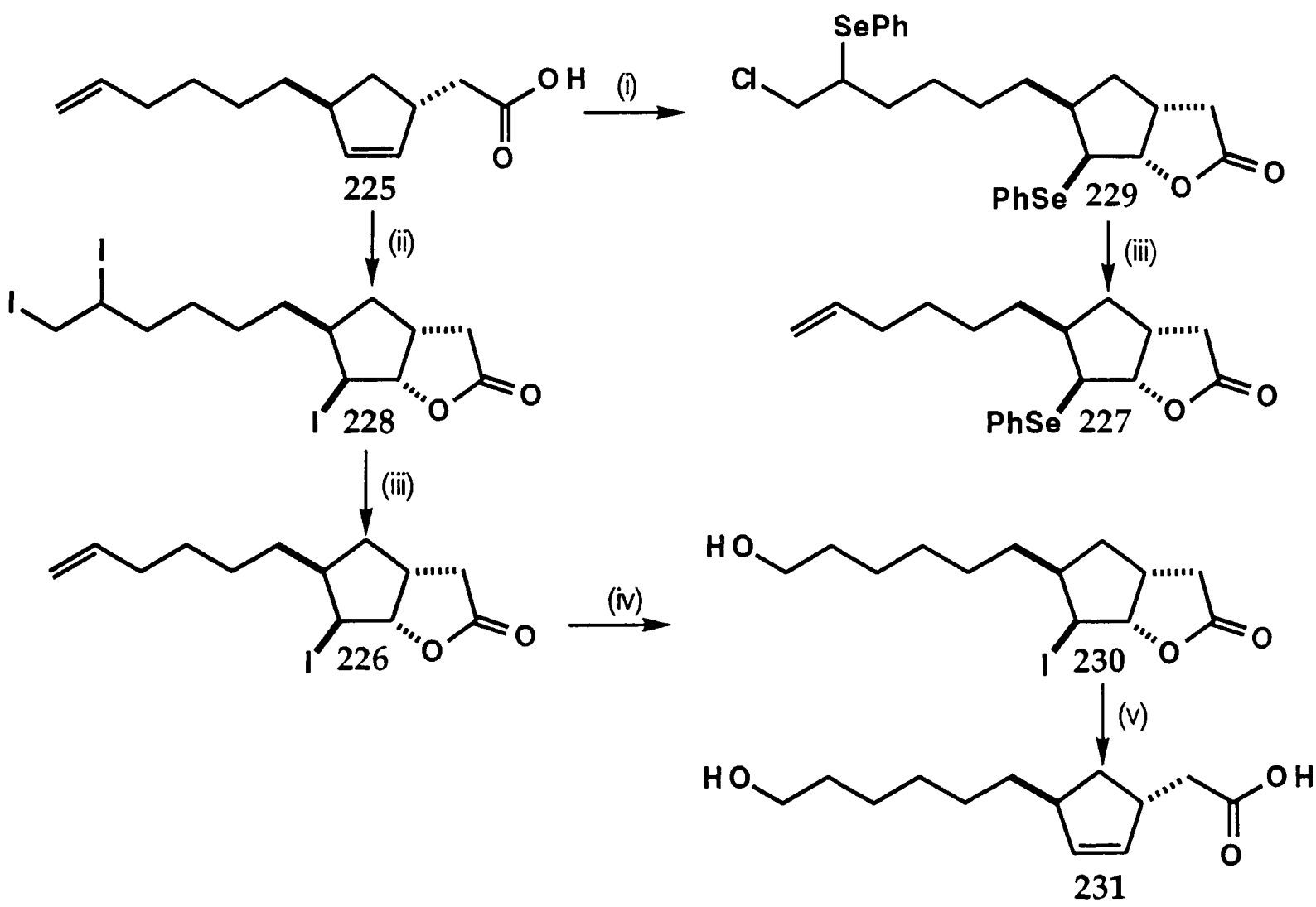
be poor (as reported by Curran[166]). However, treatment of **207** with the monoalkyl cuprate gave only one product, the desired *trans*-substrate **225** in good yield (Scheme 91).



Conditions: (i) ^{t}BuLi, Et_2O, Me_2S, $CuBr.SMe_2$, [153] -78°C to -20°C, 30mins; -78°C to RT, 15h; 82%.

Scheme 91

In order to transform the terminal alkene to the alcohol, the carboxylic acid and di-substituted alkene had first to be protected in the form of an iodo-[175] **226** or seleno[173]-lactone **227** (Scheme 92).

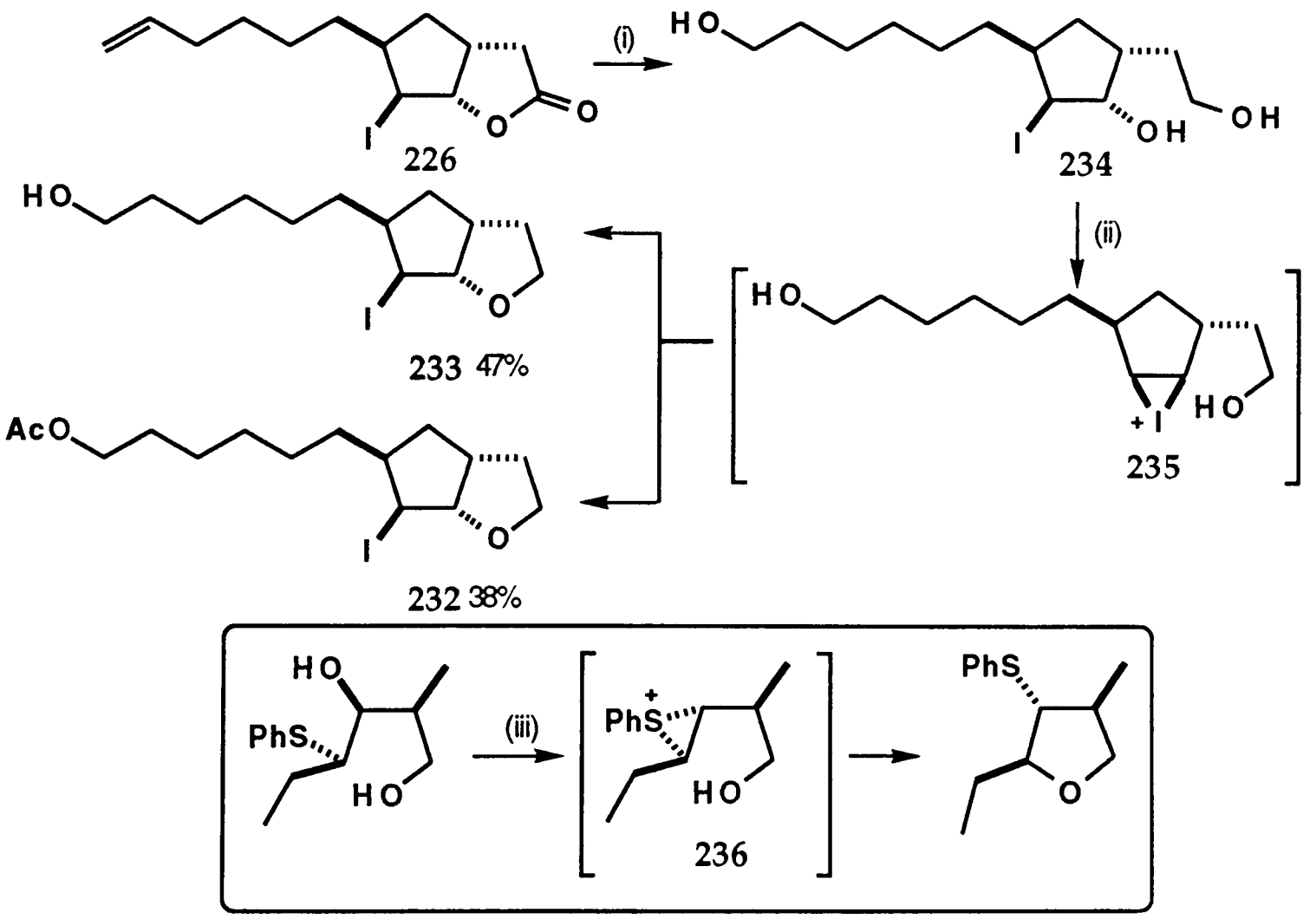


Conditions: (i) PhSeCl, DCM, 0°C to RT, 13h.[173] (ii) $KHCO_3$, KI, I_2, H_2O, Et_2O, 13h.[175] (iii) SiO_2; **227**: 57% from **225**, **226**: 92% from **225**. (iv) BH_3.THF, THF, 0°C to RT, 15h; NaOH, EtOH, H_2O_2, 1h; H_2SO_4, 1h; 84%.[154] (v) Zn, EtOH, Δ; 15h; 81%.

Scheme 92

In both lactone-forming reactions, the intermediate crude products were observed to be the addition products **228** and **229** (Appendix C), and the desired lactones **226** and **227** were only obtained after column chromatography; only the iodo-lactones were used in subsequent steps.

Reduction of **226**, solely to the alkylborane intermediate necessary for formation of **230**, was found to depend on the amount of BH_3.THF used. Addition of 2.2 eq. rather than 1.5 eq. to **226** resulted, after oxidative work-up, in a single very polar product. This was treated with acid in acetonitrile to generate the corresponding ether with (**232**) or without (**233**) an acetate functionality. The intermediate was assigned as the triol **234** (Appendix C) and its formation rationalised by a β-iodo accelerated cyclisation of the primary alcohol (Scheme 93).



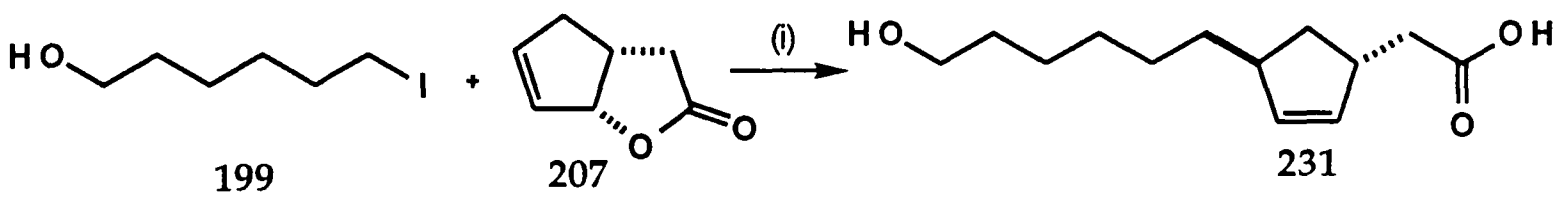
Conditions: (i) BH_3.THF, THF, 0°C to RT, 15h; NaOH, EtOH, H_2O_2, 1h; 96%.[154] (ii) conc. H_2SO_4, MeCN, 15h. (iii) TsOH, PhH, 10mins; 85%.[177]

Scheme 93

The *exo*-iodonium intermediate **235** bears some similarity to the *endo*-phenylthionium intermediate **236** proposed by Warren *et al.*[177] in their work on the synthesis of cyclic ethers.

6.4.4.2. The Second Generation Series

We decided to apply the methodology described in Section **6.3.4.2.** to this route in order to reduce the overall number of steps. Consequently the *trans*-hydroxy acid **231**, which had been previously synthesised in four steps (**6.4.4.1.**), was synthesised in one step from the oxabicycle **207** (Scheme 94); no other regio- or stereo-isomers were observed.



199 207 231

Conditions: (i) ^{n}BuLi, Et_2O, 15mins, -78°C; ^{t}BuLi, 15mins; Me_2S, CuBr.SMe_2, -78°C to -20°C, 20mins; -78°C to RT, 15h; 80%.

Scheme 94

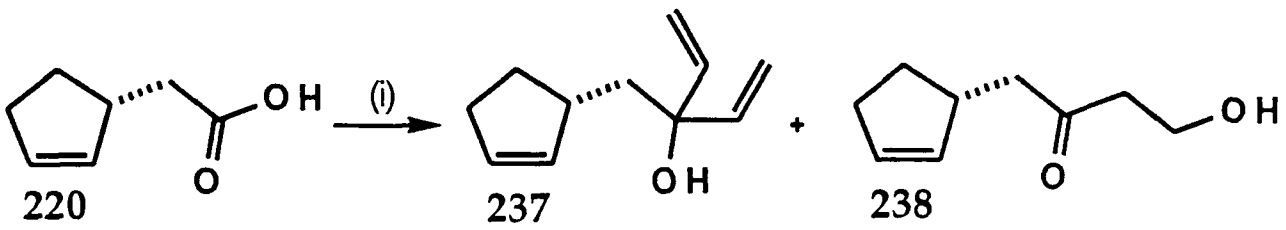
We were then concerned with developing methods to convert the carboxylic acid functionality of **231** to the vinyl ketone unit required in our free-radical precursor, and proposed three general strategies. These are summarised as follows:

- Addition of vinyllithium to the acid, generating an enone in one step (**6.4.4.3.**).
- Addition of vinylmagnesium bromide to the corresponding Weinreb amide (**6.4.4.4.**).
- Reduction of the acid to an aldehyde, addition of vinylmagnesium bromide and final oxidation to the enone (**6.4.4.5.**).

6.4.4.3. Model Study: Vinyllithium Addition

Vinyllithium is not commercially available in small quantities and so we had to consider which of the methods of generation was most suitable.[178]

Vinyllithium has been prepared by metallation of vinyl chloride,[179a] tetravinyltin[180] and vinyl bromide,[179b] and by direct metallation of ethene.[179c] Of these methods the tetravinyltin route seemed to be the most practical so, following the work of Seyferth and Weiner,[180] vinyllithium was prepared and added to the model 2-cyclopentene-acetic acid **220** (Scheme 95). Floyd had reported the preparation of vinyl ketones from carboxylic acids using vinyllithium in 1,2-dimethoxyethane,[181] however, repeats of the procedure led to the di-addition product **237** (Appendix C) and the β-hydroxyketone **238** (Appendix C). An alternative milder work-up procedure led again to **237**, **238** and only trace amounts of the enone, so work on this approach was suspended.



Conditions: (i) Vinyllithium (2.5 eq.),[177,179] DME, 5°C, 10mins, 40°C, 18h. Work-up: Add to 1M aq. HCl (0°C), 15mins; **237**: 52%, **238**: 19%.

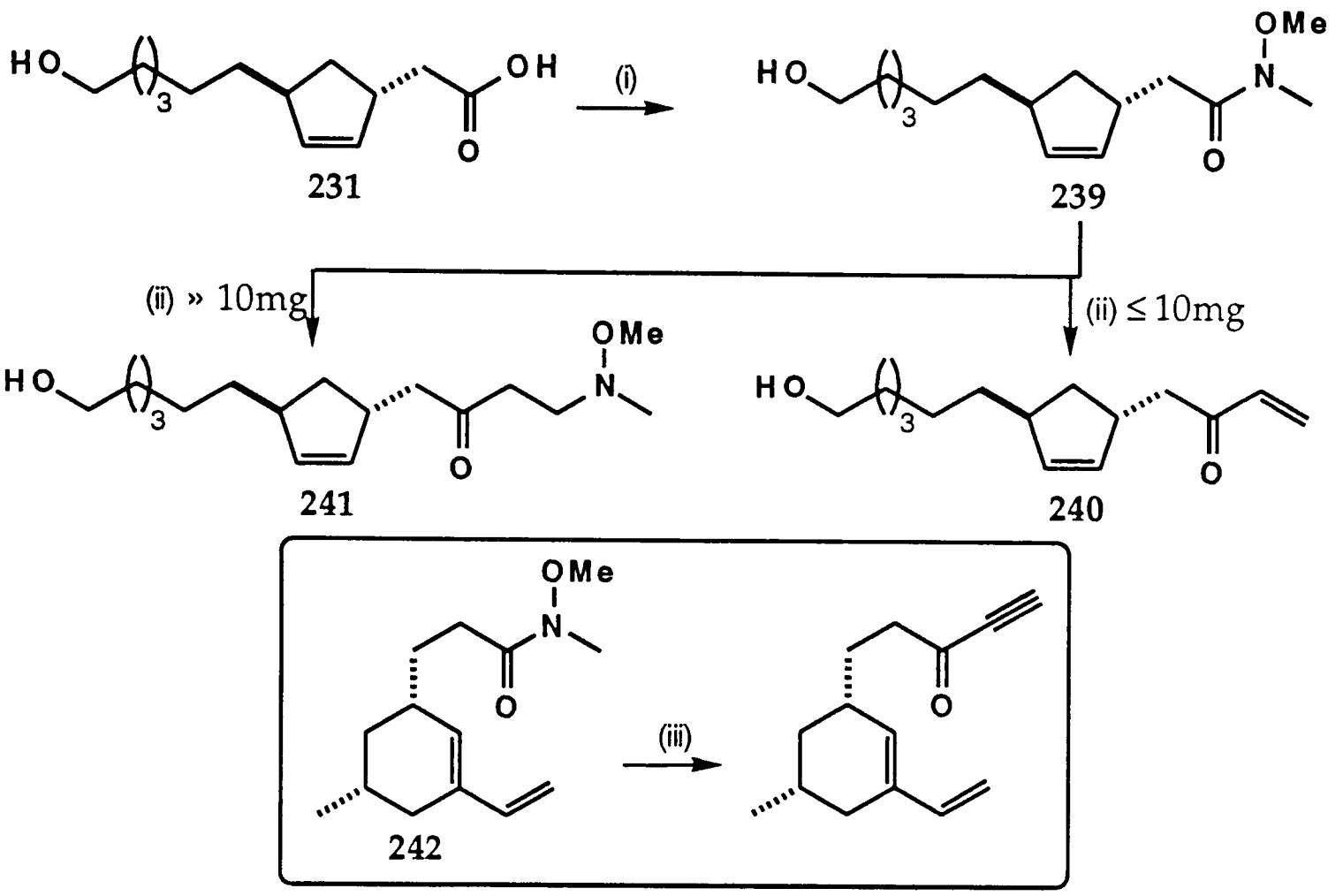
Scheme 95

6.4.4.4. The Second Generation Series: Vinylmagnesium Bromide Addition

We decided to use derivatives of the *trans*- hydroxy acid **231** in model studies to ensure that the method was compatible with the other functionality present.

Initially, addition of vinylmagnesium bromide (2.2 eq.) to the Weinreb amide[182,183] **239** resulted in isolation of the required enone **240**. However, scaling the reaction above 10mg (of the starting amide), generally resulted in isolation of the β-aminoketone **241** (Appendix C).[184] Further studies showed that inconsistent results were obtained between 10mg and 50mg; on larger scales the β-aminoketone **241** was always isolated. Attempts to convert the β-aminoketone **241** back to the enone **240** (with, for example, 15 eq. MeI) proved unsuccessful.

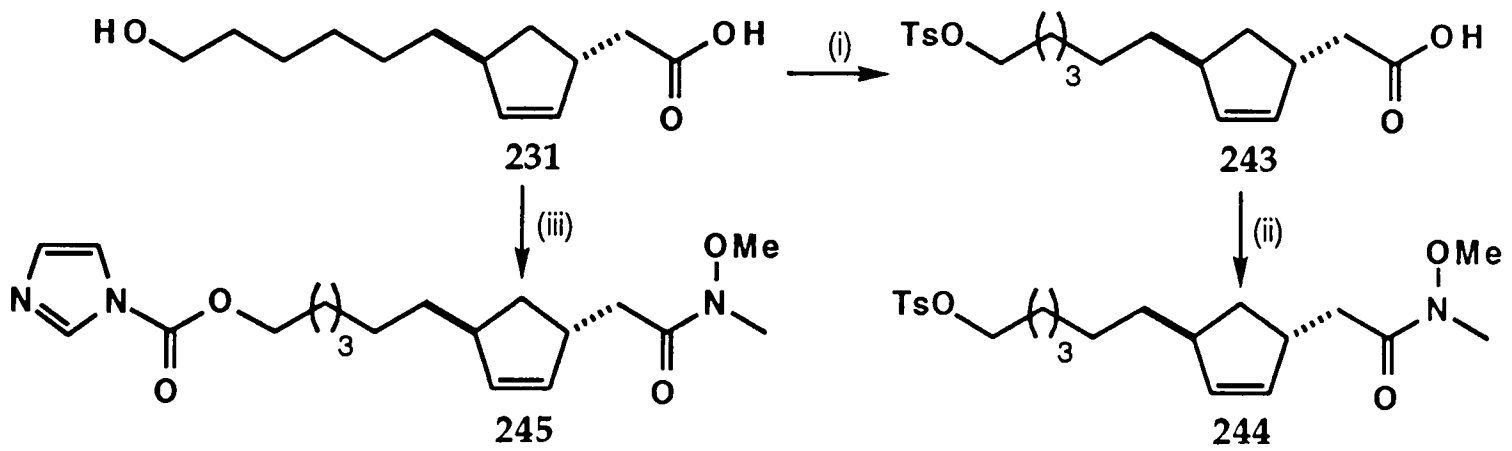
Interestingly, for comparison, Heathcock *was* able to add lithium acetylide to the amide[183] **242** (Scheme 96).



Conditions: (i) Im_2CO, MeN(OMe)H.HCl, DCM, 15h; 93%. (ii) Vinylmagnesium bromide; THF or Et_2O, -78°C to RT; **240**: 76%, **241**: 89%. (iii) Lithium acetylide-EDA complex, THF.[183b]

Scheme 96

Further investigations to effect the transformation on two other systems **244** and **245** failed (Scheme 97) and this strategy was also abandoned.

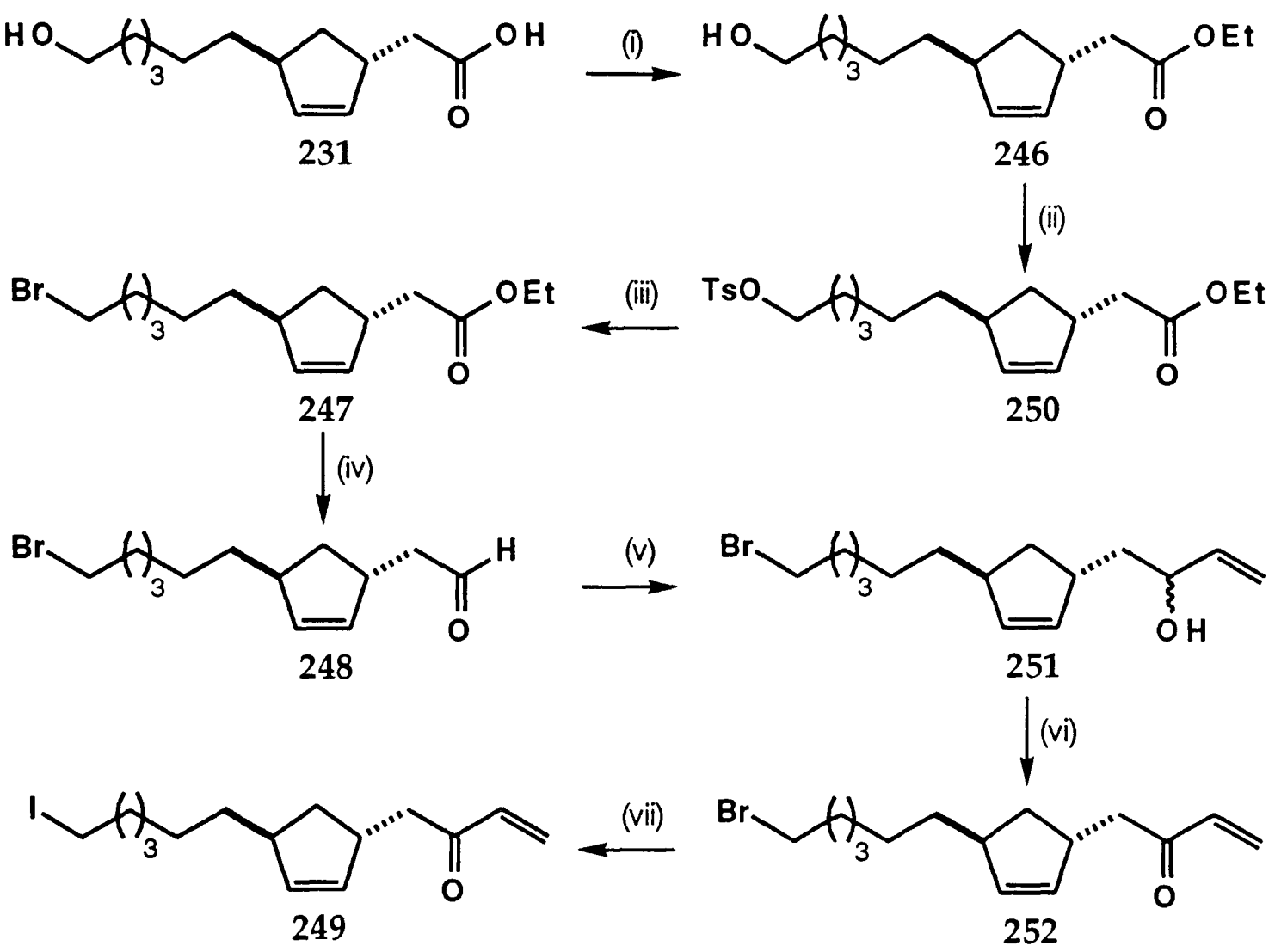


Conditions: (i) TsCl, py, DCM, 15h; 88%. (ii) Im_2CO, MeN(OMe)H.HCl, DCM, 15h; 90%. (iii) Im_2CO (2.1 eq.), MeN(OMe)H.HCl, DCM, 15h; 85%.

Scheme 97

6.4.4.5. The Second Generation Series: Reduction, Addition, Oxidation

We were therefore restricted to the approach involving addition of vinylmagnesium bromide to an aldehyde with subsequent oxidation. Accordingly the hydroxylester **246**, after conversion to the bromide **247**, was reduced with diisobutylaluminium hydride[185] to give the aldehyde **248**. This then led to the *trans*-iodoenone[189] **249** (Scheme 98) in a lengthy but efficient process.



Conditions: (i) H_2SO_4, EtOH, 15h; 93%. (ii) TsCl, py, 15h; 91%. (iii) LiBr, acetone, Δ, 4h; 94%. (iv) DIBALH, PhMe, -78°C, 3h; 87%. (v) Vinylmagnesium bromide, THF, -78°C to RT, 15h; 75% (1:1 mixture of diastereomers). (vi) Jones' reagent, acetone, 10mins; 81%. (vii) NaI, acetone, 15h; 97%.[189]

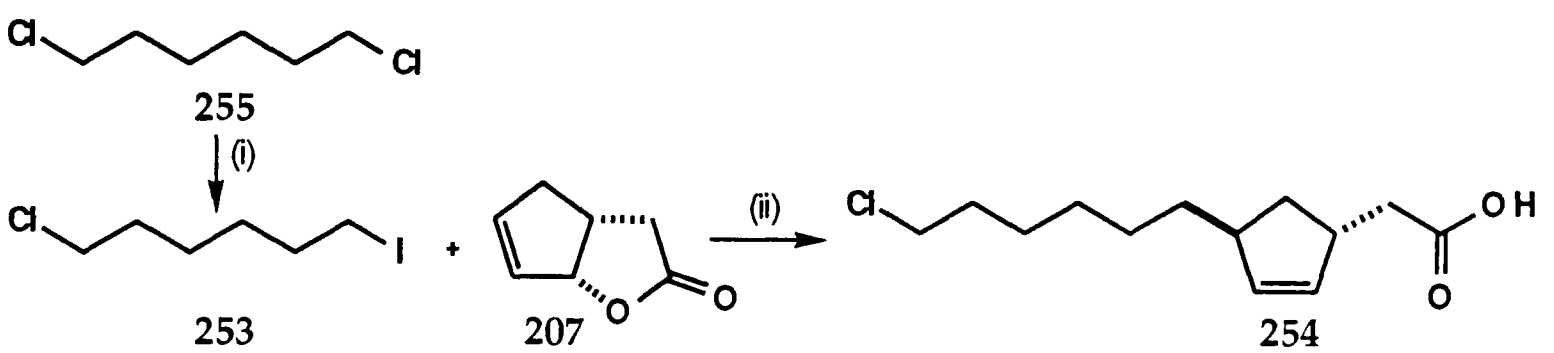
Scheme 98

6.4.4.6. The Third Generation Series: Reduction, Addition, Oxidation

We needed to improve the lengthy synthesis of the iodoenone **249** (**6.4.4.5.**). Previously, attempts to metallate the silyl-protected chloro-alcohol

(**6.3.3.2.**) (^{t}BuLi) had resulted in recovered starting material; i.e. the chloride had not been affected. We therefore expected that 1-chloro-6-iodohexane **253**[186] could be selectively metallated to give chlorohexyllithium .

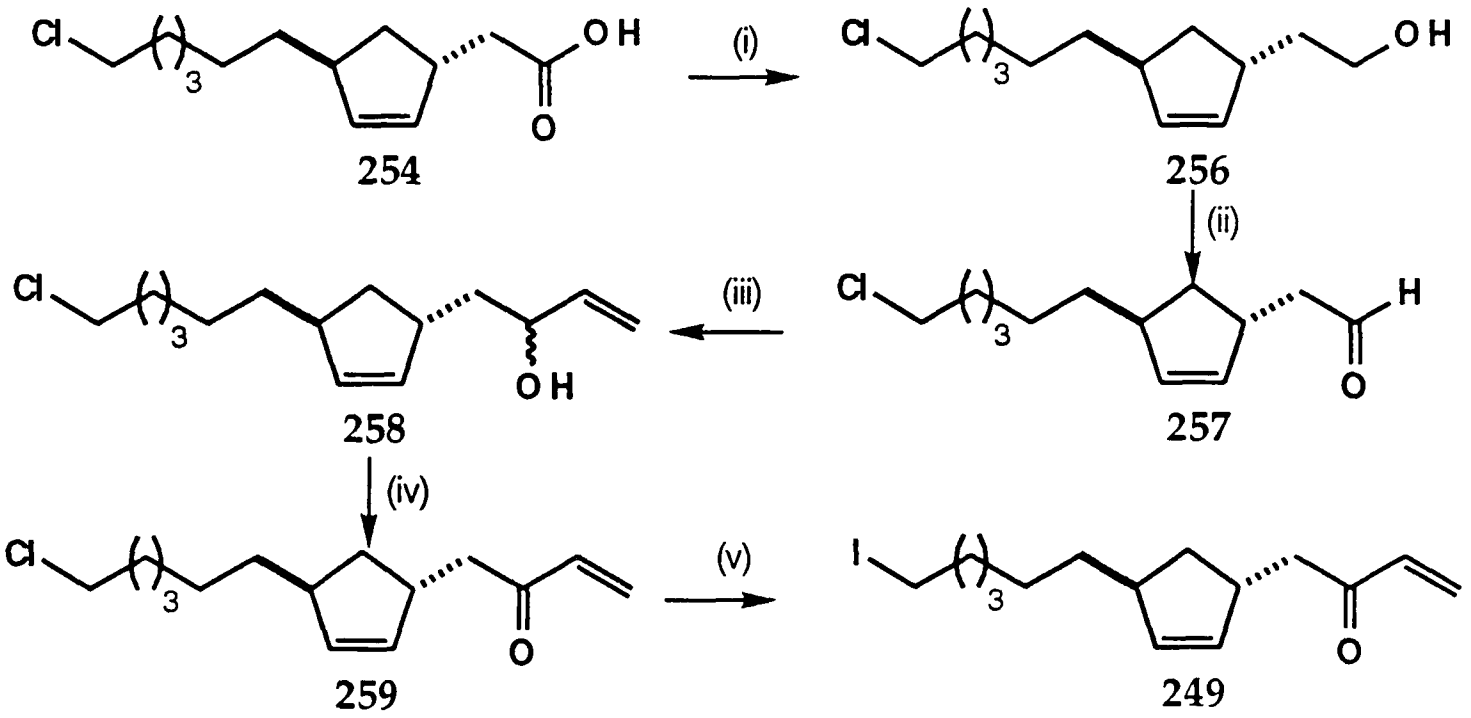
Thus, 1-chloro-6-iodohexane **253**, prepared using a known procedure,[186] was subjected to metallation, cupration conditions to generate, on addition of the oxabicycle **207**, the *trans*-chloro acid **254** (n.O.e. in Appendix D) as a single product (Scheme 99).



Conditions: (i) NaI, acetone, slow addition, 7h, Δ; fractional distillation; 77%.[186] (ii) ^{t}BuLi, Et_2O, 15mins, -78°C; Me_2S, CuBr.SMe_2, -78°C to -20°C, 20mins; -78°C to RT, 15h; 79%.

Scheme 99

Further elaboration to the *trans*- iodoenone **249** is shown in Scheme 100.



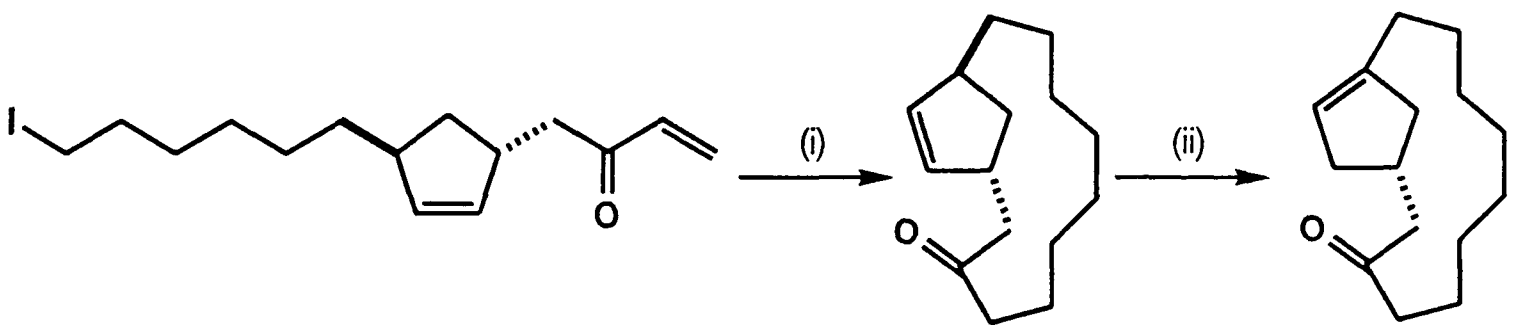
Conditions: (i) $LiAlH_4$, THF, 0°C to RT, 15h; 80%.[187] (ii) PDC, DCM, 4ÅMolS., 4h;94%.[188,189] (iii) Vinylmagnesium bromide, THF, -78°C to RT, 15h; 95% (1:1 mixture of diastereomers).[189] (iv) Jones' reagent, acetone, 10mins; 80%.[189] (v) NaI, MEK, Δ, 15h; 82%.[189]

Scheme 100

Due to inconsistent results in the diisobutylaluminium hydride reductions, possibly due to the quality of reagent, it was decided to reduce the acid to the alcohol[187] **256** and then oxidise to the aldehyde[188] **257**. Reduction of **254** could only be driven to completion using tetrahydrofuran, rather than ether.

6.4.4.7. Free-Radical Macrocyclisation

Initially at a concentration of 5mM, cyclisation was not observed and the directly reduced hexylenone was recovered.[189] Lowering the concentration to 2mM and adding the tributyltin hydride over an extended period (10h) led to a crude product which, by ^{1}H NMR and GCMS analysis (Appendix C), appeared to be the cyclised material **260**; no olefinic peaks, associated with the enone, were observed. Addition of thiophenol,[134] followed by repeated column chromatography showed that the spot (on t.l.c.) associated with the crude product was gradually diminished with concomitant increase in intensity of a lower spot. This lower spot was finally isolated and shown from full characterisation (including ^{1}H-^{1}H COSY) to be the macrocycle **261** (Scheme 101).



249 **260** **261**

Conditions: (i) ^{n}BuSn$_3$H, PhH, 2mM, slow addition 10h, then 3h, Δ. (ii) SiO_2; 37%.

Scheme 101

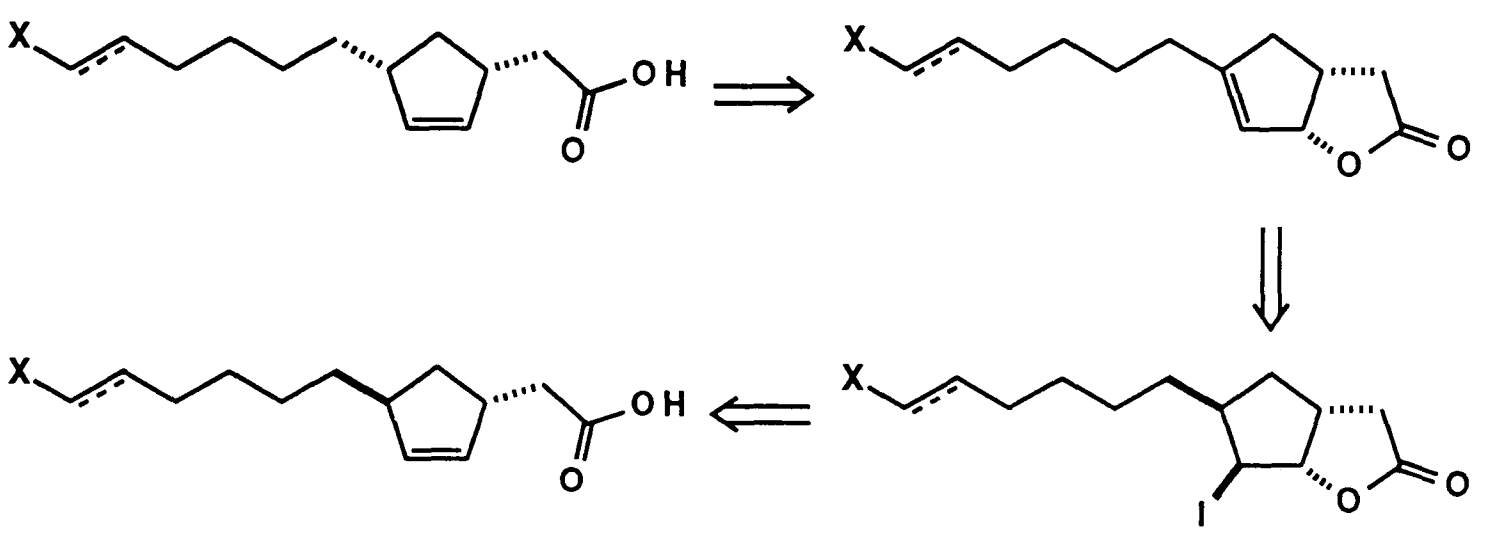
We envisaged that the corresponding *cis*- macrocycle **205** should be more stable than both the *trans*- **260** and the *pseudoplanar*- macrocycle **261** and therefore sought to prepare it *via* isomerisation of the alkene in **261**. Initial attempts with $RhCl_3.H_2O$[190] led to recovered starting material. Treatment of

261 with acid in acetonitrile, however, showed that, after stirring overnight, olefinic peaks associated with the *cis*- macrocycle **205** had started to form (~30% by ^{1}H NMR) at the expense of starting material.

6.4.5. The *Cis*-Cyclopentene Model Series

6.4.5.1. Retrosynthetic Analysis

We were still attracted to developing methodology for generating the corresponding *cis*- substrates. We considered an approach, from the *trans*-acids, based on the retrosynthetic analysis shown (Figure 13).



X = -Cl, -OH, -H (olefinic)

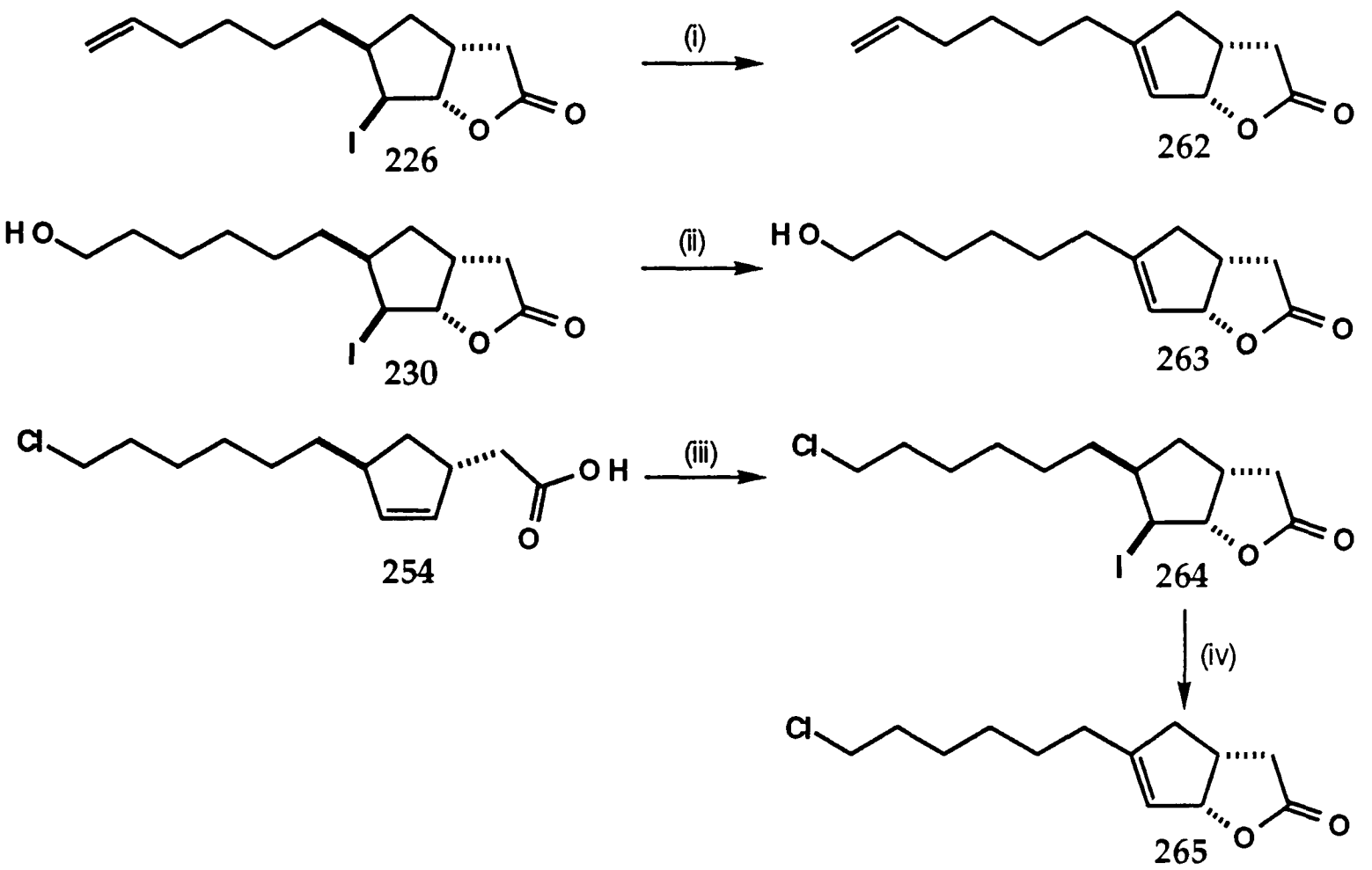
Figure 13

The crucial transformation can be seen as an overall *anti*- S_N2' addition of hydride; three methods that we thought appropriate were:

- Use of a copper hydride source such as $[(Ph_3P)CuH]_6$.[191]
- Use of palladium and ammonium formate.[192]
- Use of borane to add regio- and stereoselectively to the alkene (top face) followed by nucleophile induced elimination of the carboxylate group.

6.4.5.2. Synthesis of Substrates

Accordingly, the necessary substrates were prepared (Scheme 102).



Conditions: (i) DBU, PhH, Δ, 1h; 95%.[193] (ii) DBU, PhH, Δ, 1h; 99%.[193]
(iii) $KHCO_3$, KI, I_2, H_2O, Et_2O, 13h; 89%.[175] (iv) DBU, PhH, Δ, 1h; 96%.[193]

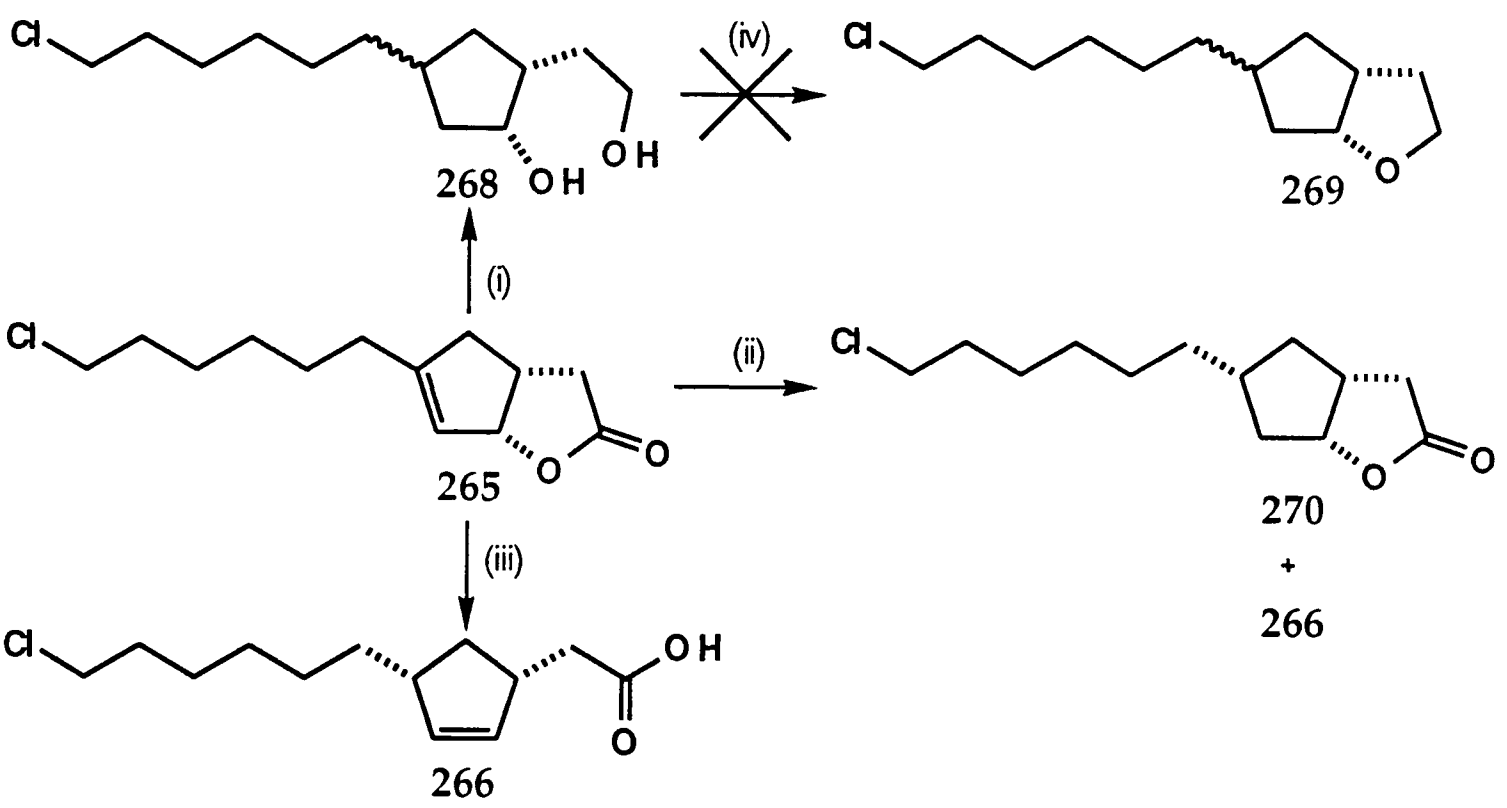
Scheme 102

6.4.5.3. Preparation of *Cis*-Alkenylacid 266

Use of the palladium methodology[192] resulted in recovered starting material and although use of the copper hydride species[191] *was* instigated, work was suspended in favour of the third approach. Addition of BH_3.THF to the alkenyllactones **262** and **263** led to complex mixtures of products on work-up with either sodium hydroxide, sodium methoxide or alkaline hydrogen peroxide; a large proportion of starting material was also recovered. However, there *was* evidence that a small amount of the *cis*- hydroxyacid had been formed. We were hopeful that, in the chloro-alkenyllactone **265**, complications arising from co-ordination of boron to the terminus of the chain and the ring would be absent. We found, however, that the lactone was very sensitive to reduction, and initially the diols **268**, (Scheme 104) were isolated. Interestingly, **268** did not form the cyclic ethers **269** under the same conditions that were

applied to the iodo-triol **234** (which *did* cyclise) supporting the involvement of iodine to accelerate the process.

Subsequent studies showed that by controlling the amount of borane-tetrahydrofuran complex added (0.5 eq.), selective addition to the alkene *could* be achieved, though the reaction was slow. Furthermore the nature of the product obtained was found to depend on which nucleophile was added to induce elimination. In the case of sodium hydroxide, a mixture was obtained, with the major component (after acid work-up) being the lactone **270**. However, addition of TBAF, a more selective nucleophile, led to formation of the desired *cis*-chloroacid **266** (n.O.e. in Appendix D) as shown in Scheme 103.



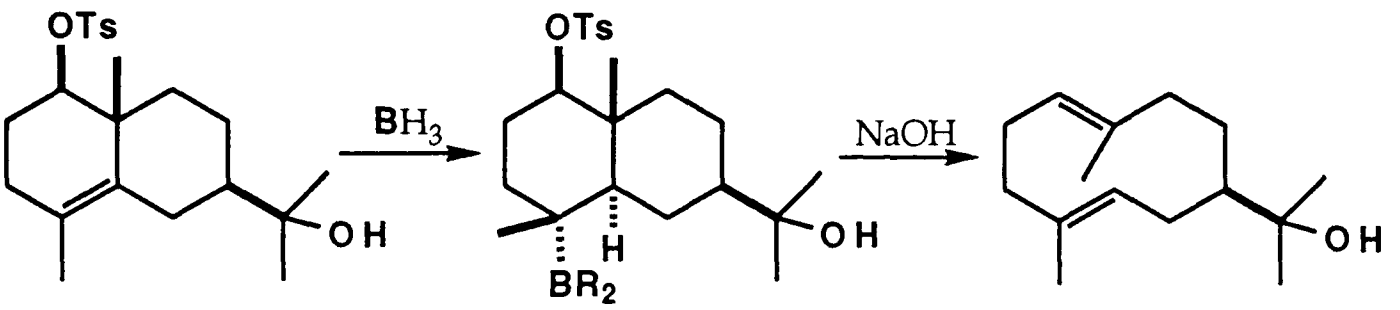
Conditions: (i) $BH_3.THF$[154] (1.0 eq.) [>20 mg **265**], THF, 18h, NaOH, 1h; 89% (4:3 mixture of diastereomers). (ii) $BH_3.THF$[154] (0.5eq.), THF, 18h, NaOH, 1h; HCl, 1h; **270**: 58%, **266**: 34%. (iii) $BH_3.THF$[154] (0.5eq.), THF, 18h, TBAF, 1h; 92%. (iv) H_2SO_4, MeCN, 15h.

Scheme 103

On a small scale (<20mg of **265**), use of 1.0 eq. of borane-tetrahydrofuran complex resulted in complete conversion to the acid **266** after 15h; on a larger scale 0.5 eq. of borane-tetrahydrofuran complex had to be used to prevent competitive lactone reduction. This meant that, after the same time period, the reaction was only half complete and, since leaving the reaction mixture for

longer did not lead to significant increases in conversion, it was considered practical to halt the reaction at this point, and separate the products.

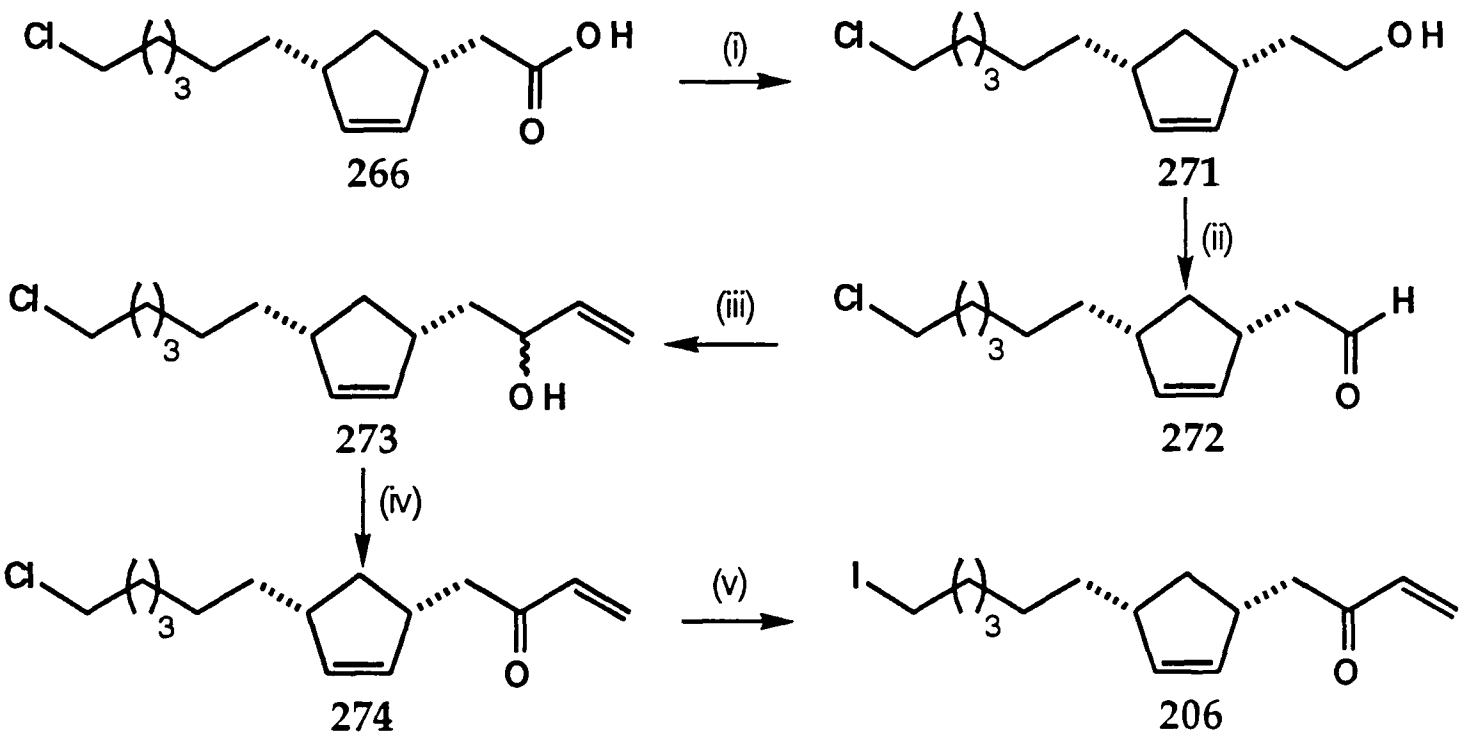
Thus we had achieved a novel conversion of the *trans*- to the *cis*-acid in three steps and overall yield of 78%. This use of a boron fragmentation bears some resemblance to work by Wharton,[194a] Marshall,[194b] Takeda[195] and Koyama,[196] as illustrated by an example in Scheme 104.[193]



Scheme 104

6.4.5.4. Preparation of the Free-Radical Precursor

With the *cis*- substrates in hand, the corresponding iodoenone **206** was prepared in an analogous manner to that described for the *trans*- in Section **6.4.4.6.** (Scheme 105).

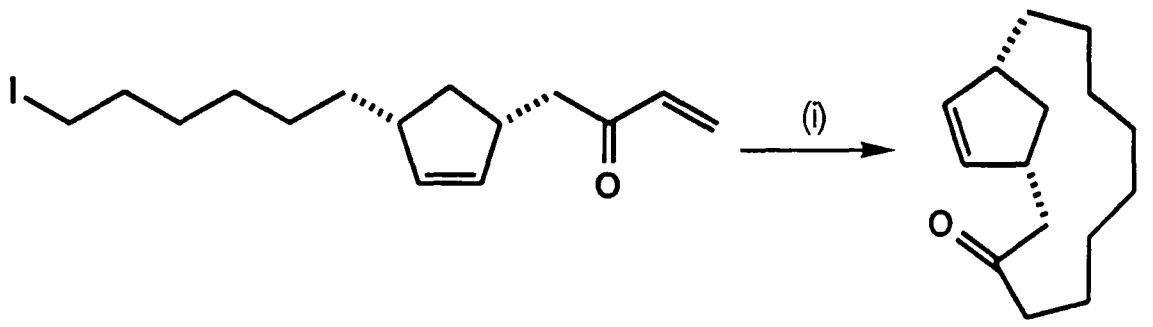


Conditions: (i) $LiAlH_4$, THF, 0°C to RT, 15h; 92%.[187] (ii) PDC, DCM, 4ÅMol.S., 4h; 84%.[188,189] (iii) Vinylmagnesium bromide, THF, -78°C to RT, 15h; 89% (1:1 mixture of diastereomers).[189] (iv) Jones' reagent, acetone, 10mins; 82%.[189] (v) NaI, MEK, Δ, 15h; 86%.[189]

Scheme 105

6.4.5.5. Free-Radical Macrocyclisation

A repeat of the conditions used previously (**6.4.4.7.**) led to a product which, by crude ^{1}H NMR and GCMS analysis, appeared to be the cyclised material **205**; no olefinic peaks, associated with the enone, were observed. Purification (using thiophenol[134]) led to isolation of the macrocycle[189] **205** (Scheme 106).



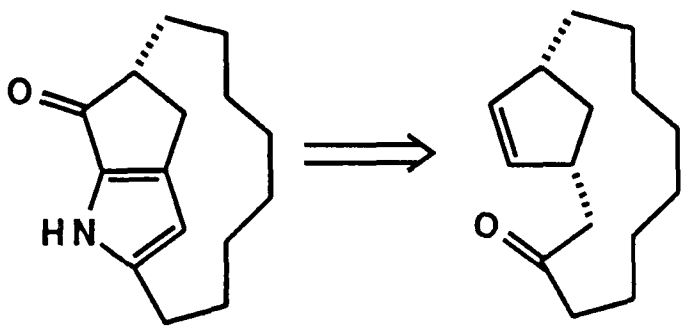
206 **205**

Conditions: (i) ^{n}BuSn$_3$H, AIBN, PhH, 2mM. slow addition 10h, then 3h, Δ; 41%.[189]

Scheme 106

6.4.5.6. Studies Towards Formation of the Model Keto-Pyrrole 275

With the model macrocyclic ketone **205** to hand, we were keen to investigate methods for formation of the model keto-pyrrole **275** (Figure 14).



275 **205**

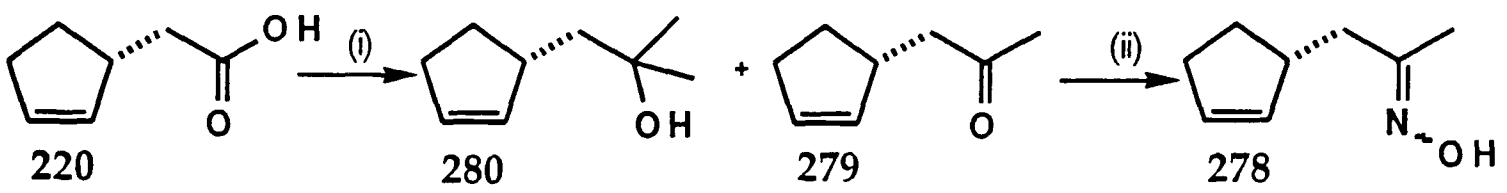
Figure 14

In the Introduction, two methods for accomplishing this transformation were proposed (**4.5.2.** and **4.5.3.**). An independent investigation in our group using the iminyl radical[24-26] approach (**4.5.2.**) was examined on a model system, and shown to be feasible (**6.4.6.**).[197] However, we were attracted to a

second approach involving nitrone formation[27] (**4.5.3.**) since the higher oxidation level in the product would facilitate generation of a pyrrole.

6.4.5.7. Model Studies: Formation of the Azabicycles 276 and 277

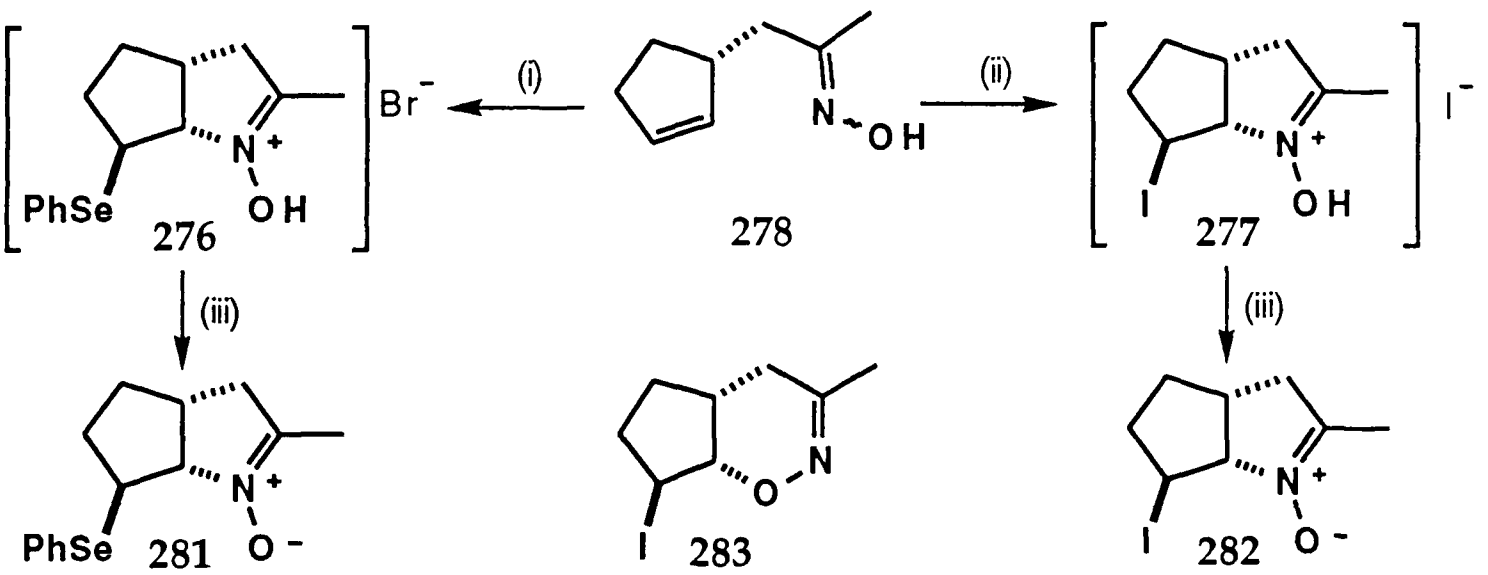
We chose to test the methodology on a simple model system, and so the oximes[24b] **278** were prepared from the known ketone[24b] **279**. The undesired tertiary alcohol **280** (Appendix C) was removed (Scheme 107).



Conditions: (i) MeLi, THF, -78°C to RT, 15h; **280**: 44%, **279**: 56%. (ii) NaOAc, $NH_2OH.HCl$, MeOH, 6h; 98%.

Scheme 107

Subjecting these oximes **278** to the conditions described by Grigg *et al.*[27] led to formation of the nitrone salts **276** and **277**, from which the free-bases were obtained with potassium carbonate (Scheme 108).



Conditions: (i) PhSeBr, DCM, 2h; 78%. (ii) I_2, DCM, 15h. (iii) K_2CO_3, DCM; **281**: quant., **282**: 96% from **278**.

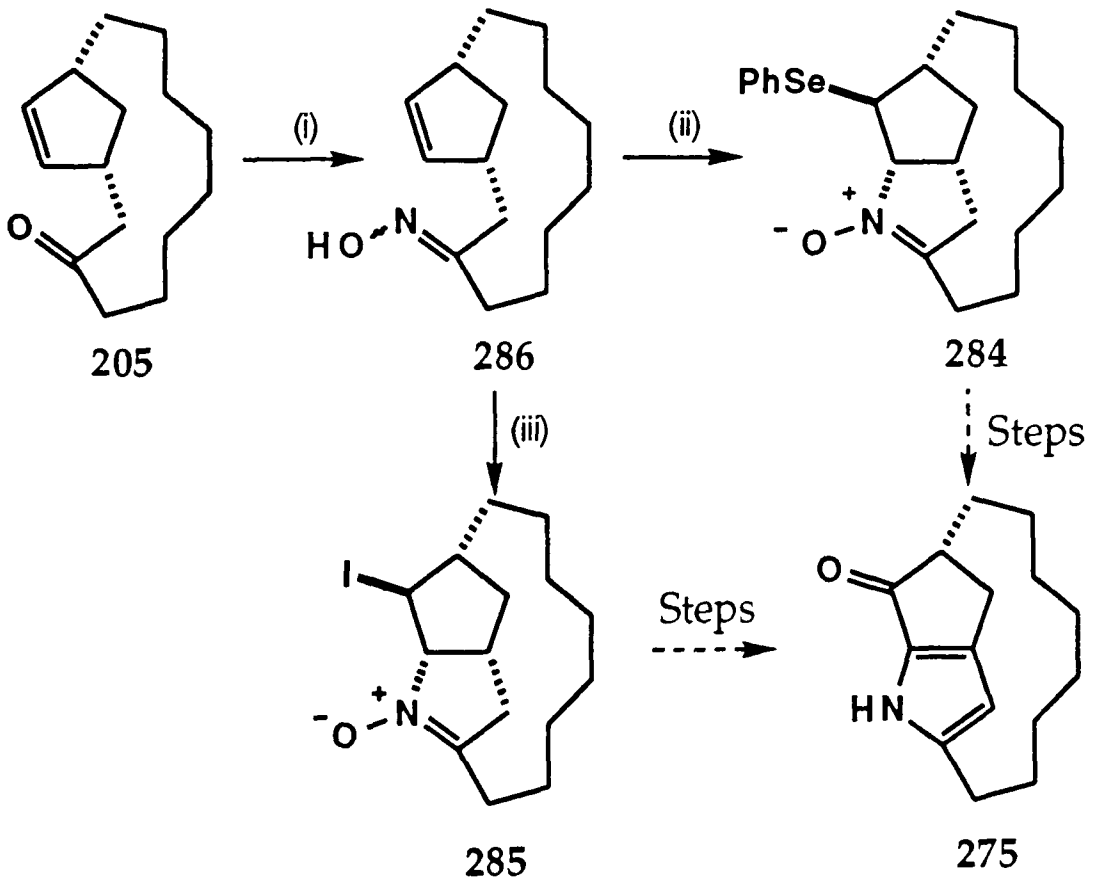
Scheme 108

The nitrones were observed to decompose on silica gel and so could not be further purified. Interestingly, a small amount (1-5%) of the iodo-oxazine **283** (Appendix C) was formed and isolated by chromatography. Attempts to

convert the nitrones **281** or **282** to the pyrroles using either tosyl chloride and DBU or chlorosulphonyl isocyanate[198] all proved inconclusive.

6.4.5.8. Model Studies: Formation of the Azatricycles 284 and 285

This approach was attempted on the macrocyclic ketone **205** to see if the third, heterocyclic, ring would still form in this more demanding case. Thus the oximes[189] **286** were prepared and subjected to the necessary conditions for nitrone formation - with either iodine or phenylselenyl bromide (Scheme 109). T.l.c analysis of the reaction mixture showed that the starting material had been consumed within 3h and a uv active spot developed on the baseline (as expected). However, ^{1}H NMR spectroscopy of the crude isolated products was inconclusive; they both had compatible mass spectra (Appendix C) and the selenide **284**, a correct high-resolution mass spectrum, thus we have tentatively assigned the products to be the nitrones **284** and **285**. The small scale of these reactions prevented reliable conclusions to be drawn.

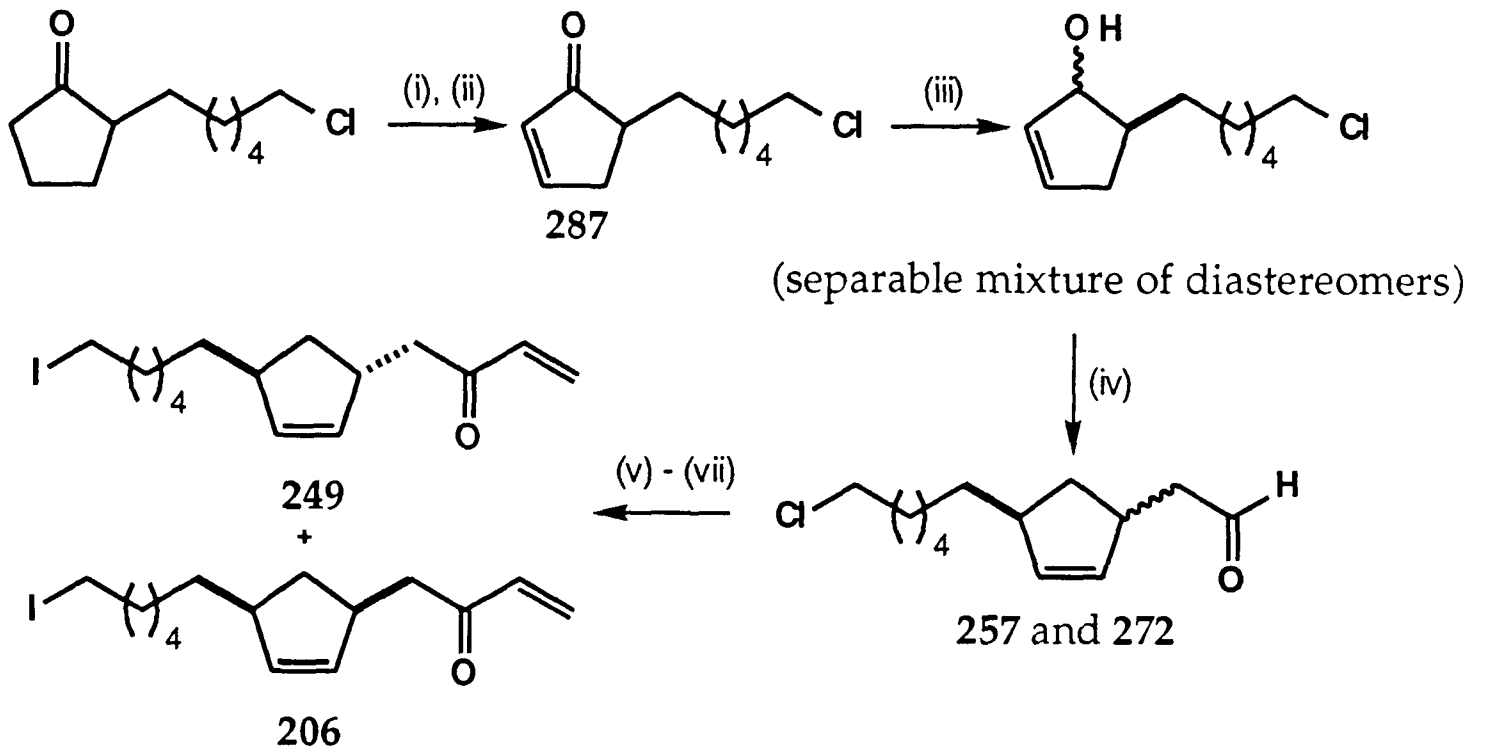


Conditions: (i) NaOAc, $NH_2OH.HCl$, MeOH, 6h; 82%.
(ii) PhSeBr, DCM, K_2CO_3; 3h. (iii) I_2, DCM, K_2CO_3, 3h.

Scheme 109

6.4.6. Alternative Approaches Within the Group

Recent investigations within the group (concurrent with the work described in Sections **6.4.4.** and **6.4.5.**) involved an alternative route towards the synthesis of the *cis*- and *trans*- substrates[199] and a model study associated with formation of the 'third' ring of Roseophilin using free-radical chemistry (Scheme 110).[197a] The key steps, in the alternative route, are the stereoselective reduction of the ketone **287** followed by a [3,3]-sigmatropic shift of an intermediate allylenol ether to the aldehydes **257** and **272**.[199]



Conditions: (i) LDA, PhSeBr, 30mins; 87%. (ii) H_2O_2, py, THF, 1h; 82%. (iii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 5mins; 93%. (iv) BVE, $Hg(OAc)_2$, 150°C, sealed tube, 17h; 69% and 63%. (v) Vinyl magnesium bromide, THF, -78°C, 1h; 96%. (vi) Jones' reagent, acetone, 5mins; 74% and 82%. (vii) NaI, MEK, Δ, 17h; 88% and 80%.

Scheme 110

For comparison, attempts to effect the cyclisation of the two radical precursors (5mM, slow addition of tributyltin hydride over 6h) led to formation of the *cis*-macrocycle **205** in 46% (from the *cis*-substrate **206**) and the directly reduced acyclic product (from the *trans*-substrate **249**).[199]

6.5. Studies on the Real System

6.5.1. Retrosynthetic Analysis

Our approach to the actual system was the same as that described in Sections **6.4.4.** and **6.4.5.** (Figure 15) except we had to prepare the isopropyloxabicycle **288**. We hoped that, due to the sensitivity of organocopper addition reactions to steric effects, the S_N2' addition of the functionalised hexylcuprate would be forced into a *syn*- mode by the *trans*- isopropyl group.

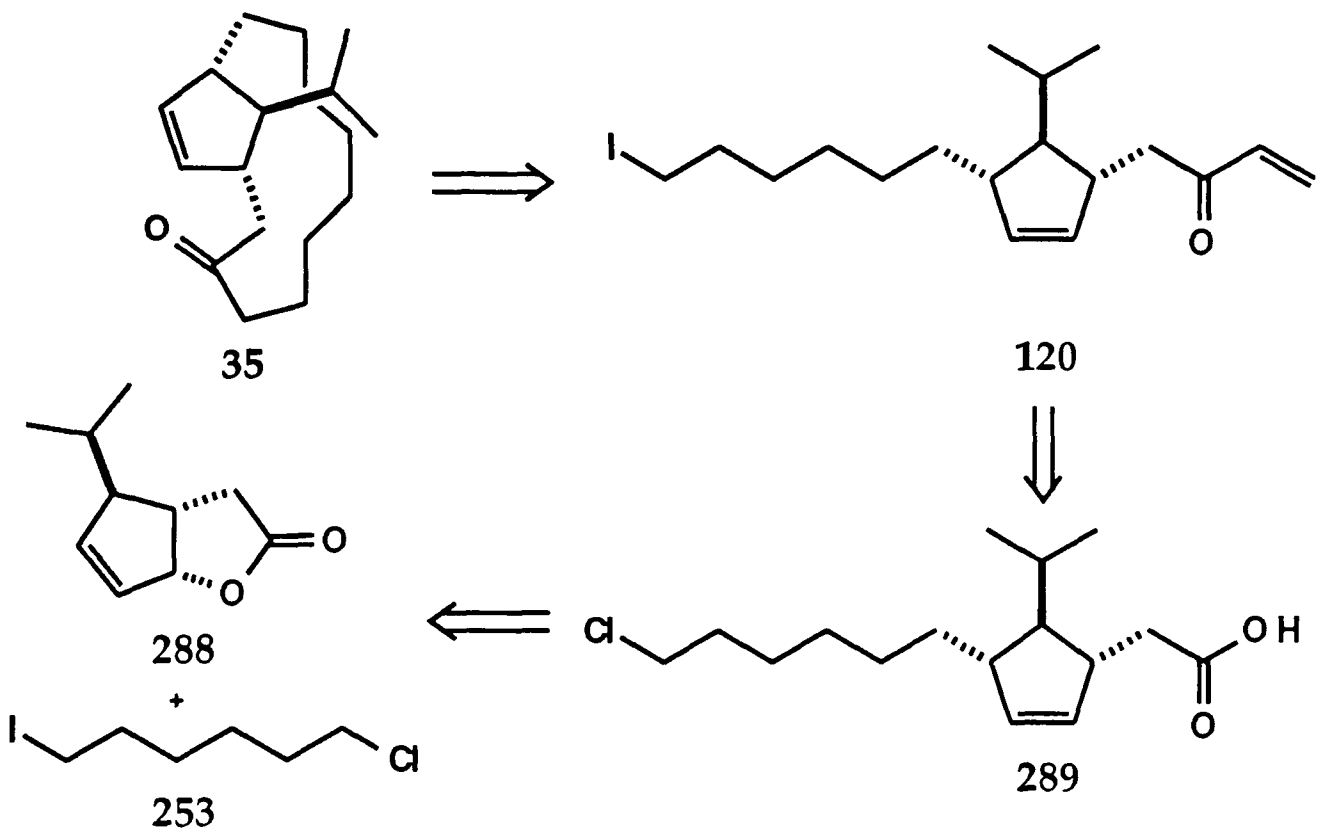
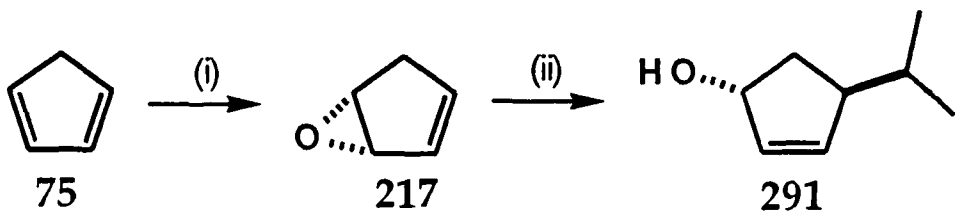


Figure 15

We proposed that formation of the isopropyloxabicycle **288** could come from the corresponding 5-isopropyl-2-cyclopentene-1-acetic acid **290** using a combination of methodology developed by Marino[171] and Clive.[200]

6.5.2. Synthesis of the Isopropyloxabicycle 288

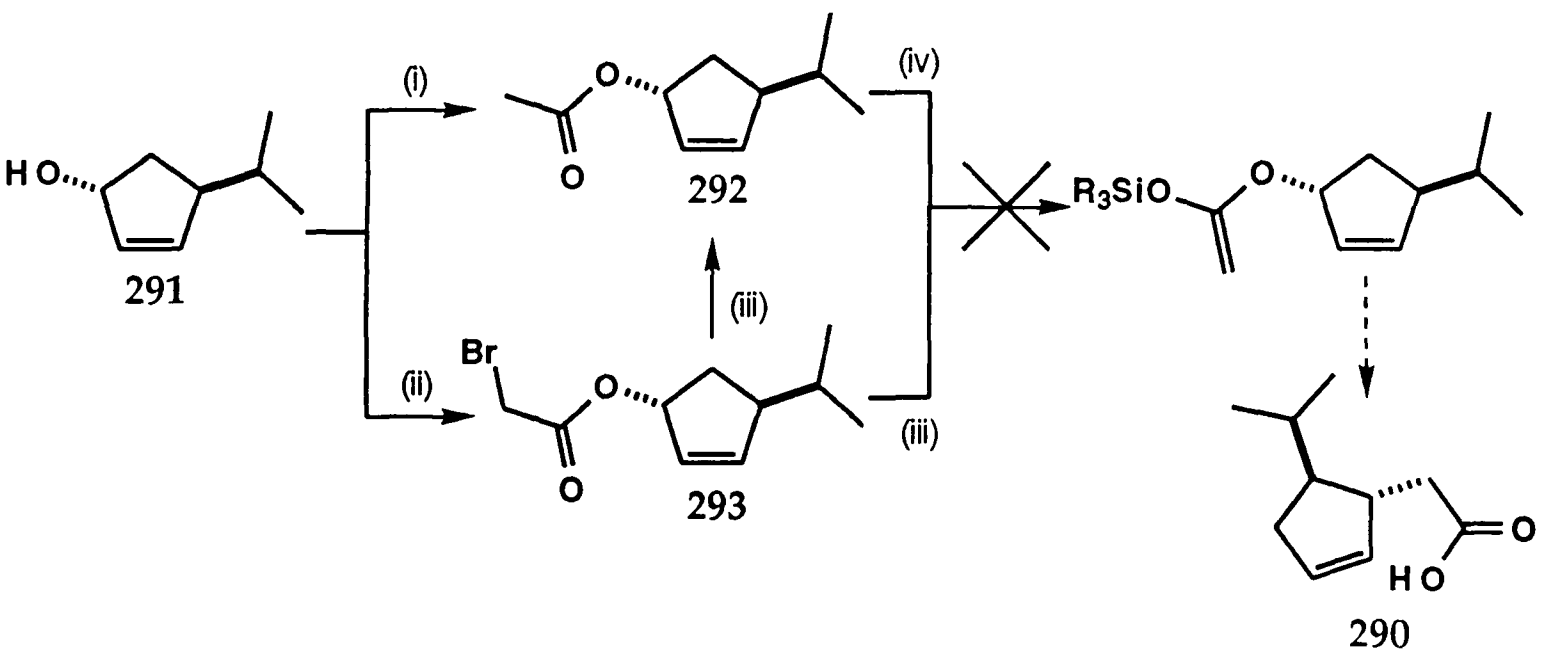
Addition of the monoalkyl-cyanocuprate, derived from isopropylmagnesium chloride,[171] to cyclopentadiene monoepoxide **217**[201] gave selectively the unreported *trans*-allylic alcohol **291** (Scheme 111).



Conditions: (i) Na_2CO_3, NaOAc, AcOOH, DCM, 0°C, 2h; 60%.[201]
(ii) ^{i}PrMgCl, CuCN (1 eq.), Et_2O, -40°C, 1h; -78°C to RT, 5h; 79%.[171]

Scheme 111

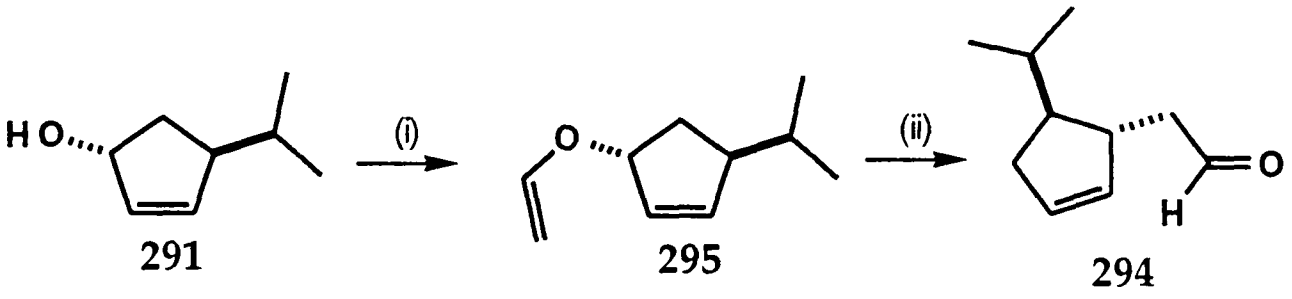
We then intended to achieve a Johnson orthoester Claisen rearrangement[202] using triethyl orthoacetate and a catalytic quantity of propionic acid,[203] however, these conditions led to decomposition of the starting material and no observable product. The use of hydroquinone, instead of propionic acid, led to similar findings.[204] Thus we sought an adaptation of the rearrangement which involved the preparation of an acetate as the precursor to the 1,5-diene silylketene acetal.[205] Accordingly the acetate **292** and bromoacetate **293** were formed, but attempts to form the silylketene acetal and achieve the cyclisation proved unsuccessful,[159,206] even with added DMPU. In fact the bromoacetate **293** reduced to give the acetate **292** under the reaction conditions (Scheme 112).



Conditions: (i) Et_3N, MeCOCl, DCM, 7h; 61%.[205] (ii) $BrCH_2CO_2H$, DMAP, DCC, THF, 15h; 72%.[105] (iii) Zn, THF, TBDMSCl or TMSCl, Δ. (iv) LDA, DMPU, TBDMSCl or TMSCl, -78°C to RT.

Scheme 112

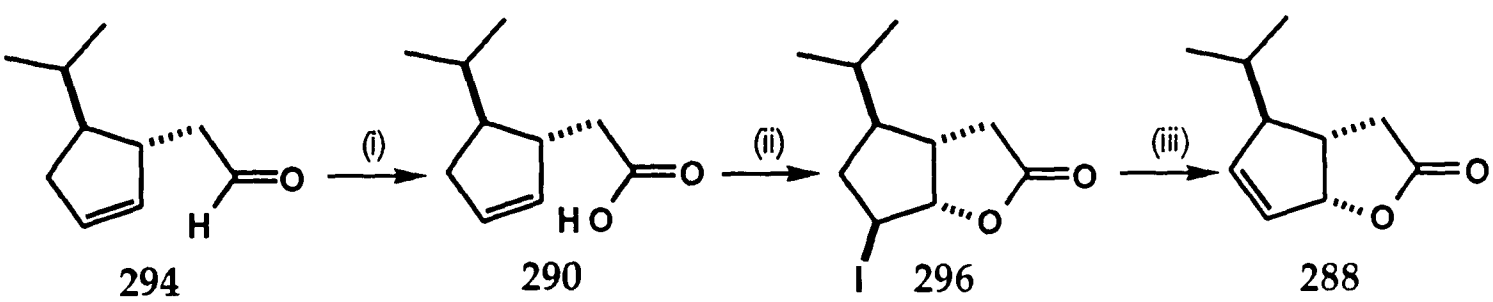
We thus chose an alternative approach that would lead to an aldehyde **294** rather than an acid.[200,206] Treating the allylic alcohol **291** with ethyl vinyl ether or *n*-butyl vinyl ether and mercury (II) acetate led, *via* the unstable allyl enol ether[207] **295**, to the *trans*-aldehyde **294** (Scheme 113). The reaction proved capricious with yields ranging from 20% to 70%; in general, however, a yield of around 60% could be readily obtained.



Conditions: (i) EVE, $Hg(OAc)_2$, 27h; 93% or BVE, $Hg(OAc)_2$, 180°C, sealed tube, 17h; 60% to give **294** directly.[207] (ii) 180°C, PhMe, sealed tube, 17h; 57%.

Scheme 113

The aldehyde **294** was then converted to the desired isopropyloxabicycle[208] **288** rather efficiently (Scheme 114). Although the iodo-lactone **296** formed plates that would have been suitable for X-ray crystallography, it was deemed unnecessary to obtain such proof of the structure since n.O.e. (Appendix D) confirmed the stereochemistry satisfactorily.

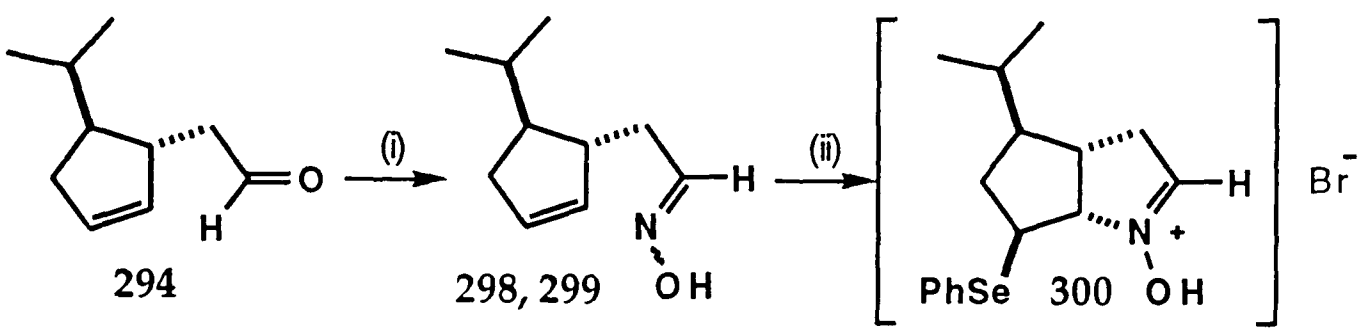


Conditions: (i) Jones' reagent, acetone, 15mins; 83%. (ii) $KHCO_3$, KI, I_2, Et_2O, H_2O, 13h; 95%. (iii) DBU, PhH, Δ, 4h; 98%.

Scheme 114

6.5.3. Attempted Synthesis of a Model Isopropylketo-pyrrole Core 297

It was hoped that the aldehyde **294** would provide a route towards a functionalised model for the keto-pyrrole core of Roseophilin. Thus the corresponding oximes **298** and **299** were subjected to phenylselenyl bromide. The ^1H NMR spectrum of the crude reaction mixture (Appendix C) was promising, however, attempts to form the free-base or purify **300**, afforded a complex mixture of products. The nitrone **300** seemed to be far more sensitive to decomposition than those dealt with earlier (Scheme 115).

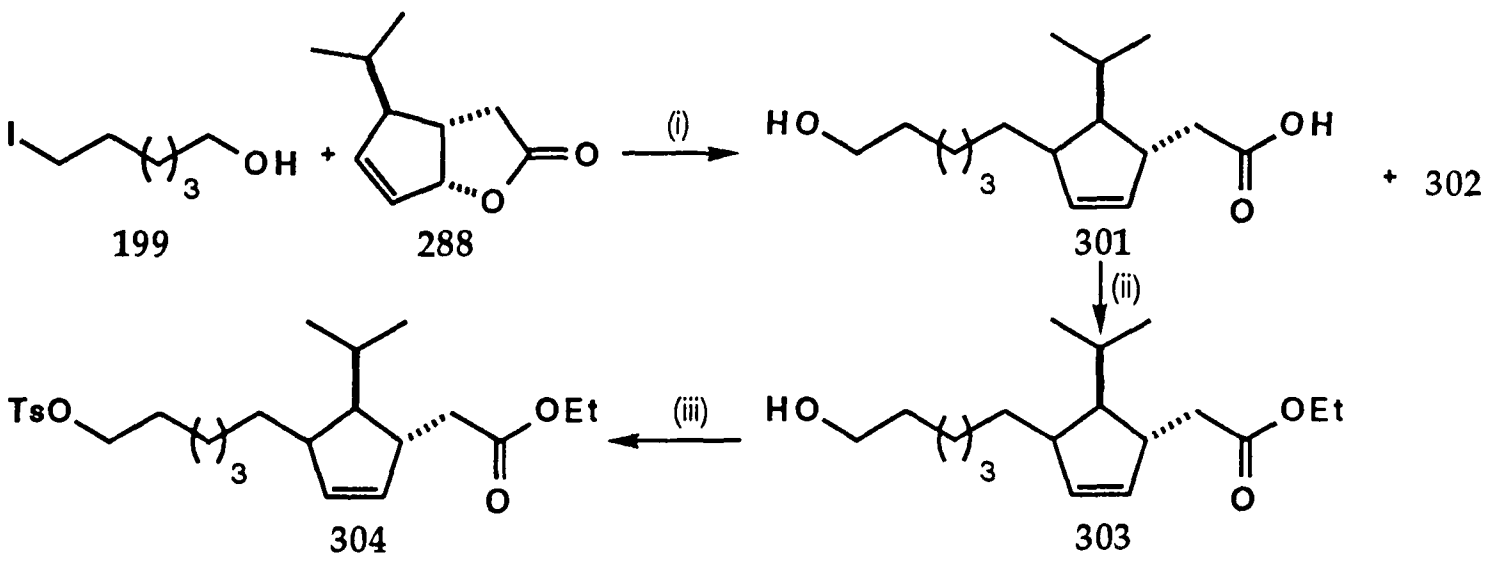


Conditions: (i) NaOAc, $NH_2OH.HCl$, MeOH, 15h; 92% (2:1 mixture). (ii) PhSeBr, DCM.

Scheme 115

6.5.4. Cuprate Addition Reactions to 288: Study I

Initially, addition of the cuprate derived from iodo-hexanol **199** was studied; the oxabicycle **288** led to two products, ratio 5.8:1 (Scheme 116).



Conditions: (i) Iodohexanol, ^nBuLi, Et_2O, 15mins, -78°C; ^tBuLi, 15mins; Me_2S, $CuBr.SMe_2$, -78°C to -20°C, 20mins; -78°C to RT, 15h; 79% (ratio of **301**:minor isomer **302**, 5.8:1). (ii) conc. H_2SO_4, EtOH, 15h; 96%. (iii) TsCl, py, 15h; 85%.

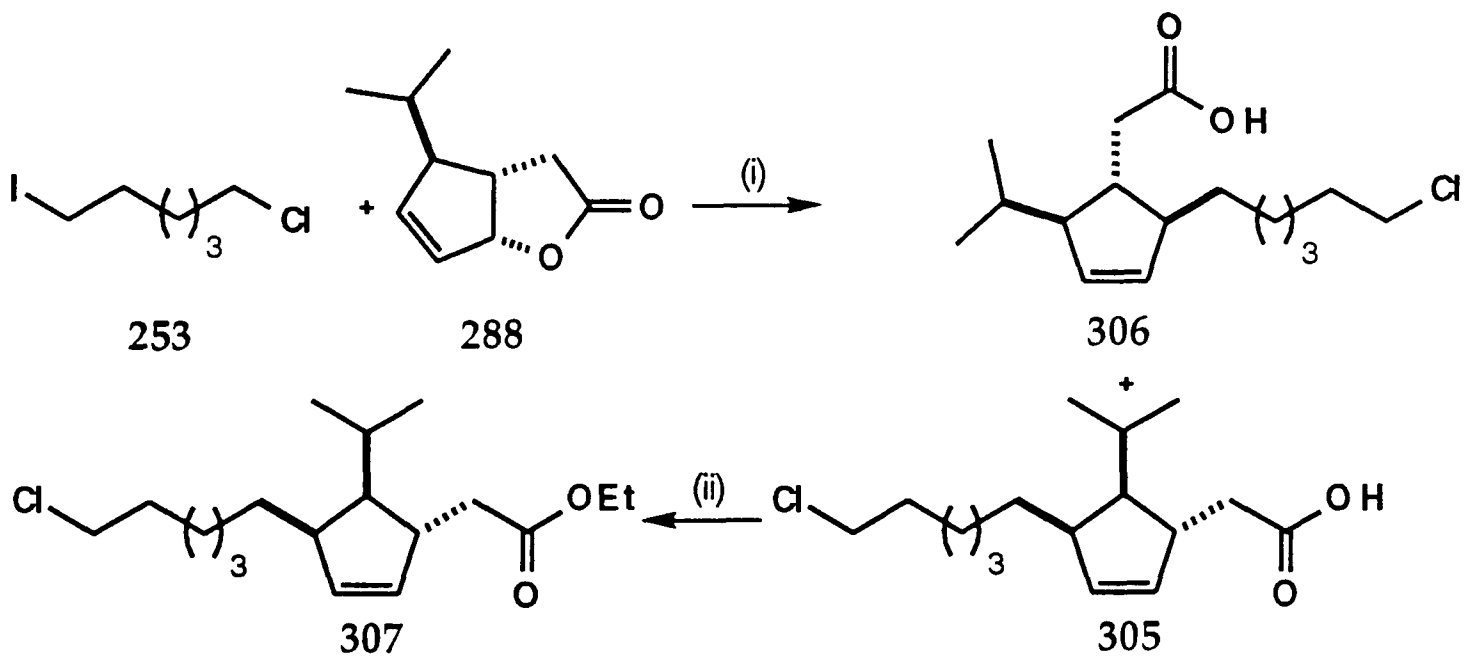
Scheme 116

The major component was shown to be the S_N2' addition product of unknown stereochemistry (though we hoped that the hexyl chain would have a *trans-* relationship to the isopropyl group).

It was initially unclear whether the minor isomer was the S_N2 or the alternative S_N2' product. The major component was converted to the tosylate **304** *en route* to the free-radical precursor. At this point (see **6.5.5.**) it was decided to make use of the chlorohexyl cuprate methodology (**6.4.4.6.**) and concentrate on identifying the exact nature of the adducts obtained.

6.5.5. Cuprate Addition Reactions to 288: Study II

Addition of the chlorohexyl cuprate (from **6.4.4.6.**) to the isopropyl oxabicycle **288** again generated two products **305** and **306**, although the ratio (**305**: **306**) decreased from 5.8:1 to 4:1. Full characterisation, including ^1H-^1H COSY and n.O.e. spectra (Appendix D) were obtained on the separated carboxylic acids **305** and **306** suggesting that the S_N2' product had in fact added in an *anti-* mode, i.e. *cis-* to the isopropyl group (Scheme 117).

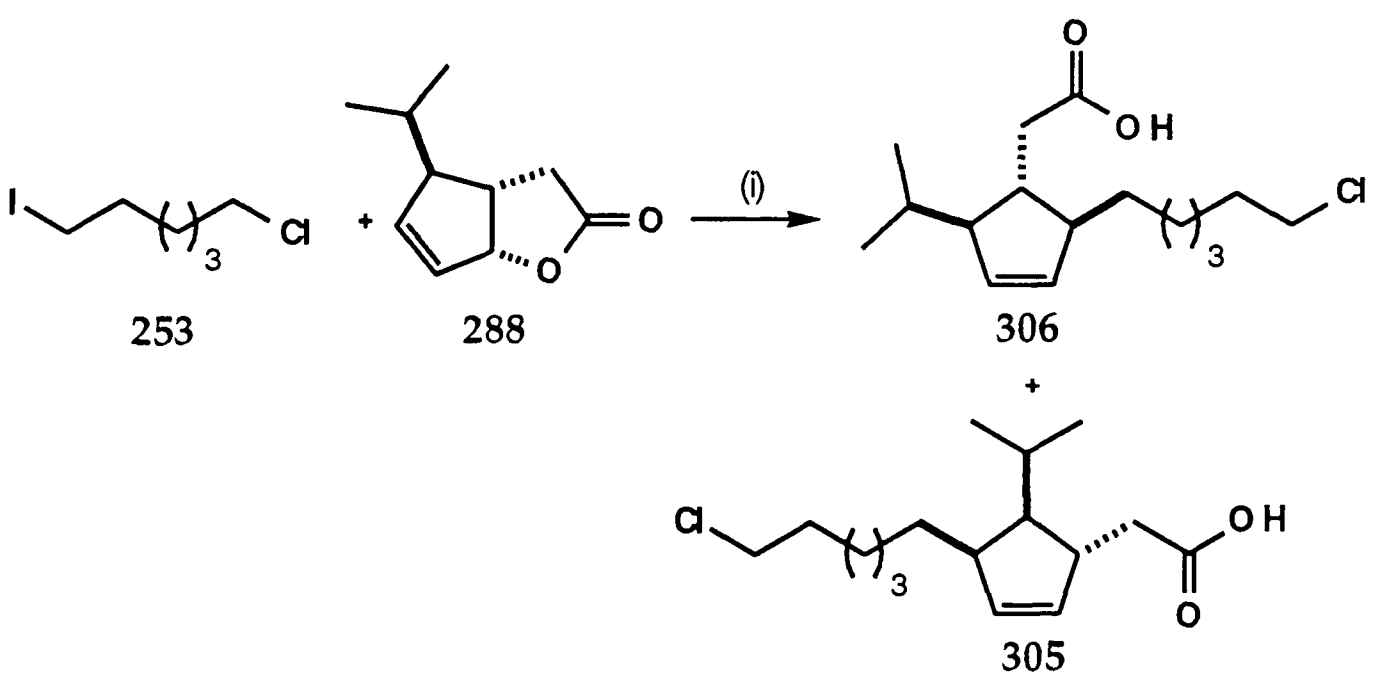


Conditions: (i) ^tBuLi, Et_2O, 15mins; Me_2S, $CuBr.SMe_2$ (1 eq.), -78°C to -20°C, 20mins; -78°C to RT, 15h; 74% (**305**:**306**, 4:1). (ii) conc. HCl, EtOH, 15h; 94%.

Scheme 117

Several of the protons in the ^1H NMR spectrum of **305** coincided, therefore the ester **307** was prepared (in order to obtain conclusive n.O.e. data). The n.O.e. spectrum of ester **307** (Appendix D) confirmed the selectivity of attack of the cuprate as *anti-*. The minor component **306** was found to be the product arising from S_N2 attack by the cuprate. This was the first time that such regioselectivity had been observed on the addition of monoalkyl cuprates (derived from $CuBr.SMe_2$) to the oxabicyclic system. Comparison with the hydroxyl analogues (**6.5.4.**) suggested that analogous products had been formed in the series derived from the hydroxyhexyl cuprate.

For comparison purposes, the oxabicycle **288** was treated with a *higher-order* cuprate (Scheme 118). This was expected to generate solely the S_N2 product, however, a small proportion of the S_N2' adduct also formed (ratio **306**:**305**, 4:1, i.e. the selectivity had reversed.)



Conditions: (i) ^tBuLi, Et_2O, 15mins; Me_2S, $CuBr.SMe_2$ (0.6 eq.), -78°C to -20°C, 20mins; -78°C to RT, 15h; 82% (**306**:**305**, 4:1).

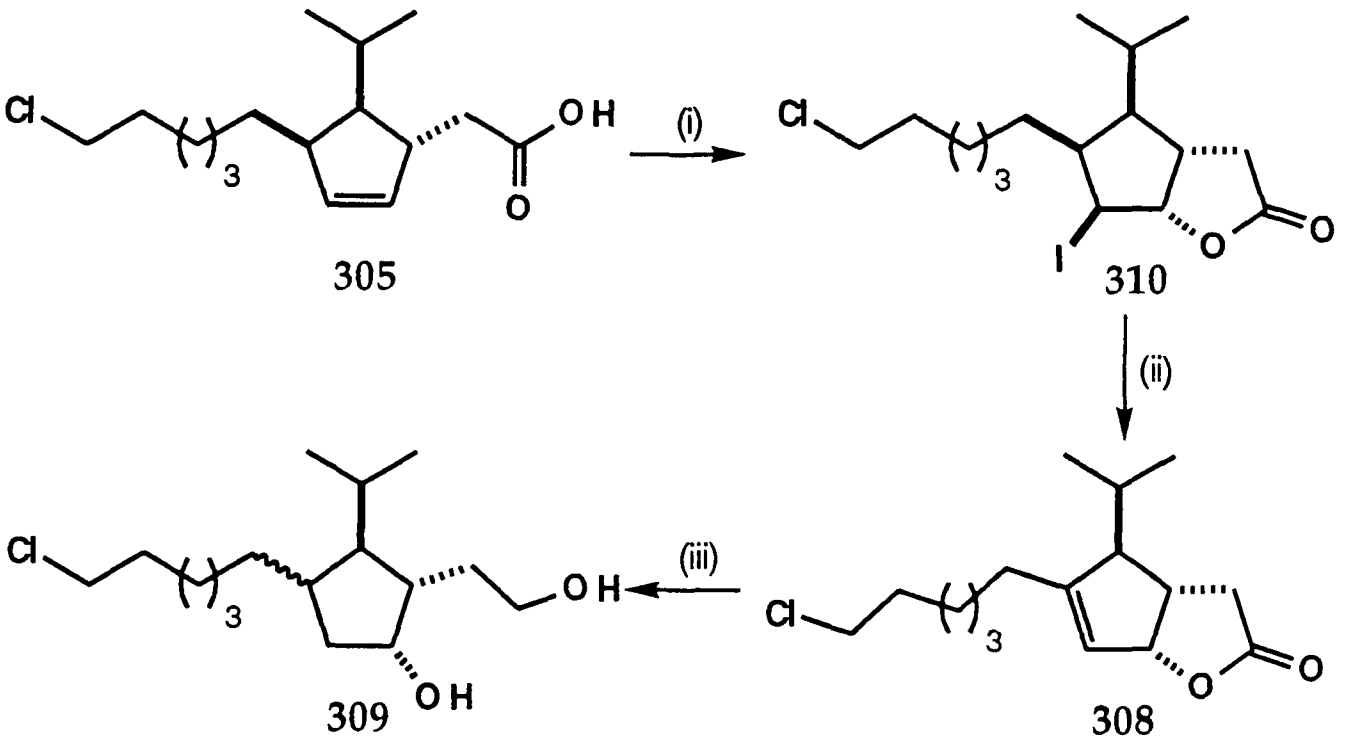
Scheme 118

6.5.6. Attempted Preparation of the *Cis-* Series

Despite our inability to isolate the *cis*-system directly, we were optimistic that our hydroboration methodology (**6.4.5.1.** and **6.4.5.3.**) would give us access

to the *cis*- series. It was interesting to note that in the ^1H NMR spectrum of the alkenyl-lactone **308** (Scheme 119), one of the methyl groups of the isopropyl substituent was significantly shielded by the adjacent alkene, δ_H 0.66 (3H, d, *J* 6.9, C**H**$_3$), 1.00 (3H, d, *J* 6.9, C**H**$_3$).

Unfortunately, the alkene in **308** could not be reduced selectively with either borane-tetrahydrofuran complex, or borane-dimethylsulphide complex[209] and under a variety of conditions only a mixture of diols **309** was obtained.

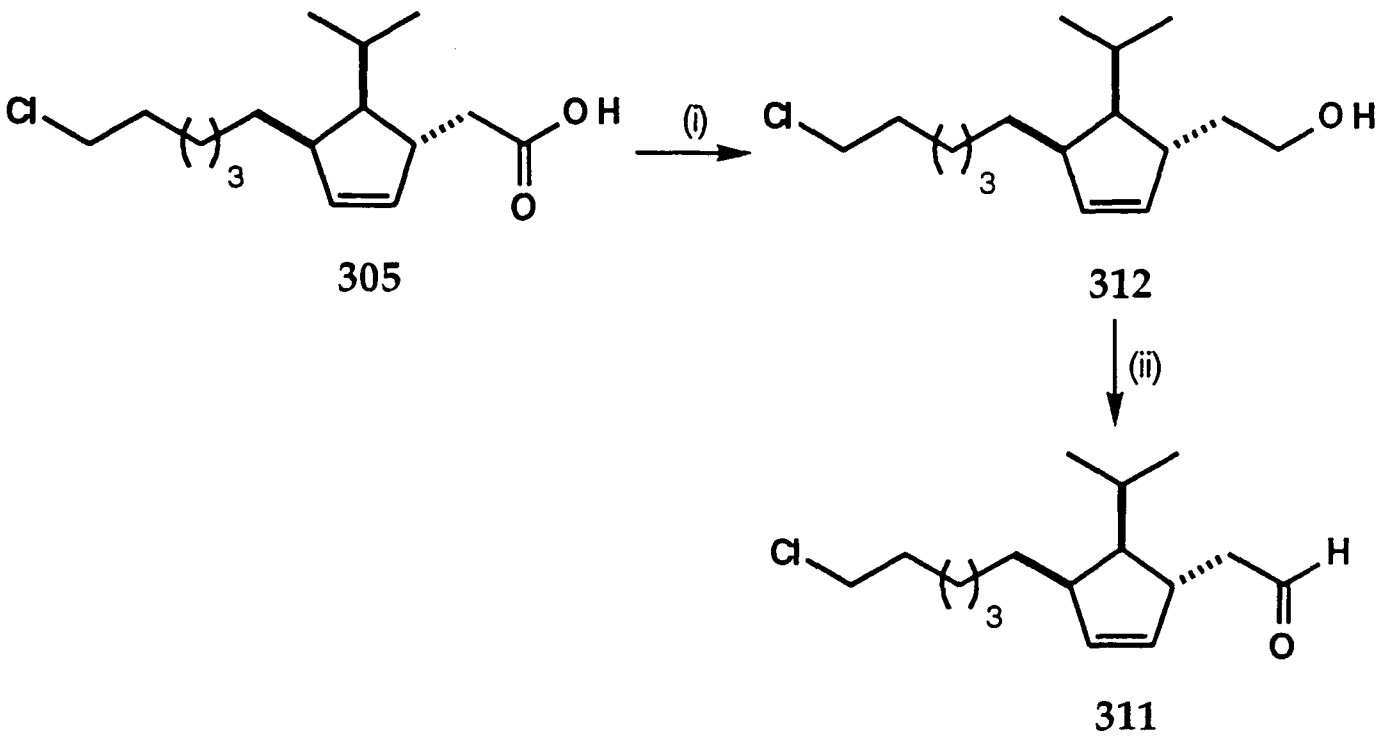


Conditions: (i) $KHCO_3$, KI, I_2, Et_2O, H_2O, 13h; 92%. (ii) DBU, PhH, Δ, 1.5h; 95%. (iii) BH_3.THF, THF, 18h; NaOH, 1h; 91% (8:3 mixture of diastereomers).

Scheme 119

6.5.7. Towards the *Trans*- Free-Radical Precursor

We decided to pursue the formation of the *trans*- radical precursor because our model study had suggested that the *trans*- cyclisation might indeed be feasible (**6.4.4.7.**). Unfortunately, due to lack of time, the intermediates were only characterised as far as the aldehyde **311** (Scheme 120).



305 312 311

Conditions: (i) $LiAlH_4$, THF, 15h, 0°C to RT; 79%. (ii) PDC, 4Å Mol.S., DCM, 4h; 88%.

Scheme 120

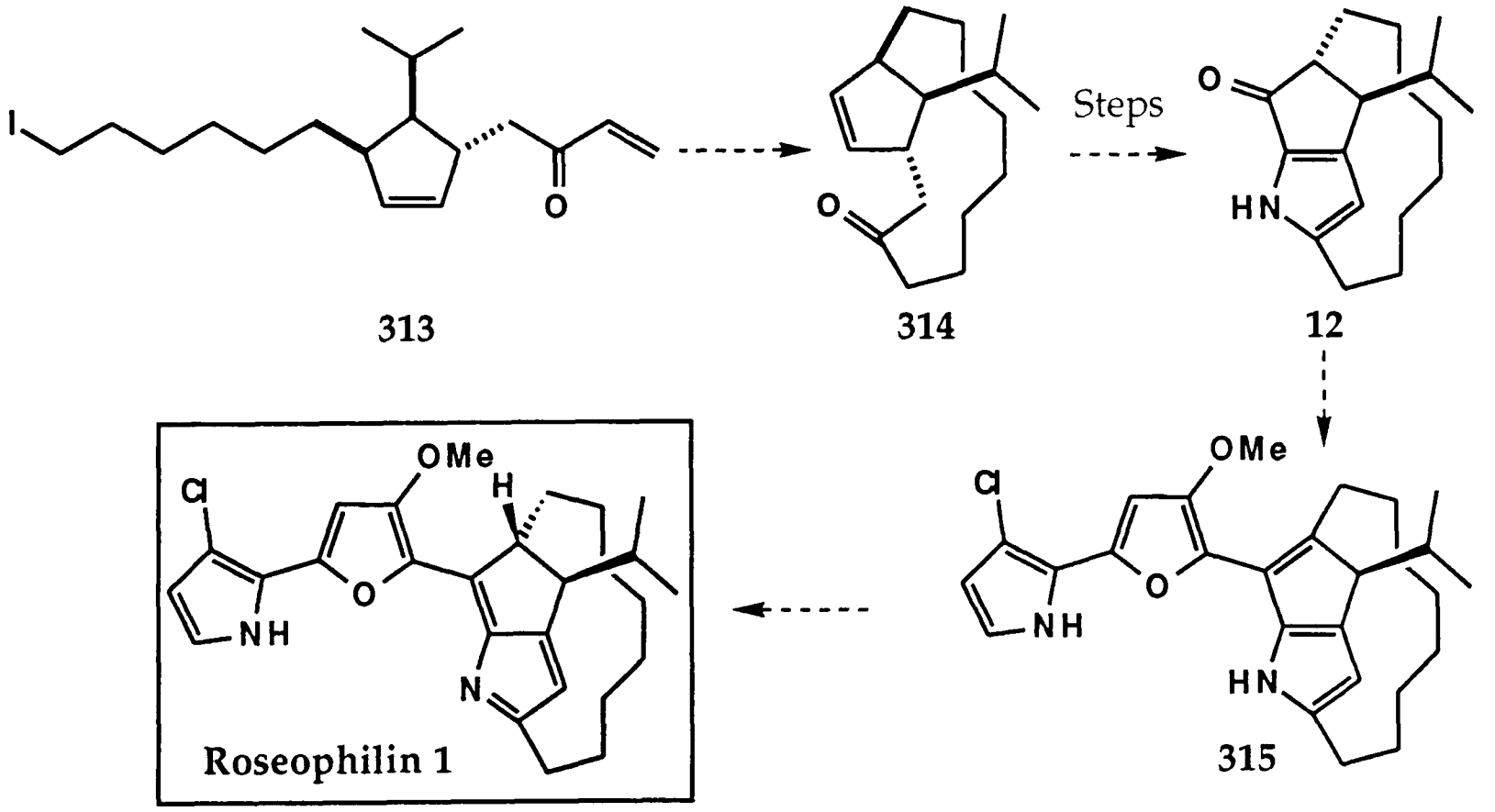
FUTURE WORK

This chapter highlights possible extensions to the methods described in this thesis together with some totally new approaches several of which are under active consideration in the group.

7.1. Macrocycle Formation: Free-Radical Approach

7.1.1. Exploitation of the Approach of Section 6.5.

Although the synthesis of the *cis*- macrocycle **120** was not achieved (**6.5.4.** to **6.5.6.**) the free-radical macrocyclisation of **313** should be viable. *Trans*-macrocycle **314** if subjected to non-acidic conditions, may then be converted to the keto-pyrrole **12** (Scheme 121).



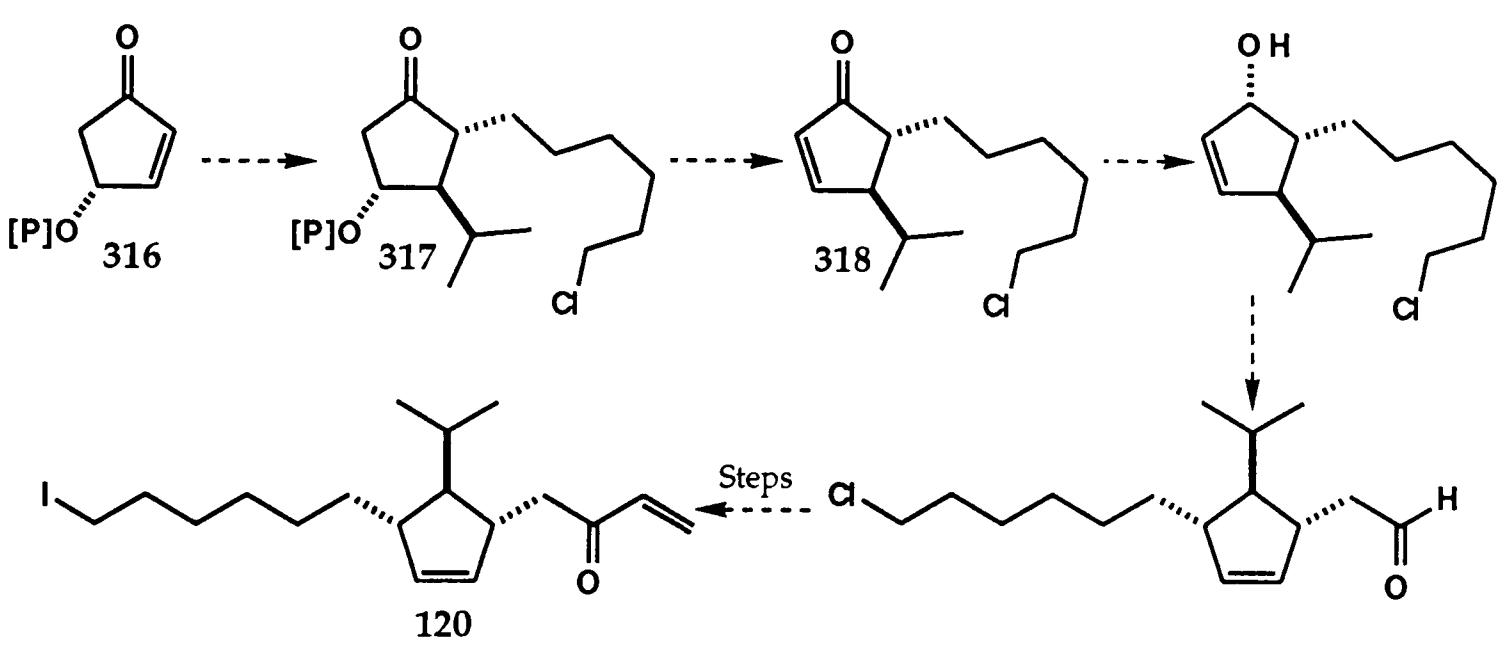
Scheme 121

Interestingly Terashima[13] has shown, from the coupling reactions on model systems (**4.4.1.**), that the azafulvene would form *via* an intermediate

alkene such as **315**; this would destroy the stereochemistry α- to the isopropyl group.

7.1.2. Exploitation of the Approach of Section 6.4.6.

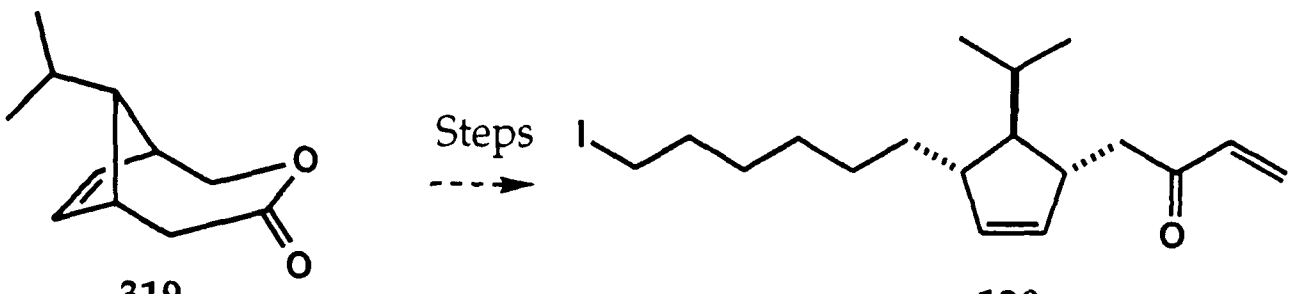
The route described in Section **6.4.6.** could be easily adapted to the real system. In fact the sequence could be performed in a stereospecific manner by making use of *O*-protected-4-hydroxy-2-cyclopentenone[210,211] **316**. The first step, a Noyori three-component coupling reaction,[212] could generate optically pure **317**, in one step, with the correct relative stereochemistry. The β-hydroxy group could be eliminated to give enone **318**. Selective reduction, Claisen rearrangement and functionalisation would lead to the desired *cis*-radical precursor **120** (Scheme 122).[213]



Scheme 122

7.1.3. An Alternative Approach to the *Cis*- Series

Current work in the group is concerned with generating the *cis*- free-radical precursor from the oxabicyclononenone **319** (Scheme 123).[214]

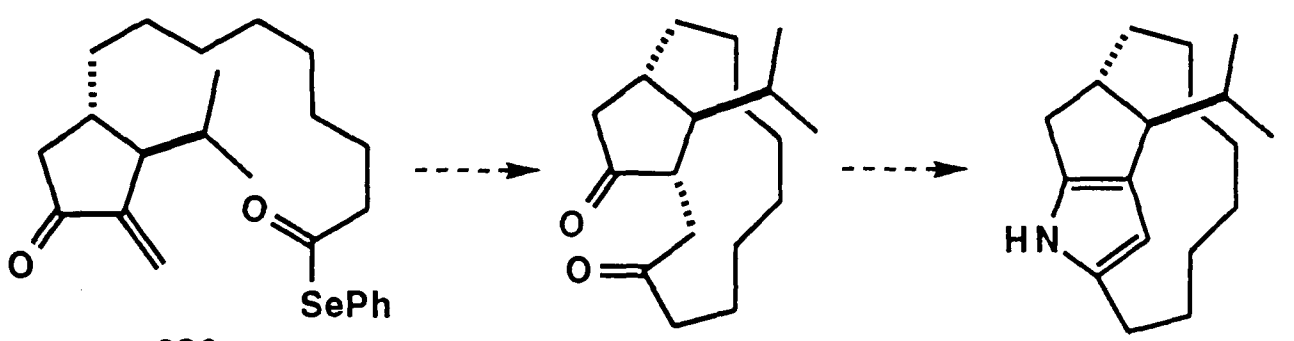


319 120

Scheme 123

7.1.4. Novel Approach for Forming the Macrocyclic Ketone 322

Boger[101] and Pattenden[123] have demonstrated that 1,4-dicarbonyl macrocyclic compounds are accessible using acyl radicals. An alternative route could therefore involve the cyclisation of **320**; the 1,4-dicarbonyl compound **321** could then be readily converted to the pyrrole **322** (Scheme 124).



320 321 322

Scheme 124

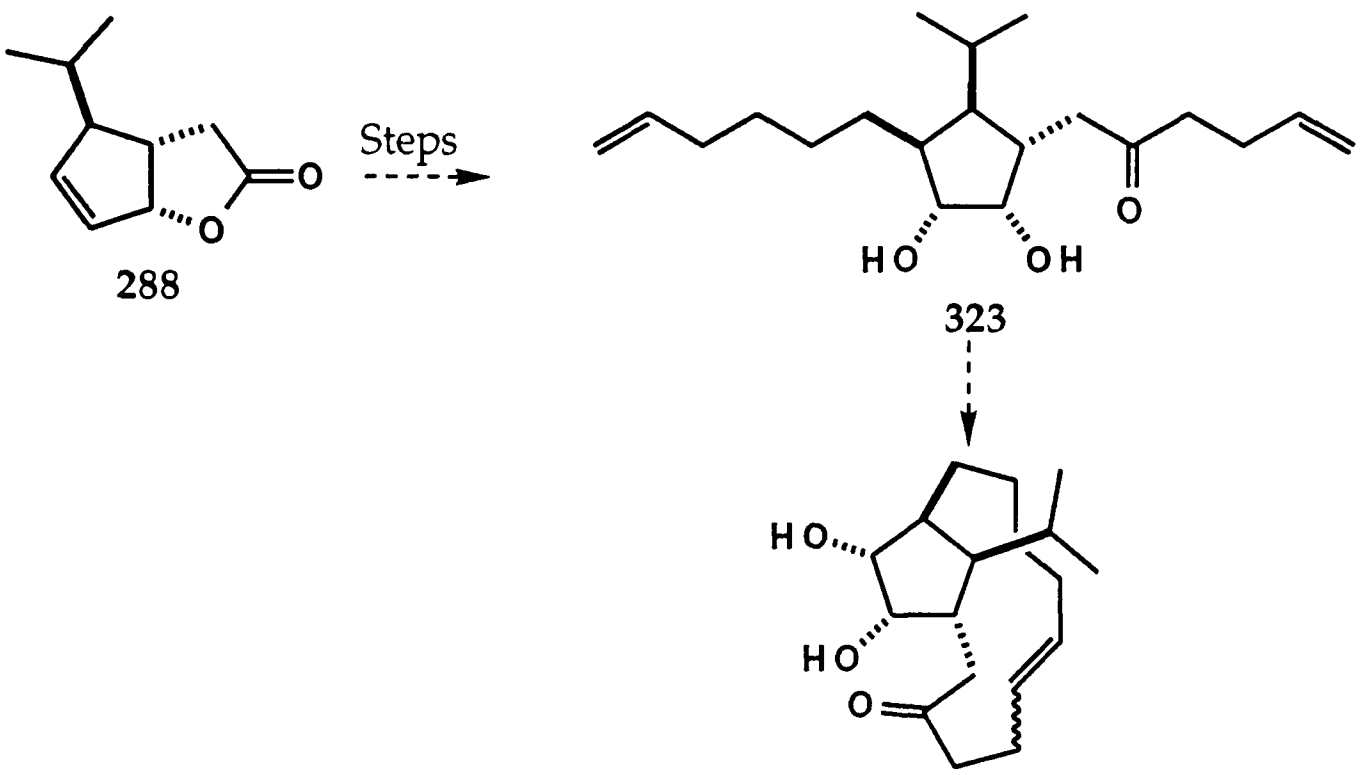
7.1.5. Alternative Strategies

All of the approaches so far involve a three fold approach: macrocyclisation, tricycle formation and finally heterocyclic coupling. This overall strategy could, of course, be altered with respect to the order of events. For instance the macrocyclisation could be attempted on a bicyclic substrate.

7.2. Macrocycle Formation: Metathesis

With the increased availability of suitable catalysts, an approach to the macrocyclic ring *via* ring-closing metathesis could be investigated.[215,216] There

are a vast number of possible cyclisation precursors; one-example, **323**, that could be derived from our work (mixture of **6.4.4.1.** and **6.5.4.** to **6.5.5.**) is shown in Scheme 125.

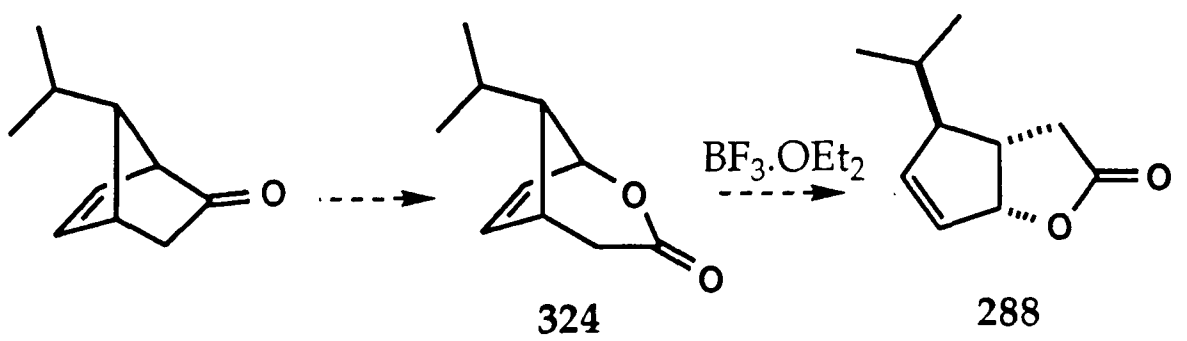


Scheme 125

7.3. Further Possibilities

7.3.1. Synthesis of the Oxabicycle 288 (*cf.* 6.5.1. and 6.5.2.)

An alternative route to the isopropyloxabicycle **288** could be developed from the methodology of Grieco and co-workers.[217] This approach relies on the rearrangement of **324**, derived from the Baeyer-Villiger oxidation of a functionalised Diels-Alder adduct (Scheme 126).



Scheme 126

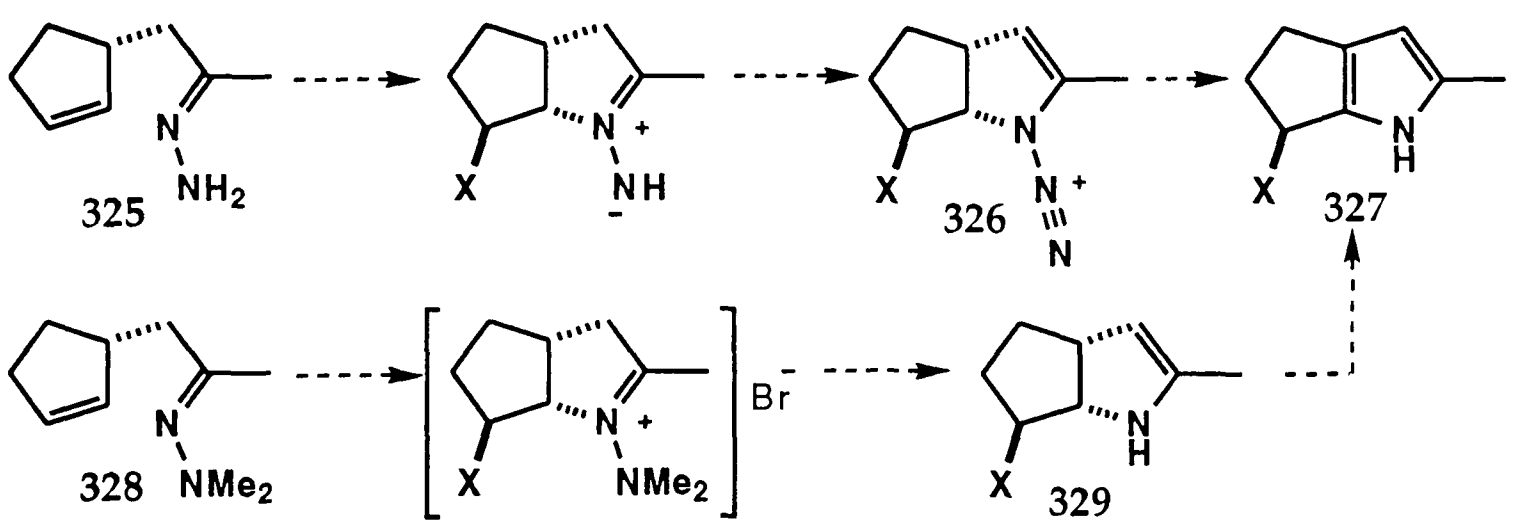
7.3.2. Asymmetric Approach

The overall sequence described in Section **6.5.2.**

could also be accomplished in an enantiomerically pure form since the manganese-salen catalysed enantioselective mono epoxidation of cyclopentadiene **75** has been recently reported.[218,219]

7.3.3. Alternatives to Oxime Cyclisation (*cf.* 6.4.5.6. to 6.4.5.8. and 6.5.3.)

It us interesting to consider whether a hydrazone **325**, in place of an oxime, could undergo electrophile induced cyclisations to 5- or 6-membered rings. After cyclisation, the terminal amine could be transformed to a diazo-species **326** which would facilitate elimination towards **327**. In the case of a functionalised hydrazone **328**, the N-N bond could be cleaved to generate **329** that could be further oxidised to **327**. These ideas are summarised in Scheme 127.



Scheme 127

EXPERIMENTAL

8.1. General Experimental

Melting points (m.p.) were measured on a Griffin Melting Point Apparatus and are uncorrected. The solvents used for recrystallisation are given in parentheses.

Boiling points (b.p.) were measured using either a short path distillation unit or a Kugelrohr distillation unit. The pressure (mmHg) is specified in each case. 'High vacuum' refers to the pressure obtained on using a Lexbold Vacuum-pump and lies within the range 0.5mbar to 2mbar. 'Water pump' refers to the pressure obtained from a standard water pump and lies within the range 15mmHg to 25mmHg.

Proton (^{1}H) NMR spectra were run on either a Varian Gemini 200 (200MHz), a Bruker AC 200 (200MHz) or a Bruker AM 500 (500MHz) spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm) downfield of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shift and coupling data[220] using COSY and n.O.e. where appropriate. Abbreviations used in the descriptions of multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet) and br (broad). Coupling constants (J) are quoted to the nearest 0.5Hz (200MHz spectrometers) and 0.1Hz (500MHz spectrometers).

Carbon-13 (^{13}C) NMR spectra were recorded on either a Varian Gemini 200 (50.3MHz), a Bruker AC 200 (50.3MHz) or a Bruker AM 500 (125MHz) spectrometer. Chemical shifts (δ_C) are quoted in parts per million (ppm) downfield of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shift using the DEPT

sequence, where appropriate, and by comparison with the data obtained from similar structures.

Infrared spectra were recorded on either a Perkin-Elmer 1750 or a Perkin-Elmer Paragon 1000 Fourier transform spectrometer, absorption maxima ($\nu_{max.}$) being recorded in wavenumbers (cm^{-1}) and classified as strong (s), medium (m), weak (w), broad (br) or a shoulder (sh).

Mass spectra were recorded on VG Micromass ZAB 1F and Masslab 20-250 spectrometers using direct chemical ionisation (C.I., NH_3) or electrospray (ES) in +ve or -ve scan mode as stated or on a VG Platform spectrometer using atmospheric pressure chemical ionisation (A.P.C.I.) from a mixed solvent system [MeOH:MeCN:H_2O, 40:40:20] in +ve or -ve scan mode as stated. GC mass spectra (GCMS) were recorded by the author on a VG TRIO-1 (DB-5 column) system under chemical ionisation (C.I., NH_3) conditions. *m/z* values are reported in Daltons and are followed by their percentage abundancies in parentheses; only peaks with a signal of 10% or greater are reported. High resolution mass spectra (HRMS) were recorded at the EPSRC Mass Spectrometry Service Centre at the University of Swansea and are calculated from the molecular formula corresponding to the observed signal using the most abundant isotopes of each element, to 4 decimal places.

Elemental (Microanalyses) analyses were carried out by Mrs V Lamburn and Mr R Prior of the Dyson Perrins Laboratory.

Thin layer chromatography (t.l.c.) was performed on Merck DC-Alufolien Kieselgel $60F_{254}$ 0.2mm precoated plates or Merck DC-Alufolien Aluminiumoxid $60F_{254}$ neutral (Typ E) 0.2mm precoated plates. Product spots were visualised by the quenching of u.v. fluorescence ($\lambda_{max.}$=254nm) then stained and heated with 5% (w/v) *dodeca*-molybdophosphoric acid in ethanol. Where retention factors (R_f) are reported, the solvent system used follows in

parentheses. Only in cases where the product formed a streak on t.l.c. or where a product spot could not be obtained under a variety of staining solutions is an R_f not quoted.

Flash column chromatography was performed by the method of Still *et al.*[221] on silica gel (Sorbsil C60 40/60 or Merck silica gel 60 (230-400 mesh ASTM)). The solvent system used follows in parentheses.

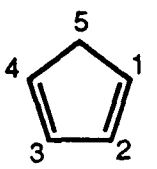
Solvents and commercially available reagents were dried and purified before use, where appropriate, using standard procedures; pyridine was distilled from, and stored over KOH; DCM, TMEDA, benzene, triethylamine, diisopropylamine, MeCN, toluene and Me_2S were heated at reflux over and distilled from calcium hydride; DMF and DMSO were obtained by reduced pressure distillation from calcium hydride. THF was obtained dry and oxygen-free by distillation from sodium benzophenone ketyl under nitrogen.[222] Anhydrous ether (99.8%) was purchased from the Aldrich Chemical company. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 30-40°C, and was distilled before use to remove involatile impurities.

CuCN was azeotropically dried by co-evaporation with toluene. $CuBr.SMe_2$[153], $Pd(PPh_3)_4$[168], PhSeBr[132], Jones' reagent[77] and $(Ph_3P)_3RhCl$[93] were all prepared and purified according to the literature procedures. $ZnCl_2$ and $ZnBr_2$ were heated on a Kugelrohr apparatus (150°C, high vacuum) for 1h before use. Mg turnings were washed with 1M aq. HCl and EtOH, and dried before use.

All non-aqueous experiments were carried out under an Ar or N_2 atmosphere unless specified and in each experimental procedure the work was performed at RT unless reported otherwise.

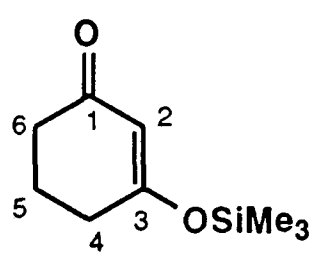
8.2. Main Experimental

Cyclopenta-1,3-diene 75[62]



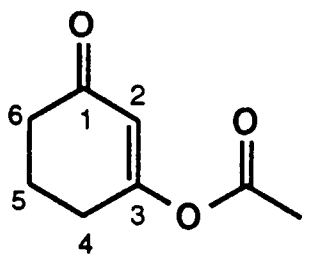
Dicyclopentadiene was cracked (170°C, A.P.) through a Vigreux column to give pure cyclopentadiene **75** (collected at -78°C). b.p. 40-44°C [lit. 38-46°C]; δ_H (200MHz, $CDCl_3$) 2.92-3.05 (2H, m, $\mathbf{H}(5)_2$), 6.43-6.50 (2H, m,), 6.54-6.61 (2H, m); *m/z* (C.I., NH_3) 67 (MH^+, 100%).

3-Trimethylsilyloxy-2-cyclohexen-1-one 78[63]



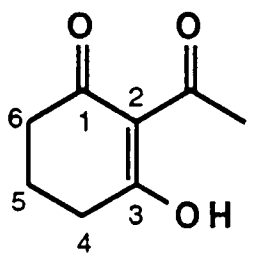
The procedure described by Ainsworth *et al.*[63] was repeated with cyclohexane-1,3-dione **80** (1.4g, 12.4mmol), imidazole (0.1g, 1.47mmol) and hexamethyldisilazane (10ml, 47.0mmol) to give the silylated compound **78** (2.0g, 87%) as a colourless oil. $\nu_{max.}$ (thin film) 2944 (w), 1629 (m), 1593 (m), 1538 (m), 1455 (m), 1408 (s), 1353 (m), 1271 (m), 1223 (s), 1183 (s), 1143 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.26 (9H, s, $Si(C\mathbf{H}_3)_3$), 1.85-2.00 (2H, q, *J* 6.5, $\mathbf{H}(5)_2$), 2.25 (2H, t, *J* 6.5, $\mathbf{H}(4)_2$), 2.35 (2H, t, *J* 6.5, $\mathbf{H}(6)_2$), 5.35 (1H, s, **H**(2)); *m/z* (C.I., NH_3) 186 ($M(^{29}Si)H^+$, 12), 185 ($M(^{28}Si)H^+$, 100) 156 (10%).

3-Acetoxy-2-cyclohexen-1-one 79[64]



A solution of cyclohexan-1,3-dione **80** (0.38g, 3.39mmol) and imidazole (23mg, 0.34mmol) in acetic anhydride (3ml) was stirred at RT. After 15h the reaction mixture was concentrated *in vacuo* and purified by distillation on a Kugelrohr apparatus (130°C, high vacuum) to afford the title compound **79** (420mg, 81%) as an oil. R_f (1:1, petrol:ether) 0.21 (uv active); $\nu_{max.}$ (thin film) 2980 (w), 1770 (m), 1644 (s), 1429 (w), 1366 (m), 1196 (m), 1123 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.00-2.15 (2H, m, **H**(5)$_2$), 2.21 (3H, s, C**H**$_3$), 2.40 (2H, t, *J* 6.5, **H**(4)$_2$), 2.53 (2H, t, *J* 6.5, **H**(6)$_2$), 5.89 (1H, s, **H**(2)); *m/z* (C.I., NH_3) 172 (MNH_4^+, 10), 155 (MH^+, 100), 113 (50%).

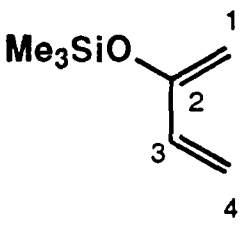
2-Acetylcyclohexane-1,3-dione 81[64]



The procedure descibed by Lakhvich *et al.*[64] was repeated using $AlCl_3$ (0.86g, 6.49mmol), DCM (20ml) and 3-acetoxy-cyclohexenone **79** (0.5ml, 3.25mmol) to give the crude title compound. Purification by flash column chromatography (2:1, petrol:ether) gave the dione **81** (460mg, 92%) as an off white solid. R_f (1:1, petrol:ether) 0.21 (uv active); m.p. (ether/petrol) 28-31°C [Lit. 29.5°C]; δ_H

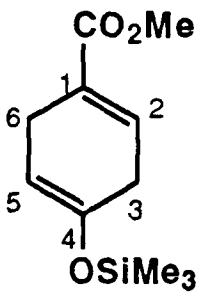
(200MHz, $CDCl_3$) 1.90-2.10 (2H, q, *J* 6.5, **H**$(5)_2$), 2.50 (2H, t, *J* 6.5, **H**$(4)_2$), 2.60 (3H, s, C**H**$_3$), 2.65 (2H, t, *J* 6.5, **H**$(6)_2$); *m/z* (C.I., NH_3) 155 (MH^+, 100), 113 (55%).

2-(Trimethylsilyloxy)buta-1,3-diene 85[68]



The procedure described by Cazeau *et al.*[68] was repeated using MVK **87** (3.0g, 3.6ml, 42.8mmol), acetonitrile (100ml), chlorotrimethylsilane (6.75ml, 53.5mmol), triethylamine (7.4ml, 53.5mmol) and NaI (8.0g, 53.5mmol) to give the title diene **85** (3.5g, 60%). $\nu_{max.}$ (thin film) 1634 (s), 1587 (m), 1593 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.24 (9H, s, Si(C**H**$_3)_3$), 4.38 (2H, s, **H**$(1)_2$), 5.10 (1H, dd, *J* 10.5, 1.0, **H**$(4)_a$), 5.49 (1H, dd, *J* 16.5, 1.0, **H**$(4)_b$), 6.22 (1H, dd, *J* 16.5, 10.5, **H**(3)); *m/z* (C.I., NH_3) 144 ($M(^{29}Si)H^+$, 15), 143 ($M(^{28}Si)H^+$, 100%).

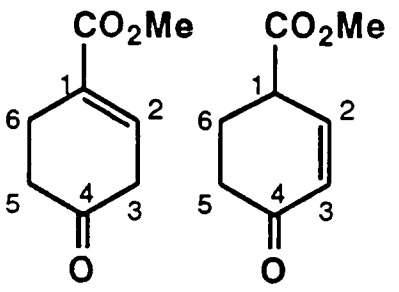
Methyl 4-trimethylsilyloxycyclohexa-1,4-diene carboxylate 84



A solution of the silyloxydiene **85** (1.5g, 10.6mmol), 1,4-dihydroxybenzene (10mg, 0.1mmol) and methyl propiolate **86** (0.9ml, 10.6mmol) in benzene (15ml) was heated at 140°C in a sealed tube for 87h. The reaction mixture was concentrated to yield the title compound **84** (720mg, 30%) as an oil. $\nu_{max.}$ (thin film) 2955 (s), 2899 (m), 2837 (w), 1720 (s), 1689 (s), 1653 (w), 1436 (s), 1378 (s),

1304 (m), 1256 (s), 1202 (s), 1090 (s), 1058 (m), 1006 (m), 957 (m), 932 (m), 885 (s), 846 (s), 804 (w), 756 (m), 729 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.20 (9H, s, $Si(CH_3)_3$), 2.81-2.89 (2H, m), 2.94-3.02 (2H, m), 3.73 (3H, s, OCH_3), 4.87-4.89 (1H, m, **H**(5)), 6.87-6.89 (1H, m, **H**(2)); δ_C (125MHz, $CDCl_3$) 0.2 ($Si(CH_3)_3$), 26.0, 31.4 ($2xCH_2$), 51.6 (OCH_3), 100.7 (**C**(5)), 127.8 (**C**(1)), 135.7 (**C**(2)), 146.2 (**C**(4)), 167.2 (CO_2Me); *m/z* (C.I., NH_3) 227 ($M(^{28}Si)H^+$, 40), 90 (100%).

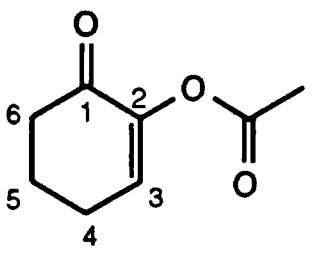
Methyl 4-oxocyclohex-1-ene carboxylate 82[66] and Methyl 4-oxocyclohex-2-ene carboxylate 83[66]



To a stirred solution of diene **84** (1.5g, 6.64mmol) in 1:1, THF:H_2O (8ml) was added conc. H_2SO_4 (0.6ml) dropwise. After 1h the reaction mixture was diluted with water (20ml) and partitioned with ether (2x20ml). The combined organic layers were washed with brine (15ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title esters (640mg, 63%) as an inseparable mixture (ratio 3:1, 1-ene **82**:2-ene **83**) of oils. R_f (1:1, petrol:ether) 0.23 (uv active); $\nu_{max.}$ (thin film) 2955 (w), 1718 (sh, s), 1654 (m), 1438 (m), 1378 (w), 1259 (s), 1193 (m), 1083 (m), 1057 (w) cm^{-1}; major isomer **82**, δ_H (200MHz, $CDCl_3$) 2.50 (2H, t, *J*, 6.5, $H(5)_2$), 2.78 (2H, br t, *J* 6.5, $H(6)_2$), 3.00-3.10 (2H, m), 3.73 (3H, s, OCH_3), 6.95-7.05 (1H, m, **H**(2)); *m/z* (C.I., NH_3) 172 (MNH_4^+, 75), 155 (MH^+, 40), 154 (MNH_4^+-H_2O, 45), 139 (30), 126 (100), 123 (55), 112 (30), 111 (24), 95 (21), 82 (19), 67 (20), 53 (11%); minor isomer **83**, δ_H (200MHz, $CDCl_3$) 2.20-2.60 (4H, m), 3.35-3.50 (1H, m, **H**(1)), 3.78 (3H, s, OCH_3), 6.08 (1H, dd, *J* 10.0, 2.0, **H**(3)), 7.06

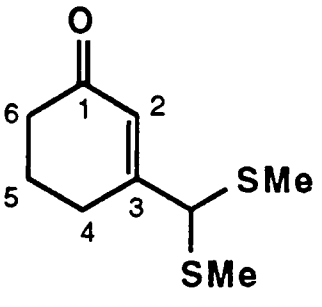
(1H, dd, *J* 10.0, 3.0, **H**(2)); *m/z* (C.I., NH_3) 172 (MNH_4^+, 65), 155 (MH^+, 100), 154 (MNH_4^+-H_2O, 45), 126 (90), 123 (15), 98 (18), 83 (13), 67 (10%).

2-Acetoxy-2-cyclohexen-1-one 92[73]



A solution of cyclohexane-1,2-dione **93** (0.4g, 3.60mmol) and imidazole (24mg, 0.36mmol) in acetic anhydride (5ml) was stirred at RT. After 15h the reaction mixture was concentrated and purified by distillation on a Kugelrohr apparatus (150°C, high vacuum) to afford the title compound **92** (424mg, 77%) as an oil. R_f (1:1, petrol:ether) 0.30 (uv active); $\nu_{max.}$ (thin film) 2947 (w), 1762 (s), 1691 (s), 1649 (w), 1431 (w), 1373 (m), 1216 (s), 1175 (w), 1108 (m), 1047 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.05-2.15 (2H, m, **H**$(5)_2$), 2.24 (3H, s, C**H**$_3$), 2.48-2.63 (4H, m, **H**$(4)_2$, **H**$(6)_2$), 6.60 (1H, t, *J* 4.5, **H**(3)); *m/z* (C.I., NH_3) 172 (MNH_4^+, 70), 155 (MH^+, 100%).

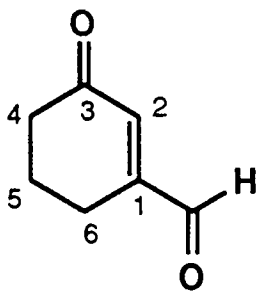
3-Bis(methylthio)methyl-2-cyclohexen-1-one 97[75]



The procedured described by Schlessinger *et al.*[75] was repeated using bis(methylthio)methane (1.5ml, 15.0mmol), THF (10ml), *n*-butyllithium (9.7ml, 1.6M in hexanes, 15.6mmol), 3-ethoxy-2-cyclohexen-1-one (2ml, 15.0mmol) and

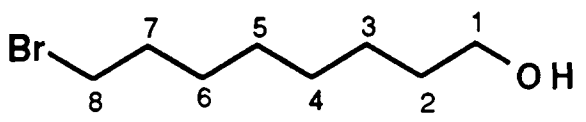
1M aq. HCl (5ml) to give the title compound **97** (2.26g, 75%) as a pungent-smelling oil. R_f (1:1, petrol:ether) 0.23 (uv active); $\nu_{max.}$ (thin film) 2918 (w), 1671 (s), 1619 (m), 1426 (m), 1346 (w), 1325 (w), 1256 (w), 1187 (w), 1134 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.05 (2H, t, *J* 6.5, **H**(5)$_2$), 2.10 (6H, s, 2xSC**H**$_3$), 2.43 (2H, t, *J* 6.5, **H**(6)$_2$), 2.52 (2H, br t, *J* 6.5, **H**(4)$_2$), 4.21 (1H, s, **H**C(SMe)$_2$), 5.98 (1H, br s, **H**(2)); *m/z* (C.I., NH_3) 203 (MH^+, 80), 174 (13), 157 (100), 155 (MH^+-HSMe, 40%).

3-Oxocyclohex-1-ene carboxaldehyde 94[75]



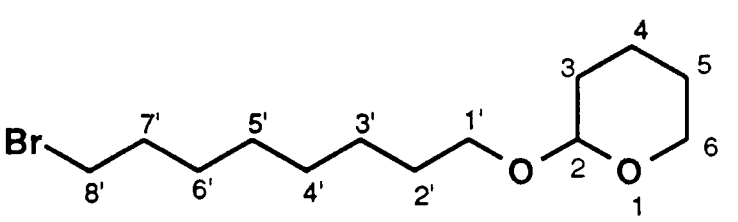
The procedured described by Schlessinger *et al.*[75] was repeated using bis(methylthio)cyclohexenone **97** (2.26g, 11.2mmol), HgO (4.9g, 23.0mmol), 4:1, THF:H_2O (20ml) and $BF_3.OEt_2$ (8.34ml, 68.0mmol) to give the aldehyde **94** (1.1g, 79%) as a colourless oil. R_f (1:1, petrol:ether) 0.18 (uv active); $\nu_{max.}$ (thin film) 2953 (m), 2873 (m), 2835 (m), 1695 (br s), 1430 (m), 1251 (m), 1237 (m), 1193 (m), 1131 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.00-2.20 (2H, q, *J* 6.5, **H**(5)$_2$), 2.39-2.70 (4H, m, **H**(4)$_2$, **H**(6)$_2$), 6.54 (1H, t, *J* 1.0, **H**(2)), 9.77 (1H, s, **H**CO); *m/z* (C.I., NH_3) 142 (MNH_4^+, 35), 125 (MH^+, 10), 124 (MNH_4^+-H_2O, 100), 96 (MNH_4^+-H_2O-CO, 70) 84 (22) 68 (70%).

8-Bromooctan-1-ol 105[81]



The procedure descibed by Kang*et al.*[81] was repeated using 1,8-octanediol **104** (46.1g, 315mmol), benzene (600ml) and 48% aq. HBr (40ml) to give the title bromo alcohol **105** (56.2g, 85%) as an oil. A small amount was purified by flash column chromatography (2:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.25; $\nu_{max.}$ (thin film) 3350 (br s), 2930 (s), 2856 (s), 1465 (m), 1245 (w), 1057 (m), 724 (w), 645 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.45 (8H, m), 1.45-1.60 (2H, m), 1.75-1.95 (2H, m), 2.12 (1H, br s, O**H**), 3.40 (2H, t, *J* 7.0, **H**$(8)_2$), 3.65 (2H, t, *J* 7.0, **H**$(1)_2$); *m/z* (C.I., NH_3) 228 ($M(^{81}Br)NH_4^+$, 30), 226 ($M(^{79}Br)NH_4^+$, 32) 148 (19), 137 (18), 111 (29), 100 (62), 82 (76), 69 (81), 58 (100%).

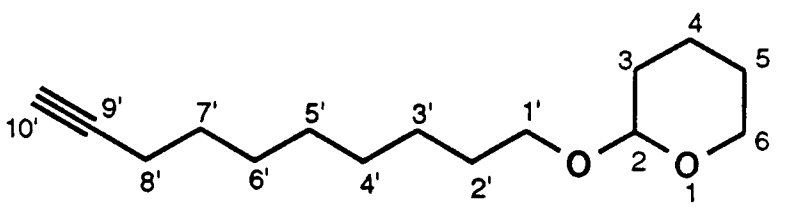
2-(8'-Bromooctyl)oxytetrahydropyran 106[82,83,84]



To a cooled (5°C) mixture of bromooctanol **105** (56g, 268mmol) and dihydropyran (26.9g, 294mmol) was added conc. HCl (4 drops). After 15mins anhydrous K_2CO_3 (8g) was added and the slurry stirred for a further 5mins. The reaction mixture was then diluted with water (100ml) and extracted with ether (250ml). The organic portion was washed with brine (100ml), dried ($MgSO_4$) and concentrated to give the desired THP-protected bromo alcohol **106** (74.9g, 95%) as a colourless oil. A small amount was retained and purified by flash column chromatography (5:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.70; $\nu_{max.}$ (thin film) 2934 (s), 2856 (m), 1455 (w), 1353 (w), 1201 (w), 1136 (m), 1121 (m), 1078 (m), 1034 (s), 987 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.45 (8H, m), 1.45-1.70 (7H, m), 1.70-1.95 (3H, m), 3.40 (2H, t, *J* 7.0, **H**$(8')_2$),

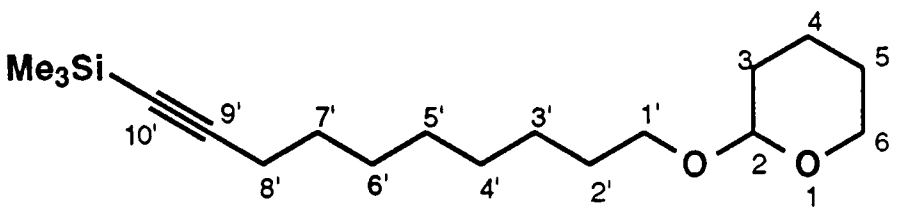
3.30-3.55 (2H, m, **H**(1')$_a$, **H**(6)$_a$), 3.65-3.92 (2H, m, **H**(1')$_b$, **H**(6)$_b$), 4.59 (1H, dd, *J* 4.0, 3.0, **H**(2)); *m/z* (C.I., NH_3) 312 (M(^{81}Br)NH_4^+, 55), 310 (M(^{79}Br)NH_4^+, 80), 295 (M(^{81}Br)H^+, 20), 293 (M(^{79}Br)H^+, 45), 102 (100), 85 (65%).

2-(Dec-9'-ynyl)oxytetrahydropyran 107 [83,84]



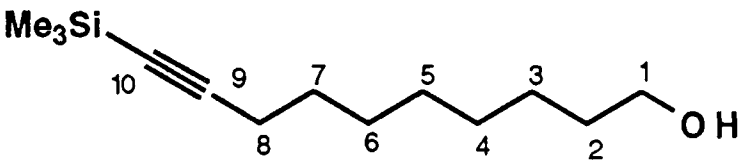
To a stirred suspension of lithium acetylide.EDA complex (13.3g, 90%, 130mmol) and NaI (0.75g, 5mmol) in THF (100ml) was added dropwise a solution of the THP-bromo-alcohol **106** (29.3g, 100mmol) in THF (80ml) followed by DMPU (61.5ml, 500mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (150ml) and extracted with ether (200ml). The organic portion was washed with water (100ml) and brine (100ml), dried ($MgSO_4$) and concentrated to give the protected alkynol **107** (22.6g, 95%) as a colourless oil. A small sample was purified by flash column chromatography (4:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.61; $\nu_{max.}$ (thin film) 2932 (s), 2857 (s), 2118 (w), 1455 (m), 1353 (m), 1261 (m), 1201 (m), 1163 (m), 1137 (s), 1121 (s), 1079 (s), 1034 (s), 989 (m), 870 (m), 724 (w), 629 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.26-1.40 (8H, m), 1.40-1.70 (7H, m), 1.70-1.90 (3H, m), 1.94 (1H, t, *J* 2.5, **H**(10')), 2.17 (2H, td, *J* 7.0, 2.5, **H**(8')$_2$), 3.22-3.55 (2H, m, **H**(1')$_a$, **H**(6)$_a$), 3.65-3.95 (2H, m, **H**(1')$_b$, **H**(6)$_b$), 4.59 (1H, dd, *J* 4.0, 3.0, **H**(2)); *m/z* (C.I., NH_3) 256 (MNH_4^+, 85), 239 (MH^+, 100), 221 (MH^+-H_2O, 11), 172 (MNH_4^+-DHP, 88), 169 (65), 137 (55), 121 (60), 118 (62%).

2-(10'-Trimethylsilyl-dec-9'-ynyl)oxytetrahydropyran 108



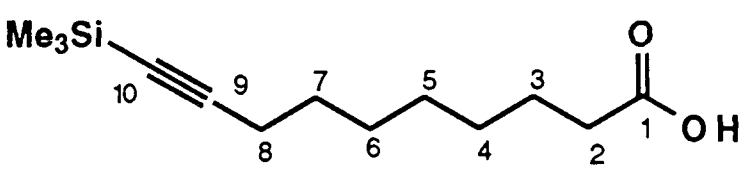
To a cooled (-78°C) solution of THP-alkynol **107** (22g, 92mmol) in THF (160ml) was added successively *n*-butyllithium (87ml, 1.6M in hexanes, 139mmol) and, after 30mins, chlorotrimethylsilane (23.5ml, 184mmol). After a further 30mins 1M aq. HCl (60ml) was added and the separated organic portion washed with water (50ml) and brine (60ml), dried ($MgSO_4$) and concentrated to give the silylated-protected alkyne **108** (27.5g, 96%) as an oil. A small fraction was purified by flash column chromatography (5:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.70; $\nu_{max.}$ (thin film) 2932 (s), 2857 (s), 2175 (m), 1455 (w), 1353 (w), 1249 (m), 1201 (m), 1185 (w), 1137 (m), 1121 (m), 1079 (m), 1034 (s), 989 (m), 843 (s), 760 (m), 641 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.15 (9H, s, $Si(C\mathbf{H}_3)_3$), 1.27-1.41 (8H, m), 1.49-1.63 (8H, m), 1.69-1.75 (1H, m), 1.81-1.86 (1H, m), 2.21 (2H, t, *J* 7.2, $\mathbf{H}(8')_2$), 3.39 (1H, dt, *J* 9.6, 6.8, $\mathbf{H}(1')_a$), 3.50 (1H, ddd, *J* 10.9, 5.3, 3.8, $\mathbf{H}(6)_a$), 3.74 (1H, dt, *J* 9.6, 6.8, $\mathbf{H}(1')_b$), 3.88 (1H, ddd, *J* 10.9, 7.5, 3.2, $\mathbf{H}(6)_b$), 4.58 (1H, dd, *J* 4.4, 2.8, **H**(2)); δ_C (125MHz, $CDCl_3$) 0.2 ($Si(\mathbf{C}H_3)_3$), 19.7, 19.8, 25.5, 26.2, 28.6, 28.7, 29.0, 29.3, 29.7, 30.8 ($10x\mathbf{C}H_2$), 62.3 (**C**(1')), 67.7 (**C**(6)), 84.3, 107.7 (**C**(9'), **C**(10')), 98.9 (**C**(2)); *m/z* (C.I., NH_3) 328 ($M(^{28}Si)NH_4^+$, 10), 311 ($M(^{28}Si)H^+$, 22), 221 (20), 102 ($(DHP)NH_4^+$, 100), 85 ($(DHP)H^+$, 88%); Microanalysis: Found C, 69.73; H, 11.49%; $C_{18}H_{34}O_2Si$ requires C, 69.62; H, 11.04%.

10-Trimethylsilyldec-9-yn-1-ol 109



A solution of the TMS-alkyne **108** (27g, 87mmol) and TsOH.H_2O (0.17g, 0.9mmol) in MeOH (150ml) was stirred at RT. After 15h the reaction mixture was diluted with 1M aq. HCl (100ml) and extracted with ether (2x100ml). The combined organic portions were washed with water (50ml) and brine (100ml), dried ($MgSO_4$) and concentrated to give the expected alcohol **109** (18.9g, 96%) as a colourless oil. A fraction was retained and purified by flash column chromatography (2:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.30; $\nu_{max.}$ (thin film) 3350 (br s), 2931 (s), 2857 (s), 2175 (s), 1465 (w), 1250 (m), 1056 (m), 1034 (s), 843 (m), 760 (m), 698 (w), 640 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.14 (9H, s, Si($\mathbf{C}H_3$)$_3$), 1.30-1.41 (8H, m), 1.48-1.59 (4H, m), 1.70 (1H, br s, O**H**), 2.21 (2H, t, *J* 7.2, **H**(8)$_2$), 3.64 (2H, t, *J* 6.7, **H**(1)$_2$); δ_C (125MHz, $CDCl_3$) 0.2 (Si($\mathbf{C}H_3$)$_3$), 19.8, 25.6, 28.6, 28.7, 29.0, 29.2, 32.7 (7x$\mathbf{C}H_2$), 63.0 (**C**(1)), 84.3, 107.7 (**C**(9), **C**(10)); *m/z* (C.I., NH_3) 244 (M(^{28}Si)NH_4^+, 25), 137 (15), 95 (25), 90 (100), 81 (31), 74 (30%); Microanalysis: Found C, 68.76; H, 11.81%; $C_{13}H_{26}OSi$ requires C, 68.96; H, 11.57%.

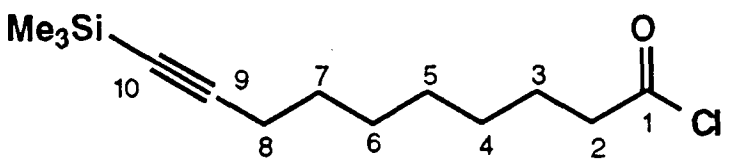
10-Trimethylsilyl-9-decynoic acid 110



To a cooled (0°C) solution of TMS-alkynol **109** (18.4g, 81mmol) in acetone (250ml) was added Jones' reagent (162ml, 2M aq. solution in H_2SO_4, 325mmol) dropwise over 30mins. After a further 30mins MeOH was added dropwise

until the solution remained green then the reaction mixture was diluted with water (100ml) and extracted with EtOAc (4x50ml) and ether (50ml). The organic portions were washed with water (100ml) and brine (100ml), dried ($MgSO_4$) and concentrated to give the acid **110** (19.4g, 90%) as a colourless oil. A small sample was purified by flash column chromatography for analysis. R_f (1:1, petrol:ether) 0.40; $\nu_{max.}$ (thin film) 3400-2800 (br), 2935 (s), 2859 (s), 2174 (m), 1713 (s), 1413 (m), 1286 (m), 1250 (m), 1079 (w), 939 (w), 844 (s), 761 (w), 639 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.15 (9H, s, $Si(C\mathbf{H}_3)_3$), 1.31-1.42 (6H, m), 1.49-1.54 (2H, m), 1.61-1.67 (2H, m), 2.21 (2H, t, *J* 7.1, $\mathbf{H}(8)_2$), 2.35 (2H, t, *J* 7.5, $\mathbf{H}(2)_2$), 8.10 (1H, br s, COO**H**); δ_C (125MHz, $CDCl_3$) 0.2 ($Si(\mathbf{C}H_3)_3$), 19.8, 24.6, 28.5, 28.5, 28.7, 28.9 ($6x\mathbf{C}H_2$), 34.0 (**C**(2)), 84.4, 107.6 (**C**(9), **C**(10)), 180.3 (**C**(1)); *m/z* (C.I., NH_3) 259 ($M(^{29}Si)NH_4^+$, 13), 258 ($M(^{28}Si)NH_4^+$, 70), 241 ($M(^{28}Si)H^+$, 25), 90 (100%); Microanalysis: Found C, 64.80; H, 10.41%; $C_{13}H_{24}O_2Si$ requires C, 64.95; H, 10.06%.

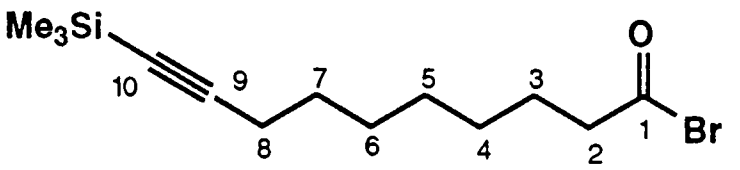
10-Trimethylsilyl-9-decynoyl chloride 103



To a cooled (5°C) solution of the acid **110** (1.03g, 4.29mmol) in benzene (20ml) was added oxalyl chloride (0.73ml, 8.60mmol) dropwise. The reaction mixture was warmed to RT then after 3h the solution was concentrated to afford the desired acid chloride **103** (1.06g, crude 95%) as an orange-red foul smelling oil. No further purification was possible. $\nu_{max.}$ (thin film) 2936 (s), 2859 (m), 2175 (m), 1801 (s), 1407 (w), 1249 (s), 1027 (w), 953 (w), 843 (s), 760 (m), 725 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.14 (9H, s, $Si(C\mathbf{H}_3)_3$), 1.20-1.40 (6H, m), 1.40-1.55 (2H, m), 1.55-1.75 (2H, m), 2.21 (2H, t, *J* 7.0, $\mathbf{H}(8)_2$), 2.88 (2H, t, *J* 7.5, $\mathbf{H}(2)_2$); δ_C (50.3MHz,

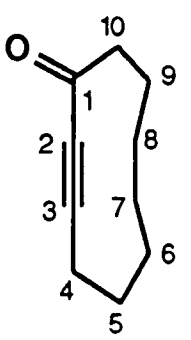
$CDCl_3$) 0.1 (Si(**C**H_3)$_3$), 19.7, 24.9, 28.2, 28.3, 28.5, 28.6 (6x**C**H_2), 47.0 (**C**(2)), 84.4, 107.3 (**C**(9), **C**(10)), 173.7 (**C**(1)); *m/z* (C.I., NH_3) 240 (M(^{28}Si)NH_4^+-HCl, 20), 90 (100%).

10-Trimethylsilyl-9-decynoyl bromide 111



To a cooled (5°C) solution of the acid **110** (200mg, 0.89mmol) in benzene (5ml) was added oxalyl bromide (0.19ml, 1.77mmol) dropwise. The reaction mixture was warmed to RT then after 3h the solution was concentrated to afford the desired acid bromide **111** (240mg, crude 90%) as a red foul smelling oil. No further purification was possible. $\nu_{max.}$ (thin film) 2935 (s), 2858 (m), 2174 (m), 1814 (m), 1412 (w), 1249 (s), 1039 (m), 844 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.14 (9H, s, Si(C**H**$_3$)$_3$), 1.25-1.40 (6H, m), 1.40-1.55 (2H, m), 1.55-1.75 (2H, m), 2.22 (2H, t, *J* 7.0, **H**(8)$_2$), 3.00 (2H, t, *J* 7.5, **H**(2)$_2$); δ_C (50.3MHz, $CDCl_3$) 0.0 (Si(**C**H_3)$_3$) 19.6, 25.2, 27.9, 28.0, 28.3, 28.6 (6x**C**H_2), 52.4 (**C**(2)), 84.5, 107.5 (**C**(9), **C**(10)), 170.0 (**C**(1)).

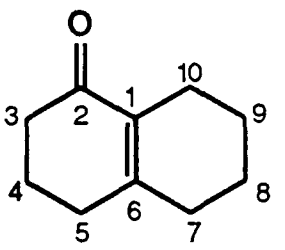
Cyclodec-2-yn-1-one 98



To a cooled (0°C) suspension of $AlCl_3$ (0.14g, 1.08mmol) in DCM (5ml) was added a solution of the acid chloride **103** (0.14g, 0.54mmol) in DCM (5ml).

After 45mins the temperature was warmed to RT, then after a further 30mins the reaction mixture was diluted with sat. aq. Na_2SO_4 (15ml) and extracted with ether (3x10ml). The combined organic portions were washed with water (10ml), brine (20ml), dried (Na_2SO_4) and concentrated to give the desired cycloalkynone **98** (66mg, 81%) as a sweet fruity smelling oil. A fraction was retained and purified by passing through a short column of neutral alumina (6:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether; alumina coated t.l.c. plate) 0.60 (uv active); $\nu_{max.}$ (thin film) 2931 (s), 2857 (m), 2210 (m), 1670 (s), 1603 (m), 1462 (m), 1327 (w), 1228 (m), 914 (w), 844 (w), 730 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.26-1.32 (2H, m), 1.56-1.59 (2H, m), 1.66-1.74 (4H, m), 1.74-1.81 (2H, m), 2.40 (2H, dd, *J* 6.5, 5.3, $\mathbf{H}(4)_2$), 2.44 (2H, t, *J* 5.8, $\mathbf{H}(10)_2$); δ_C (125MHz, $CDCl_3$) 20.5, 22.0, 24.2, 24.5, 25.3 (5x$\mathbf{C}H_2$), 27.4 (**C**(4)), 42.8 (**C**(10)), 82.5 (**C**(2)), 102.9 (**C**(3)), 190.2 (**C**(1)); *m/z* (C.I., NH_3) 168 (MNH_4^+, 35), 151 (MH^+, 100), 150 (MNH_4^+-H_2O, 40), 135 (30), 104 (30), 91 (25%); Accurate Mass: Found 168.1388, $C_{10}H_{18}NO$ (MNH_4^+) requires 168.138830.

Bicyclo[4.4.0]dec-1(6)-en-2-one 112[88]

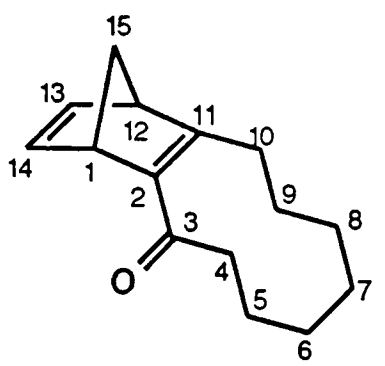


Cyclodec-2-yn-1-one **98** (70mg, 0.47mmol) was subjected to flash column chromatography (6:1, petrol:ether) to give the purified starting material **98** (12mg, 17%) as a minor component and the title enone **112** (50mg, 71%) as the major component. R_f (1:1, petrol:ether) 0.50 (uv active); $\nu_{max.}$ (thin film) 2932 (s), 2860 (m), 1713 (m), 1665 (s), 1633 (w), 1451 (w), 1387 (w), 1284 (w), 1193 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.40 (2H, m,), 1.50-1.60 (4H, m), 1.95 (2H, t, *J* 6.5,

H(10)$_2$), 2.10-2.30 (4H, m, **H**(5)$_2$, **H**(7)$_2$), 2.40 (2H, t, *J* 6.5, **H**(3)$_2$); *m/z* (C.I., NH_3) 151 (MH^+, 100), 150 (MNH_4^+-H_2O, 15), 135 (12), 122 (11%).

Tricyclo[10.2.1.0^{2,11}]pentadeca-2(11),13-dien-3-one 113

Method 1

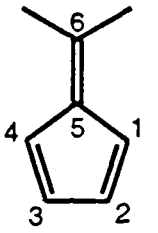


To a suspension of $AlCl_3$ (0.26g, 1.93mmol) in DCM (20ml) was added successively cyclopentadiene **75** (0.3ml, 4.5mmol) and after 15mins a solution of the acid chloride **103** (0.25g, 0.96mmol) in DCM (20ml). After 3h the reaction mixture was diluted with sat. aq. Na_2SO_4 (20ml), filtered and extracted with ether (2x20ml). The combined organic portions were washed with water (10ml), brine (25ml), dried ($MgSO_4$) and concentrated to give the title adduct **113** (100mg, 48%) as an oil. Purification by column chromatography (neutral alumina) afforded 30mg (15%) of pure cycloadduct. R_f (1:1, petrol:ether; alumina coated t.l.c. plate) 0.57 (uv active); $\nu_{max.}$ (thin film) 2932 (s), 2857 (m), 1709 (m), 1601 (w), 1460 (w), 1066 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.27-1.35 (4H, m), 1.35-1.42 (1H, m), 1.45-1.55 (1H, m), 1.53-1.58 (4H, m), 1.94-1.95 (2H, m, **H**(15)$_2$), 2.52 (2H, t, *J* 7.4, **H**(10)$_2$), 2.56-2.67 (2H, m, **H**(4)$_2$), 3.50 (1H, d, *J* 3.8, **H**(1)), 3.90 (1H, br s, **H**(12)), 6.70 (1H, t, *J* 3.8, **H**(14)), 6.86 (1H, dd, *J* 3.8, 1.9, **H**(13)); δ_C (125MHz, $CDCl_3$) 21.1, 21.9, 22.0, 23.2, 25.9 (5x**C**H_2), 27.6 (**C**(10)), 41.7 (**C**(4)), 51.9 (**C**(12)), 56.0 (**C**(1)), 70.7 (**C**(15)), 140.9, 141.6 (**C**(13), **C**(14)), 150.2 (**C**(2)), 161.8 (**C**(11)), 206.5 (**C**(3)); *m/z* (C.I., NH_3) 217 (MH^+, 100), 201 (12), 91 (11%); Accurate Mass: Found 217.1592, $C_{15}H_{21}O$ (MH^+) requires 217.159240.

Method 2

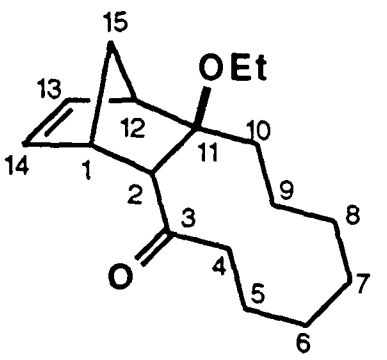
To a cooled (-78°C) suspension of $AlCl_3$ (1.0g, 7.57mmol) in DCM (50ml) was added successively cyclopentadiene **75** (1ml, 15mmol) and after 1h a solution of the acid chloride **103** (0.98g, 3.78mmol) in DCM (10ml). After 1h the temperature of the reaction mixture was warmed to RT and additional cyclopentadiene **75** (1ml, 15mmol) was added. After 15h anhydrous Na_2CO_3 (2g) was added and the mixture filtered. The solution was diluted with sat. aq. Na_2SO_4 (40ml) and extracted with ether (2x40ml). The organic portions were washed with water (30ml) and brine (40ml), dried ($MgSO_4$) and concentrated to give the desired cycloadduct **113** (650mg, 79% crude) as an oil. This proved to be identical to the compound described previously.

6, 6-Dimethylfulvene 114[89]



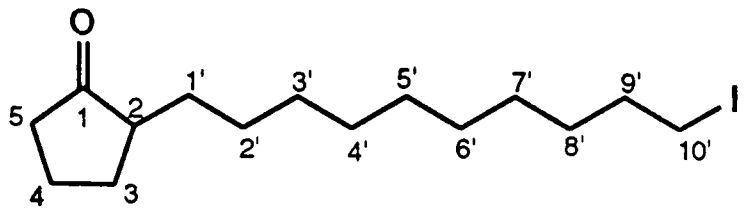
The procedure described by Stone and Little[89] was repeated using acetone (1ml, 13.6mmol), cyclopentadiene **75** (2.25ml, 34.0mmol), EtOH (4ml), pyrrolidine (1.70ml, 20.4mmol) and acetic acid (1.17ml, 20.4mmol) to give the title triene **114** (1.17g, 81%) as an orange-red unpleasant smelling oil. δ_H (200MHz, $CDCl_3$) 2.19 (6H, s, 2xCH_3), 6.45-6.55 (4H, m); *m/z* (C.I., NH_3) 107 (MH^+, 100%).

rel-(1*S*, 2*S*, 11*S*, 12*R*)-Tricyclo[10.2.1.0^{2,11}]-11-ethoxypentadec-13-en-3-one 116



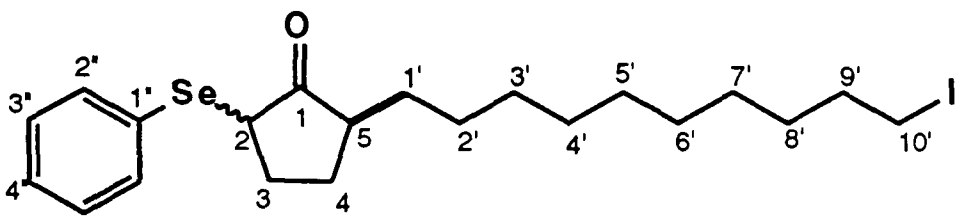
A stirred solution of the tricycle **113** (15mg, 0.069mmol) and NaOH (8mg, 0.2mmol) in ethanol (2ml) was stirred at RT. After 37h the reaction mixture was diluted with water (5ml) and extracted with ether (4x5ml). The combined organic fractions were washed with brine (5ml), dried ($MgSO_4$) and concentrated to give the title ethoxy-ketone **116** (12mg, crude 74%) as an oil. Purification by flash column chromatography (20:1, petrol:ether) gave a low recovery (3.5mg, 22%) of the purified product **115**. R_f (1:1, petrol:ether) 0.60; $\nu_{max.}$ (thin film) 2971 (s), 2935 (s), 2869 (m), 1707 (m), 1468 (w), 1364 (w), 1280 (w), 1188 (w), 1100 (w), 1062 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.0, C**H**$_3$), 1.00-1.47 (9H, m), 1.40 (1H, dt, *J* 8.2, 1.7), 1.70-1.79 (2H, m), 1.85 (1H, d, *J* 8.2), 1.98 (1H, dddd, *J* 16.0, 14.2, 5.0, 3.1), 2.44 (1H, ddd, *J* 17.7, 8.1, 1.8, **H**(4)$_a$), 2.79 (1H, ddd, *J* 17.7, 6.7, 1.4, **H**(4)$_b$), 2.81 (1H, br s, **H**(12)), 2.97 (1H, dd, *J* 3.4, 1.6, **H**(1)), 3.16 (1H, d, *J* 8.2, **H**(2)), 3.42 (1H, dq, *J* 8.9, 7.0, OC**H**$_a$H$_b$CH$_3$), 3.55 (1H, dq, *J* 8.9, 7.0, OCH$_a$**H**$_b$CH$_3$), 5.94 (1H, dd, *J* 5.6, 3.4, **H**(14)), 6.45 (1H, dd, *J* 5.6, 2.9, **H**(13)); δ_C (125MHz, $CDCl_3$) 16.0 (**C**H$_3$), 20.8, 22.6, 23.0, 27.0, 27.2, 29.4, 45.0 (7x**C**H$_2$), 46.5, 47.0 (**C**(1), **C**(12)), 50.8 (**C**(15)), 57.5 (**C**(2)), 66.4 (O**C**H$_2$CH$_3$), 91.6 (**C**(11)), 130.9 (**C**(14)), 138.9 (**C**(13)), 213.3 (**C**(3)); *m/z* (C.I., NH_3) 217 (MH^+-EtOH, 100), 151 (MH^+-EtOH-cyclopentadiene, 15), 117 (11) 105 (10) 91 (23) 66 (31%).

2-(10'-Iododecyl)cyclopentanone 165



To a cooled (-78°C) solution of diisopropylamine (0.95ml, 6.78mmol) in THF (30ml) was added dropwise *n*-butyllithium (5.9ml, 1.2M in hexanes, 7.07mmol) and after 15mins cyclopentanone **160** (0.5ml, 5.65mmol). After a further 25 mins DMPU (20ml, 167mmol) was added followed, after 10mins, by a solution of 1,10-diiododecane (11.1g, 28.25mmol) in THF (30ml) *via* a cannula to create a thick, viscous mixture. After 15h the solution was diluted with 1M aq. HCl (25ml) and extracted with ether (2x15ml). The combined organic layers were washed with brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (20:1, petrol:ether) to give the recovered diiododecane (10.2g, 25.9mmol) and the desired iodoketone **165** [0.5g, 25% (63% based on recovered diiododecane)] as a pale yellow oil. R_f (1:1, petrol:ether) 0.55 (uv active); $\nu_{max.}$ (thin film) 2926 (s), 2853 (s), 1738 (s), 1463 (m), 1156 (w), 1074 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.28-1.40 (15H, m), 1.52 (1H, dtd, *J* 12.5, 10.5, 6.5, **H**$(1')_a$), 1.72-1.83 (2H, m), 1.80-1.82 (2H, m), 1.96-2.05 (2H, m), 2.10 (1H, ddd, *J* 18.7, 10.3, 8.7, **H**$(5)_a$), 2.21 (1H, dtdd, *J* 9.6, 6.5, 6.5, 2.8, **H**(2)), 2.30 (1H, dddt, *J* 18.7, 8.4, 3.1, 1.5, **H**$(5)_b$), 3.19 (2H, t, *J* 7.2, **H**$(10')_2$); δ_C (125MHz, $CDCl_3$) 7.8 (**C**(10')), 21.2, 28.0, 28.9, 29.8, 29.8, 29.9, 30.0, 30.0, 30.1 (9x**C**H_2), 30.9, 34.0, 38.6 (**C**(3), **C**(4), **C**(5)), 49.6 (**C**(2)), 222.1 (**C**(1)); *m/z* (C.I., NH_3) 240 (MNH_4^+-HI, 55), 223 (MH^+-HI, 50), 205 (12), 84 (100%); Accurate Mass: Found 368.1456, $C_{15}H_{31}INO$ (MNH_4^+) requires 368.145564.

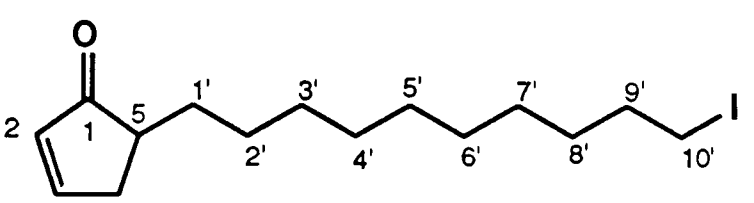
cis- and _trans_-5-(10'-Iododecyl)-2-(phenylseleno)cyclopentanone 161 and 162



To a cooled (-78°C) solution of diisopropylamine (0.19ml, 1.37mmol) in THF (5ml) was added dropwise *n*-butyllithium (1.1ml, 1.25M in hexanes, 1.37mmol), then after 30mins a solution of iododecyl-ketone **165** (0.38g, 1.09mmol) in THF (3ml), and, after a further 15mins, a solution of phenylselenyl bromide (228mg, 1.25mmol) in THF (3ml). After 3h the solution was diluted with water (20ml) and extracted with ether (2x20ml). The combined organic portions were washed with brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (20:1, petrol:ether) to give diphenyl diselenide (45mg, R_f (1:1, petrol:ether) 0.63), the *cis*-selenide **161** (0.16g, 29%) and *trans*-selenide **162** (0.23g, 42%) as yellow oils. *cis*-Isomer **161**, R_f (1:1, petrol:ether) 0.60 (uv active); $\nu_{max.}$ (thin film) 2926 (s), 2853 (m), 1728 (s), 1639 (w), 1579 (w), 1477 (w), 1460 (w), 1438 (w), 1163 (w), 740 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.27-1.35 (10H, m), 1.35-1.41 (4H, m), 1.69-1.76 (2H, m), 1.80-1.86 (2H, m), 2.00-2.12 (2H, m), 2.13-2.23 (3H, m), 3.20 (2H, t, *J* 7.0, **H**(10')$_2$), 3.87 (1H, d, *J* 6.7, **H**(2)), 7.26-7.35 (3H, m, 2x**H**(2"), **H**(4")), 7.59-7.62 (2H, m, 2x**H**(3")); δ_C (125MHz, $CDCl_3$) 7.3 (**C**(10')), 27.4, 27.7, 28.5, 28.7, 29.4, 29.4, 29.4, 29.4, 30.5 (9x**C**H_2), 31.6, 33.5 (**C**(3), **C**(4)), 46.4 (C(5)), 49.6 (**C**(2)), 128.0 (**C**(1")), 128.4 (**C**(4")), 129.1 (2x**C**(2")), 135.3 (2x**C**(3")), 215.2 (**C**(1)); *m/z* (A.P.C.I., +ve) 507 (M(^{80}Se)H^+, 55), 505 (M(^{78}Se)H^+, 32), 349 (MH^+-PhSeH, 28), 307 (40), 305 (41), 149 (100%); Microanalysis (on mixture): Found C, 49.80; H, 6.05%; $C_{21}H_{31}IOSe$ requires C, 49.91; H, 6.18%. *trans*-Isomer **162**, R_f (1:1, petrol:ether) 0.62 (uv active); $\nu_{max.}$ (thin film) 2925 (s), 2853 (m), 1732 (m), 1579 (w), 1476 (w), 1462 (w), 1438 (m), 1157 (w), 1022 (w)

cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.21-1.35 (10H, m), 1.36-1.44 (4H, m), 1.51 (1H, dddd, *J* 16.3, 13.0, 9.3, 6.9, **H**(1')$_a$), 1.71-1.79 (1H, m), 1.79-1.92 (3H, m), 1.95-2.10 (2H, m), 2.19 (1H, dddd, *J* 12.6, 8.6, 6.9, 4.0, **H**(4)$_a$), 2.37 (1H, dddd, *J* 14.9, 8.0, 6.9, 4.0, **H**(5)), 3.19 (2H, t, *J* 7.1, **H**(10')$_2$), 3.68 (1H, t, *J* 8.3, **H**(2)), 7.25-7.44 (3H, m, 2x**H**(2''), **H**(4'')), 7.60-7.68 (2H, m, 2x**H**(3'')); δ_C (125MHz, $CDCl_3$) 7.3 (**C**(10')), 27.3, 27.8, 28.5, 28.8, 29.3, 29.3, 29.4, 29.4, 30.5 (9x**C**H_2), 33.5, 33.5 (**C**(3), **C**(4)), 46.2 (**C**(5)), 47.4 (**C**(2)), 128.3 (**C**(1'')), 129.0 (**C**(4'')), 129.0 (2x**C**(2'')), 135.4 (2x**C**(3'')), 216.7 (**C**(1)); *m/z* (A.P.C.I., +ve) 507 (M(^{80}Se)H$^+$, 55), 505 (M(^{78}Se)H$^+$, 32), 349 (MH$^+$-PhSeH, 28), 307 (40), 305 (41), 149 (100%); Microanalysis (on mixture): Found C, 49.80; H, 6.05%; $C_{21}H_{31}IOSe$ requires C, 49.91; H, 6.18%.

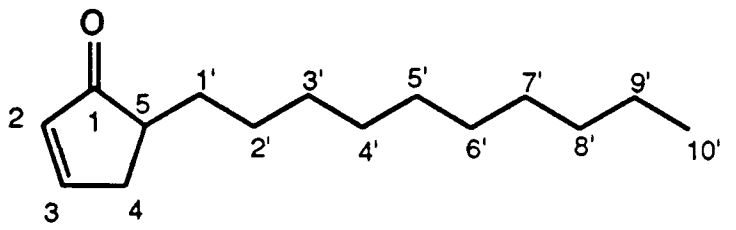
5-(10'-Iododecyl)-2-cyclopenten-1-one 159



To a cooled (0°C) solution of phenylselenoketones **161** and **162** (91mg, 0.15mmol) in DCM (5ml) was added H_2O_2 (42µl, 30% aq. solution, 0.37mmol). After 15h the reaction mixture was diluted with water (20ml) and extracted with ether (2x15ml). The combined organic portions were washed with water (10ml), brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (5:1, petrol:ether) to give the iodo-enone **159** (72mg, 86%) as an oil. R_f (1:1, petrol:ether) 0.35 (uv active); $\nu_{max.}$ (thin film) 2925 (s), 2853 (s), 1707 (s), 1589 (w), 1464 (m), 1369 (w), 1345 (w), 1172 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.27-1.41 (16H, m), 1.79-1.86 (2H, m), 2.30-2.33 (1H, m), 2.38 (1H, dddd, *J* 19.2, 2.4, 2.4, 2.4, **H**(4)$_a$), 2.87 (1H, ddt, *J* 19.2, 6.4, 2.4, **H**(4)$_b$), 3.20 (2H, t, *J* 7.0, **H**(10')$_2$), 6.18 (1H, dt, *J* 5.7, 2.4, **H**(2)), 7.68 (1H, dt, *J* 5.7, 2.4, **H**(3)); δ_C (125MHz,

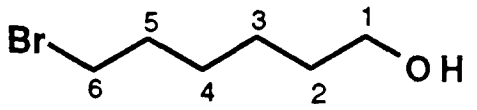
$CDCl_3$) 7.3 (**C**(10')), 27.2, 28.5, 29.4, 29.4, 29.5, 29.5, 30.5, 31.3, 33.5 (9x**C**H_2), 35.7 (**C**(4)), 44.9 (**C**(5)), 133.9 (**C**(2)), 163.4 (**C**(3)), 213.2 (**C**(1)); *m/z* (C.I., NH_3) 366 (MNH_4^+, 50), 349 (MH^+, 100), 238 (MNH_4^+-HI, 30), 221 (MH^+-HI, 20), 95 (21), 82 (43), 58 (20%); Accurate Mass: Found 366.1300, $C_{15}H_{29}INO$ (MNH_4^+) requires 366.129914.

5-(Decyl)-2-cyclopenten-1-one 166



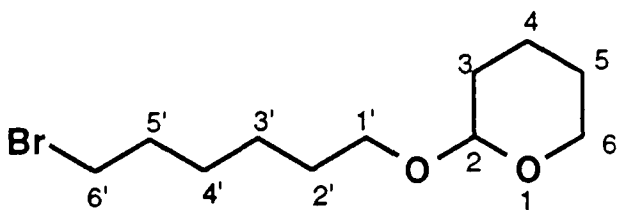
To a solution of iodo-enone **159** (27mg, 0.078mmol) and AIBN (1mg, 0.006mmol) in degassed benzene (25ml) heated at reflux was added a solution of tri-*n*-butyltin hydride (23µl, 0.085mmol) and AIBN (1mg, 0.006mmol) in degassed benzene (2ml) over a period of 3h using a syringe pump. After a further 3h the reaction mixture was concentrated and thiophenol (9.5mg, 0.0086mmol) added. Purification by flash column chromatography (100:1, petrol:ether) gave the directly reduced product **166** (8mg, 50%) as an oil. R_f (1:1, petrol:ether) 0.50 (uv active); $\nu_{max.}$ (thin film) 2925 (s), 2853 (s), 1709 (s), 1590 (w), 1466 (w), 1345 (w), 1170 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, **H**(10')$_3$), 1.26-1.40 (16H, m), 1.79-1.86 (2H,m), 2.29-2.33 (1H, m), 2.38 (1H, dddd, *J* 19.3, 2.4, 2.4, 2.4, **H**(4)$_a$), 2.89 (1H, ddt, *J* 19.3, 6.5, 2.4, **H**(4)$_b$), 6.19 (1H, dt, *J* 5.7, 2.4, **H**(2)), 7.67 (1H, dt, *J* 5.7, 2.4, **H**(3)); δ_C (125MHz, $CDCl_3$) 14.1 (**C**(10')), 22.7, 27.3, 29.3, 29.5, 29.6, 29.6, 29.6, 31.3, 31.9 (9x**C**H_2), 35.7 (**C**(4)), 44.9 (**C**(5)), 133.9 (**C**(2)), 163.4 (**C**(3)), 212.7 (**C**(1)); *m/z* (C.I., NH_3) 240 (MNH_4^+, 12), 223 (MH^+, 100), 95 (30), 82 (100%); Accurate Mass: Found 233.2062, $C_{15}H_{27}O$ (MH^+) requires 223.206190.

6-Bromohexan-1-ol 174[81]



The procedure described by Kang *et al.*[81] was repeated using 1,6-hexanediol **173** (5.09g, 43mmol), benzene (100ml) and 48% aq. HBr (5ml) to give the title bromo-alcohol **174** (6.79g, 87%) as an oil. A small amount was purified by flash column chromatography (2:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.24; $\nu_{max.}$ (thin film) 3339 (br s), 2935 (s), 2859 (m), 1462 (w), 1432 (w), 1260 (w), 1054 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.30-1.70 (6H, m), 1.80-1.95 (2H, m), 3.42 (2H, t, *J* 6.5, **H**$(6)_2$), 3.65 (2H, t, *J* 6.5, **H**$(1)_2$); *m/z* (C.I., NH_3) 200 ($M(^{81}Br)NH_4^+$, 20), 198 ($M(^{79}Br)NH_4^+$, 20), 100 (12), 83 (65), 81 (65), 67 (21), 58 (100%).

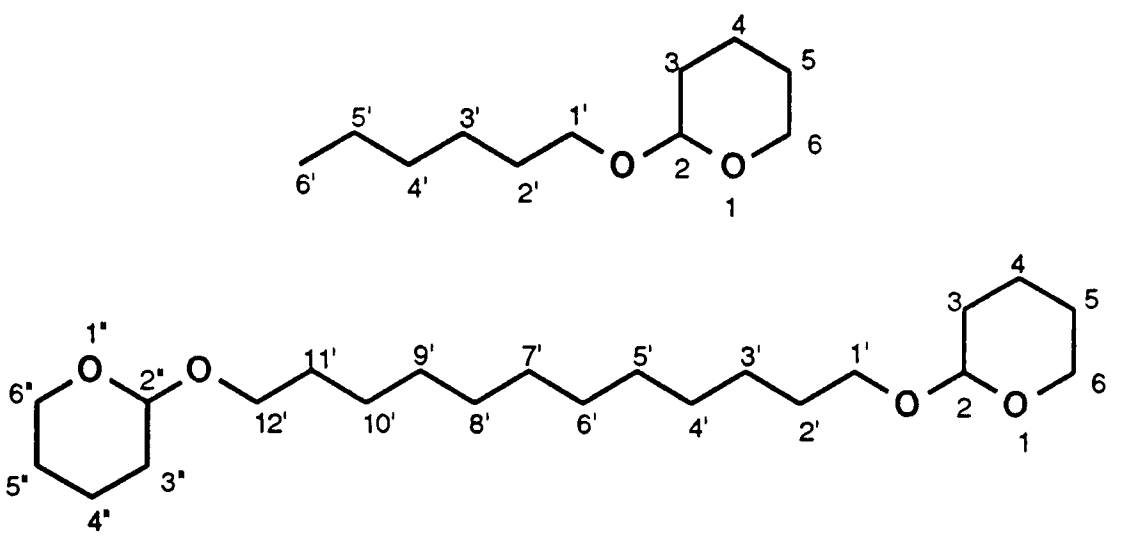
2-(6'-Bromohexyl)oxytetrahydropyran 172[135,136]



To a cooled (5°C) mixture of bromo-hexanol **174** (6.58g, 36.6mmol) and DHP (3.67g, 40.2mmol) was added conc. HCl (2 drops). After 15mins anhydrous K_2CO_3 (1.5g) was added and the slurry stirred for a further 5mins. The reaction mixture was then diluted with water (20ml) and extracted with ether (50ml). The organic portion was washed with brine (30ml), dried ($MgSO_4$) and concentrated to give the title compound **172** (9.5g, 98%) as a colourless oil. A small amount was retained and purified by flash column chromatography (5:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.70; $\nu_{max.}$ (thin film) 2939 (s), 2865 (m), 1441 (w), 1353 (w), 1201 (w), 1136 (m), 1120 (m), 1078 (m),

1034 (s), 870 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.35-1.77 (10H, m), 1.77-1.95 (4H, m), 3.42 (2H, t, *J* 6.5, $\mathbf{H}(6')_2$), 3.35-3.60 (2H, m, $\mathbf{H}(1')_a$, $\mathbf{H}(6)_a$), 3.75 (1H, dt, *J* 9.5, 7.0, $\mathbf{H}(1')_b$), 3.82-3.92 (1H, m, $\mathbf{H}(6)_b$), 4.58 (1H, dd, *J* 4.0, 3.0, **H**(2)); *m/z* (C.I., NH_3) 284 ($M(^{81}Br)NH_4^+$, 81), 282 ($M(^{79}Br)NH_4^+$, 87), 267 ($M(^{81}Br)H^+$, 48), 265 ($M(^{79}Br)H^+$, 100) 200 (33), 198 (32), 169 (91), 165 (88), 163 (93%).

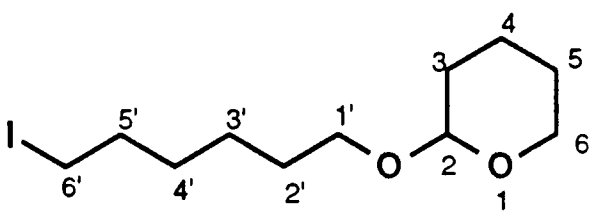
2-(Hexyl)oxytetrahydropyran 176[140] and 2-(12'-(tetrahydropyran-2-yloxy)dodecyl)oxytetrahydropyran 177



A suspension of the THP-bromohexanol **172** (10mg, 0.037mmol), Mg turnings (13mg, 0.53mmol) and I_2 (1 crystal) in THF (0.5ml) was heated to reflux in short bursts with a heat gun. The mixture was allowed to stir vigorously and continued to be heated until the I_2 had decolourised. To the grey suspension formed, after cooling to RT, was added dropwise a solution of the remainder of the starting material **172** (125mg, 0.47mmol) in THF (1ml) over a period of 20mins. After 3h the cooled (5°C) reaction mixture was diluted with water (5ml) and extracted with ether (2x15ml). The combined organic portions were washed with 1M aq. HCl (10ml), water (10ml) and brine (15ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (10:1, petrol:ether) to give the reduced monomer **176** (39mg, 41%) and the dimer **177** (42mg, 45%)

both as colourless oils. Reduced THP-bromide **176**: R_f (1:1, petrol:ether) 0.64; $\nu_{max.}$ (thin film) 2937 (s), 2871 (s), 1467 (w), 1353 (w), 1201 (w), 1127 (m), 1080 (m), 1034 (s), 988 (w), 870 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, **H**(6')$_3$), 1.26-1.39 (6H, m), 1.49-1.62 (6H, m), 1.69-1.74 (1H, m), 1.80-1.87 (1H, m), 3.39 (1H, dt, *J* 9.6, 6.7, **H**(1')$_a$), 3.50 (1H, ddd, *J* 10.9, 5.3, 3.8, **H**(6)$_a$), 3.73 (1H, dt, *J* 9.6, 7.3, **H**(1')$_b$), 3.88 (1H, ddd, *J* 10.9, 7.5, 3.2, **H**(6)$_b$), 4.58 (1H, dd, *J* 4.4, 2.8, **H**(2)); δ_C (125MHz, $CDCl_3$) 14.0 (**C**(6')), 19.7, 22.6, 25.5, 25.9, 29.7, 30.8, 31.7 (7x**C**H_2), 62.3 (**C**(1')), 67.7 (**C**(6)), 98.8 (**C**(2)); *m/z* (C.I., NH_3) 187 (MH^+, 10), 169 (15), 102 (100), 85 (90%). Dimer **177**: R_f (1:1, petrol:ether) 0.71; $\nu_{max.}$ (thin film) 2927 (s), 2854 (m), 1454 (w), 1441 (w), 1353 (w), 1201 (w), 1122 (m), 1078 (m), 1034 (m), 989 (w), 666 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.26-1.38 (16H, m), 1.51-1.62 (12H, m), 1.69-1.74 (2H, m), 1.80-1.87 (2H, m), 3.38 (2H, dt, *J* 9.6, 6.9, **H**(1')$_a$, **H**(12')$_a$), 3.48-3.53 (2H, m, **H**(6)$_a$, **H**(6")$_a$), 3.72 (2H, dt, *J* 9.6, 6.9, **H**(1')$_b$, **H**(12')$_b$), 3.87 (2H, ddd, *J* 11.0, 7.5, 3.3, **H**(6)$_b$, **H**(6")$_b$), 4.58 (2H, dd, *J* 4.4, 2.8, **H**(2), **H**(2")); δ_C (125MHz, $CDCl_3$) 19.7, 25.5, 26.2, 29.5, 29.6, 29.6, 29.8, 30.8 (8x(2x**C**H_2)), 62.3 (**C**(1'), **C**(12')), 67.7 (**C**(6), **C**(6")), 98.8 (**C**(2), **C**(2")); *m/z* (C.I., NH_3) 388 (MNH_4^+, 22), 220 (31), 102 (100), 85 (98%).

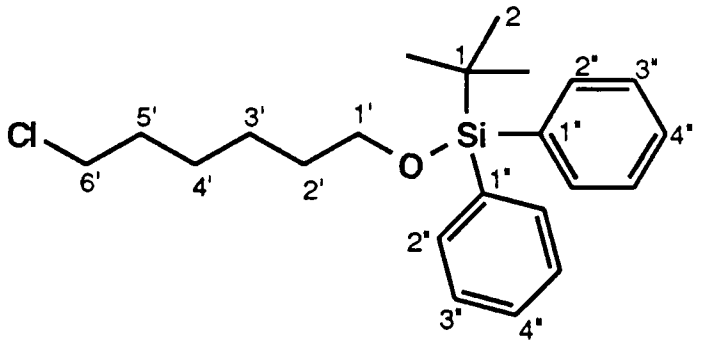
2-(6'-Iodohexyl)oxytetrahydropyran 178[141]



A solution of THP-bromohexanol **172** (1.45g, 5.51mmol) and NaI (2.06g, 13.8mmol) in acetone (20ml) was stirred at RT. After 15h the reaction mixture was diluted with water (20ml) and extracted with ether (30ml). The organic portion was washed with sat. aq. $Na_2S_2O_3$ (5ml), water (10ml) and brine (30ml),

dried ($MgSO_4$) and concentrated to give the title compound **178** (1.65g, 96%) as a colourless oil which did not need further purification. R_f (1:1, petrol:ether) 0.71 (uv active); $\nu_{max.}$ (thin film) 2937 (s), 2862 (m), 1453 (w), 1440 (w), 1352 (w), 1201 (m), 1169 (m), 1134 (s), 1078 (s), 1034 (s), 989 (w), 870 (w), 667 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.36-1.50 (4H, m), 1.50-1.63 (6H, m), 1.65-1.75 (1H, m), 1.79-1.86 (3H, m), 3.19 (2H, t, *J* 7.0, **H**(6')$_2$), 3.38 (1H, dt, *J* 9.6, 6.5, **H**(1')$_a$), 3.50 (1H, ddd, *J* 10.9, 6.4, 5.3, **H**(6)$_a$), 3.73 (1H, dt, *J* 9.6, 6.8, **H**(1')$_b$), 3.86 (1H, ddd, *J* 10.9, 7.4, 3.2, **H**(6)$_b$), 4.57 (1H, dd, *J* 4.1, 2.6, **H**(2)); δ_C (125MHz, $CDCl_3$) 7.0 (**C**(6')), 19.7, 25.2, 25.5, 29.5, 30.3, 30.7, 33.4 (7x**C**H_2), 62.3 (**C**(1')), 67.4 (**C**(6)), 98.9 (**C**(2)); *m/z* (C.I., NH_3) 330 (MNH_4^+, 100), 313 (MH^+, 12), 311 (30), 279 (18), 211 (45), 185 (MH^+-HI, 45), 169 (32), 118 (23%).

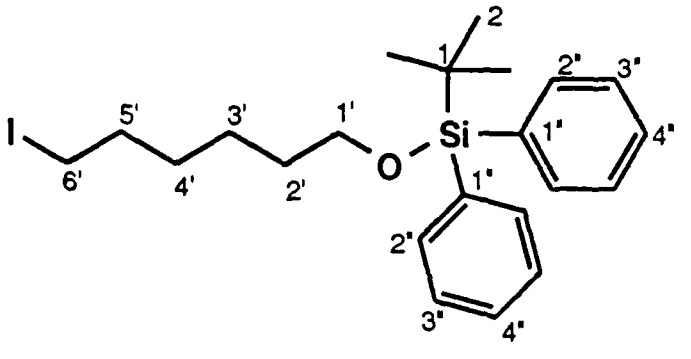
(6'-Chlorohexyl)oxy-1,1-dimethylethyl-diphenylsilane 180



To a solution of 6-bromohexan-1-ol **174** (1.0g, 5.55mmol) and imidazole (0.76g, 11.1mmol) in DMF (30ml) was added dropwise *t*-butylchlorodiphenylsilane (1.9ml, 7.22mmol). After 15h the reaction mixture was concentrated and purified by flash column chromatography (10:1, petrol:ether) to give the title compound **180** (2.0g, 96%) as an oil. R_f (1:1, petrol:ether) 0.61 (uv active); δ_H (200MHz, $CDCl_3$) 1.10 (9H, s, 3x**C**H_3), 1.30-1.50 (4H, m), 1.50-1.70 (2H, m), 1.70-1.90 (2H, m, **H**(5')$_2$), 3.55 (2H, t, *J* 6.5, **H**(6')$_2$), 3.75 (2H, t, *J* 6.0, **H**(1')$_2$), 7.39-7.50 (6H, m, 4x**H**(2''), 2x**H**(4'')), 7.70-7.80 (4H, m, 4x**H**(3'')); δ_C (50.3MHz, $CDCl_3$) 19.1 (**C**(1)), 25.0, 26.5 27.8, 32.7 (4x**C**H_2), 26.8 (3x**C**H_3), 45.1 (**C**(6')), 63.7 (**C**(1')), 127.8

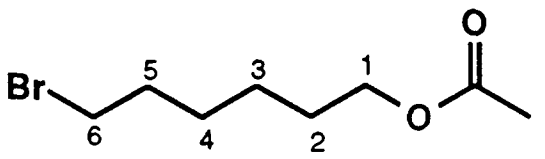
(4x**C**(2")), 129.8 (2x**C**(4")), 134.3 (2x**C**(1")), 135.8 (4x**C**(3")); *m/z* (C.I., NH_3) 377 ($M(^{37}Cl^{28}Si)H^+$, 15), 376 ($M(^{35}Cl^{29}Si)H^+$, 20), 375 ($M(^{35}Cl^{28}Si)H^+$, 60), 341 ($M(^{30}Si)H^+$-HCl, 15), 340 ($M(^{29}Si)H^+$-HCl, 11), 339 ($M(^{28}Si)H^+$-HCl, 40), 281 (22), 256 (24), 234 (23), 217 (25), 196 (30), 100 (32), 91 (35), 83 (MH^+-HCl-^{t}BuPh$_2$SiOH, 100%.)

(6'-Iodohexyl)oxy-1,1-dimethylethyl-diphenyl silane 179



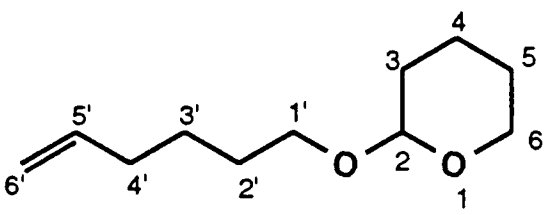
A solution of the protected chloro-alcohol **180** (0.36g, 0.96mmol) and NaI (0.39g, 2.60mmol) in acetone (20ml) was heated at reflux. After 15h the reaction mixture was diluted with water (20ml) and extracted with ether (2x15ml). The combined organic portions were washed with water (10ml) and brine (20ml), dried ($MgSO_4$) and concentrated to give the title compound **179** (0.39g, 87%) as an oil which did not need further purification. R_f (1:1, petrol:ether) 0.68 (uv active); $\nu_{max.}$ (thin film) 2999 (w), 2931 (s), 2857 (s), 1728 (m), 1472 (m), 1428 (m), 1390 (w), 1170 (w), 1112 (m), 824 (w), 740 (w), 702 (m), 613 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.07 (9H, s, 3x**C**H$_3$), 1.37-1.43 (4H, m), 1.55-1.61 (2H, m), 1.68-1.85 (2H, m), 3.18 (2H, t, *J* 7.3, **H**(6')$_2$), 3.68 (2H, t, *J* 6.4, **H**(1')$_2$), 7.38-7.46 (6H, m, 4x**H**(2"), 2x**H**(4")), 7.67-7.69 (4H, m, 4x**H**(3")); δ_C (125MHz, $CDCl_3$) 7.1 (**C**(6')), 19.2 (**C**(1)), 24.7, 30.2, 32.3, 33.5 (4x**C**H$_2$), 26.9 (3x**C**H$_3$), 63.7 (**C**(1')), 127.6 (4x**C**(2")), 129.5 (2x**C**(4")), 134.1 (2x**C**(1")), 135.6 (4x**C**(3")); *m/z* (C.I., NH_3) 341 ($M(^{30}Si)H^+$-HI, 32), 340 ($M(^{29}Si)H^+$-HI, 30), 339 ($M(^{28}Si)H^+$-HI, 100), 256 (40), 196 (25), 100 (21), 83 (16%).

6-Bromohexyl acetate 183[145]



A solution of bromo-hexanol **174** (1.0g, 5.56mmol) and imidazole (38mg, 0.56mmol) in acetic anhydride (10ml) was stirred at RT. After 15h the reaction mixture was concentrated and purified by flash column chromatography (2:1, petrol:ether) to give the title compound **183** (1.02g, 82%) as a colourless oil. R_f (1:1, petrol:ether) 0.3; $\nu_{max.}$ (thin film) 2938 (m), 2860 (w), 1738 (s), 1462 (w), 1366 (m), 1240 (s), 1046 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.36-1.42 (2H, m), 1.45-1.51 (2H, m), 1.62-1.68 (2H, m), 1.85-1.91 (2H, m), 2.05 (3H, s, C**H**$_3$), 3.41 (2H, t, *J* 6.8, **H**(6)$_2$), 4.07 (2H, t, *J* 6.7, **H**(1)$_2$); δ_C (125MHz, $CDCl_3$) 21.0 (**C**H$_3$), 25.1, 27.8, 28.4, 32.6 (4x**C**H$_2$), 33.6 (**C**(6)), 64.3 (**C**(1)), 171.2 (**C**=O); *m/z* (C.I., NH_3) 242 (M(^{81}Br)NH_4^+, 70), 240 (M(^{79}Br)NH_4^+, 100), 220 (40), 100 (10%).

2-(Hex-5'-enyl)oxytetrahydropyran 184[146]

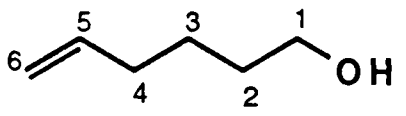


A solution of the THP-bromide **172** (2.0g, 7.60mmol) and KOBu^t (1.02g, 8.40mmol) in DMSO (40ml) was stirred at RT. After 15h the reaction mixture was diluted with water (40ml) and extracted with ether (2x30ml). The combined organic portions were washed with water (20ml) and brine (30ml), dried ($MgSO_4$) and concentrated to give the desired alkene **184** (1.34g, 96%) as a colourless oil. R_f (1:1, petrol:ether) 0.55; $\nu_{max.}$ (thin film) 2940 (s), 2869 (s), 1641 (w), 1456 (w), 1353 (w), 1201 (w), 1121 (m), 1078 (m), 1035 (s), 906 (w), 668 (w)

cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.35-1.90 (10H, m), 2.09 (2H, q, *J* 7.0, **H**(4')$_2$), 3.30-3.60 (2H, m, **H**(1')$_a$, **H**(6)$_a$), 3.65-3.95 (2H, m, **H**(1')$_b$, **H**(6)$_b$), 4.58 (1H, br s, **H**(2)), 4.93 (1H, d, *J* 10.0, **H**(6')$_a$), 5.00 (1H, d, *J* 15.5, **H**(6')$_b$), 5.81 (1H, dddd, *J* 15.5, 10.0, 7.0, 7.0, **H**(5')); δ_C (50.3MHz, $CDCl_3$) 19.5, 19.5, 25.4, 29.1, 30.6, 33.5 (6x**C**H_2), 62.2 (**C**(1')), 67.4 (**C**(6)), 98.9 (**C**(2)), 114.6 (**C**(6')), 139.0 (**C**(5')); *m/z* (C.I., NH_3) 102 (80), 85 (100%).

Hex-5-en-1-ol 185[147]

Method 1



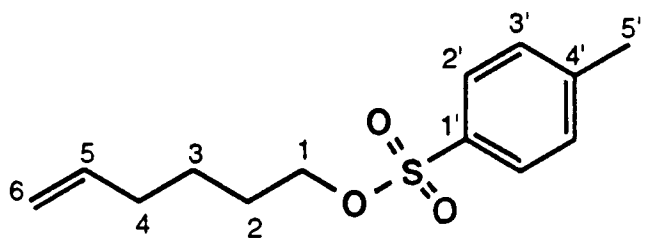
A solution of THP-alkene **184** (1.34g, 7.28mmol) and TsOH.H_2O (0.139g, 0.73mmol) in MeOH (30ml) was stirred at RT. After 15h the reaction mixture was diluted with water (30ml) and extracted with ether (2x20ml). The combined organic portions were washed with brine (20ml) and concentrated to give the pure alkenol **185** (0.40g, 55%) as a colourless oil. R_f (1:1, petrol:ether) 0.23; $\nu_{max.}$ (thin film) 3449 (br s), 2927 (m), 1654 (w), 1559 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.35-1.70 (4H, m), 1.95-2.20 (3H, m, **H**(4)$_2$, O**H**), 3.62 (2H, t, *J* 6.0, **H**(1)$_2$), 4.93 (1H, d, *J* 10.0, **H**(6)$_a$), 4.93 (1H, d, *J* 17.0, **H**(6)$_b$), 5.80 (1H, dddd, *J* 17.0, 10.0, 6.5, 6.5, **H**(5)); *m/z* (C.I., NH_3) 82 (80), 67 (61), 54 (100%).

Method 2

A solution of 6-bromohexanol **174** (4.4g, 16.7mmol) and KOBu^t (4.5g, 36.8mmol) in DMSO (40ml) was stirred at RT. After 20h the reaction mixture was diluted with water (40ml) and extracted with ether (2x30ml). The organic fractions were combined, washed with 1M aq. HCl (20ml), water (20ml) and brine (30ml), dried ($MgSO_4$) and concentrated to give starting material **174**

(1.0g, 5.5mmol) and the title alkenol **185**. The desired product was separated and purified by distillation on a Kugelrohr apparatus (RT, high vacuum) to give **185** [1.08g, 65% (95% based on recovered starting material)] as a colourless volatile oil. This compound proved to be identical to that described above.

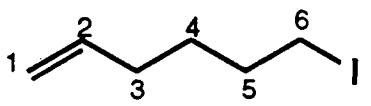
Hex-5-enyl *para*-toluenesulphonate 186[147]



To a stirred solution of hexenol **185** (0.38g, 3.8mmol) and TsCl (0.87g, 4.56mmol) in DCM (20ml) was added pyridine (0.45ml, 5.7mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (30ml) and extracted with ether (2x20ml). The combined organic portions were washed with 1M aq. HCl (20ml), sat. aq. $CuSO_4$ (10ml), water (10ml) and brine (20ml), dried ($MgSO_4$) and concentrated to give the tosylate **186** (0.77g, 85%) as a yellow oil. R_f (1:1, petrol:ether) 0.53; $\nu_{max.}$ (thin film) 2932 (s), 2863 (m), 1641 (w), 1598 (m), 1454 (w), 1359 (s), 1176 (s), 1098 (m), 1019 (m), 996 (m), 936 (m), 815 (m), 665 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.38-1.50 (2H, m), 1.60-1.72 (2H, m), 1.90-2.10 (2H, m, $\mathbf{H}(4)_2$), 2.45 (3H, s, $\mathbf{H}(5')_3$), 4.03 (2H, t, *J* 6.5, $\mathbf{H}(1)_2$), 4.90-4.92 (1H, m, $\mathbf{H}(6)_a$), 4.96-5.01 (1H, m, $\mathbf{H}(6)_b$), 5.75 (1H, dddd, *J* 17.0, 10.0, 6.5, 6.5, **H**(5)), 7.35 (2H, d, *J* 8.0, 2x**H**(3')), 7.79 (2H, d, *J* 8.0, 2x**H**(2')); *m/z* (C.I., NH_3) 272 (MNH_4^+, 100), 218 (10), 82 (20%).

6-Iodohex-1-ene 182[147]

Method 1

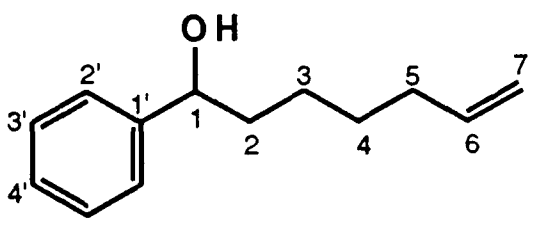


To a cooled (0°C) solution of hexenol **185** (0.87g, 8.70mmol), PPh_3 (2.51g, 9.57mmol) and imidazole (0.66g, 9.57mmol) in acetonitrile:ether, 3:1 (20ml) was added I_2 (2.43g, 9.57mmol). After 15h the reaction mixture was filtered and the residue washed with ether (2x10ml). The filtrate was concentrated, then triturated with ether (3x15ml). The combined extracts were washed with sat. aq. $Na_2S_2O_3$ (5ml), water (10ml) and brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (petrol) to give iodohexene **182** (1.02g, 56%) as a colourless oil. R_f (1:1, petrol:ether) 0.75 (uv active); $\nu_{max.}$ (thin film) 2933 (s), 2858 (m), 1642 (m), 1441 (w), 1218 (w), 1117 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.40-1.60 (2H, m), 1.80-1.95 (2H, m), 2.05-2.10 (2H, m, $\mathbf{H}(3)_2$), 3.21 (2H, t, *J* 7.0, $\mathbf{H}(6)_2$), 4.95-4.96 (1H, m, $\mathbf{H}(1)_a$), 4.98-5.10 (1H, m, $\mathbf{H}(1)_b$), 5.80 (1H, dddd, *J* 17.0, 10.0, 6.5, 6.5, **H**(2)); *m/z* (C.I., NH_3) 200 (10), 183 (45), 101 (MNH_4^+-HI, 70), 82 (100), 67 (26), 55 (38%).

Method 2

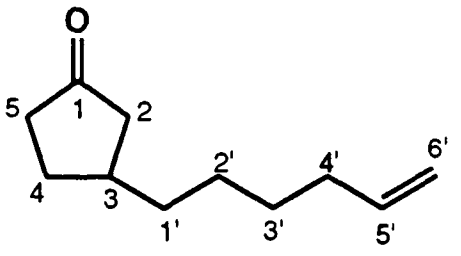
A solution of the tosylate **186** (0.7g, 2.76mmol) and NaI (0.82g, 5.51mmol) in acetone (10ml) was stirred at RT. After 15h the reaction mixture was diluted with water (20ml) and extracted with ether (2x20ml). The combined organic layers were washed with 1M aq. HCl (20ml) and brine (20ml), dried ($MgSO_4$) and concentrated to afford iodohexene **182** (0.52g, 91%) as a colourless oil. This compound proved to be identical to that described above.

1-Phenylhept-6-en-1-ol 187



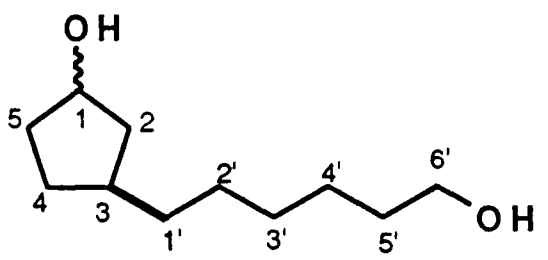
To a cooled (-78°C) solution of iodohexene **182** (50mg, 0.24mmol) in ether (5ml) was added dropwise *t*-butyllithium (300µl, 1.6M in pentane, 0.49mmol) and, after 5mins, benzaldehyde **175** (20µl, 0.2mmol). After 4h the reaction mixture was warmed to RT and diluted with 1M aq. HCl (10ml) and partitioned with ether (2x10ml). The combined organic fractions were washed with water (5ml) and brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (5:1, petrol:ether) to give the alcohol **187** (30mg, 85%) as a colourless oil. R_f (1:1, petrol:ether) 0.45 (uv active); $\nu_{max.}$ (thin film) 3366 (br s), 3064 (w), 3029 (w), 2976 (w), 2932 (s), 2858 (m), 1641 (w), 1494 (w), 1454 (m), 1119 (m), 1089 (m), 1028 (m), 995 (m), 911 (m), 761 (m), 701 (s), 667 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.30-1.40 (1H, m), 1.41-1.48 (3H, m), 1.69-1.76 (1H, m), 1.79-1.85 (1H, m), 2.03-2.08 (2H, m, **H**(5)$_2$), 4.68 (1H, dd, *J* 7.6, 5.8, **H**(1)), 4.94 (1H, dddd, *J* 10.2, 2.3, 1.7, 1.3, **H**(7)$_a$), 4.99 (1H, dddd, *J* 17.0, 1.7, 1.7, 1.7, **H**(7)$_b$), 5.80 (1H, dddd, *J* 17.0, 10.2, 6.7, 6.7, **H**(6)), 7.27-7.30 (1H, m, **H**(4')), 7.34-7.38 (4H, m, 2x**H**(3'), 2x**H**(2')); δ_C (125MHz, $CDCl_3$) 25.3, 28.8, 33.7, 38.9 (4x**C**H_2), 74.6 (**C**(1)), 114.4 (**C**(7)), 125.9 (2x**C**(2')), 127.5 (**C**(4')), 128.4 (2x**C**(3')), 138.8 (**C**(6)), 144.9 (**C**(1')); *m/z* (C.I., NH_3) 208 (MNH_4^+, 10), 191 (MH^+, 10), 190 (MNH_4^+-H_2O, 60), 173 (MH^+-H_2O, 100%).

3-(Hex-5'-enyl)cyclopentanone 188



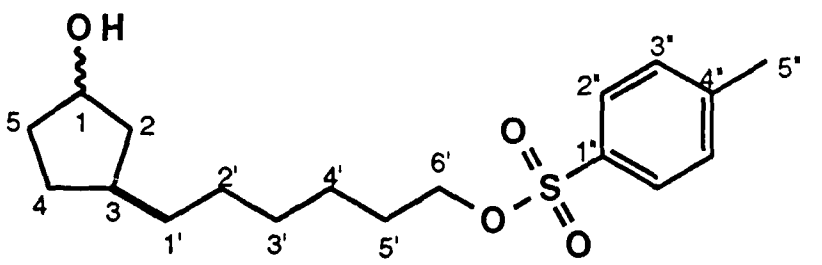
To a cooled (-78°C) solution of iodohexene **182** (0.88g, 4.20mmol) in ether (10ml) was added dropwise *t*-butyllithium (5.0ml, 1.7M in pentane, 8.60mmol) and, after a further 10mins, a solution of $CuBr.SMe_2$ (0.86g, 4.20mmol) in Me_2S (5ml) *via* a cannula. The mixture was warmed to -30°C and stirred vigorously. After 30mins the dark blue solution was re-cooled to -78°C, iodotrimethylsilane (0.89ml, 6.30mmol) was added followed, after 10mins, by cyclopentenone **170** (0.35ml, 4.20mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (20ml) and extracted with ether (3x15ml). The combined organic portions were washed with water (20ml) and brine (25ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (5:1, petrol:ether) to give the title ketone **188** (0.7g, 97%) as an oil. R_f (1:1, petrol:ether) 0.50; $\nu_{max.}$ (thin film) 3077 (w), 2927 (s), 2856 (m), 1743 (s), 1641 (w), 1462 (w), 1406 (w), 1159 (m), 994 (w), 910 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.33-1.54 (8H, m), 1.79 (1H, ddd, *J* 18.1, 9.6, 1.0, $\mathbf{H}(5)_a$), 2.04-2.09 (2H, m, $\mathbf{H}(4')_2$), 2.10-2.19 (2H, m, $\mathbf{H}(2)_a$, $\mathbf{H}(3)$), 2.29 (1H, dd, *J* 15.7, 7.8, $\mathbf{H}(2)_b$), 2.38 (1H, ddd, *J* 18.1, 7.3, 1.7, $\mathbf{H}(5)_b$), 4.95 (1H, dd, *J* 10.1, 1.5, $\mathbf{H}(6')_a$), 5.00 (1H, dddd, *J* 17.0, 1.7, 1.7, 1.5 $\mathbf{H}(6')_b$), 5.81 (1H, dddd, *J* 17.0, 10.1, 6.7, 6.7, $\mathbf{H}(5')$); δ_C (125MHz, $CDCl_3$) 27.3, 28.9, 29.5, 33.7, 35.5 (5x$\mathbf{C}H_2$), 37.2 ($\mathbf{C}(3)$), 38.5, 45.3 ($\mathbf{C}(2)$, $\mathbf{C}(5)$), 114.4 ($\mathbf{C}(6')$), 138.8 ($\mathbf{C}(5')$), 219.9 ($\mathbf{C}(1)$); *m/z* (C.I., NH_3) 184 (MNH_4^+, 100), 166 (MNH_4^+-H_2O, 10%); Accurate Mass: Found 184.1701, $C_{11}H_{22}NO$ (MNH_4^+) requires 184.170139.

cis- and _trans_-3-(6'-Hydroxyhexyl)cyclopentan-1-ol 189



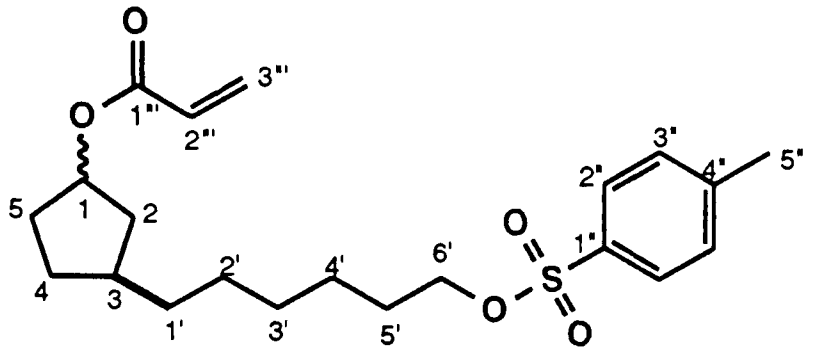
To a cooled (0°C) solution of hexenyl-cyclopentanone **188** (0.30g, 1.81mmol) in THF (5ml) was added dropwise BH_3.THF (5.4ml, 1.0M in THF, 5.40mmol) and, after 15h, EtOH (0.5ml), 1M aq. NaOH (1ml) and H_2O_2 (1ml, 60% aq. solution). After a further 5h the reaction mixture was diluted with 1M aq. HCl (5ml) and extracted with ether (2x15ml). The combined organic portions were washed with water (10ml) and brine (15ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (2:1, petrol:EtOAc) to give the title diols **189** (0.26g, 77%) as an inseparable mixture (ratio 1:1) of oils. R_f (EtOAc) 0.35; $\nu_{max.}$ (thin film) 3338 (br s), 2927 (s), 2855 (m), 1463 (w), 1343 (w), 1173 (w), 1058 (w) cm^{-1}; first isomer: δ_H (500MHz, $CDCl_3$) 1.09-1.17 (1H, m), 1.26-1.39 (8H, m), 1.52-1.64 (3H, m), 1.72-1.83 (3H, m), 1.92-1.99 (1H, m), 2.13-2.18 (1H, m), 3.64 (2H, t, *J* 6.6, **H**(6')$_2$), 4.29 (1H, q, *J* 6.2, **H**(1)); second isomer: as above except 4.34 (1H, sept, *J* 2.8, **H**(1)); δ_C (125MHz, $CDCl_3$) 25.7, 28.5, 29.6, 30.3/30.5, 32.8, 35.2/35.5, 36.1/36.7 (7x**C**H_2), 37.4/38.5 (**C**(3)), 42.5/42.7 (**C**H_2), 63.0 (**C**(6')), 73.1 (**C**(1)); *m/z* (C.I., NH_3) 204 (MNH_4^+, 100), 187 (MH^+, 10), 186 (MNH_4^+-H_2O, 12), 169 (MH^+-H_2O, 20), 151 (MH^+-2H_2O, 15%); Accurate Mass: Found 204.1964, $C_{11}H_{26}NO_2$ (MNH_4^+) requires 204.196354.

cis- and _trans_ 3-(6'-_para_Toluenesulphonyloxyhexyl)cyclopentan-1-ol 191



To a solution of the diol **189** (0.12g, 0.75mmol) in pyridine (2ml) was added TsCl (0.16g, 0.75mmol) in one portion. After 15h the reaction mixture was diluted with 1M aq. HCl (25ml) and extracted with ether (3x10ml). The combined organic portions were washed with sat. aq. $CuSO_4$ (10ml), water (10ml) and brine (15ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (3:1, petrol:ether) to give the undesired ditosylates **190** (27mg, 10%), which were not characterised, and the title tosylates **191** (0.15g, 60%) as an inseparable mixture (ratio 1:1) of oils. R_f (EtOAc) 0.55 (uv active); $\nu_{max.}$ (thin film) 3401 (br s), 2928 (s), 2857 (m), 1599 (m), 1463 (m), 1359 (s), 1307 (w), 1189 (s), 1177 (s), 1098 (m), 1020 (w), 957 (m), 816 (m), 665 (m) cm^{-1}; first isomer: δ_H (500MHz, $CDCl_3$) 1.07-1.14 (1H, m), 1.24-1.41 (6H, m), 1.42-1.60 (4H, m), 1.61-1.67 (2H, m), 1.70-1.82 (2H, m), 1.90-1.99 (1H, m), 2.07-2.17 (1H, m), 2.46 (3H, s, **H**(5")$_3$), 4.03 (2H, t, *J* 6.5, **H**(6')$_2$), 4.28-4.30 (1H, m, **H**(1)) 7.35 (2H, d, *J* 6.4, 2x**H**(3")), 7.81 (2H, d, *J* 6.4, 2x**H**(2")); second isomer: as above except 4.34-4.37 (1H, m, **H**(1)); δ_C (125MHz, $CDCl_3$) 21.6 (**C**(5")), 25.3, 28.3, 28.8, 29.1, 30.2/30.5, 35.2/35.4, 36.0/36.6 (7x**C**H_2), 37.3/38.4 (**C**(3)), 42.5/42.7 (**C**H_2), 70.7 (**C**(6')), 73.8 (**C**(1)), 127.9 (2x**C**(3")), 129.8 (2x**C**(2")), 133.3 (**C**(4")), 144.6 (**C**(1")); *m/z* (C.I., NH_3) 358 (MNH_4^+, 55), 341 (MH^+, 20), 340 (MNH_4^+-H_2O, 100), 151 (MH^+-H_2O-TsOH, 30%); Accurate Mass: Found 358.2052, $C_{18}H_{32}NO_4S$ (MNH_4^+) requires 358.205204.

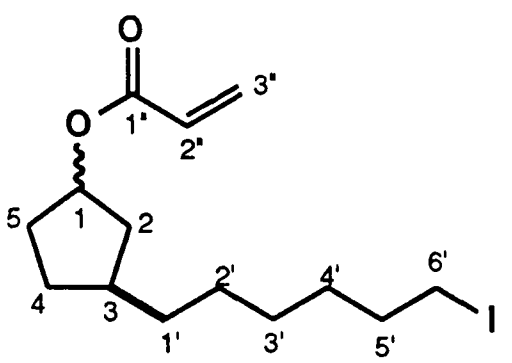
cis- and *trans* 3-(6'-*para*Toluenesulphonyloxyhexyl)cyclopentan-1-yl propenoate 192



To a cooled (10°C) solution of the tosylates **191** (0.12g, 0.35mmol) in benzene (6ml) was added successively triethylamine (52µl, 0.37mmol) and acryloyl chloride (29µl, 0.37mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (5ml) and extracted with ether (2x10ml). The combined organic portions were washed with water (10ml) and brine (15ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (6:1, petrol:ether) to give the title esters **192** (98mg, 71%) as an inseparable mixture (ratio 1:1) of oils. R_f (1:1, petrol:ether) 0.40 (uv active); $\nu_{max.}$ (thin film) 3036 (w), 2928 (s), 2857 (m), 1719 (s), 1636 (w), 1619 (w), 1599 (w), 1463 (w), 1407 (m), 1360 (s), 1296 (m), 1276 (m), 1190 (br s, sh), 1177 (s), 1098 (m), 1049 (m), 1006 (m), 962 (m), 919 (m), 814 (m), 779 (m), 665 (s) cm^{-1}; first isomer: δ_H (500MHz, $CDCl_3$) 1.19-1.35 (12H, m), 1.60-1.65 (2H, m), 1.74-1.82 (1H, m), 1.83-1.92 (1H, m), 1.99-2.10 (1H, m), 2.44 (3H, s, $\mathbf{H}(5'')_2$), 4.01 (2H, t, *J* 6.5, $\mathbf{H}(6')_2$), 5.20-5.24 (1H, m, $\mathbf{H}(1)$), 5.78 (1H, dd, *J* 10.4, 1.7, $\mathbf{H}(3''')_a$), 6.08 (1H, dd, *J* 17.3, 10.4, $\mathbf{H}(2''')$), 6.36 (1H, dd, *J* 17.3, 1.7, $\mathbf{H}(3''')_b$), 7.34 (2H, d, *J* 7.2, 2x$\mathbf{H}(3'')$), 7.78 (2H, d, *J* 7.2, 2x$\mathbf{H}(2'')$), second isomer: as above except 1.12 (1H, dq, *J* 12.7, 8.8, $\mathbf{H}(2)_a$), 1.39 (1H, ddd, *J* 14.1, 10.0), 5.14-5.19 (1H, m, $\mathbf{H}(1)$); δ_C (125MHz, $CDCl_3$) 21.6 ($\mathbf{C}(5'')$), 25.2, 28.2, 28.7, 29.0, 30.5/30.6, 32.1/32.3, 35.5/36.0 (7x$\mathbf{C}H_2$), 37.8/38.3 ($\mathbf{C}(3)$), 39.0/39.5 ($\mathbf{C}H_2$), 70.6 ($\mathbf{C}(6')$), 76.6/77.0 ($\mathbf{C}(1)$), 127.8 ($\mathbf{C}(2''')$), 129.0 (2xd, 2x$\mathbf{C}(2'')$), 129.7 (2xd, 2x$\mathbf{C}(3'')$), 130.1 ($\mathbf{C}(3''')$), 133.2 ($\mathbf{C}(4'')$), 144.6 ($\mathbf{C}(1'')$), 166.0 ($\mathbf{C}(1''')$); *m/z*

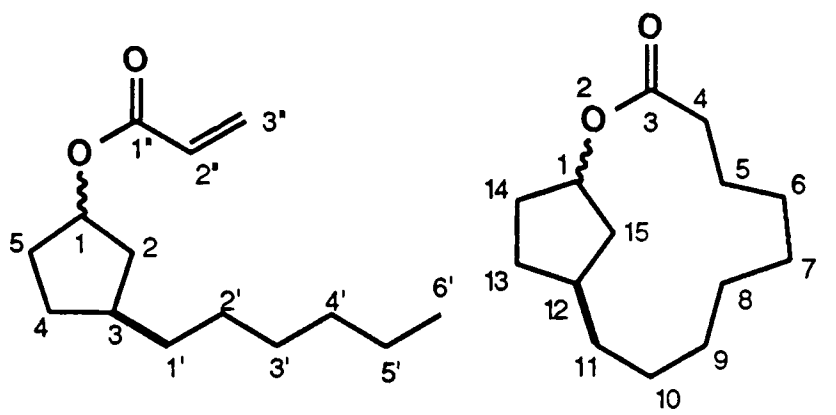
(A.P.C.I., +ve) 151 (100%); Accurate Mass: Found 412.2157, $C_{21}H_{34}NO_5S$ (MNH_4^+), requires 412.215700.

cis- and _trans_ 3-(6'-Iodohexyl)cyclopentan-1-yl propenoate 171



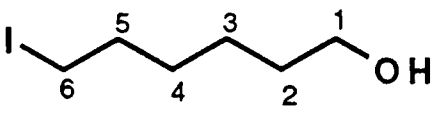
To a solution of the tosylates **192** (86mg, 0.22mmol) in acetone (4ml) was added NaI (65mg, 0.44mmol) and the mixture stirred at RT. After 15h the reaction mixture was diluted with water (5ml) and extracted with ether (2x10ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (12:1, petrol:ether) to give the title iodides **171** (68mg, 89%) as an inseparable mixture (ratio 1:1) of oils. R_f (1:1, petrol:ether) 0.55 (uv active); $\nu_{max.}$ (thin film) 2926 (s), 2853 (m), 1723 (s), 1639 (w), 1463 (w), 1406 (w), 1296 (w), 1274 (w), 1197 (m), 1119 (w), 1048 (w), 985 (w) cm^{-1}; first isomer: δ_H (500MHz, $CDCl_3$) 1.24-1.34 (7H, m), 1.35-1.46 (4H, m), 1.65-1.71 (1H, m), 1.71-1.96 (4H, m), 2.02-2.18 (1H, m), 3.19 (2H, t, *J* 7.0, **H**(6')$_2$), 5.16-5.20 (1H, m, **H**(1)), 5.80 (1H, dd, *J* 10.4, 1.5, **H**(3")$_a$), 6.09 (1H, dd, *J* 17.3, 10.4, **H**(2")), 6.36 (1H, dd, *J* 17.3, 1.5, **H**(3")$_b$), second isomer: as above except 1.15 (1H, dq, *J* 12.7, 8.8, **H**(2)$_a$), 5.22-5.25 (1H, m, **H**(1)); δ_C (125MHz, $CDCl_3$) 7.3 (**C**(6')), 28.3, 28.7, 30.4, 30.6, 32.1/32.4, 33.4, 35.6/36.1 (7xCH_2), 37.9/38.4 (**C**(3)), 39.1/39.6 (CH_2), 76.6/77.0 (**C**(1)), 129.0 (**C**(2")), 130.2 (**C**(3")), 166.1 (**C**(1")); *m/z* (C.I., NH_3) 368 (MNH_4^+, 100), 351 (MH^+, 10), 276 (70), 240 (MNH_4^+-HI, 15), 151 (55), 109 (19), 95 (45), 81 (30) 55 (82%); Accurate Mass: Found 368.1092, $C_{14}H_{27}INO_2$ (MNH_4^+) requires 368.109179.

rel-(1*S*, 3*S*)- and *rel*-(1*R*, 3*S*)-3-Hexylcyclopentan-1-yl propenoate 193 and *rel*-(1*R*, 12*S*)- and *rel*-(1*S*, 12*S*)-2-Oxabicyclo[10.2.1]pentadecan-3-one 168



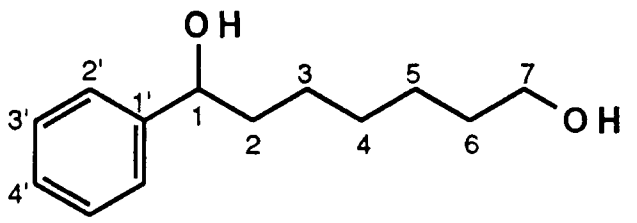
To a solution of the iodides **171** (62mg, 0.18mmol) and AIBN (2mg, 0.011mmol) in degassed benzene (75ml) at reflux was added, *via* syringe pump over 10h, a solution of $^{n}Bu_3SnH$ (70µl, ~75% pure by ^1H NMR, 0.19mmol) in degassed benzene (4ml). After a further 3h the reaction mixture was concentrated, thiophenol (25µl, 0.2mmol) was added and the mixture purified by flash column chromatography (200:1, petrol:ether) to give the title macrocycles **168** and the directly reduced products **193** (31mg, 78%) as a mixture (ratio **168**:**193**, 1:1.3) of oils. Reduced **193**: R_f (1:1, petrol:ether) 0.60 (uv active); $\nu_{max.}$ (thin film) 2926 (s), 2855 (s), 1729 (s), 1637 (w), 1463 (m), 1383 (m), 1296 (w), 1261 (m), 1188 (s), 1153 (s), 1049 (m), 987 (w), 812 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, **H**(6')$_3$), 1.11-1.51 (12H, m), 1.52-1.94 (4H, m), 2.00-2.10 (1H, m), 5.11-5.20 (1H, m, **H**(1)), 5.79 (1H, dd, *J* 10.4, 1.5, **H**(3")$_a$), 6.10 (1H, dd, *J* 17.3, 10.4, **H**(2")), 6.10 (1H, dd, *J* 17.3, 1.5, **H**(3")$_b$); Macrocycles **168**: R_f (1:1, petrol:ether) 0.52; δ_H (500MHz, $CDCl_3$) 1.11-1.51 (14H, m), 1.52-1.94 (6H, m), 2.00-2.10 (1H, m), 2.20-2.32 (2H, m, **H**(4)$_2$), 5.11-5.20 (1H, m, **H**(1)); *m/z* (C.I., NH_3) 242 (MNH_4^+, 100), 225 (MH^+, 50%); Accurate Mass: Found 242.2120, $C_{14}H_{28}NO_2$ (MNH_4^+) requires 242.212004.

6-Iodohexan-1-ol 199[156]



To a stirred solution of bromohexanol **174** (0.52g, 2.87mmol) in acetone (15ml) was added NaI (0.86g, 5.75mmol). After 15h the reaction mixture was diluted with water (20ml) and partitioned with ether (2x20ml). The combined organic extracts were washed with sat. aq. $Na_2S_2O_3$ (5ml), water (10ml) and brine (20ml), dried ($MgSO_4$) and concentrated to give the desired iodo-alcohol **199** (0.61g, 93%) as an oil that needed no further purification. R_f (ether) 0.47 (uv active); $\nu_{max.}$ (thin film) 3350 (br s), 2931 (s), 2857 (m), 1461 (w), 1427 (w), 1201 (w), 1167 (w), 1073 (m), 1056 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.39-1.55 (4H, m), 1.56-1.63 (2H, m), 1.82-1.89 (2H, m), 3.21 (2H, t, *J* 7.0, **H**(6)$_2$), 3.66 (2H, t, *J* 6.5, **H**(1)$_2$); *m/z* (C.I., NH_3) 246 (MNH_4^+, 100), 211 (MH^+-H_2O, 12), 118 (MNH_4^+-HI, 25), 100 (MNH_4^+-HI-H_2O, 42), 83 (MH^+-HI-H_2O, 50), 71 (31), 58 (74%).

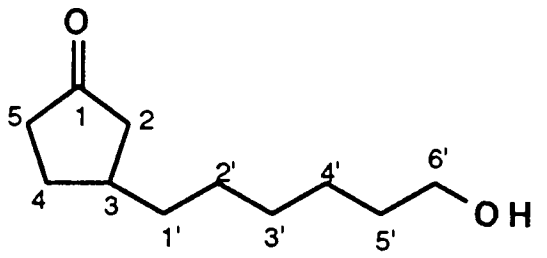
1-Phenylheptan-1,7-diol 200



To a cooled (-78°C) solution of iodohexanol **199** (100mg, 0.44mmol) in ether (3ml) was added dropwise *n*-butyllithium (0.27ml, 1.6M in hexanes, 0.44mmol), and, after 15mins, *t*-butyllithium (0.52ml, 1.7M in pentane, 0.88mmol) then, after a further 15mins, benzaldehyde **175** (40μl, 0.40mmol). After 3h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x10ml). The combined organic portions were washed with water (5ml) and

brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (2:1, petrol:ether) to give the diol **200** (30mg, 53%) as a colourless oil. R_f (EtOAc) 0.50 (uv active); $\nu_{max.}$ (thin film) 3350 (br s), 3063 (w), 3029 (w), 2932 (s), 2858 (m), 1494 (w), 1455 (m), 1203 (w), 1055 (m), 913 (w), 762 (m), 701 (s), 666 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.27-1.40 (5H, m), 1.40-1.46 (1H, m), 1.50-1.56 (2H, m), 1.67-1.74 (1H, m), 1.76-1.84 (1H, m), 3.59 (2H, t, *J* 6.6, **H**(7)$_2$), 4.65 (1H, dd, *J* 7.5, 5.8, **H**(1)), 7.25-7.28 (1H, m, **H**(4')), 7.29-7.36 (4H, m, 2x**H**(3'), 2x**H**(2')); δ_C (125MHz, $CDCl_3$) 25.6, 25.7, 29.2, 32.6, 38.9 (5x**C**H_2), 62.8 (**C**7)), 74.5 (**C**(1)), 125.8 (2x**C**(2')), 127.4 (**C**(4')), 128.4 (2x**C**(3')), 144.9 (**C**(1')); *m/z* (C.I., NH_3) 226 (MNH_4^+, 8), 209 (MH^+, 11), 208 (MNH_4^+-H_2O, 100), 191 (MH^+-H_2O, 40), 190 (MNH_4^+-$2H_2O$, 50), 173 (48), 131 (22), 117 (49), 105 (68), 104 (75), 91 (79), 79 (38); Accurate Mass: Found 208.1700, $C_{13}H_{22}NO$ (MNH_4^+-H_2O) requires 208.170139.

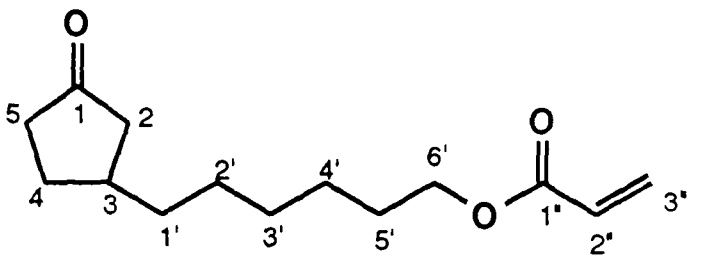
3-(6'-Hydroxyhexyl)cyclopentanone 201



To a cooled (-78°C) suspension of iodo-hexanol **199** (1.0g, 4.39mmol) in ether (10ml) was added dropwise *n*-butyllithium (2.7ml, 1.6M in hexanes, 4.40mmol) and, after 15mins, *t*-butyllithium (5.6ml, 1.6M in pentane, 8.99mmol) then, after a further 15mins, a solution of $CuBr.SMe_2$ (0.90g, 4.40mmol) in Me_2S (5ml). The mixture was warmed to -20°C and stirred vigorously. After 20mins the dark blue solution was cooled to -78°C and iodotrimethylsilane (0.93ml, 6.60mmol) added, followed, after 10mins, by cyclopentenone **170** (0.36ml, 4.40mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (20ml)

and extracted with ether (3x15ml). The combined organic portions were washed with water (20ml) and brine (25ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (2:1, petrol:ether) to give recovered iodo-hexanol (0.4g), 1,12-dodecanediol (0.2g) and the title ketone **201** [0.12g, 40% (based on recovered starting material)] as an oil. R_f (EtOAc) 0.44; $\nu_{max.}$ (thin film) 3427 (br s), 2927 (s), 2856 (m), 1739 (s), 1462 (w), 1404 (w), 1241 (w), 1161 (m), 1057 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.26-1.50 (9H, m), 1.50-1.57 (2H, m), 1.57-1.74 (1H, m), 1.77 (1H, ddd, *J* 18.1, 9.8, 1.0, **H**$(2)_a$), 2.08-2.16 (2H, m, **H**(3), **H**$(5)_a$), 2.25-2.30 (1H, m, **H**$(5)_b$), 2.36 (1H, ddd, *J* 18.1, 7.4, 1.6,**H**$(2)_b$), 3.62 (2H, t, *J* 6.6, **H**$(6')_2$); δ_C (125MHz, $CDCl_3$) 25.6, 27.7, 29.4, 29.4, 32.6, 35.5 (6x**C**H_2), 37.1 (**C**(3)), 38.4, 45.2 (**C**(2), **C**(5)), 62.8 (**C**(6')), 219.9 (**C**(1)); *m/z* (C.I., NH_3) 202 (MNH_4^+, 80), 186 (10), 185 (MH^+, 100), 149 (15), 83 (65%); Accurate Mass: Found 202.1807, $C_{11}H_{24}NO_2$ (MNH_4^+) requires 202.180704.

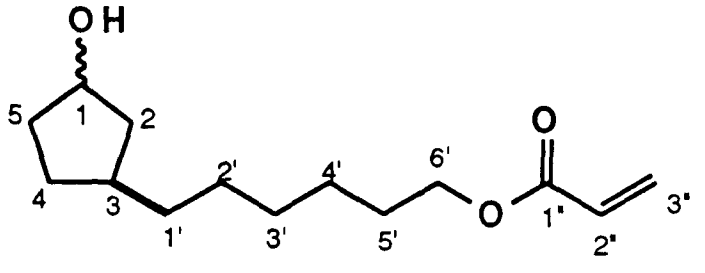
3-(6'-Propenoyloxyhexyl)cyclopentanone 202



To a cooled (0°C) solution of the alcohol **201** (40mg, 0.22mmol) in DCM (1ml) was added successively triethylamine (46µl, 0.33mmol) and acryloyl chloride (26µl, 0.33mmol). After 7h the reaction mixture was diluted with 1M aq. HCl (3ml) and extracted with ether (2x5ml). The combined organic portions were washed with water (5ml) and brine (5ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the title acrylate **202** (42mg, 82%) as an oil. R_f (ether) 0.57 (uv active); $\nu_{max.}$ (thin film) 2928 (s), 2857 (m), 1741 (s), 1724 (s), 1637 (w), 1408 (m), 1274 (m), 1194 (m) cm^{-1};

δ_H (500MHz, $CDCl_3$) 1.33-1.51 (9H, m), 1.64-1.70 (2H, m), 1.78 (1H, ddd, *J* 18.8, 9.7, 1.2, **H**(2)$_a$), 2.09-2.17 (3H, m), 2.25-2.30 (1H, m), 2.36 (1H, dd, *J* 18.8, 7.4, **H**(2)$_b$), 4.15 (2H, t, *J* 6.7, **H**(6')$_2$), 5.80 (1H, dd, *J* 10.4, 1.5, **H**(3")$_a$), 6.12 (1H, dd, *J* 17.4, 10.4, **H**(2")), 6.38 (1H, dd, *J* 17.4, 1.5, **H**(3")$_b$); δ_C (125MHz, $CDCl_3$) 25.8, 27.7, 28.5, 29.2, 29.5, 35.5 (6x**C**H_2), 37.1 (**C**(3)), 38.4, 45.2 (**C**(2), **C**(5)), 64.5 (**C**(6')), 128.6 (**C**(2")), 130.4 (**C**(3")), 166.2 (**C**(1")), 219.8 (**C**(1)); *m/z* (C.I., NH_3) 256 (MNH_4^+, 95), 239 (MH^+, 100), 109 (12), 83 (23), 55 (38%); Accurate Mass: Found 256.1913, $C_{14}H_{26}NO_3$ (MNH_4^+) requires 256.191269.

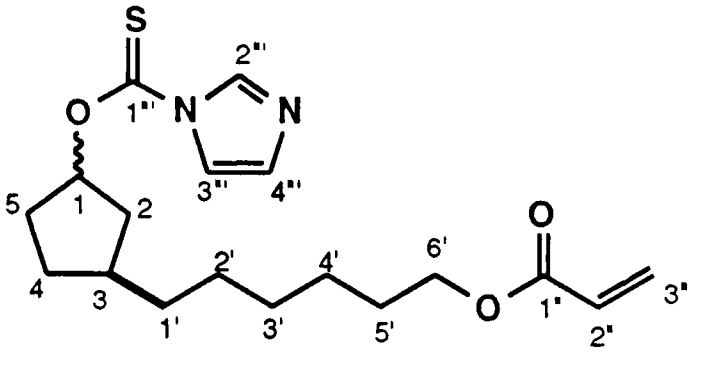
***cis* and *trans* 3-(6'-Propenoyloxyhexyl)cyclopentan-1-ol 203**



To a solution of the ketone **202** (30mg, 0.13mmol) in EtOH (1ml) was added $NaBH_4$ (7mg, 0.19mmol). After 4h the reaction mixture was diluted with water (3ml) and extracted with ether (2x5ml). The combined organic portions were washed with water (5ml) and brine (5ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (2:1, petrol:ether) to give the title alcohols **203** (28mg, 92%) as an inseparable mixture (ratio 3:2) of oils. R_f (1:1, petrol:ether) 0.21 (uv active); $\nu_{max.}$ (thin film) 3405 (br s), 2928 (s), 2856 (m), 1726 (s), 1637 (w), 1463 (w), 1409 (m), 1296 (w), 1274 (w), 1194 (s), 1062 (m), 986 (m), 812 (w) cm^{-1}; major isomer: δ_H (500MHz, $CDCl_3$) 1.14-1.20 (1H, m), 1.35-1.44 (6H, m), 1.60-1.67 (2H, m), 1.68-1.75 (2H, m), 1.76-1.87 (3H, m), 1.96-2.03 (1H, m), 2.13-2.22 (1H, m), 4.19 (2H, t, *J* 6.7, **H**(6')$_2$), 4.31-4.35 (1H, m, **H**(1)), 5.86 (1H, dd, *J* 10.5, 1.1, **H**(3")$_a$), 6.17 (1H, dd, *J* 17.3, 10.5, **H**(2")), 6.44 (1H, dd, *J* 17.3, 1.1, **H**(3")$_b$); minor isomer: as above except 4.39 (1H, dddd, *J* 5.6, 5.6, 2.8, 2.8, **H**(1));

δ_C (125MHz, $CDCl_3$) 25.9, 28.4, 28.6, 29.4, 30.2/30.5, 35.2/35.4 (6x**C**H_2), 37.3/38.4 (**C**(3)), 36.1/36.7, 42.4/42.7 (**C**(2), **C**(5)), 64.7 (**C**(6')), 73.8 (**C**(1)), 128.6 (**C**(2")), 130.4 (**C**(3")), 166.3 (**C**(1")); *m/z* (A.P.C.I., +ve) 223 (MH^+-H_2O, 13), 151 (MH^+-H_2O-H_2C=$CHCO_2H$, 100), 124 (39), 122 (88), 109 (40%); Accurate Mass: Found 223.1698, $C_{14}H_{23}O_2$ (MH^+-H_2O) requires 223.169805.

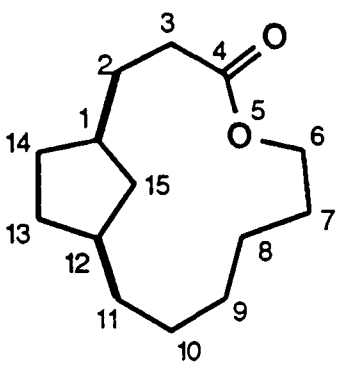
***cis*- and *trans*- 3-(6'-Propenoyloxyhexyl)-1-(*N*-imidazolyl-thiocarbonyl)oxy-cyclopentane 195**



To a solution of the alcohols **203** (20mg, 0.083mmol) in DCM (1ml) was added thiocarbonyldiimidazole (16mg, 0.09mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (1ml) and extracted with ether (2x5ml). The combined organic portions were washed with water (5ml) and brine (5ml), dried ($MgSO_4$) and concentrated to give the title compounds **195** (27mg, 93%) as an inseparable mixture (ratio 3:2) of oils. R_f (1:1, petrol:ether) 0.20 (uv active); $\nu_{max.}$ (thin film) 2927 (s), 2855 (m), 1724 (s), 1636 (w), 1620 (w), 1532 (w), 1466 (m), 1408 (m), 1386 (s), 1336 (m), 1284 (s), 1234 (s), 1192 (s), 1096 (m), 1061 (m), 977 (m), 811 (w), 745 (w), 658 (w) cm^{-1}; major isomer: δ_H (500MHz, $CDCl_3$) 1.14-1.46 (6H, m), 1.47-1.60 (2H, m), 1.61-1.69 (2H, m), 1.74-1.79 (1H, m), 1.87-1.96 (2H, m), 1.98-2.03 (2H, m), 2.07-2.17 (1H, m), 2.24-2.25 (1H, m), 4.15 (2H, t, *J* 6.8, **H**(6')$_2$), 5.76 (1H, ddd, *J* 9.8, 6.5, 4.2, **H**(1)), 5.81 (1H, d, *J* 10.4, **H**(3")$_a$), 6.12 (1H, dd, *J* 17.3, 10.4, **H**(2")), 6.39 (1H, dd, *J* 17.3, 1.4, **H**(3")$_b$), 7.03, 7.62 (2x1H, 2xbr s, **H**(3"'), **H**(4"')), 8.33 (1H, s, **H**(2"')); minor isomer: as above except 2.39-

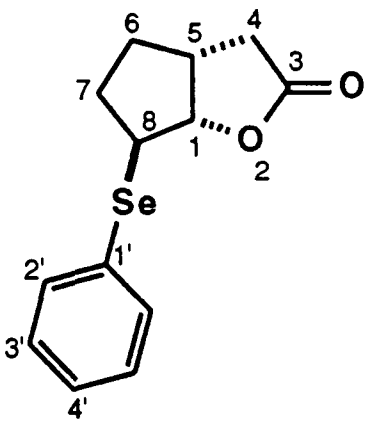
2.45 (1H, m), 5.80-5.83 (1H, m, **H**(1)); δ_C (125MHz, $CDCl_3$) 25.8, 28.3, 28.5, 29.3, 29.3, 30.6/30.8, 31.8/32.3, 36.0, (8x**C**H_2), 38.5/38.7 (**C**(3)), 64.6 (**C**(6')), 86.8/87.3 (**C**(1)), 117.9 (**C**(3''')), 128.5 (**C**(2")), 130.5 (**C**(3")), 130.5 (**C**(4''')), 136.7 (C(2''')), 166.3 (C(1")), 183.6 (**C**(1''')); *m/z* (A.P.C.I., +ve) 351 (MH^+, 11), 129 ((HOCSIm)H^+, 100%); Accurate Mass: Found 351.1742, $C_{18}H_{27}N_2O_3S$ (MH^+) requires 351.1742399.

***rel*-(1*S*, 12*S*)-5-Oxabicyclo[10.2.1]pentadecan-4-one 204**



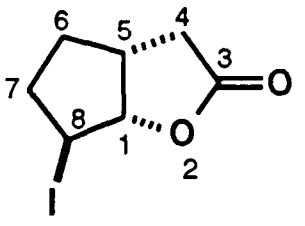
To a solution of acrylate **195** (25mg, 0.071mmol) and AIBN (1mg, 0.006mmol) in degassed benzene (28ml) at reflux was added, *via* syringe pump over 10h, a solution of $^nBu_3SnH$ (28µl, ~75% pure by ^1H NMR, 0.078mmol) in degassed benzene (4ml). After a further 3h the reaction mixture was concentrated, thiophenol (10µl, 0.08mmol) was added and the mixture purified by flash column chromatography (200:1, petrol:ether) to give the title macrocycle **204** (6mg, 38%) as an oil. R_f (1:1, petrol:ether) 0.40; $\nu_{max.}$ (thin film) 2928 (s), 2855 (s), 1734 (s), 1640 (w), 1464 (m), 1389 (w), 1153 (br s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.80-1.00 (1H, m), 1.20-1.40 (9H, m), 1.45-1.70 (8H, m), 2.00-2.10 (2H, m), 2.20-2.40 (2H, m, **H**$(3)_2$), 4.08 (2H, t, *J* 7.0, **H**$(6)_2$); *m/z* (C.I., NH_3) 242 (MNH_4^+, 100), 151 (11), 69 (40%); Accurate Mass: Found 242.2120, $C_{14}H_{28}NO_2$ (MNH_4^+) requires 242.212004.

rel-(1*S*, 5*R*, 8*S*)-8-Phenylseleno-2-oxabicyclo[3.3.0]octan-3-one 218[173]



The procedure described by Nicolaou *et al.*[173] was repeated using 2-cyclopentene-1-acetic acid **220** (2.0g, 15.8mmol), DCM (40ml), PhSeCl (3.3g, 17.4mmol) to give the desired seleno-lactone **218** (3.8g, 85%) as a pale yellow oil. R_f (DCM) 0.30 (uv active); $\nu_{max.}$ (thin film) 2960 (s), 1776 (s), 1579 (w), 1479 (w), 1438 (w), 1302 (w), 1176 (m), 1007 (m), 741 (m), 692 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.52-1.64 (1H, m), 1.76-1.93 (1H, m), 2.17-2.29 (2H, m), 2.35 (1H, dd, *J* 18.0, 2.5, **H**(4)$_a$), 2.83 (1H, dd, *J* 18.0, 10.0, **H**(4)$_b$), 3.10-3.15 (1H, m, **H**(5)), 3.90 (1H, br d, *J* 3.0, **H**(8)), 4.91 (1H, d, *J* 6.5, **H**(1)), 7.29-7.35 (3H, m, 2x**H**(2'), **H**(4')), 7.53-7.58 (2H, m, 2x**H**(3')); *m/z* (C.I., NH_3) 285 (M(^{82}Se)H$^+$, 20), 283 (M(^{80}Se)H$^+$, 100), 281 (M(^{78}Se)H$^+$, 55), 280 (M(^{77}Se)H$^+$, 40), 279 (M(^{76}Se)H$^+$, 25) 125 (MH$^+$-PhSeH, 30), 78 (43%).

rel-(1*S*, 5*R*, 8*S*)-8-Iodo-2-oxabicyclo[3.3.0]octan-3-one 219[174]

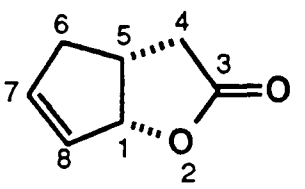


To a vigorously stirred solution of the acid **220** (2.5g, 19.8mmol) in water (60ml) at RT was added successively $KHCO_3$ (12g, 119mmol), KI (20.1g, 119mmol), ether (20ml) and, after 10mins, I_2 (10.2g, 39.7mmol). After 13h conc. HCl was

added dropwise until the pH fell below 7.0 at which point the mixture was diluted with ether (40ml) and the organic layer separated. The ether fraction was washed with sat. aq. $Na_2S_2O_3$ (15ml), water (40ml) and brine (40ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (4:1, petrol:ether) afforded the iodo-lactone **219** (4.7g, 94%) as a colourless oil. R_f (1:1, petrol:ether) 0.36 (uv active); $\nu_{max.}$ (thin film) 2966 (m), 2876 (w), 1785 (s), 1457 (m), 1443 (m), 1416 (m), 1347 (m), 1321 (m), 1303 (m), 1259 (w), 1222 (m), 1164 (s), 1081 (w), 1045 (m), 1005 (s), 974 (m), 943 (w), 909 (w), 876 (s), 820 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.50-1.70 (1H, m), 1.95-2.30 (2H, m), 2.30-2.60 (1H, m), 2.40 (1H, dd, *J* 18.5, 2.0, **H**$(4)_a$), 2.92 (1H, dd, *J* 18.5, 10.5, **H**$(4)_b$), 3.10-3.30 (1H, m, **H**(5)), 4.50 (1H, d, *J* 5.0, **H**(8)), 5.22 (1H, d, *J* 6.0, **H**(1)); *m/z* (C.I., NH_3) 270 (MNH_4^+, 100), 142 (MNH_4^+-HI, 25), 125 (MH^+-HI, 70), 107 (30), 97 (20), 81 (MH^+-HI-CO_2, 60), 67 (17), 58 (18), 55 (24%).

rel-(1*R*, 5*R*)-2-Oxabicyclo[3.3.0]oct-7-en-3-one 207[158,173]

Method 1



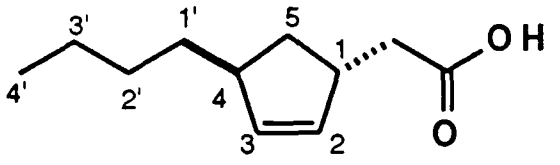
The procedure described by Nicolaou *et al.*[173] was repeated using phenylseleno-lactone **218** (3.8g, 13.5mmol), DCM (20ml) and H_2O_2 (1.6ml, 60% aq. solution, 28.4mmol) to give the alkenyl lactone **207** (1.53g, 92%) as a colourless oil. R_f (DCM) 0.17; $\nu_{max.}$ (thin film) 2962 (s), 2857 (s), 1772 (s), 1616 (w), 1479 (w), 1449 (w), 1417 (w), 1362 (m), 1338 (m), 1305 (w), 1290 (w), 1269 (w), 1170 (s), 1109 (w), 1022 (s), 1008 (s), 957 (w), 917 (w), 859 (w), 741 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.32 (1H, dd, *J* 17.5, 5.0, **H**$(4)_a$), 2.27-2.36 (1H, m, **H**$(6)_a$), 2.85 (1H, dd, *J* 17.5, 10.5, **H**$(4)_b$), 2.71-2.78 (1H, m, **H**$(6)_b$), 3.05-3.26 (1H, m, **H**(5))

5.54 (1H, d, *J* 7.5, **H**(1)), 5.87-5.91 (1H, m, **H**(8)), 6.08-6.12 (1H, m, **H**(7)); *m/z* (C.I., NH_3) 142 (MNH_4^+, 10), 125 (MH^+, 20), 108 (70), 80 (30), 66 (100%).

Method 2

To a stirred solution of the iodolactone **219** (4.7g, 18.7mmol) in benzene (40ml) was added DBU (4.2ml, 28mmol) and the mixture heated at reflux. After 3h the reaction mixture was diluted with 1M aq. HCl (30ml) and extracted with ether (2x20ml). The combined organic portions were washed with brine (30ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (1:1, petrol:ether) to give the alkenyl-lactone **207** (2.08g, 90%) as an oil. This proved to be identical to the compound described above.

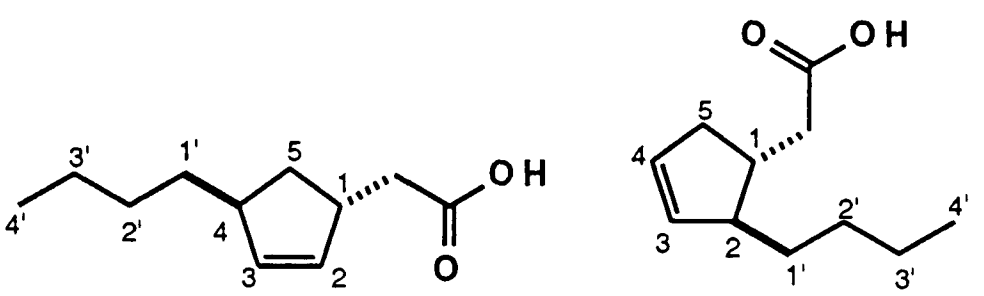
***trans*-4-Butylcyclopent-2-ene-1-acetic acid 221**



To a cooled (-20°C) suspension of $CuBr.SMe_2$ (166mg, 0.81mmol) in THF (10ml) was added successively Me_2S (2ml), *n*-butylmagnesium chloride (0.4ml, 2.0M in hexanes, 0.8mmol) dropwise and after 15mins a solution of the alkenyllactone **207** (50mg, 0.40mmol) in THF (1ml) dropwise. After 15h the reaction mixture was diluted with ether (20ml) and extracted with sat. aq. $NaHCO_3$ (2x20ml). The combined aqueous fractions were acidified by dropwise addition of conc. HCl until the pH fell below 7.0 then extracted with ether (3x15ml). The combined ether layers were washed with brine (20ml), dried ($MgSO_4$) and concentrated to give the *trans*-1,4-addition product **221** (54mg, 74%) as a colourless oil. R_f (DCM) 0.05; $\nu_{max.}$ (thin film) 3053 (m), 2957 (m), 2926 (m), 2854 (m), 1708 (s), 1410 (w), 1285 (w), 1225 (w), 951 (w) cm^{-1}; δ_H

(500MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.9, **H**(4')$_3$), 1.25-1.35 (5H, m), 1.36-1.41 (1H, m), 1.69-1.78 (2H, m, **H**(5)$_2$), 2.33 (1H, dd, *J* 15.3, 8.1, C**H**$_a$H$_b$CO$_2$H), 2.41 (1H, dd, *J* 15.3, 6.9, CH$_a$**H**$_b$CO$_2$H), 2.69-2.72 (1H, m, **H**(4)), 3.10-3.15 (1H, m, **H**(1)), 5.68 (1H, dt, *J* 5.6, 2.0, **H**(2)), 5.75 (1H, dt, *J* 5.6, 1.9, **H**(3)); δ_C (125MHz, $CDCl_3$) 14.1 (**C**(4')), 22.9, 30.1, 35.5 (**C**(1'), **C**(2'), **C**(3')), 36.4 (**C**(5)), 40.1 (**C**H$_2$CO$_2$H), 41.1 (**C**(4)), 44.6 (**C**(1)), 132.6 (**C**(2)), 136.5 (**C**(3)), 179.1 (**C**O$_2$H); *m/z* (C.I., NH_3) 200 (MNH_4^+, 100), 183 (MH^+, 80), 137 (28), 123 (MH^+-MeCO$_2$H, 85), 109 (12), 94 (22), 80 (51), 67 (25), 55 (16%); Microanalysis: Found C, 72.44; H, 9.84%; $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%.

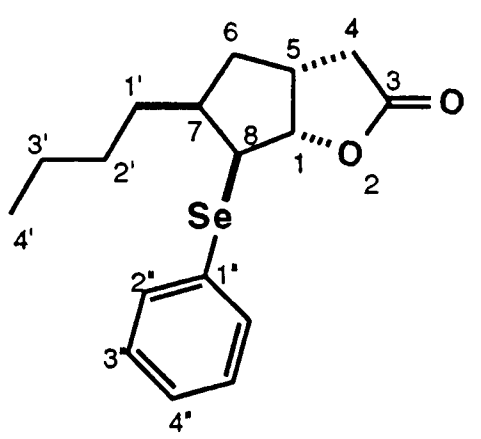
trans-4-Butylcyclopent-2-ene-1-acetic acid 221 and _trans_-2-Butylcyclopent-3-ene-1-acetic acid 222



To a cooled (-78°C) suspension of CuCN (56mg, 0.73mmol) in THF (10ml) was added dropwise *n*-butyllithium (0.4ml, 1.6M in hexanes, 0.73mmol). The temperature was raised to -20°C, carefully maintained and observed until the solution was homogeneous, then quickly re-cooled to -78°C. To this cooled solution of *n*-butyl cuprate was added dropwise a solution of the alkenyl-lactone **207** (60mg, 0.48mmol) in THF (1ml). After 15h the reaction mixture was diluted with 1M aq. HCl (15ml) and ether (20ml), and the layers separated. The combined organic portions were washed with brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (5:1, petrol:ether) to give an inseparable mixture (ratio 1:1) of the 1,2 addition product **222** and the 1,4 addition product **221** (60mg, 69%) as colourless oils. 1,2 Addition

product **222**: R_f (DCM) 0.05; $\nu_{max.}$ (thin film) 3053 (m), 2957 (m), 2926 (m), 2854 (m), 1708 (s), 1410 (w), 1285 (w), 1225 (w), 951 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8, **H**(4')$_3$), 1.25-1.36 (5H, m), 1.36-1.44 (1H, m), 2.02 (1H, dddd, *J* 16.9, 5.1, 1.9, 1.9, **H**(5)$_a$), 2.23-2.30 (1H, m), 2.30-2.33 (1H, m), 2.34 (1H, dd, *J* 15.3, 6.4, C**H**$_a$H$_b$CO$_2$H), 2.51 (1H, dd, *J* 15.3, 5.9, CH$_a$**H**$_b$CO$_2$H), 2.63-2.69 (1H, m, **H**(2)), 5.63-5.66 (2H, m, **H**(3), **H**(4)); δ_C (125MHz, $CDCl_3$) 14.0 (**C**(4')), 22.9, 29.8, 34.7 (3x**C**H$_2$), 38.4 (**C**(5)), 39.6 (**C**(1)), 40.1 (**C**H$_2$CO$_2$H), 51.5 (**C**(2)), 128.6, 133.9 (**C**(3), **C**(4)), 179.5 (**C**O$_2$H); *m/z* (C.I., NH_3) 200 (MNH_4^+, 100), 183 (MH^+, 80), 137 (28), 123 (MH^+-MeCO$_2$H, 85), 109 (12), 94 (22), 80 (51), 67 (25), 55 (16%); Microanalysis (on mixture of isomers): Found C, 72.44; H, 9.84%; $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%. The data for the 1,4 addition product **221** were identical to that described above.

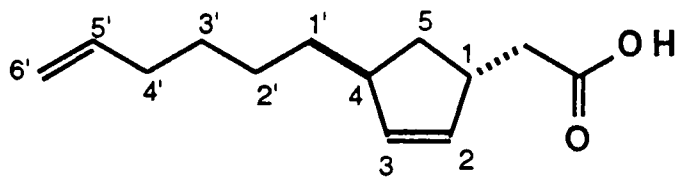
***rel*-(1*S*, 5*R*, 7*S*, 8*S*)-7-Butyl-8-phenylseleno-2-oxabicyclo[3.3.0]octan-3-one 223**



To a cooled (-78°C) solution of phenylselenyl chloride (24mg, 0.12mmol) in DCM (4ml) was added dropwise a solution of acid **221** (20mg, 0.11mmol) in DCM (1ml). After 3h the orange/red colour had dissipated and the solution was warmed to RT, diluted with ether (15ml) and 1M aq. HCl (5ml), and the layers separated. The organic portion was washed with water (10ml) and brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the desired seleno-lactone **223**

(31mg, 84%) as a pale yellow oil. R_f (1:1, petrol:ether) 0.44 (uv active); $\nu_{max.}$ (thin film) 3057 (w), 2956 (m), 2926 (m), 2857 (w), 1777 (s), 1579 (w), 1478 (w), 1456 (w), 1438 (w), 1164 (m), 999 (w), 740 (w), 691 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.9, **H**(4')$_3$), 1.27-1.44 (5H, m), 1.46-1.59 (1H, m), 1.67 (1H, dd, *J* 13.1, 6.9, **H**(6)$_a$), 1.92 (1H, ddd, *J* 13.1, 9.7, 9.7, **H**(6)$_b$), 2.29-2.36 (1H, m, **H**(7)), 2.34 (1H, dd, *J* 18.6, 2.4, **H**(4)$_a$), 2.84 (1H, dd, *J* 18.6, 10.5, **H**(4)$_b$), 3.16-3.22 (1H, m, **H**(5)), 3.92 (1H, d, *J* 5.2, **H**(8)), 4.93 (1H, d, *J* 6.3, **H**(1)), 7.28-7.32 (3H, m, 2x**H**(2''), **H**(4'')), 7.53-7.56 (2H, m, 2x**H**(3'')); δ_C (125MHz, $CDCl_3$) 14.0 (**C**(4')), 22.7, 30.6, 31.7 (3x**C**H_2), 35.6 (**C**(7)), 36.7 (**C**(6)), 39.3 (**C**(4)), 40.9 (**C**(5)), 52.7 (**C**(8)), 90.3 (**C**(1)), 127.7 (**C**(4'')), 128.1 (**C**(1'')), 129.4 (2x**C**(2'')), 133.7 (2x**C**(3'')), 177.3 (**C**(3)); *m/z* (C.I., NH_3) 339 (M(^{82}Se)H^+, 15), 337 (M(^{80}Se)H^+, 30), 198 (MNH_4^+-PhSeH, 30), 181 (MH^+-PhSeH, 70), 137 (MH^+-PhSeH-CO_2, 75), 78 (100%); Accurate Mass: Found 339.0863, $C_{17}H_{23}O_2Se$ (MH^+) requires 339.086325.

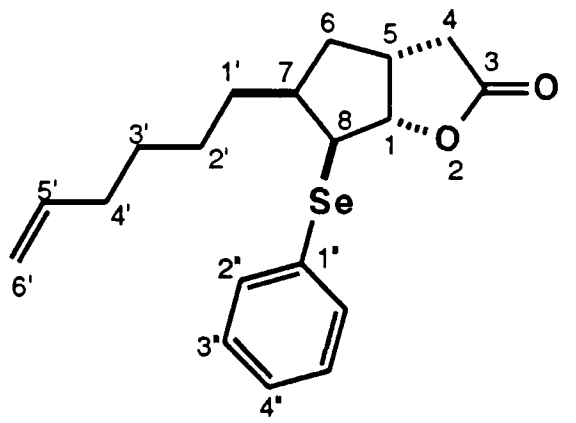
***trans*-4-(Hex-5'-enyl)cyclopent-2-ene-1- acetic acid 225**



To a cooled (-78°C) suspension of iodo-hexene **182** (0.9g, 4.30mmol) in ether (6ml) was added dropwise *t*-butyllithium (5.3ml, 1.7M in pentane, 9.00mmol) and, after a further 15mins, a solution of CuBr.SMe_2 (0.88g, 4.30mmol) in Me_2S (5ml) *via* a cannula. The mixture was warmed to -20°C and stirred vigorously. After 30mins the dark blue solution was cooled again to -78°C and a solution of the alkenyl lactone **207** (0.44g, 3.60mmol) in ether (2ml) added dropwise. After 15h the reaction mixture was diluted with ether (30ml) and extracted with sat. aq. $NaHCO_3$ (3x15ml). The combined aqueous portions were acidified by the

dropwise addition of conc. HCl and then extracted with ether (4x15ml). The combined organic fractions were washed with brine (25ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the title acid **225** (605mg, 82%) as an oil. R_f (EtOAc) 0.55; $\nu_{max.}$ (thin film) 3049 (w), 2926 (s), 2855 (m), 1708 (s), 1641 (w), 1413 (m), 1364 (w), 1280 (m), 1208 (w), 993 (w), 910 (m), 744 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.26-1.43 (6H, m), 1.67-1.78 (2H, m, **H**(5)$_2$), 2.03-2.08 (2H, m, **H**(4')$_2$), 2.33 (1H, dd, *J* 15.3, 8.0, $CH_aH_bCO_2H$), 2.41 (1H, dd, *J* 15.3, 6.8, $CH_a\mathbf{H}_bCO_2H$), 2.70-2.72 (1H, m, **H**(4)), 3.10-3.14 (1H, m, **H**(1)), 4.95 (1H, dd, *J* 10.2, 1.6, **H**(6')$_a$), 5.00 (1H, ddd, *J* 17.0, 3.4, 1.6, **H**(6')$_b$), 5.68 (1H, dt, *J* 5.7, 1.8, **H**(2)), 5.74 (1H, dt, *J* 5.7, 1.9, **H**(3)), 5.81 (1H, dddd, *J* 17.0, 10.2, 6.7, 6.7, **H**(5')); δ_C (125MHz, $CDCl_3$) 27.4, 29.1, 33.7, 35.6, 36.4 (5xCH_2), 40.1 (**C**H_2CO_2H), 41.1 (**C**(4)), 44.6 (**C**(1)), 114.2 (**C**(6')), 132.7 (**C**(2)), 136.4 (**C**(3)), 139.0 (**C**(5')), 179.0 (**C**O_2H); *m/z* (C.I., NH_3) 226 (MNH_4^+, 100), 209 (MH^+, 20), 178 (70), 149 (MH^+-AcOH, 50), 148 (90), 119 (19), 105 (31), 93 (38), 79 (70), 58 (26%); Accurate Mass: Found 226.1807, $C_{13}H_{24}NO_2$ (MNH_4^+) requires 226.180692.

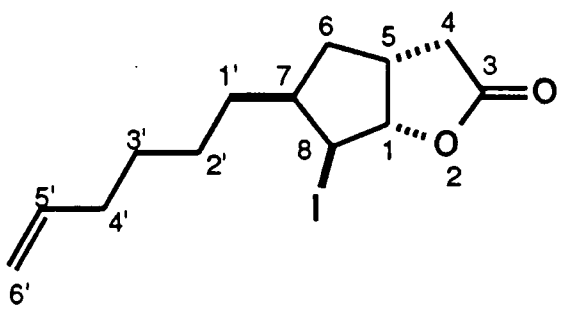
***rel*-(1*S*, 5*R*, 7*S*, 8*S*)-7-(Hex-5'-enyl)-8-phenylseleno-2-oxabicyclo[3.3.0]octan-3-one 227**



To a cooled (0°C) solution of the alkenyl acid **225** (50mg, 0.24mmol) in DCM (5ml) was added dropwise a solution of PhSeCl (93mg, 0.49mmol) in DCM (2ml). After 13h the solution was diluted with 1M aq. HCl (5ml) and extracted

with ether (15ml). The organic portion was washed with water (5ml) and brine (15ml), dried ($MgSO_4$) and concentrated to give the crude diselenide addition product **229**. Subsequent purification by flash column chromatography (petrol then DCM) gave the desired seleno-lactone **227** (50mg, 57%) as a yellow oil. R_f (DCM) 0.33 (uv active); $\nu_{max.}$ (thin film) 3072 (w), 2927 (m), 2854 (w), 1777 (s), 1640 (w), 1580 (w), 1478 (w), 1453 (m), 1438 (w), 1164 (m), 1022 (w), 998 (w), 740 (w), 666 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.30-1.60 (6H, m), 1.67 (1H, dd, *J* 13.4, 6.9, **H**$(6)_a$), 1.91 (1H, ddd, *J* 13.4, 13.0, 9.7, **H**$(6)_b$), 2.05-2.09 (2H, m, **H**$(4')_2$), 2.31-2.36 (1H, m, **H**(7)), 2.33 (1H, dd, *J* 18.6, 2.4, **H**$(4)_a$), 2.84 (1H, dd, *J* 18.6, 10.5, **H**$(4)_b$), 3.18 (1H, dddd, *J* 10.5, 9.7, 6.3, 2.4, **H**(5)), 3.91 (1H, br d, *J* 5.2, **H**(8)), 4.93 (1H, d, *J* 6.3, **H**(1)), 4.96 (1H, ddd, *J* 10.2, 1.7, 1.0, **H**$(6')_a$), 5.02 (1H, ddd, *J* 17.0, 3.4, 1.7, **H**$(6')_b$), 5.81 (1H, dddd, *J* 17.0, 10.2, 6.7, 6.7, **H**(5')), 7.28-7.53 (3H, m, 2x**H**(2''), **H**(4'')), 7.53-7.61 (2H, m, 2x**H**(3'')); δ_C (125MHz, $CDCl_3$) 27.9, 28.9, 31.9, 33.6, 35.6, (5xCH_2), 36.7 (**C**(7)), 39.3 (**C**(4)), 40.9 (**C**(5)), 52.8 (**C**(8)), 90.3 (**C**(1)), 114.5 (**C**(6')), 127.7 (**C**(4'')), 128.1 (**C**(1'')), 129.4 (2x**C**(2'')), 133.8 (2x**C**(3'')), 138.7 (**C**(5')), 177.2 (**C**(3)); *m/z* (C.I., NH_3) 365 (M(^{80}Se)H^+, 60), 363 (M(^{78}Se)H^+, 45), 224 (23), 207 (MH^+-PhSeH, 100), 147 (MH^+-PhSeH-AcOH, 55%); Accurate Mass: Found 365.1020, $C_{19}H_{25}O_2Se$ (MH^+) requires 365.101975.

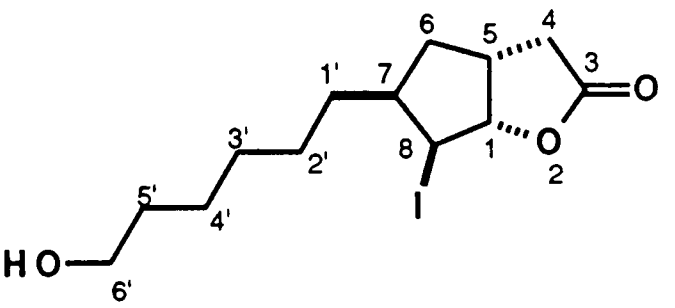
***rel*-(1*S*, 5*R*, 7*S*, 8*S*)-7-(Hex-5'-enyl)-8-iodo-2-oxabicyclo[3.3.0]octan-3-one 226**



To a vigorously stirred solution of the acid **225** (150mg, 0.72mmol) in water (10ml) was added successively $KHCO_3$ (0.44g, 4.32mmol), KI (0.73g, 4.32mmol),

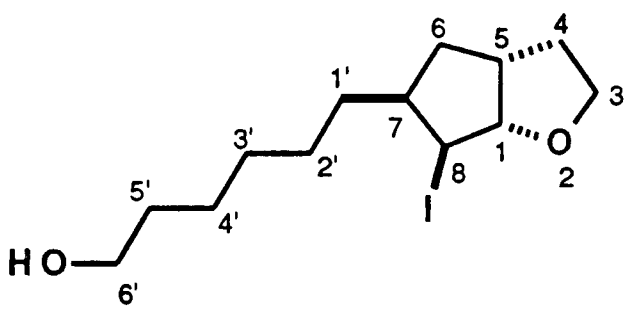
ether (5ml) and, after 5mins, I_2 (0.37g, 1.44mmol). After 13h conc. HCl was added dropwise until the pH fell below 7.0 at which point the mixture was diluted with ether (20ml) and the organic layer separated. The ether fraction was washed with sat. aq. $Na_2S_2O_3$ (5ml), water (10ml) and brine (15ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of the desired iodo-lactone **226** and the triiodide **228**. Flash column chromatography (petrol then DCM) afforded the iodo-lactone **226** (0.22g, 92%) as a colourless oil. R_f (DCM) 0.29; $\nu_{max.}$ (thin film) 3074 (w), 2927 (m), 2854 (w), 1782 (s), 1640 (w), 1454 (w), 1416 (w), 1342 (w), 1323 (w), 1297 (w), 1256 (w), 1216 (w), 1160 (m), 998 (m), 911 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.21-1.38 (4H, m), 1.39-1.49 (3H, m), 1.55 (1H, dd, *J* 13.6, 6.5, **H**$(6)_a$), 1.92 (1H, ddd, *J* 13.6, 9.9, 9.9, **H**$(6)_b$), 2.04-2.17 (2H, m, **H**$(4')_2$), 2.37 (1H, dd, *J* 18.5, 2.0, **H**$(4)_a$), 2.89 (1H, dd, *J* 18.5, 10.3, **H**$(4)_b$), 3.18 (1H, dddd, *J* 10.0, 10.0, 6.2, 2.0, **H**(5)), 4.53 (1H, d, *J* 3.8, **H**(8)), 4.96 (1H, dd, *J* 10.1, 1.5, **H**$(6')_a$), 5.0 (1H, ddd, *J* 17.0, 3.4, 1.5, **H**$(6')_b$), 5.30 (1H, d, *J* 6.2, **H**(1)), 5.80 (1H, dddd, *J* 17.0, 10.1, 6.7, 6.7, **H**(5')); δ_C (125MHz, $CDCl_3$) 27.2, 28.0, 33.5, 35.1, 35.1 (5x$\mathbf{C}H_2$), 36.5 (**C**(8)), 38.3 (**C**(7)), 41.4 (**C**(4)), 41.9 (**C**(5)), 92.1 (**C**(1)), 114.6 (**C**(6')), 138.6 (**C**(5')), 176.7 (**C**(3)); *m/z* (C.I., NH_3) 352 (MNH_4^+, 45), 226 (38), 207 (MH^+-HI, 65), 147 (MH^+-HI-AcOH, 100), 107 (22), 91 (24), 81 (36), 67 (26%); Accurate Mass: Found 352.0775, $C_{13}H_{23}INO_2$ (MNH_4^+) requires 352.0775272.

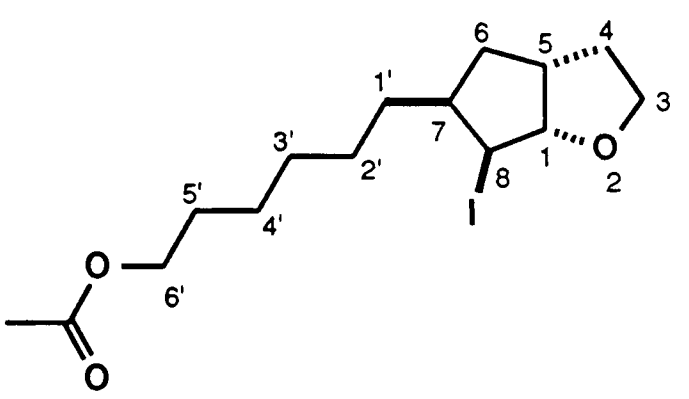
rel-(1*S*, 5*R*, 7*S*, 8*S*)-7-(6'-Hydroxyhexyl)-8-iodo-2-oxabicyclo[3.3.0]octan-3-one 230



To a cooled (0°C) solution of iodo-lactone **226** (68mg, 0.20mmol) in THF (5ml) was added BH_3.THF (0.30ml, 1.0M in THF, 0.30mmol) dropwise, followed by, after 15h, ethanol (500µl), 1M NaOH (500µl) and H_2O_2 (500µl, 60% aq. solution) and, after a further 1h, conc. H_2SO_4 (2 drops). After 1h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x15ml). The ether fractions were washed with brine (10ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (2:1 petrol:EtOAc) afforded the alcohol **230** (60mg, 84%) as a colourless oil. R_f (EtOAc) 0.43 (uv active); $\nu_{max.}$ (thin film) 3401 (br m), 2928 (m), 2854 (m), 1778 (s), 1454 (w), 1162 (m), 1056 (w), 995 (w), 666 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.22-1.31 (5H, m,), 1.41-1.47 (2H, m), 1.49-1.60 (3H, m), 1.92 (1H, ddd, *J* 12.3, 12.3, 10.0, **H**$(6)_a$), 2.37 (1H, dd, *J* 18.5, 2.0, **H**$(4)_a$), 2.89 (1H, dd, *J* 18.5, 10.0, **H**$(4)_b$), 3.17 (1H, dddd, *J* 10.0, 10.0, 6.2, 2.0, **H**(5)), 3.65 (2H, t, *J* 6.6, **H**$(6')_2$), 4.53 (1H, d, *J* 3.8, **H**(8)), 5.30 (1H, d, *J* 6.2, **H**(1)); δ_C (125MHz, $CDCl_3$) 25.6, 27.7, 29.4, 32.6, 35.1 (5x**C**H_2), 35.2 (**C**(8)), 36.5 (**C**(6)), 38.3 (**C**(4)), 41.4 (**C**(7)), 41.9 (**C**(5)), 62.9 (**C**(6')), 92.1 (**C**(1)), 176.8 (**C**(3)); *m/z* (C.I., NH_3) 370 (MNH_4^+, 100), 353 (MH^+, 10), 242 (MNH_4^+-HI, 50), 225 (MH^+-HI, 45), 207 (MH^+-HI-H_2O, 50), 181 (38), 147 (20), 81 (18%); Accurate Mass: Found 370.0884, $C_{13}H_{25}INO_3$ (MNH_4^+) requires 370.088444.

rel-(1*S*, 5*R*, 7*S*, 8*S*)-7-(6'-Hydroxyhexyl)-8-iodo-2-oxabicyclo[3.3.0]octane 233 and rel-(1*S*, 5*R*, 7*S*, 8*S*)-7-(6'-Acetoxyhexyl)-8-iodo-2-oxabicyclo[3.3.0]octane 232



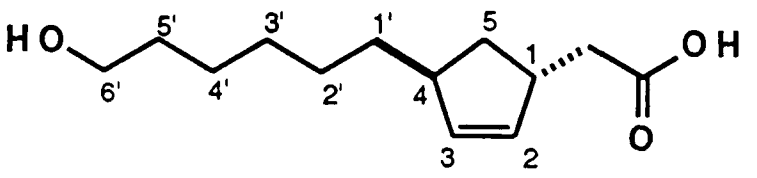


To a cooled (0°C) solution of iodo-lactone **226** (90mg, 0.25mmol) in THF (5ml) was added dropwise BH_3.THF (0.55ml, 1.0M in THF, 0.55mmol) and, after 15h, ethanol (500µl), 1M NaOH (500µl) and H_2O_2 (500µl, 60% aq. solution). After 1h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x20ml). The combined extracts were washed with brine (15ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the iodo-triol **234** (85mg, 96%) which was dissolved in acetonitrile (2ml) and conc. H_2SO_4 (one drop) added. After 15h the reaction mixture was diluted with 1M aq. HCl (10ml) and ether (20ml) and the layers separated. The organic portion was washed with brine (10ml), concentrated and purified by flash column chromatography (4:1, petrol:ether) to afford the alcohol **233** (38mg, 47%) and the acetate **232** (32mg, 38%) as colourless oils. Alcohol **233**, R_f (EtOAc) 0.54 (uv active); $\nu_{max.}$ (thin film) 3400 (br s), 2927 (s), 2855 (m), 1654 (w), 1543 (w), 1508 (w), 1456 (w), 1437 (w), 1116 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.16-1.50 (10H, m), 1.55-1.70 (3H, m), 1.75 (1H, ddd, *J* 12.3, 12.3, 10.0, **H**$(6)_a$), 2.19 (1H, dddd, *J* 15.5, 12.4, 7,1, 6.8, **H**$(4)_a$), 2.93-3.0 (1H, m, **H**(5)), 3.68 (2H, t, *J* 6.6, **H**$(6')_2$), 3.88 (1H, ddd, *J* 8.6, 6.8, 6.7, **H**$(3)_a$), 3.80 (1H, ddd, *J* 8.6, 7.1, 6.0, **H**$(3)_b$), 4.46 (1H, d, *J* 4.1, **H**(8)), 4.84 (1H, d, *J* 6.0, **H**(1)); δ_C (125MHz, $CDCl_3$) 26.1, 28.4, 29.9, 33.2, 36.3 (5x**C**H_2), 35.3, 38.1, 40.5, 43.2 (**C**(4), (**C**(6), **C**(7), **C**(8)), 47.5 (**C**(5)), 63.4 (**C**(6')), 70.0 (**C**(3)), 93.5 (**C**(1)); *m/z* (C.I., NH_3) 356 (MNH_4^+, 10), 339 (MH^+, 8), 228 (22), 211 (MH^+-HI, 100), 193 (MH^+-HI-H_2O, 100), 181 (27%); Accurate Mass: Found 356.1092, $C_{13}H_{27}INO_2$ (MNH_4^+) requires 356.109179. The acetate **232**, R_f (EtOAc) 0.72 (uv active); $\nu_{max.}$ (thin film) 2927 (s), 2855 (m), 1739 (s), 1454 (w), 1365 (w), 1241 (s), 1041 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.18-1.45 (9H, m), 1.51-1.70 (4H, m), 1.73 (1H, ddd, *J* 12.3, 12.3, 10.0, **H**$(6)_a$), 2.09 (3H, s, C**H**$_3$), 2.19 (1H, dddd, *J* 15.5, 12.4, 7,1, 6.8, **H**$(4)_a$), 2.93-3.0 (1H, m, **H**(5)), 3.80 (1H, ddd, *J* 8.4, 7.1, 5.3, **H**$(3)_a$), 3.88 (1H, ddd, *J* 8.4, 6.8, 6.8, **H**$(3)_b$), 4.10 (2H, t, *J* 6.8, **H**$(6')_2$), 4.46 (1H, d, *J* 4.0, **H**(8)), 4.84 (1H,

d, *J* 6.0, **H**(1)); δ_C (125MHz, $CDCl_3$) 21.5 (**C**H_3), 26.3, 28.3, 29.0, 29.7, 36.2 (5x**C**H_2), 35.3, 38.2, 40.5, 43.1 (**C**(4), C(6), **C**(7), **C**(8)), 47.5 (**C**(5)), 65.0 (**C**(6')), 70.0 (**C**(3)), 93.5 (**C**(1)), 171.6 (**C**=O); *m/z* (C.I., NH_3) 398 (MNH_4^+, 10), 381 (MH^+, 15), 253 (MH^+-HI, 85), 235 (MH^+-HI-H_2O, 100), 270 (MNH_4^+-HI, 10%); Accurate Mass: Found 381.0932, $C_{15}H_{26}IO_3$ (MH^+) requires 381.093195.

trans-4-(6'-Hydroxyhexyl)cyclopent-2-ene-1-acetic acid 231

Method 1:



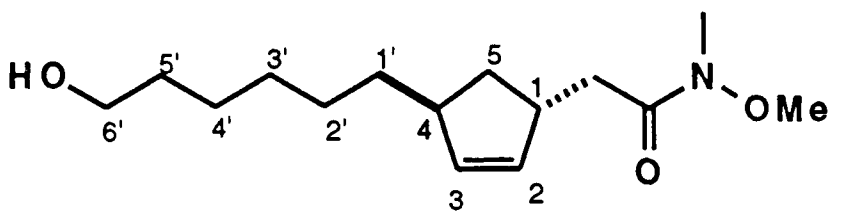
To a cooled (-78°C) suspension of iodo-hexanol **199** (2.55g, 11.8mmol) in ether (30ml) was added dropwise *n*-butyllithium (7.43ml, 1.6M in hexanes, 11.9mmol) and, after 15mins, *t*-butyllithium (14.7ml, 1.6M in pentane, 24.8mmol) followed by, after a further 15mins, a solution of $CuBr.SMe_2$ (2.44g, 11.8mmol) in Me_2S (15ml). The mixture was warmed to -20°C and stirred vigorously. After 20mins the dark blue solution was cooled to -78°C and a solution of the alkenyl-lactone **207** (0.88g, 7.10mmol) in ether (3ml) added dropwise. After 15h the reaction mixture was diluted with ether (40ml) and extracted with sat. aq. $NaHCO_3$ (3x30ml). The combined aqueous portions were acidified by the dropwise addition of conc. HCl until the pH fell below 7.0 then extracted with ether (4x20ml). The combined organic portions were washed with brine (40ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (1:1, EtOAc:petrol) to give the title hydroxy-acid **231** (1.2g, 80%) as a white solid. m.p. (EtOAc/petrol) 27-30°C; R_f (EtOAc) 0.24; $\nu_{max.}$ (KBr) 3406 (br), 2927 (s), 2856 (s), 1708 (s), 1407 (w), 1271 (w), 1168 (w), 1054 (w), 910 (s), 736 (s), 650 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.24-1.41 (8H, m), 1.54-1.60 (2H, m), 1.71-1.76 (2H, m), 2.35 (1H, dd, *J* 14.0, 6.9, C**H**$_a$H$_b$CO$_2$H), 2.41

(1H, dd, *J* 14.0, 8.6, $CH_aH_bCO_2H$), 2.68-2.73 (1H, m, **H**(4)), 3.09-3.16 (1H, m, **H**(1)), 3.65 (2H, t, *J* 6.6, **H**(6')$_2$), 5.66-5.74 (2H, m, **H**(2), **H**(3)); δ_C (125MHz, $CDCl_3$) 25.7, 27.8, 29.5, 32.7, 35.7 (5xCH_2), 36.4 (**C**(5)), 41.2 (**C**(4)), 44.6 (CH_2CO_2H), 44.6 (**C**(1)), 63.0 (**C**(6')), 132.8 (**C**(2)), 136.8 (**C**(3)), 178.7 (CO_2H); *m/z* (C.I., NH_3) 244 (MNH_4^+, 100), 227 (MH^+, 15), 209 (MH^+-H_2O, 30%); Microananlysis: Found C, 69.12; H, 10.16%; $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%.

Method 2:

A suspension of the iodo-lactone **230** (25mg, 0.071mmol) and zinc dust (10mg, 0.14mmol) in EtOH (2ml) was heated at reflux. After 15h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (3x5ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (1:1, EtOAc:petrol) to give the title hydroxy-acid **231** (13mg, 81%) as a white solid. The data for this compound were identical to that described above.

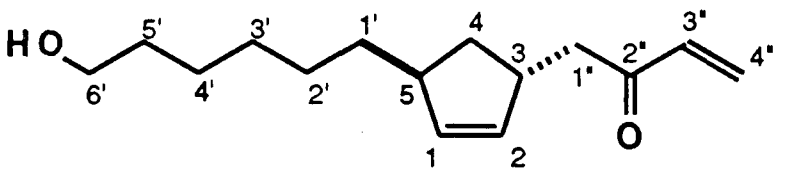
trans-4-(6'-Hydroxyhexyl)cyclopent-2-ene-1-_N_-methyl-_N_-methoxyacetamide 239



To a solution of hydroxy acid **231** (0.3g, 1.32mmol) in DCM was added carbonyl diimidazole (235mg, 1.45mmol) and, after 30mins, HN(OMe)Me.HCl (154mg, 1.58 mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (20ml) and extracted with ether (2x20ml). The combined organic extracts were washed with water (10ml) and brine (20ml), dried ($MgSO_4$) and

concentrated to give the title amide **239** (0.33g, 93%) as a colourless oil. A small portion was purified by flash column chromatography (2:1, ether:petrol) for analysis. R_f (EtOAc) 0.34; $\nu_{max.}$ (thin film) 3417 (br s), 2927 (s), 2855 (s), 1646 (s), 1463 (m), 1176 (m), 1057 (m), 1003 (m), 740 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.25-1.41 (8H, m), 1.54-1.60 (2H, m), 1.65-1.80 (2H, m), 2.39 (1H, dd, *J* 15.5, 7.0, CH_aH_bCO-), 2.47 (1H, dd, *J* 15.5, 6.9, CH_aH_bCO-), 2.68-2.70 (1H, m, **H**(4)), 3.14-3.18 (1H, m, **H**(1)), 3.19 (3H, br s, NCH_3), 3.64 (2H, t, *J* 6.7, **H**(6')$_2$), 3.67 (3H, s, $NOCH_3$), 5.68-5.73 (2H, m, **H**(2), **H**(3)); δ_C (125MHz, $CDCl_3$) 25.7, 27.8, 29.6, 32.8, 35.8 (5xCH_2), 32.1 (NCH_3), 36.6 (**C**(5)), 37.9 (CH_2CO-), 40.9 (**C**(4)), 44.6 (**C**(1)), 61.2 ($NOCH_3$), 63.0 (**C**(6')), 133.8 (**C**(2)), 135.7 (**C**(3)), 174.0 (**C**=O); *m/z* (C.I., NH_3) 270 (MH^+, 55), 240 (85), 238 (MH^+-MeOH, 70), 167 (18), 138 (24), 110 (22), 103 (16), 81 (31), 73 (100%); Accurate Mass: Found 270.2069, $C_{15}H_{28}NO_3$ (MH^+) requires 270.206919.

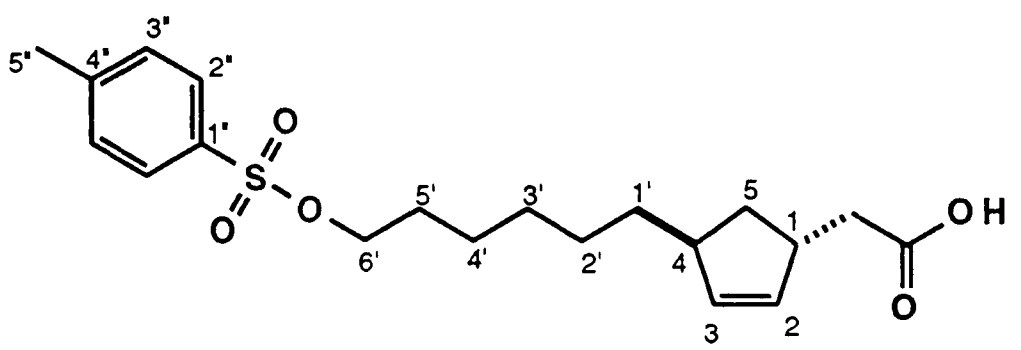
***trans*-5-(6'-Hydroxyhexyl)-3-(2"-oxobut-3"-enyl)cyclopentene 240**



To a cooled (-78°C) solution of the amide **239** (3mg, 1μmol) in THF (1ml) was added dropwise vinylmagnesium bromide (30μl, 1.0M in THF, 3μmol). After 15h the reaction mixture was diluted with 1M aq. HCl (2ml) and extracted with ether (3x5ml). The combined organic portions were washed with brine (5ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (3:1, petrol:ether) to give the title compound **240** (2mg, 76%) as an oil. R_f (EtOAc) 0.60 (uv active); $\nu_{max.}$ (thin film) 3383 (m), 3046 (w), 2927 (s), 2855 (s), 1684 (sh s), 1616 (m), 1402 (w), 1052 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.22-1.39 (8H, m), 1.58-1.60 (2H, m), 1.63 (1H, ddd, *J* 13.2, 11.7, 8.2, **H**(4)$_a$), 1.74 (1H, ddd, *J*

13.2, 8.3, 5.3, **H**(4)$_b$), 2.57 (1H, dd, *J* 16.2, 7.9, **H**(1")$_a$), 2.65 (1H, dd, *J* 16.2, 6.7, **H**(1")$_b$), 2.64-2.71 (1H, m, **H**(5)), 3.13-3.20 (1H, m, **H**(3)), 3.65 (2H, t, *J* 6.6, **H**(6')$_2$), 5.65 (1H, dt, *J* 5.7, 2.1, **H**(2)), 5.71 (1H, dt, *J* 5.7, 2.0, **H**(1)), 5.83 (1H, dd, *J* 10.6, 1.1, **H**(4")$_a$), 6.22 (1H, dd, *J* 17.7, 1.1, **H**(4")$_b$), 6.36 (1H, dd, *J* 17.7, 10.6, **H**(3")); δ_C (125MHz, $CDCl_3$) 25.7, 27.8, 29.5, 32.7, 35.7 (5x**C**H_2), 36.5 (**C**(4)), 40.5 (**C**(5)), 44.6 (**C**(3)), 45.6 (**C**(1")), 63.0 (**C**(6')), 128.1 (**C**(4")), 133.3 (**C**(2)), 135.8 (**C**(1)), 136.8 (**C**(3")), 200.4 (**C**(2")); *m/z* (C.I., NH_3) 237 (MH^+, 95), 219 (MH^+-H_2O, 40), 201 (20), 167 (28), 148 (30), 135 (47), 107 (15), 93 (23), 80 (56), 55 (100%); Accurate Mass: Found 237.1855, $C_{15}H_{25}O_2$ (MH^+) requires 237.185455.

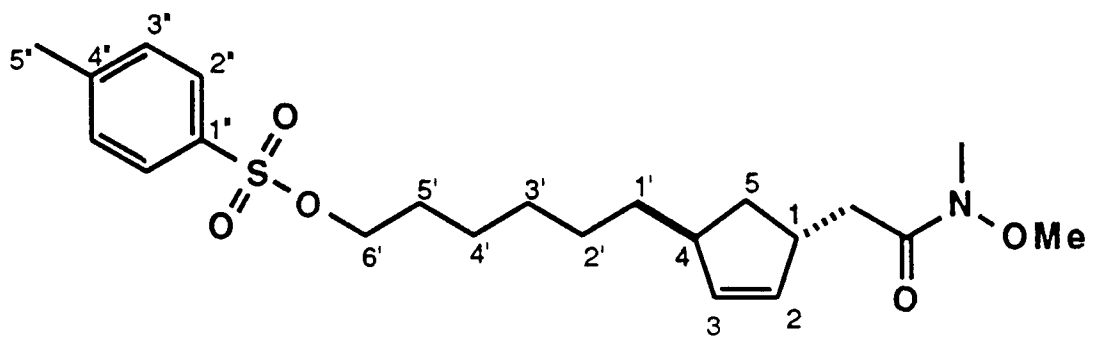
trans-4-(6'-_para_-toluenesulphonyloxyhexyl)-cyclopent-2-ene-1-acetic acid 243



To a stirred solution of hydroxy acid **231** (50mg, 0.21mmol) and TsCl (60mg, 0.32mmol) in DCM (5ml) was added pyridine (25μl). After 15h the reaction mixture was diluted with ether (20ml), washed successively with 1M aq. HCl (2x15ml), sat. aq. $CuSO_4$ solution (5ml), water (10ml) and brine (15ml) then dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (4:1, petrol:ether) afforded the title compound **243** (70mg, 88%) as an orange oil. R_f (EtOAc) 0.56 (uv active); $\nu_{max.}$ (thin film) 3400 (br), 3047 (w), 2927 (s), 1708 (s), 1599 (w), 1361 (s), 1177 (s), 816 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.21-1.42 (8H, m), 1.60-1.67 (2H, m), 1.69-1.77 (2H, m), 2.28-2.42 (2H, m, CH_2CO_2H), 2.45 (3H, s, **H**(5")$_3$), 2.62-2.70 (1H, m, **H**(4)), 3.08-3.15 (1H, m, **H**(1)), 4.02 (2H, t, *J* 6.5, **H**(6')$_2$), 5.64-5.67 (1H, m, **H**(2)), 5.70-5.73 (1H, m,

H(3)), 7.34 (2H, d, *J* 8.2, 2x**H**(3")), 7.79 (2H, d, *J* 8.2, 2x**H**(2")); δ_C (125MHz, $CDCl_3$) 21.6 (**C**(5")), 25.3, 27.6, 28.8, 29.1, 35.6 (5xCH_2), 36.3 (**C**(5)), 40.0 (**C**(4)), 41.1 (CH_2CO_2H), 44.5 (**C**(1)), 70.6 (**C**(6')), 127.9 (2x**C**(3")), 129.8 (2x**C**(2")), 132.8 (**C**(2)), 136.2 (**C**(4")), 133.3 (**C**(3)), 144.6 (**C**(1")), 178.7 (CO_2H); *m/z* (C.I., NH_3) 398 (MNH_4^+, 100), 380 (MNH_4^+-H_2O, 40), 381 (MH^+, 20), 363 (MH^+-H_2O, 10), 334 (11), 148 (15), 94 (14%); Accurate Mass: Found 398.2001, $C_{20}H_{32}NO_5S$ (MNH_4^+) requires 398.200119.

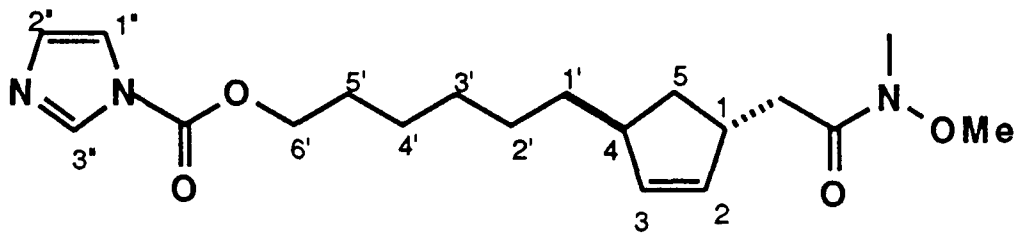
***trans*-4-(6'-*para*-toluenesulphonyloxyhexyl)cyclopent-2-ene-1-*N*-methyl-*N*-methoxyacetamide 244**



To a solution of the acid **243** (90mg, 0.24mmol) in DCM (4ml) was added carbonyl diimidazole (42mg, 0.26mmol) and, after 30mins, HN(OMe)Me.HCl (25mg, 0.26mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x10ml). The combined organic portions were washed with water (5ml) and brine (10ml) then dried ($MgSO_4$) and concentrated to give the title amide **244** (0.105g, 90%) as a colourless oil. R_f (EtOAc) 0.59 (uv active); $\nu_{max.}$ (thin film) 3045 (w), 2927 (s), 2856 (s), 1662 (s), 1599 (w), 1360 (s), 1177 (s), 817 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.18-1.33 (8H, m), 1.59-1.63 (2H, m), 1.64-1.72 (2H, m, **H**(5)$_2$), 2.29 (1H, dd, *J* 15.4, 8.1, C**H**$_a$H$_b$CO-), 2.36 (1H, dd, *J* 15.4, 7.0, CH$_a$**H**$_b$CO-), 2.43 (3H, s, **H**(5")$_3$), 2.61-2.70 (1H, m, **H**(4)), 3.13-3.16 (1H, m, **H**(1)), 3.17 (3H, br s, NC**H**$_3$), 3.65 (3H, s, NOC**H**$_3$), 4.00 (2H, t, *J* 6.5, **H**(6')$_2$), 5.65-5.69 (2H, m, **H**(2), **H**(3)), 7.33 (2H, d, *J* 8.1, 2x**H**(3")),

7.77 (2H, d, *J* 8.1, 2x**H**(2")); δ_C (125MHz, $CDCl_3$) 21.5 (**C**(5")), 25.2, 27.5, 28.7, 29.0, 35.6 (5x**C**H_2), 32.0 (N**C**H_3), 36.5 (**C**(5)), 40.9 (**C**(4)), 41.1 (CH_2CO-), 44.5 (**C**(1)), 61.1 (NO**C**H_3), 70.6 (**C**(6')), 127.8 (2x**C**(3")), 129.7 (2x**C**(2")), 133.7 (**C**(2)), 133.2 (**C**(4")), 135.5 (**C**(3)), 144.5 (**C**(1")), 173.9 (**C**=O); *m/z* (C.I., NH_3) 424 (MH^+, 100), 380 (MNH_4^+-HN(OMe)Me, 10); Accurate Mass: Found 424.2158, $C_{22}H_{34}NO_5S$ (MH^+) requires 424.215769.

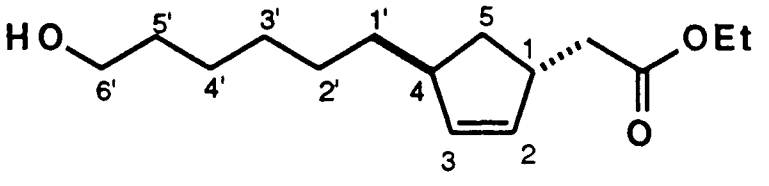
trans-4-(6'-(_N_-Imidazolylcarbonyloxy)hexyl)cyclopent-2-ene-1-_N_-methyl-_N_-methoxyacetamide 245



To a solution of hydroxy acid **231** (200mg, 0.88mmol) in DCM (10ml) was added carbonyl diimidazole (300mg, 1.84mmol) and, after 20mins, HN(OMe)Me.HCl (188mg, 1.93mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (30ml) and extracted with ether (2x20ml). The combined organic portions were washed with water (10ml) and brine (30ml), dried ($MgSO_4$) and concentrated to give the title compound **245** (0.27g, 85%) as an oil. R_f (EtOAc) 0.39 (uv active); $\nu_{max.}$ (thin film) 3451 (w), 3126 (w), 2927 (s), 2856 (m), 1763 (s), 1666 (s), 1471 (m), 1407 (s), 1377 (m), 1319 (m), 1291 (s), 1241 (s), 1177 (m), 1096 (m), 1058 (w), 1003 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.22-1.41 (8H, m), 1.64-1.74 (2H, m, **H**$(5)_2$), 1.74-1.80 (2H, m), 2.39 (1H, dd, *J* 15.4, 8.5, C**H**$_a$H$_b$CO-), 2.45 (1H, dd, *J* 15.4, 6.5, CH$_a$**H**$_b$CO-), 2.66-2.68 (1H, m, **H**(4)), 3.14-3.19 (1H, m, **H**(1)), 3.17 (3H, br s, NC**H**$_3$), 3.65 (3H, s, NOC**H**$_3$), 4.39 (2H, t, *J* 6.8, **H**$(6')_2$), 5.66-5.69 (2H, m, **H**(2), **H**(3)), 7.05, 7.41 (2H, 2xbr s, **H**(1"), **H**(2")), 8.12 (1H, br s, **H**(3")); δ_C (125MHz, $CDCl_3$) 25.6, 27.6, 28.4, 29.2, 35.6 (5x**C**H_2),

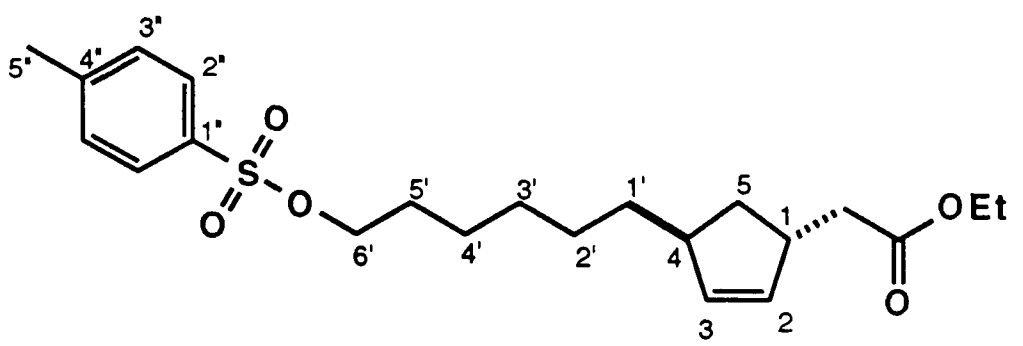
32.0 (NCH_3), 36.5 (**C**(5)), 37.8 (CH_2CO-), 40.9 (**C**(4)), 44.5 (**C**(1)), 61.1 ($NOCH_3$), 68.4 (**C**(6')), 117.0, 130.5 (**C**(2''), **C**(1'')), 133.8 (**C**(2)), 135.4 (**C**(3)), 137.0 (**C**(3'')), 148.7 (**C**=O), 173.9 (**C**ON(OMe)Me); *m/z* (C.I., NH_3) 364 (MH^+, 100), 303 (MH^+-HN(OMe)Me, 10), 270 (30%); Accurate Mass: Found 364.2236, $C_{19}H_{30}N_3O_4$ (MH^+) requires 364.223632.

Ethyl *trans*-4-(6'-hydroxyhexyl)cyclopent-2-ene-1-acetate 246



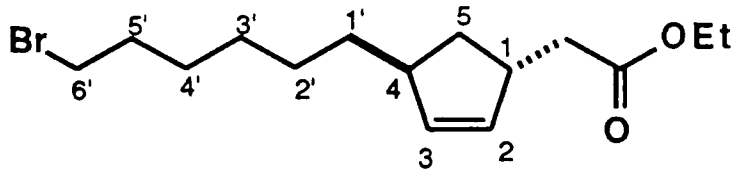
To a stirred solution of hydroxy acid **231** (540mg, 2.37mmol) in EtOH (20ml) was added conc. H_2SO_4 (two drops). After 15h the reaction mixture was concentrated and the residue purified by flash column chromatography (1:1, petrol:ether) to afford the ester **246** (564mg, 93%) as a colourless oil. R_f (1:1, petrol:ether) 0.16; $\nu_{max.}$ (thin film) 3366 (br, s), 3047 (w), 2927 (s), 2856 (s), 1736 (s), 1464 (m), 1372 (m), 1299 (m), 1161 (s), 1032 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.21-1.39 (8H, m), 1.25 (3H, t, *J* 7.1, CH_3), 1.52-1.58 (2H, m), 1.64-1.70 (2H, m, **H**$(5)_2$), 2.25 (1H, dd, *J* 15.0, 8.1, $CH_aH_bCO_2Et$), 2.32 (1H, dd, *J* 15.0, 6.9, $CH_aH_bCO_2Et$), 2.66-2.69 (1H, m, **H**(4)), 3.08-3.11 (1H, m, **H**(1)), 3.62 (2H, t, *J* 6.6, **H**$(6')_2$), 4.12 (2H, q, *J* 7.1, OCH_2CH_3), 5.63 (1H, dt, *J* 5.7, 2.0, **H**(2)), 5.70 (1H, dt, *J* 5.7, 1.9, **H**(3)); δ_C (125MHz, $CDCl_3$) 14.2 (CH_3), 25.7, 27.8, 29.5, 32.7, 35.7 (5xCH_2), 36.3 (**C**(5)), 40.4 (**C**(4)), 41.3 (CH_2CO_2Et), 44.5 (**C**(1)), 60.2 (**C**(6')), 62.9 (OCH_2CH_3), 133.0 (**C**(2)), 136.0 (**C**(3)), 173.0 (CO_2Et); *m/z* (C.I., NH_3) 272 (MNH_4^+, 15), 255 (MH^+, 100), 209 (MH^+-EtOH, 10%); Accurate Mass: Found 255.1960, $C_{15}H_{27}O_3$ (MH^+) requires 255.196020.

Ethyl *trans*-4-(6'-*para*-toluenesulphonyloxyhexyl)cyclopent-2-ene-1-acetate 250



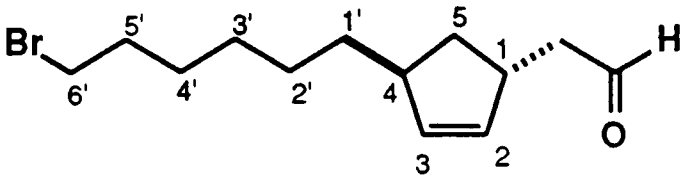
To a stirred solution of ethyl ester **246** (200mg, 0.78mmol) in pyridine (5ml) was added a solution of TsCl (160mg, 0.86mmol) in pyridine (1ml). After 15h the reaction mixture was diluted with ether (30ml), washed successively with 1M aq. HCl (2x30ml), sat. aq. $CuSO_4$ (10ml), water (25ml) and brine (30ml), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (10:1, petrol:ether) gave the title compound **250** (290mg, 91%) as an orange oil. R_f (1:1, petrol:ether) 0.60 (uv active); $\nu_{max.}$ (thin film) 3047 (w), 2927 (s), 2856 (m), 1733 (s), 1447 (w), 1367 (w), 1178 (s), 1098 (w), 1032 (w), 816 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.11-1.40 (8H, m), 1.27 (3H, t, *J* 7.0, CH_3), 1.51-1.77 (4H, m), 2.19-2.41 (2H, m, CH_2CO_2Et), 2.46 (3H, s, **H**(5")$_3$), 2.61-2.66 (1H, m, **H**(4)), 3.08-3.14 (1H, m, **H**(1)), 4.03 (2H, t, *J* 6.5, **H**(6')$_2$), 4.15 (2H, q, *J* 7.0, OCH_2CH_3), 5.63-5.72 (2H, m, **H**(2), **H**(3)), 7.36 (2H, d, *J* 8.0, 2x**H**(3")), 7.80 (2H, d, *J* 8.0, 2x**H**(2")); δ_C (50.3MHz, $CDCl_3$) 14.1 (CH_3), 21.5 (**C**(5")), 25.2, 27.5, 28.6, 28.9, 35.5 (5xCH_2), 36.2 (**C**(5)), 40.3 (**C**(4)), 41.3 (CH_2CO_2Et), 44.5 (**C**(1)), 60.2 (OCH_2CH_3), 70.7 (**C**(6')), 128.0 (2x**C**(3")), 130.0 (2x**C**(2")), 133.2 (**C**(2)), 133.3 (**C**(4")), 136.1 (**C**(3)), 144.9 (**C**(1")), 173.3 (CO_2Et); *m/z* (C.I., NH_3) 426 (MNH_4^+, 70), 409 (MH^+, 100), 380 (MNH_4^+-EtOH, 30), 363 (MH^+-EtOH, 50), 334 (20), 321 (15), 273 (16), 255 (35), 148 (28), 107 (16), 94 (12%); Accurate Mass: Found 409.2049, $C_{22}H_{33}O_5S$ (MH^+) requires 409.204870.

Ethyl *trans*-4-(6'-bromohexyl)cyclopent-2-ene-1-acetate 247



To a stirred solution of the tosylate **250** (140mg, 0.34mmol) in acetone (5ml) was added LiBr (60mg, 0.67mmol) and the mixture heated at reflux for 4h. The reaction mixture was diluted with water (10ml) and extracted with ether (2x15ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (10:1, petrol:ether) to yield the title compound **247** (102mg, 94%) as an oil. R_f (1:1, petrol:ether) 0.57; $\nu_{max.}$ (thin film) 3047 (w), 2927 (s), 2855 (m), 1735 (s), 1464 (w), 1371 (w), 1256 (w), 1160 (m), 1033 (w), 816 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.40 (8H, m), 1.25 (3H, t, *J* 7.0, C**H**$_3$), 1.60-1.70 (2H, m), 1.70-1.90 (2H, m), 2.20 (1H, dd, *J* 14.0, 7.0, C**H**$_a$H$_b$CO$_2$Et), 2.40 (1H, dd, *J* 14.0, 7.0, CH$_a$**H**$_b$CO$_2$Et), 2.60-2.80 (1H, m, **H**(4)), 3.00-3.20 (1H, m, **H**(1)), 3.46 (2H, t, *J* 7.0, **H**(6')$_2$), 4.10 (2H, q, *J* 7.0, OC**H**$_2$CH$_3$), 5.55-5.70 (2H, m, **H**(2), **H**(3)); δ_C (50.3MHz, $CDCl_3$) 14.2 (**C**H$_3$), 27.6, 28.1, 28.9, 32.7, 35.6 (5x**C**H$_2$), 33.9 (**C**(6')), 36.3 (**C**(5)), 40.3 (**C**(4)), 41.3 (**C**H$_2$CO$_2$Et), 44.5 (**C**(1)), 60.1 (O**C**H$_2$CH$_3$), 133.0 (**C**(2)), 135.9 (**C**(3)), 172.9 (**C**O$_2$Et); *m/z* (C.I., NH_3) 334 (M(^{79}Br)NH_4^+, 10), 319 (M(^{81}Br)H^+, 68), 317 (M(^{79}Br)H^+, 70), 272 (30), 255 (100) 149 (20), 80 (25%); Accurate Mass: Found 317.1116, $C_{15}H_{26}BrO_2$ (MH^+) requires 317.111616.

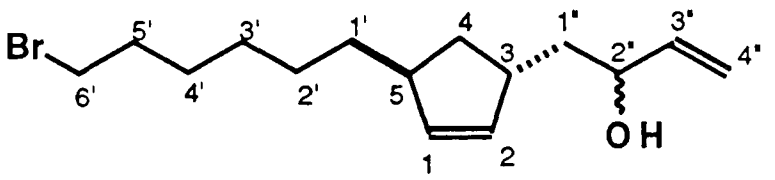
***trans*-4-(6'-Bromohexyl)cyclopent-2-ene-1-acetaldehyde 248**



To a cooled (-78°C) solution of the ester **247** (40mg, 0.13mmol) in toluene (5ml) was added dropwise DIBALH (0.14ml, 1.0M in hexane, 0.14mmol). After 3h

sat. aq. potassium sodium tartrate (3ml) was added and the solution stirred vigorously for 1h. The mixture was diluted with ether (20ml), washed with sat. aq. potassium sodium tartrate (10ml), water (10ml) and brine (15ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (8:1, petrol:ether) to give the aldehyde **248** (30mg, 87%) as an oil. R_f (1:1, petrol:ether) 0.50; $\nu_{max.}$ (thin film) 3046 (w), 2927 (s), 2855 (s), 1724 (s), 1463 (w), 1367 (w), 1254 (w), 1160 (m), 1035 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.40 (8H, m), 1.50-1.90 (4H, m), 2.30-2.60 (2H, m, CH_2CHO), 2.60-2.80 (1H, m, **H**(4)), 3.10-3.30 (1H, m, **H**(1)), 3.40 (2H, t, *J* 7.0, **H**(6')$_2$), 5.60-5.80 (2H, m, **H**(2), **H**(3)), 9.80 (1H, br t, *J* 1.0, C**H**O); δ_C (50.3MHz, $CDCl_3$) 27.6, 28.0, 28.8, 32.7, 35.5 (5xCH_2), 33.9 (**C**(6')), 36.3 (**C**(5)), 38.9 (**C**(4)), 44.6 (**C**(1)), 49.8 (**C**H_2CHO), 132.9 (**C**(2)), 136.4 (**C**(3)), 202.9 (**C**HO); *m/z* (C.I., NH_3) 292 (M(^{81}Br)NH_4^+, 18), 290 (M(^{79}Br)NH_4^+, 20), 273 (M(^{79}Br)H^+, 10), 228 (100), 193 (MH^+-HBr, 50), 149 (29), 109 (43), 80 (77%); Accurate Mass: Found 290.1120, $C_{13}H_{25}BrNO$ (MNH_4^+) requires 290.111950.

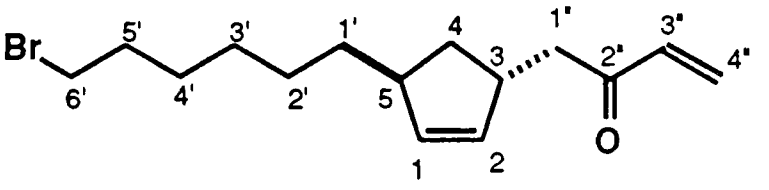
trans-5-(6'-Bromohexyl)-3-(2''-hydroxybut-3''-enyl)cyclopentene 251



To a cooled (-78°C) solution of aldehyde **248** (30mg, 0.11mmol) in THF (2ml) was added dropwise vinylmagnesium bromide (0.15ml, 1.0M in THF, 0.15mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (5ml) and extracted with ether (2x10ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$) and concentrated to give the allylic alcohols **251** (25mg, 75%) as an inseparable mixture (ratio 1:1) of oils. R_f (1:1, petrol:ether) 0.43; $\nu_{max.}$ (thin film) 3367 (br s), 2926 (s), 2855 (s), 1439 (m), 1369 (m), 1255 (m), 1056 (m), 922 (m), 739 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.22-1.58

(8H, m), 1.62-1.71 (3H, m), 1.82-1.88 (2H, m), 2.20-2.40 (1H, m), 2.65-2.67 (1H, m, **H**(5)), 2.81-2.86 (1H, m, **H**(3)), 3.40 (2H, t, *J* 6.8, **H**(6')$_2$), 4.12-4.17 (1H, m, **H**(2")), 5.10 (1H, dd, *J* 10.3, 1.2, **H**(4")$_a$), 5.23 (1H, ddt, *J* 17.0, 3.3, 1.2, **H**(4")$_b$), 5.63-5.72 (2H, m, **H**(1), **H**(2)), 5.87 (1H, ddd, *J* 17.0, 10.3, 6.3, **H**(3")); δ_C (125MHz, $CDCl_3$) 25.6, 27.7/27.8, 28.1/28.9, 32.7, 35.8 (5x**C**H_2), 34.0 (**C**(6')), 36.7/36.9 (**C**(4)), 41.1/41.4 (**C**(5)), 43.2 (**C**(1")), 44.5/44.6 (**C**(3)), 72.2/72.4 (**C**(2")), 114.4/114.6 (**C**(4")), 134.0/134.3 (**C**(2)), 135.0/135.2 (**C**(1)), 141.3/141.4 (**C**(3")); *m/z* (C.I., NH_3) 320 (M(^{81}Br)NH_4^+, 12), 318 (M(^{79}Br)NH_4^+, 20), 302 (M(^{81}Br)NH_4^+-H_2O, 15), 300 (M(^{79}Br)NH_4^+-H_2O, 15), 230 (90), 221 (MH^+-HBr, 50), 212 (100), 167 (65), 149 (22), 119 (61), 108 (18), 91 (65), 80 (50%); Accurate Mass: Found 300.1327, $C_{15}H_{27}BrN$ (MNH_4^+-H_2O) requires 300.132685.

trans-5-(6'-Bromohexyl)-3-(2"-oxobut-3"-enyl)cyclopentene 252

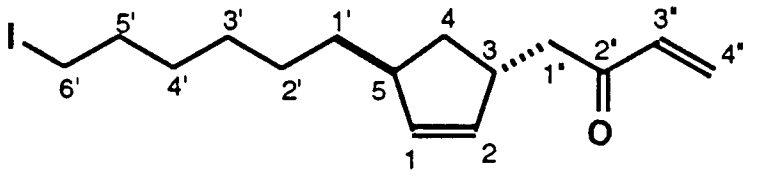


To a stirred solution of the allylic alcohols **251** (25mg, 0.083mmol) in acetone (3ml) was added dropwise Jones' reagent (63µl, 2.0M aq. solution, 0.13mmol). After 10mins MeOH (1ml) was added and the resulting green solution diluted with water (10ml). The mixture was extracted with ether (2x15ml) and the combined organic portions washed with brine (15ml), dried ($MgSO_4$) and concentrated to give the title compound **252** (20mg, 81%) as an oil. R_f (1:1, petrol:ether) 0.60 (uv active); $\nu_{max.}$ (thin film) 3046 (w), 2928 (s), 2856 (m), 1703 (s), 1684 (s), 1615 (m), 1462 (m), 1402 (m), 1256 (w), 1181 (w), 986 (w), 964 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.20-1.43 (8H, m), 1.58-1.65 (1H, m, **H**(4)$_a$), 1.69-1.77 (1H, m, **H**(4)$_b$), 1.80-1.91 (2H, m), 2.56 (1H, dd, *J* 16.2, 7.9, **H**(1")$_a$), 2.64 (1H, dd, *J* 16.2, 6.7, **H**(1")$_b$), 2.60-2.70 (1H, m, **H**(5)), 3.15-3.20 (1H, m, **H**(3)), 3.40 (2H, t, *J* 6.8, **H**(6')$_2$), 5.63-5.70 (2H, m, **H**(1), **H**(2)), 5.82 (1H, dd, *J* 10.5, 1.0, **H**(4")$_a$), 6.20

(1H, dd, *J* 17.7, 1.0, **H**(4")$_b$), 6.34 (1H, dd, *J* 17.7, 10.5, **H**(3")); δ_C (125MHz, $CDCl_3$) 27.6, 28.1, 28.9, 32.7, 35.6 (5xCH_2), 33.9 (**C**(6')), 36.5 (**C**(4)), 40.4 (**C**(5)), 44.5 (**C**(3)), 45.6 (**C**(1")), 128.1 (**C**(4")), 133.3 (**C**(2)), 135.7 (**C**(1)), 136.8 (**C**(3")), 200.5 (**C**(2")); *m/z* (C.I., NH_3) 301 (M(^{81}Br)H$^+$, 10), 221 (100), 219 (MH$^+$-HBr, 50), 149 (29), 135 (17), 119 (15), 107 (17), 93 (29), 80 (51), 55 (43%); Accurate Mass: Found 316.1276, $C_{15}H_{27}BrNO$ (MNH_4^+) requires 316.127600.

trans-5-(6'-Iodohexyl)-3-(2"-oxobut-3"-enyl)cyclopentene 249[189]

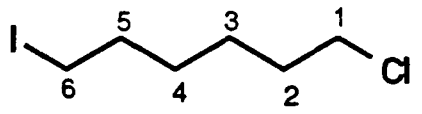
Method 1:



To a stirred solution of bromide **252** (15mg, 0.05mmol) in acetone (2ml) was added NaI (11mg, 0.075mmol). After 15h the reaction mixture was diluted with water (5ml) and extracted with ether (2x10ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (20:1, petrol:ether) to give the title compound **249** (17mg, 97%) as an oil. R_f (1:1, petrol:ether) 0.60 (uv active); $\nu_{max.}$ (thin film) 3045 (w), 2926 (s), 2854 (m), 1708 (sh s), 1615 (m), 1462 (w), 1402 (w), 1367 (w), 1168 (w), 912 (w), 735 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.27-1.41 (8H, m), 1.63 (1H, ddd, *J* 13.1, 8.2, 4.9, **H**(4)$_a$), 1.74 (1H, ddd, *J* 13.1, 8.3, 5.4, **H**(4)$_b$), 1.80-1.86 (2H, m), 2.57 (1H, dd, *J* 16.2, 7.9, **H**(1")$_a$), 2.65 (1H, dd, *J* 16.2, 6.6, **H**(1")$_b$), 2.65-2.71 (1H, m, **H**(5)), 3.12-3.20 (1H, m, **H**(3)), 3.19 (2H, t, *J* 7.1, **H**(6')$_2$), 5.65 (1H, dt, *J* 5.7, 2.1, **H**(2)), 5.71 (1H, dt, *J* 5.7, 2.0, **H**(1)), 5.83 (1H, dd, *J* 10.7, 1.0, **H**(4")$_a$), 6.21 (1H, dd, *J* 17.7, 1.0, **H**(4")$_b$), 6.36 (1H, dd, *J* 17.7, 10.7, **H**(3")); δ_C (125MHz, $CDCl_3$) 7.2 (**C**(6')), 27.7, 28.7, 30.5, 33.5, 35.7 (5xCH_2), 36.6 (**C**(4)), 40.5 (**C**(5)), 44.6 (**C**(3)), 45.7 (**C**(1")), 128.0 (**C**(4")), 133.4 (**C**(2)), 135.8 (**C**(1)), 136.8 (**C**(3")), 200.4 (**C**(2")); *m/z* (C.I., NH_3) 364 (MNH_4^+, 30), 347 (MH$^+$, 100), 219 (MH$^+$-HI, 60), 149

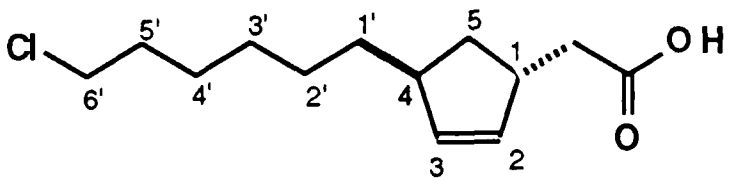
(44), 108 (40), 93 (55), 80 (88), 55 (17%); Accurate Mass: Found 364.1143, $C_{15}H_{27}INO$ (MNH_4^+) requires 364.114264.

1-Chloro-6-iodohexane 253[186]



To a solution of 1,6-dichlorohexane **255** (12g, 77.0mmol) in acetone (50ml) at reflux was added a solution of NaI (5.80g, 39.0mmol) in acetone (25ml), over a period of 3h, *via* a syringe pump. After 4h the reaction mixture was concentrated, diluted with water (100ml) and extracted with ether (2x40ml). The combined organic portions were washed with brine (60ml), dried ($MgSO_4$), concentrated and separated by fractional distillation (Vigreux column) to give recovered dichloride **255** (7.5g), b.p. 100-115°C (water pump), [lit. b.p. 86-88°C (15mmHg)] and the iodo-chloride **253** (5.57g, 30% [77% based on recovered starting material]), b.p. 134-148°C (water pump), [lit. 73-74°C (0.7mmHg)]; R_f (1:1, petrol:ether) 0.90 (uv active); $\nu_{max.}$ (thin film) 2934 (m), 2857 (m), 1461 (m), 1428 (m), 1308 (w), 1270 (w), 1248 (w), 1208 (w), 1184 (w), 1163 (w), 1070 (w), 725 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.35-1.52 (4H, m,), 1.70-1.95 (4H, m), 3.20 (2H, t, *J* 6.5, $\mathbf{H}(6)_2$), 3.54 (2H, t, *J* 6.5, $\mathbf{H}(1)_2$); *m/z* (C.I., NH_3) 82 (100), 69 (22), 58 (70%).

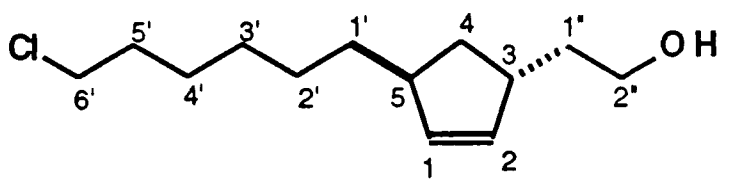
***trans*-4-(6'-Chlorohexyl)cyclopent-2-ene-1-acetic acid 254**



To a cooled (-78°C) solution of chloroiodohexane **253** (1.96g, 7.94mmol) in ether (30ml) was added dropwise *t*-butyllithium (11.1ml, 1.5M in pentane, 16.7mmol)

and, after a further 15mins, a solution of $CuBr.SMe_2$ (2.12g, 10.3mmol) in Me_2S (20ml). The mixture was warmed to -20°C and stirred vigorously. After 20mins the solution was cooled to -78°C and a solution of the alkenyl-lactone **207** (0.4g, 3.17mmol) in ether (2ml) added dropwise. After 15h the reaction mixture was diluted with ether (40ml) and extracted with sat. aq. $NaHCO_3$ (3x20ml). The combined aqueous portions were acidified by the dropwise addition of conc. HCl until the pH fell below 7.0 and then extracted with ether (3x20ml). The combined organic extracts were washed with brine (30ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the title chloro-acid **254** (0.61g, 79%) as an oil. R_f (1:1, petrol:ether) 0.28; $\nu_{max.}$ (thin film) 3047 (w), 2927 (s), 2856 (m), 1708 (s), 1409 (w), 1282 (w), 1205 (w), 941 (w), 743 (w), 652 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.30-1.40 (6H, m), 1.40-1.51 (2H, m), 1.74-1.85 (4H, m), 2.37 (1H, dd, *J* 15.4, 8.1, $CH_aH_bCO_2H$), 2.46 (1H, dd, *J* 15.4, 6.8, $CH_aH_bCO_2H$), 2.68-2.73 (1H, m, **H**(4)), 3.09-3.15 (1H, m, **H**(1)), 3.58 (2H, t, *J* 6.8, **H**(6')$_2$), 5.68 (1H, dt, *J* 5.7, 2.0, **H**(2)), 5.74 (1H, dt, *J* 5.7, 1.9, **H**(3)); δ_C (125MHz, $CDCl_3$) 26.9, 27.7, 29.1, 32.6, 35.6, 36.4 (6xCH_2), 40.0 (**C**(4)), 41.1 (CH_2CO_2H), 44.6 (**C**(6')), 45.1 (**C**(1)), 132.8 (**C**(2)), 136.3 (**C**(3)), 178.8 (CO_2H); *m/z* (C.I., NH_3) 264 ($M(^{37}Cl)NH_4^+$, 35), 262 ($M(^{35}Cl)NH_4^+$, 100), 226 (MNH_4^+-HCl, 12), 201 (25), 199 (82), 187 ($M(^{37}Cl)H^+$-AcOH, 20), 185 ($M(^{35}Cl)H^+$-AcOH, 70), 121 (16), 94 (18), 80 (52), 67 (17), 58 (30%); Accurate Mass: Found 262.1574, $C_{13}H_{25}ClNO_2$ (MNH_4^+) requires 262.157381.

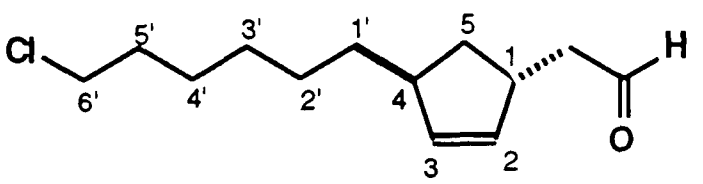
trans-5-(6'-Chlorohexyl)-3-(2"-hydroxyethyl)cyclopentene 256



To a cooled (0°C) suspension of $LiAlH_4$ (62mg, 1.64mmol) in THF (9ml) was added dropwise a solution of acid **254** (0.2g, 0.82mmol) in THF (1ml). After 15h

aq. sat. potassium sodium tartrate (2ml) was added and the mixture stirred vigorously. After a further 1h the reaction mixture was diluted with potassium sodium tartrate (5ml) and ether (10ml) and the layers separated. The organic portion was washed with 1M aq. NaOH (5ml), water (5ml) and brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the alcohol **256** (0.15g, 80%) as a colourless oil. R_f (1:1, petrol:ether) 0.25; $\nu_{max.}$ (thin film) 3355 (br m), 3043 (w), 2927 (s), 2855 (m), 1446 (m), 1367 (w), 1310 (w), 1051 (m), 737 (m), 651 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.23-1.39 (6H, m), 1.40-1.50 (2H, m), 1.53-1.61 (1H, m), 1.62-1.70 (3H, m), 1.71-1.82 (3H, m), 2.65-2.70 (1H, m, **H**(5)), 2.77-2.83 (1H, m, **H**(3)), 3.54 (2H, t, *J* 6.7, **H**(6')$_2$), 3.68 (1H, dt, *J* 10.5, 6.8, **H**(2")$_a$), 3.72 (1H, dt, *J* 10.5, 6.6, **H**(2")$_b$), 5.68 (1H, dt, *J* 5.6, 1.7, **H**(2)), 5.69 (1H, dt, *J* 5.6, 1.7, **H**(1)); δ_C (125MHz, $CDCl_3$) 26.7, 27.6, 28.9, 32.4, 35.7 (5x**C**H_2), 36.6 (**C**(1")), 38.7 (**C**(4)), 41.2 (**C**(5)), 44.5 (**C**(3)), 45.0 (**C**(6')), 61.3 (**C**(2")), 134.3 (**C**(2)), 135.1 (**C**(1)); *m/z* (A.P.C.I., +ve) 247 (30), 245 (100), 231 (MH^+, 18), 229 (45), 227 (85), 213 (10), 211 (20), 144 (22), 122 (26%); Accurate Mass: Found 248.1781, $C_{13}H_{27}ClNO$ (MNH_4^+) requires 248.178116.

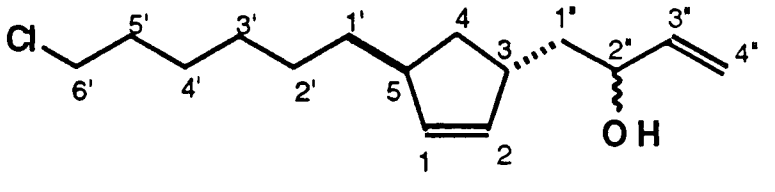
trans-4-(6'-Chlorohexyl)cyclopent-2-ene-1-acetaldehyde 257[189]



A suspension of alcohol **256** (0.15g, 0.65mmol), molecular sieves (0.4g, 4Å powdered) and PDC (0.34g, 0.98mmol) in DCM (10ml) was stirred at RT. After 4h the mixture was diluted with ether (10 ml) and filtered through Celite®. The organic layer was washed with sat. aq. $CuSO_4$ (5ml), 1M aq. HCl (5ml) and brine (10ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the aldehyde **257** (0.14g, 94%) as an oil. R_f (1:1, petrol:ether) 0.50; $\nu_{max.}$ (thin film) 2928 (s), 2856 (m), 1725 (s), 1463 (w), 1071 (w), 733 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.26-1.59

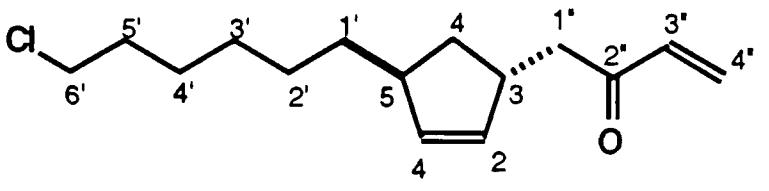
(8H, m), 1.64-1.80 (4H, m), 2.42 (1H, ddd, *J* 16.5, 8.0, 2.0, CH_aH_bCHO), 2.50 (1H, ddd, *J* 16.5, 6.5, 2.0, CH_aH_bCHO), 2.60-2.75 (1H, m, **H**(4)), 3.10-3.30 (1H, m, **H**(1)), 3.53 (2H, t, *J* 7.0, **H**$(6')_2$), 5.60-5.70 (2H, m, **H**(2), **H**(3)), 9.79 (1H, t, *J* 2.0, CHO); *m/z* (A.P.C.I., +ve) 245 (30), 243 (60), 229 (M(38), 227 (100), 211 (38), 185 ($M(^{35}Cl)H^+$-MeCHO, 15), 149 (13), 122 (78), 107 (28%).

trans-5-(6'-Chlorohexyl)-3-(2"-hydroxybut-3"-enyl)cyclopentene 258[189]



To a cooled (-78°C) solution of aldehyde **257** (0.14g, 0.61mmol) in THF (10ml) was added dropwise vinylmagnesium bromide (0.8ml, 1.0M in THF, 0.80mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x15ml). The combined organic portions were washed with brine (20ml), dried ($MgSO_4$) and concentrated to give the allylic alcohols **258** (0.15g, 95%) as an inseparable mixture (ratio 1:1) of oils. R_f (1:1, petrol:ether) 0.43; $\nu_{max.}$ (thin film) 3392 (br m), 3045 (w), 2927 (s), 2855 (m), 1446 (w), 1061 (w), 993 (w), 739 (w), 651 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.85 (13H, m), 2.20-2.40 (1H, m), 2.60-3.00 (2H, m, **H**(5), **H**(3)), 3.54 (2H, t, *J* 7.0, **H**$(6')_2$), 4.10-4.30 (1H, m, **H**(2")), 5.10-5.15 (1H, m, **H**$(4")_a$), 5.20-5.40 (1H, m, **H**$(4")_b$), 5.65-5.75 (2H, m, **H**(1), **H**(2)), 5.80-6.00 (1H, m, **H**(3")); *m/z* (A.P.C.I., +ve) 241 ($M(^{37}Cl)H^+$-H_2O, 42), 239 ($M(^{35}Cl)H^+$-H_2O, 100), 187 (15), 185 (20), 149 (15), 124 (40), 122 (96), 104 (25%).

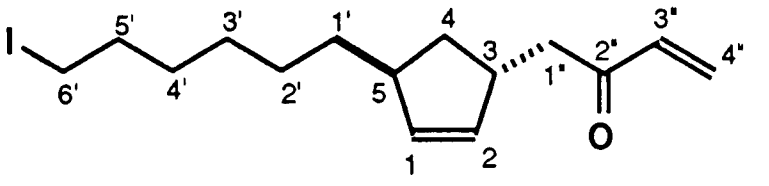
trans-5-(6'-Chlorohexyl)-3-(2"-oxobut-3"-enyl)cyclopentene 259[189]



To a stirred solution of the alcohols **258** (0.14g, 0.55mmol) in acetone (5ml) was added Jones' reagent (0.33ml, 2.0M aq. solution, 0.66mmol) dropwise. After 10mins MeOH (1ml) was added and the resulting green solution diluted with water (15ml). The mixture was extracted with ether (2x20ml) and the combined organic portions washed with brine (15ml), dried ($MgSO_4$) and concentrated to give the title enone **259** (0.11g, 80%) as an oil. R_f (1:1, petrol:ether) 0.55 (uv active); $\nu_{max.}$ (thin film) 3047 (w), 2927 (s), 2856 (s), 1705 (s), 1683 (sh s), 1616 (s), 1447 (m), 1402 (w), 1365 (w), 1160 (m), 986 (w), 741 (m), 651 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.52 (8H, m), 1.50-1.70 (2H, m), 1.70-1.90 (2H, m, **H**(5')$_2$), 2.50-2.80 (3H, m, **H**(1")$_2$, **H**(5)), 3.10-3.30 (1H, m, **H**(3)), 3.53 (2H, t, *J* 7.0, **H**(6')$_2$), 5.60-5.80 (2H, m, **H**(1), **H**(2)), 5.80-5.95 (1H, m, **H**(4")$_a$), 6.15-6.50 (2H, m, **H**(4")$_b$, **H**(3")); *m/z* (C.I., NH_3) 274 (M(^{37}Cl)NH_4^+, 30), 272 (M(^{35}Cl)NH_4^+, 12), 257 (40), 255 (M(^{35}Cl)H^+, 42), 238 (50), 221 (100), 219 (MH^+-HCl, 20), 185 (25), 149 (38), 80 (39%).

trans-5-(6'-Iodohexyl)-3-(2"-oxobut-3"-enyl)cyclopentene 249[189]

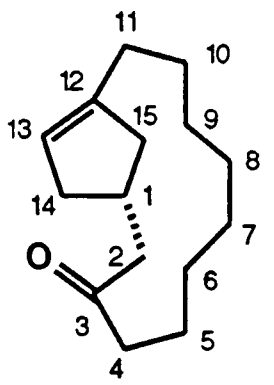
Method 2



To a stirred solution of chloride **259** (60mg, 0.24mmol) in MEK (5ml) was added NaI (105mg, 0.71mmol) and the mixture heated at reflux. After 15h the reaction mixture was diluted with water (10ml) and extracted with ether (2x10ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography

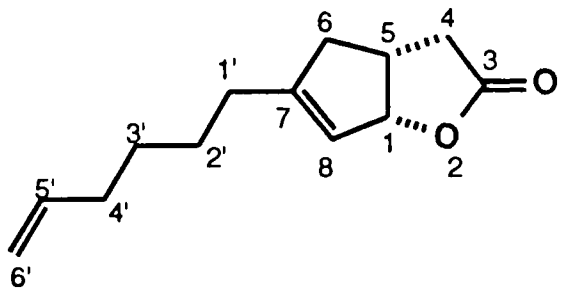
(20:1, petrol:ether) to give the title compound **249** (68mg, 82%) as an oil. The data were identical to the compound described above.

Bicyclo[10.2.1]pentadec-12-en-3-one 261



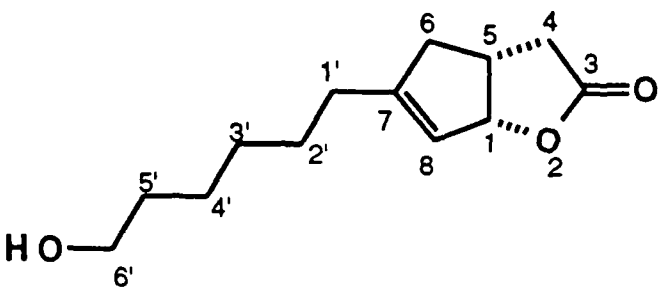
To a solution of enone **249** (56mg, 0.16mmol) and AIBN (2mg, 0.01mmol) in degassed benzene (80ml) at reflux was added, *via* syringe pump over 10h, a solution of $^{n}Bu_3SnH$ (70µl, ~75% pure by ^1H NMR, 0.19mmol) in degassed benzene (4ml). After a further 3h the reaction mixture was concentrated, thiophenol (25µl, 0.22mmol) was added and the mixture purified by flash column chromatography (200:1, petrol:ether) to give the title macrocycle **261** (13mg, 37%) as an oil. R_f (1:1, petrol:ether) 0.50; $\nu_{max.}$ (thin film) 2927 (s), 2856 (m), 1718 (s), 1656 (w), 1446 (m), 1127 (m), 1041 (m), 877 (w), 666 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.20-1.33 (8H, m), 1.37-1.44 (2H, m, $\mathbf{H}(10)_2$), 1.67-1.74 (2H, m, $\mathbf{H}(15)_a$, $\mathbf{H}(5)_a$), 1.87-1.93 (1H, m, $\mathbf{H}(14)_a$), 2.00 (1H, dddd, *J* 14.1, 8.6, 5.6, 5.6, $\mathbf{H}(5)_b$), 2.04 (2H, t, *J* 8.0, $\mathbf{H}(11)_2$), 2.21-2.25 (2H, m, $\mathbf{H}(4)_2$), 2.31 (1H, dd, *J* 15.3, 6.8, $\mathbf{H}(2)_a$), 2.48 (1H, dd, *J* 15.3, 6.2, $\mathbf{H}(2)_b$), 2.58 (1H, dd, *J* 16.7, 9.5, $\mathbf{H}(14)_b$), 2.81 (1H, tq, *J* 9.5, 6.5, **H**(1)), 3.02-3.10 (1H, m, $\mathbf{H}(15)_b$), 5.19 (1H, d, *J* 1.6, **H**(13)); δ_C (125MHz, $CDCl_3$) 22.6, 25.9, 27.6, 29.1, 29.7, 30.9, 31.7, 34.3, 37.1, 42.8 (10x$\mathbf{C}H_2$), 42.9 (**C**(1)), 43.9 (**C**(2)), 126.6 (**C**(13)), 144.9 (**C**(12)), 214.4 (**C**(3)); *m/z* (C.I., NH_3) 238 (MNH_4^+, 100), 221 (MH^+, 30), 150 (12%); Accurate Mass: Found 238.2171, $C_{15}H_{28}NO$ (MNH_4^+) requires 238.217089.

rel-(1*R*, 5*R*)-7-(Hex-5'-enyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one 262



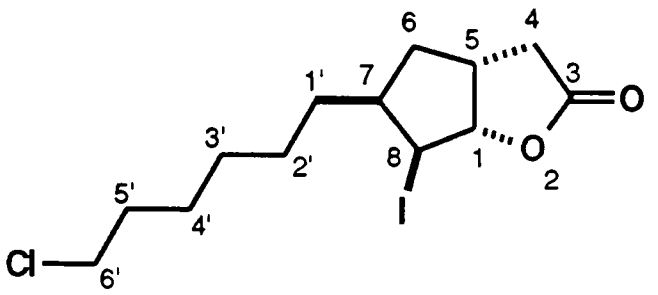
To a stirred solution of the iodo-lactone **226** (0.22g, 0.66mmol) in benzene (10ml) was added DBU (0.2ml, 1.3mmol) and the mixture heated at reflux. After 1h 1M aq. HCl (10ml) was added and the mixture extracted with ether (2x10ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$) and concentrated to give the alkenyl-lactone **262** (0.13g, 95%) as an oil which needed no further purification. R_f (1:1, petrol:ether) 0.17; $\nu_{max.}$ (thin film) 3075 (w), 2929 (s), 2856 (m), 1771 (s), 1642 (w), 1445 (w), 1417 (w), 1349 (w), 1306 (w), 1171 (m), 1004 (m), 933 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.37-1.43 (2H, m), 1.46-1.53 (2H, m), 2.04-2.09 (2H, m, **H**(4')$_2$), 2.12 (2H, td, *J* 7.3, 1.0, **H**(1')$_2$), 2.20 (1H, dd, *J* 17.0, 1.4, **H**(6)$_a$), 2.31 (1H, dd, *J* 18.3, 5.5, **H**(4)$_a$), 2.67 (1H, ddd, *J* 17.0, 8.4, 0.7, **H**(6)$_b$), 2.82 (1H, dd, *J* 18.3, 10.5, **H**(4)$_b$), 3.13 (1H, dddd, *J* 16.0, 10.5, 5.5, 3.1, **H**(5)), 4.96 (1H, ddd, *J* 10.2, 1.7, 1.0, **H**(6')$_a$), 5.00 (1H, ddd, *J* 17.0, 3.4, 1.7, **H**(6')$_b$), 5.47 (1H, d, *J* 7.4, **H**(1)), 5.52 (1H, dd, *J* 3.4, 1.7, **H**(8)), 5.79 (1H, dddd, *J* 17.0, 10.2, 6.7, 6.7, **H**(5')); δ_C (125MHz, $CDCl_3$) 26.7, 28.5, 30.8, 33.4 (4xCH_2), 35.5 (**C**(6)), 36.4 (**C**(4)), 42.0 (**C**(5)), 90.1 (**C**(1)), 114.6 (**C**(6')), 122.2 (**C**(8)), 138.5 (**C**(5')), 152.2 (**C**(7)), 177.4 (**C**(3)); *m/z* (C.I., NH_3) 224 (MNH_4^+, 35), 207 (MH^+, 45), 163 (MH^+-CO_2, 100%); Accurate Mass: Found 224.1651, $C_{13}H_{22}NO_2$ (MNH_4^+) requires 224.1650426.

rel-(1*R*, 5*R*)-7-(6'-Hydroxyhexyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one 263



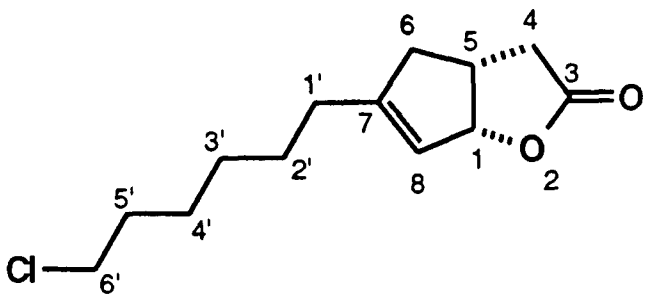
To a stirred solution of the iodo-lactone **230** (0.58g, 1.65mmol) in benzene (30ml) was added DBU (0.62ml, 4.12mmol) and the mixture heated at reflux. After 1h the reaction mixture was diluted with 1M aq. HCl (20ml) and extracted with ether (2x20ml). The combined organic extracts were washed with brine (20ml), dried ($MgSO_4$) and concentrated to give the alkenyl-lactone **263** (0.37g, 99%) as an oil which needed no further purification. R_f (EtOAc) 0.37; $\nu_{max.}$ (thin film) 3416 (br s), 2927 (s), 2855 (m), 1767 (s), 1649 (w), 1446 (w), 1350 (w), 1171 (m), 1073 (w), 665 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.29-1.40 (4H, m), 1.41-1.50 (2H, m), 1.52-1.60 (2H, m), 2.12 (2H, td, *J* 8.1, 0.9, **H**(1')$_2$), 2.20 (1H, dd, *J* 17.0, 1.3, **H**(6)$_a$), 2.32 (1H, dd, *J* 18.3, 5.5, **H**(4)$_a$), 2.67 (1H, ddt, *J* 17.0, 8.4, 0.8, **H**(6)$_b$), 2.82 (1H, dd, *J* 18.3, 10.5, **H**(4)$_b$), 3.13 (1H, dddd, *J* 16.0, 10.5, 5.5, 3.1, **H**(5)), 3.65 (2H, t, *J* 6.5, **H**(6')$_2$), 5.48 (1H, dd, *J* 7.4, 0.8, **H**(1)), 5.53 (1H, dd, *J* 3.4, 1.6, **H**(8)); δ_C (125MHz, $CDCl_3$) 25.5, 27.2, 29.1, 30.9, 32.6 (5x**C**H_2), 35.5 (**C**(6)), 36.4 (**C**(4)), 42.0 (**C**(5)), 62.9 (**C**(6')), 90.2 (**C**(1)), 122.1 (**C**(8)), 152.3 (**C**(7)), 177.5 (**C**(3)); *m/z* (C.I., NH_3) 242 (MNH_4^+, 100), 225 (MH^+, 65), 207 (MH^+-H_2O, 70), 181 (MH^+-CO_2, 100%); Accurate Mass: Found 242.1756, $C_{13}H_{24}NO_3$ (MNH_4^+) requires 242.1756059.

rel-(1*S*, 5*R*, 7*S*, 8*S*)-7-(6'-Chlorohexyl)-8-iodo-2-oxabicyclo[3.3.0]octan-3-one 264



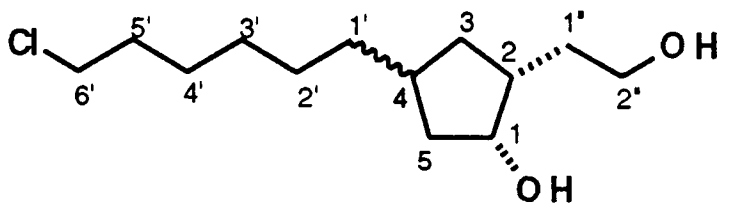
To a vigorously stirred solution of the acid **254** (550mg, 2.20mmol) in water (30ml) was added successively $KHCO_3$ (1.46g, 13.3mmol), KI (2.25g, 13.3mmol) and, after 5mins, I_2 (1.15g, 4.44mmol) followed by ether (15ml). After 13h conc. HCl was added dropwise until the pH fell below 7 at which point the mixture was diluted with ether (30ml) and the organic layer separated. The ether fraction was washed with sat. aq. $Na_2S_2O_3$ (5ml), water (10ml) and brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo.* Flash column chromatography (3:1, petrol:ether) afforded the iodo-lactone **264** (820mg, 89%) as a colourless oil. R_f (1:1, petrol:ether) 0.32 (uv active); $\nu_{max.}$ (thin film) 2929 (s), 2855 (s), 1780 (s), 1455 (m), 1342 (w), 1298 (m), 1215 (m), 1160 (s), 995 (s), 871 (m), 725 (w), 650 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.20-1.30 (3H, m), 1.32-1.37 (4H, m), 1.43-1.47 (2H, m), 1.56 (1H, dd, *J* 13.0, 6.4, **H**$(6)_a$), 1.74-1.80 (2H, m, **H**$(5')_2$), 1.91 (1H, ddd, *J* 13.0, 13.0, 10.0, **H**$(6)_b$), 2.37 (1H, dd, *J* 18.5, 2.0, **H**$(4)_a$), 2.90 (1H, dd, *J* 18.5, 10.3, **H**$(4)_b$), 3.17 (1H, dddd, *J* 10.0, 10.0, 6.1, 2.0, **H**(5)), 3.54 (2H, t, *J* 6.7, **H**$(6')_2$), 4.53 (1H, d, 3.8, **H**(8)), 5.30 (1H, d, *J* 6.1, **H**(1)); δ_C (125MHz, $CDCl_3$) 26.6, 27.5, 28.8, 32.4, 35.0 (5x**C**H_2), 35.1 (**C**(8)), 36.4 (**C**(6)), 38.3 (**C**(4)), 41.4 (**C**(7)), 41.8 (**C**(5)), 45.0 (**C**(6')), 92.2 (**C**(1)), 177.1 (**C**(3)); *m/z* (A.P.C.I., +ve) 243 ($M(^{35}Cl)H^+$-HI, 10), 189 (MH^+-HI-HCl-H_2O, 20), 173 (100%); Accurate Mass: Found 243.1165, $C_{13}O_2H_{20}Cl$ (MH^+-HI) requires 243.115182.

rel-(1*R*, 5*R*)-7-(6'-Chlorohexyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one 265



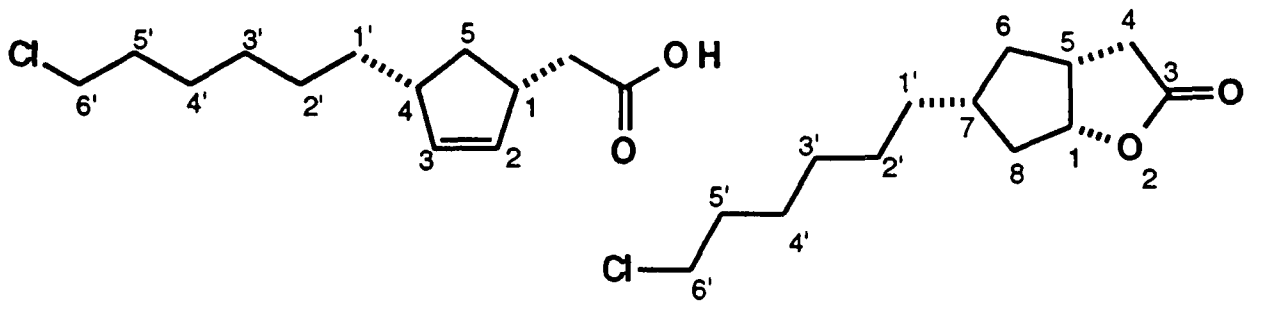
To a stirred solution of the iodo-lactone **264** (750mg, 2.02mmol) in benzene (20ml) was added DBU (333µl, 2.23mmol) and the mixture heated at reflux. After 1h the reaction mixture was diluted with 1M aq. HCl (20ml) and extracted with ether (2x15ml). The combined organic portions were washed with brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (1:1, petrol:ether) to give the alkenyl-lactone **265** (471mg, 96%) as an oil. R_f (1:1, petrol:ether) 0.18; $\nu_{max.}$ (thin film) 2932 (s), 2857 (m), 1771 (s), 1649 (w), 1446 (w), 1348 (w), 1307 (m), 1172 (s), 1004 (s), 931 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.32-1.37 (2H, m), 1.43-1.52 (4H, m), 1.75-1.80 (2H, m, **H**(5')$_2$), 2.12 (2H, t, *J* 7.3, **H**(1')$_2$), 2.20 (1H, dd, *J* 17.0, 1.6, **H**(6)$_a$), 2.32 (1H, dd, *J* 18.3, 5.5, **H**(4)$_a$), 2.67 (1H, ddd, *J* 17.0, 8.4, 1.0, **H**(6)$_b$), 2.82 (1H, dd, *J* 18.3, 10.5, **H**(4)$_b$), 3.09-3.16 (2H, m, **H**(5)), 3.53 (2H, t, *J* 6.7, **H**(6')$_2$), 5.48 (1H, d, *J* 8.2, **H**(1)), 5.53 (1H, ddd, *J* 3.4, 3.4, 1.6, **H**(8)); δ_C (50.3MHz, $CDCl_3$) 26.5, 27.0, 28.5, 30.8, 32.3 (5xCH_2), 35.4 (**C**(6)), 36.3 (**C**(4)), 42.0 (**C**(5)), 45.0 (**C**(6')), 90.2 (**C**(1)), 122.3 (**C**(8)), 152.5 (**C**(7)), 177.8 (**C**(3)); *m/z* (A.P.C.I., +ve) 259 (40), 257 (95), 245 ($M(^{37}Cl)H^+$, 45), 243 ($M(^{35}Cl)H^+$, 100), 227 ($M(^{37}Cl)H^+$-H_2O, 15), 225 ($M(^{35}Cl)H^+$-H_2O, 40), 199 (50), 183 (77), 153 (96), 125 (47) 107 (20%); Accurate Mass: Found 243.1156, $C_{13}H_{20}ClO_2$ (MH^+) requires 243.115182.

rel-(1*R*, 2*R*, 4*R*)- and (1*R*, 2*R*, 4*S*)-2-(2''-Hydroxyethyl)-4-(6'-chlorohexyl)-cyclopentan-1-ol 268



To a solution of lactone **265** (60mg, 0.25mmol) in THF (6ml) was added BH_3.THF (0.25ml, 1.0M in THF, 0.25mmol) and, after a further 18h, 1M NaOH (1ml). After 1h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (20ml). The organic portion was washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (5:1, petrol:EtOAc) to give the title diols **268** (55mg, 89%) as a mixture (ratio 4:3) of oils. R_f (EtOAc) 0.38, 0.32; $\nu_{max.}$ (thin film) 3354 (s), 2927 (s), 2856 (m), 1631 (w), 1445 (m), 1311 (w), 1055 (sh m), 726 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.85-0.95 (1H, m), 1.21-1.60 (7H, m), 1.60-1.77 (3H, m), 1.77-1.95 (4H, m), 2.00-2.15 (2H, m), 2.15-2.29 (1H, m), 3.57 (2H, t, *J* 6.8, **H**(6')$_2$), 3.67-3.73 (2H, m, **H**(2'')$_2$), 3.89-3.92 (1H, m, **H**(1)); δ_C (125MHz, $CDCl_3$) 26.8, 28.0/28.3, 29.0/29.2, 32.6, 33.6/34.4, 36.1/36.3, 36.7, 39.1/39.9 (8x**C**H_2), 40.8/41.3 (**C**(4)), 45.1 (**C**(6')), 47.7/49.0 (**C**(2)), 61.9/62.4 (**C**(2'')), 78.1/78.6 (**C**(1)); *m/z* (A.P.C.I., +ve) 279 (80), 263 (10), 249 (12), 247 (52), 233 (M(^{37}Cl)H^+-H_2O, 20), 231 (M(^{35}Cl)H^+-H_2O, 50), 215 (M(^{37}Cl)H^+-2H_2O, 40), 213 (M(^{35}Cl)H^+-2H_2O, 100), 157 (56), 109 (74%); Accurate Mass: Found 231.1516, $C_{13}H_{24}ClO$ (MH^+-H_2O) requires 231.151567.

cis-4-(6'-Chlorohexyl)cyclopent-2-ene-1-acetic acid 266 and _rel_-(1_R_, 5_R_, 7_R_)-(6'-Chlorohexyl)-2-oxabicyclo[3.3.0]octan-3-one 270

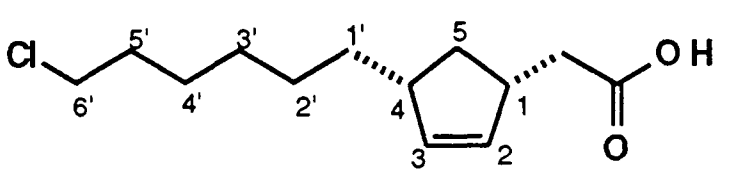


To a solution of lactone **265** (40mg, 0.17mmol) in THF (4ml) was added BH_3.THF (85µl, 1.0M in THF, 0.085mmol) then, after 18h, 1M NaOH (0.5ml) and, after a further 1h, conc. HCl (2 drops). After 1h the reaction mixture was diluted with 1M aq. HCl (5ml) and extracted with ether (10ml). The organic extract was washed with brine (5ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (12:1, petrol:ether) to give the recovered starting material **265** (20mg), the reduced lactone **270** (12mg, [58% based on recovered starting material]) and the *cis*-acid **266** (7mg, [34% based on recovered starting material]) as oils. Reduced lactone **270**: R_f (1:1, petrol:ether) 0.21; $\nu_{max.}$ (thin film) 2931 (s), 2850 (m), 1769 (s), 1417 (w), 1166 (m), 1037 (w), 730 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.20-1.36 (5H, m), 1.36-1.51 (5H, m), 1.74-1.80 (2H, m), 1.84-1.92 (1H, m), 2.10-2.18 (1H, m), 2.30-2.39 (2H, m), 2.69-2.77 (2H, m, **H**(4)$_2$), 3.54 (2H, t, *J* 6.7, **H**(6')$_2$), 4.91 (1H, ddd, *J* 11.2, 6.9, 4.3, **H**(1)); δ_C (125MHz, $CDCl_3$) 26.8, 28.3, 29.0, 32.5, 34.9, 35.3, 39.1 (7x**C**H_2), 39.1, 39.3, 39.9 (**C**(4), **C**(5), **C**(7)), 45.1 (**C**(6')), 85.8 (**C**(1)), 177.4 (**C**(3)); *m/z* (A.P.C.I., +ve) 245 (M(^{35}Cl)H^+, 25), 227 (M(^{35}Cl)H^+-H_2O, 15), 187 (M(^{37}Cl)H^+-AcOH, 13) 185 (M(^{35}Cl)H^+-AcOH, 40), 124 (32), 122 (100%); Accurate Mass: Found 245.1308, $C_{13}H_{22}ClO_2$ (MH^+) requires 245.130832; *cis*-acid **266**: R_f (1:1, petrol:ether) 0.28; $\nu_{max.}$ (thin film) 3054 (w), 2929 (s), 2862 (m), 1706 (s), 1545 (w), 1530 (w), 1380 (w), 1331 (w), 1261 (w), 1134 (w), 1092 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.00 (1H, dt, *J* 12.8, 7.7, **H**(5)$_a$), 1.20-1.39 (6H, m), 1.41-1.49 (2H, m), 1.72-1.81 (2H, m), 2.35 (1H, dd, *J* 15.5, 7.8, C**H**$_a$H$_b$CO$_2$H), 2.37 (1H, dt, *J* 12.8, 8.0, **H**(5)$_b$), 2.49 (1H, dd, *J* 15.5, 6.9,

$CH_aH_bCO_2H$), 2.61-2.68 (1H, m, **H**(4)), 3.03-3.09 (1H, m, **H**(1)), 3.54 (2H, t, *J* 6.7, **H**(6')$_2$), 5.65 (1H, dt, *J* 5.5, 2.0, **H**(2)), 5.72 (1H, dt, *J* 5.5, 2.1, **H**(3)); δ_C (125MHz, $CDCl_3$) 26.8, 27.7, 29.0, 32.6, 36.5 (5x**C**H_2), 37.1 (**C**(5)), 40.9 (**C**H_2CO_2H), 41.7 (**C**(4)), 45.2 (**C**(1)), 45.7 (**C**(6')), 132.8 (**C**(2)), 136.3 (**C**(3)), 178.7 (**C**O_2H); *m/z* (C.I., NH_3) 264 (M(^{37}Cl)NH_4^+, 35), 262 (M(^{35}Cl)NH_4^+, 90), 247 (M(^{37}Cl)H^+, 30), 245 (M(^{35}Cl)H^+, 80), 211 (35), 209 (MH^+-HCl, 25), 187 (M(^{37}Cl)H^+-AcOH, 11), 185 (M(^{35}Cl)H^+-AcOH, 40), 151 (32), 149 (40), 140 (100), 107 (28), 94 (32), 81 (50), 67 (33), 55 (48%); Accurate Mass: Found 262.1442, $C_{13}H_{25}ClNO_2$ (MNH_4^+) requires 262.157381 (Deteriorated in transit).

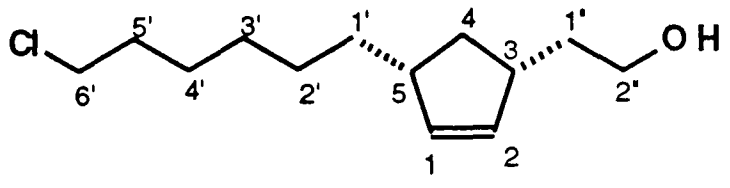
cis-4-(6'-Chlorohexyl)cyclopent-2-ene-1-acetic acid 266

Method 2



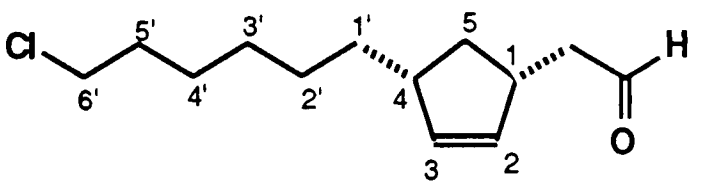
To a solution of lactone **265** (0.57g, 2.35mmol) in THF (50ml) was added dropwise BH_3.THF (1.2ml, 1.0M in THF, 1.20mmol) and, after a further 18h, TBAF (2.4ml, 1.0M in THF, 2.40mmol). After 1h the reaction mixture was diluted with water (20ml) and extracted with ether (30ml). The organic portion was washed with 1M aq. HCl (20ml) and brine (30ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (DCM) to give the starting material **265** (0.28g) and the *cis*-acid **266** (0.27g, [92% based on recovered starting material]) as an oil. The data for this compound were identical to that described earlier.

cis-5-(6'-Chlorohexyl)-3-(2''-hydroxyethyl)cyclopentene 271



To a cooled (0°C) suspension of $LiAlH_4$ (22mg, 0.57mmol) in THF (5ml) was added a solution of *cis*-acid **266** (70mg, 0.29mmol) in THF (1ml). After 15h sat. aq. potassium sodium tartrate (1ml) was added and the mixture stirred vigorously. After a further 1h the reaction mixture was diluted with sat. aq. potassium sodium tartrate (3ml) and ether (5ml) and the layers separated. The organic portion was washed with 1M aq. NaOH (5ml), water (5ml) and brine (5ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the *cis*-alcohol **271** (65mg, 92%) as an oil. R_f (1:1, petrol:ether) 0.25; $\nu_{max.}$ (thin film) 3368 (br m), 3045 (w), 2927 (s), 2855 (w), 1446 (m), 1051 (m), 737 (w), 669 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.95 (1H, dt, *J* 12.6, 7.8, **H**$(4)_a$), 1.26-1.40 (5H, m), 1.41-1.49 (3H, m), 1.54-1.61 (1H, dddd, *J* 13.8, 13.8, 6.9, 6.6, **H**$(1'')_a$), 1.71-1.81 (3H, m, **H**$(1'')_b$, **H**$(5')_2$), 2.28 (1H, dt, *J* 12.6, 8.0, **H**$(4)_b$), 2.58-2.64 (1H, m, **H**(5)), 2.70-2.76 (1H, m, **H**(3)), 3.54 (2H, t, *J* 6.7, **H**$(6')_2$), 3.69 (1H, dt, *J* 10.5, 6.9, **H**$(2'')_a$), 3.73 (1H, dt, *J* 10.5, 6.6, **H**$(2'')_b$), 5.66 (1H, dt, *J* 5.7, 1.9, **H**(2)), 5.67 (1H, dt, *J* 5.7, 1.9, **H**(1)); δ_C (125MHz, $CDCl_3$) 26.8, 27.8, 29.0, 32.5, 36.6 (5x**C**H_2), 37.3 (**C**(1")), 39.6 (**C**(4)), 42.2 (**C**(5)), 45.1 (**C**(3)), 45.6 (**C**(6')), 61.7 (**C**(2")), 134.3 (**C**(2)), 135.4 (**C**(1)); *m/z* (C.I., NH_3) 250 (M(^{37}Cl)NH_4^+, 25), 248 (M(^{35}Cl)NH_4^+, 90), 212 (MNH_4^+-HCl, 50), 195 (MH^+-HCl, 65), 177 (19), 165 (25), 111 (27), 93 (100), 81 (21%); Accurate Mass: Found 248.1781, $C_{13}H_{27}ClNO$ (MNH_4^+) requires 248.178116.

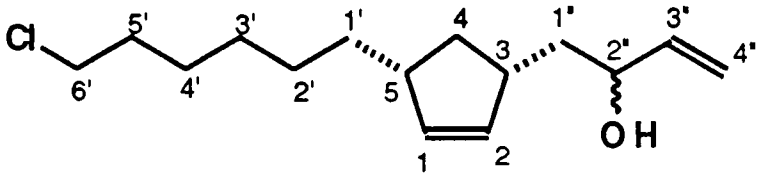
cis-4-(6'-Chlorohexyl)cyclopent-2-ene-1-acetaldehyde 272[189]



A suspension of alcohol **271** (60mg, 0.26mmol), molecular sieves (0.15g, 4Å powdered) and PDC (0.11g, 0.31mmol) in DCM (5ml) was stirred at RT. After 4h the solution was diluted with ether (5ml) and filtered through Celite®. The

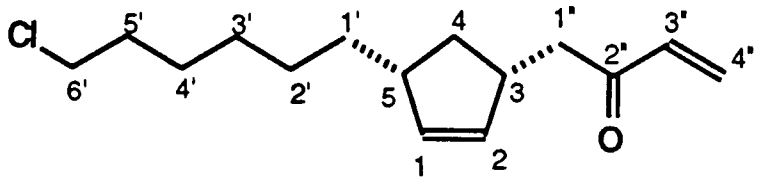
organic layer was washed with sat. aq. $CuSO_4$ (5ml), 1M aq. HCl (5ml) and brine (5ml) then dried ($MgSO_4$) and concentrated *in vacuo* to give the *cis*-aldehyde **272** (50mg, 84%) as an oil. R_f (1:1, petrol:ether) 0.50; $\nu_{max.}$ (thin film) 2927 (s), 2855 (s), 1724 (s), 1446 (w), 1100 (w), 738 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.95 (1H, dt, *J* 13.0, 7.5, **H**$(5)_a$), 1.25-1.50 (8H, m), 1.65-1.82 (2H, m, **H** $(5')_2$), 2.37 (1H, dt, *J* 13.0, 8.0, **H**$(5)_b$), 2.40-2.70 (3H, m, CH_2CHO, **H**(4)), 3.05-3.15 (1H, m, **H**(1)), 3.53 (2H, t, *J* 7.0, **H**$(6')_2$), 5.55-5.65 (1H, m, **H**(2)), 5.65-5.72 (1H, m, **H**(3)); *m/z* (A.P.C.I., +ve) 245 (15), 227 (15), 144 (11), 124 (36), 122 (100%).

cis-5-(6'-Chlorohexyl)-3-(2"-hydroxybut-3"-enyl)cyclopentene 273[189]



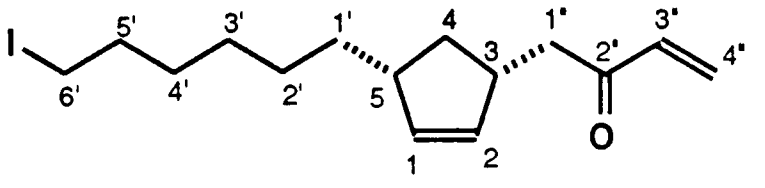
To a cooled (-78°C) solution of aldehyde **272** (30mg, 0.13mmol) in THF (2ml) was added vinylmagnesium bromide (160µl, 1.0M in THF, 0.16mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (2ml) and extracted with ether (2x5ml). The combined organic fractions were washed with brine (5ml), dried ($MgSO_4$) and concentrated to give the allylic alcohols **273** (30mg, 89%) as an inseparable mixture (ratio 1:1) of oils. R_f (1:1, petrol:ether) 0.43; $\nu_{max.}$ (thin film) 3407 (br m), 2927 (s), 2855 (m), 1446 (w), 1070 (w), 736 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.85-1.00 (1H, m, **H**$(4)_a$), 1.20-1.50 (10H, m), 1.60-1.80 (2H, m, **H**$(5')_2$), 2.20-2.40 (1H, m, **H**$(4)_b$), 2.50-2.80 (2H, m, **H**(5), **H**(3)), 3.54 (2H, t, *J* 7.0, **H**$(6')_2$), 4.10-4.25 (1H, m, **H**(2")), 5.05-5.35 (2H, m, **H**$(4")_2$), 5.60-5.75 (2H, m, **H**(1), **H**(2)), 5.75-6.00 (1H, m, **H**(3")); *m/z* (A.P.C.I., +ve) 255 (10), 253 (20), 245 (40), 241 ($M(^{37}Cl)H^+$-H_2O, 11), 239 ($M(^{35}Cl)H^+$-H_2O, 25), 185 (18), 122 (100%).

cis-5-(6'-Chlorohexyl)-3-(2"-oxobut-3"-enyl)cyclopentene 274[189]



To a stirred solution of the allylic alcohols **273** (90mg, 0.35mmol) in acetone (3ml) was added Jones' reagent (0.20ml, 2.0M aq. solution, 0.4mmol) dropwise. After 10mins MeOH (0.5ml) was added and the resulting green solution diluted with water (5ml). The mixture was extracted with ether (2x10ml) and the combined organic portions washed with brine (10ml), dried ($MgSO_4$) and concentrated to give the title enone **274** (73mg, 82%) as an oil. R_f (1:1, petrol:ether) 0.55 (uv active); $\nu_{max.}$ (thin film) 3046 (w), 2927 (s), 2856 (s), 1712 (s), 1615 (s), 1446 (m), 1404 (m), 1369 (m), 1265 (m), 1165 (m), 990 (w), 812 (w), 739 (m), 651 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.85-1.00 (1H, m, **H**$(4)_a$), 1.24-1.50 (8H, m), 1.70-1.90 (2H, m, **H**$(5')_2$), 2.25-2.50 (1H, m, **H**$(4)_b$), 2.50-2.80 (3H, m, **H**$(1")_2$, **H**(5)), 3.10-3.20 (1H, m, **H**(3)), 3.53 (2H, t, *J* 7.0, **H**$(6')_2$), 5.60-5.75 (2H, m, **H**(1), **H**(2)), 5.82 (1H, dd, *J* 10.5, 0.5, **H**$(4")_a$), 6.20 (1H, dd, *J* 17.5, 0.5, **H**$(4")_b$), 6.36 (1H, dd, *J* 17.5, 10.5, **H**(3")); *m/z* (A.P.C.I., +ve) 271 (25), 269 (70), 257 ($M(^{37}Cl)H^+$, 13), 255 ($M(^{35}Cl)H^+$, 20), 187 ($M(^{37}Cl)H^+$-MVK, 30), 185 ($M(^{35}Cl)H^+$-MVK, 100), 144 (81), 122 (49%).

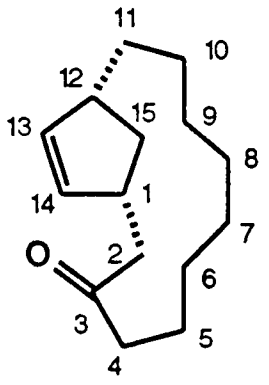
cis-5-(6'-Iodohexyl)-3-(2"-oxobut-3"-enyl)cyclopentene 206[189]



To a stirred solution of chloride **274** (29mg, 0.11mmol) in MEK (3ml) was added NaI (51mg, 0.34mmol) and the mixture heated at reflux. After 15h the reaction mixture was diluted with water (5ml) and extracted with ether (2x10ml). The combined organic portions were washed with brine (5ml), dried ($MgSO_4$),

concentrated and purified by flash column chromatography (20:1, petrol:ether) to give the title compound **206** (34mg, 86%) as an oil. R_f (1:1, petrol:ether) 0.60 (uv active); $\nu_{max.}$ (thin film) 2926 (s), 2854 (w), 1708 (sh s), 1615 (w), 1445 (m), 1128 (s), 1044 (m), 739 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.92 (1H, dt, *J* 13.0, 7.5, **H**$(4)_a$), 1.19-1.45 (8H, m), 1.80-1.90 (2H, m, **H**$(5')_2$), 2.30-2.40 (1H, m, **H**$(4)_b$), 2.50-2.75 (3H, m, **H**$(1'')_2$, **H**(5)), 3.05-3.15 (1H, m, **H**(3)), 3.19 (2H, t, *J* 7.0, **H**$(6')_2$), 5.55-5.64 (1H, m, **H**(2)), 5.64-5.70 (1H, m, **H**(1)), 5.82 (1H, dd, *J* 10.5, 1.0, **H**$(4'')_a$), 6.21 (1H, dd, *J* 18.0, 1.0, **H**$(4'')_b$), 6.36 (1H, dd, *J* 18.0, 10.5, **H**(3'')); *m/z* (A.P.C.I., +ve) 361 (25), 347 (MH^+, 100), 277 (MH^+-MVK, 55), 219 (MH^+-HI, 11), 149 (18), 124 (27), 122 (96%).

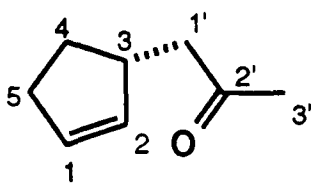
***rel*-(1*R*, 12*R*)-Bicyclo[10.2.1]pentadec-13-en-3-one 205**[189]



To a solution of enone **206** (33mg, 0.1mmol) and AIBN (1mg, 5μmol) in degassed benzene (50ml) at reflux was added, *via* syringe pump over 10h, a solution of $^nBu_3SnH$ (45μl, ~75% pure by ^1H NMR, 0.12mmol) in degassed benzene (4ml). After a further 3h the reaction mixture was concentrated, thiophenol (15μl, 0.13mmol) was added and the mixture purified by flash column chromatography (200:1, petrol:ether) to give the title macrocycle **205** (8.5mg, 41%) as an oil. R_f (1:1, petrol:ether) 0.60; $\nu_{max.}$ (thin film) 2927 (s), 2856 (m), 1709 (m), 1632 (w), 1461 (w), 1361 (w), 1221 (m), 738 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.02-1.70 (14H, m), 1.76-1.85 (1H, m), 2.13 (1H, dt, *J* 14.0, 9.1, **H**$(15)_a$), 2.29 (1H, ddd, *J* 14.0, 9.4, 4.4, **H**$(4)_a$), 2.47 (1H, ddd, *J* 14.0, 7.6, 4.4, **H**$(4)_b$), 2.52 (1H, dd, *J* 17.2, 4.3, **H**$(2)_a$), 2.57-2.64 (1H, m, **H**(12)), 2.65 (1H, dd, *J* 17.2, 10.7,

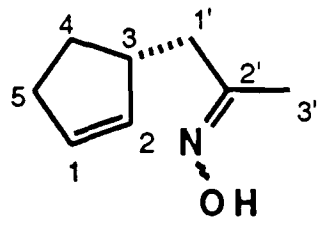
H(2)$_b$), 3.06-3.12 (1H, m, **H**(1)), 5.65 (1H, dt, *J* 5.7, 2.0, **H**(14)), 5.70 (1H, dt, *J* 5.7, 2.0, **H**(13)); *m/z* (C.I., NH_3) 238 (MNH_4^+, 20), 221 (MH^+, 100%).

3-(2'-Oxopropyl)cyclopentene 279[24b]



To a cooled (-78°C) solution of 2-cyclopentene-1-acetic acid **220** (1.0g, 7.90mmol) in THF (20ml) was added dropwise methyllithium (24.4ml, 1.3M in ether, 31.7mmol). After 15h the reaction mixture was diluted with 1M aq. HCl (20ml) and extracted with ether (20ml). The combined organic portions were washed with water (20ml) and brine (25ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (5:1, petrol:ether) to give the undesired tertiary alcohol **280** (0.5g, 44%), which was not characterised, and the title ketone **279** (0.55g, 56%) as an oil. R_f (1:1, petrol:ether) 0.51; $\nu_{max.}$ (thin film) 3052 (w), 2927 (m), 1714 (s), 1405 (w), 1362 (m), 1253 (w), 1160 (m), 721 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.30-1.50 (2H, m, **H**(4)$_2$), 2.12 (3H, s, **H**(3')$_3$), 2.20-2.40 (2H, m, **H**(5)$_2$), 2.40-2.60 (2H, m, **H**(1')$_2$), 3.02-3.20 (1H, m, **H**(3)), 5.61-5.70 (1H, m, **H**(2)), 5.70-5.80 (1H, m, **H**(1)); *m/z* (C.I., NH_3) 142 (MNH_4^+, 100), 125 (MH^+, 70), 124 (12), 109 (11), 65 (11%).

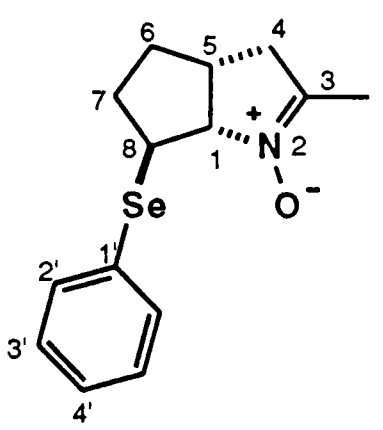
3-(2'-Oxopropyl)cyclopentene oxime 278[24b]



To a solution of the ketone **279** (0.3g, 2.40mmol) and NaOAc (0.22g, 2.70mmol) in MeOH (5ml) was added $NH_2OH.HCl$ (0.19g, 2.7mmol). After 6h the

reaction mixture was diluted with water (10ml) and extracted with ether (2x15ml). The combined organic components were washed with brine (15ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (8:1, petrol:ether) to give the title oximes **278** (0.33g, 98%) as a mixture of oils. R_f (1:1, petrol:ether) 0.46, 0.32; $\nu_{max.}$ (thin film) 3246 (br s), 3055 (w), 2926 (s), 2854 (s), 1708 (w), 1665 (w), 1459 (br s), 1370 (s), 1289 (m), 1141 (w), 1069 (m), 956 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.30-1.50 (2H, m, **H**(4)$_2$), 1.91 (3H, s, **H**(3')$_3$), 1.95-2.50 (4H, m, **H**(5)$_2$, **H**(1')$_2$), 2.85-3.10 (1H, m, **H**(3)), 5.60-5.70 (1H, m, **H**(2)), 5.70-5.80 (1H, m, **H**(1)); δ_C (50.3MHz, $CDCl_3$) 19.7 (**C**H_3), 29.1 (**C**(4)), 31.8 (**C**(5)), 41.5 (**C**(1')), 42.5 (**C**(3)), 131.7 (**C**(2)), 133.3 (**C**(1)), 165.6 (**C**(2')); *m/z* (C.I., NH_3) 160 (18), 158 (70), 140 (MH^+, 30), 125 (30), 124 (MNH_4^+-NH_2OH, 100), 122 (MH^+-H_2O, 35), 108 (32), 94 (13), 58 (13), 57 (20%).

***rel*-(1*S*, 5*R*, 8*R*)-8-Phenylseleno-3-methyl-2-azabicyclo[3.3.0]oct-2-ene *N*-oxide 276**

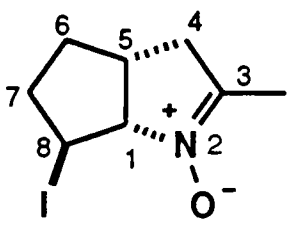


To a solution of the oxime **278** (100mg, 0.72mmol) in DCM (5ml) was added dropwise a solution of PhSeBr (140mg, 0.84mmol) in DCM (2ml). After 2h the reaction mixture was concentrated, diluted with acetonitrile (10ml) and extracted with petrol (4x5ml). The acetonitrile layer was concentrated to give the hydrogen bromide salt of the title nitrone **276** (210mg, 78%) as a yellow/orange oil. $\nu_{max.}$ (thin film) 3366 (br s), 2959 (w), 2871 (w), 2642 (m), 2428 (br s), 1667 (m), 1578 (m), 1477 (s), 1460 (m), 1448 (m), 1437 (s), 1411 (m), 1302 (w), 1163 (s), 1072 (m), 1022 (m), 999 (w), 742 (s), 692 (s), 670 (w) cm^{-1}; δ_H

(500MHz, $CDCl_3$) 1.64-1.68 (1H, m), 1.83-1.87 (1H, m), 2.13-2.20 (1H, m), 2.22-2.29 (1H, m), 2.47 (3H, s, C**H**$_3$), 2.82 (1H, d, *J* 20.0, **H**(4)$_a$), 3.10-3.20 (1H, m, **H**(5)), 3.44 (1H, dd, *J* 20.0, 9.1, **H**(4)$_b$), 4.40 (1H, d, *J* 5.0, **H**(8)), 4.80 (1H, d, *J* 5.5, **H**(1)), 7.26-7.28 (3H, m, **H**(4'), 2x**H**(2')), 7.55-7.57 (2H, m, 2x**H**(3')); δ_C (125MHz, $CDCl_3$) 16.7 (**C**H$_3$), 30.1, 33.2, 34.1 (3x**C**H$_2$), 41.4, 42.2 (**C**(5), **C**(8)), 83.0 (**C**(1)), 128.0 (**C**(4')), 129.0 (**C**(1')), 129.3 (2x**C**(2')), 134.0 (2x**C**(3')), 178.6 (**C**(3)); *m/z* (ES, +ve) 298 (M(^{82}Se)H$^+$-HBr, 22), 296 (M(^{80}Se)H$^+$-HBr, 100), 294 (M(^{78}Se)H$^+$-HBr, 55), 292 (M(^{76}Se)H$^+$-HBr, 20%).

A solution of the nitrone salt **276** (210mg, 0.57mmol) in DCM (2ml) was then eluted through a sinta funnel containing anhydrous K_2CO_3 (~0.5g) to yield (quant.) the free-based nitrone **281**: $\nu_{max.}$ (thin film) 3052 (w), 2955 (w), 1621 (w), 1578 (m), 1477 (m), 1437 (s), 1301 (w), 1215 (w), 1072 (w), 1022 (m), 1000 (w), 797 (w), 739 (s), 691 (s), 666 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.50-2.00 (2H, m), 2.05 (3H, s, C**H**$_3$), 2.10-2.40 (3H, m), 2.85-3.20 (2H, m), 4.40 (1H, d, *J* 5.0, **H**(8)), 4.55 (1H, d, *J* 5.0, **H**(1)), 7.20-7.35 (3H, m, **H**(4'), 2x**H**(2')), 7.55-7.70 (2H, m, 2x**H**(3')); δ_C (50.3MHz, $CDCl_3$) 14.9 (**C**H$_3$), 30.3, 33.5, 33.8 (3x**C**H$_2$), 41.4, 42.4 (**C**(5), **C**(8)), 83.4 (**C**(1)), 127.8 (**C**(4')), 129.2 (**C**(1')), 129.3 (2x**C**(2')), 131.4 (**C**(3)), 133.8 (2x**C**(3')); *m/z* (A.P.C.I., +ve) 298 (M(^{82}Se)H$^+$, 20), 296 (M(^{80}Se)H$^+$, 100), 294 (M(^{78}Se)H$^+$, 52), 292 (M(^{76}Se)H$^+$, 18), 280 (12), 138 (21), 122 (10%); Accurate Mass: Found 296.0568, $C_{14}H_{18}NOSe$ (MH$^+$) requires 296.055359.

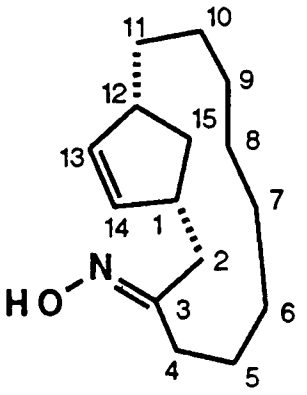
rel-(1*S*, 5*R*, 8*R*)-8-Iodo-3-methyl-2-azabicyclo[3.3.0]oct-2-ene *N*-oxide 282



To a solution of the oxime **278** (120mg, 0.86mmol) in DCM (5ml) was added dropwise a solution of I_2 (0.24g, 0.95mmol) in DCM (2ml). After 15h

anhydrous K_2CO_3 (0.25g, 1.81mmol) was added and the reaction stirred for a further 1h. The reaction mixture was diluted with water (5ml) and extracted with ether (4x5ml). The ether layers were washed with sat. aq. $Na_2S_2O_3$ (5ml), water (5ml) and brine (10ml) and concentrated to give the title iodo nitrone **282** (0.23g, 96%) as an oil. $\nu_{max.}$ (thin film) 2960 (m), 1618 (m), 1441 (m), 1391 (w), 1288 (w), 1249 (m), 1217 (s), 1165 (m), 1040 (w), 876 (w), 735 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.50-1.70 (1H, m), 1.70-1.90 (1H, m), 1.95 (3H, s, CH_3), 1.90-2.10 (1H, m), 2.20-2.55 (2H, m), 2.90-3.15 (2H, m), 4.70-4.85 (1H, m, **H**(8)), 4.95 (1H, d, *J* 5.0, **H**(1)); δ_C (50.3MHz, $CDCl_3$) 12.8 (CH_3), 26.6 (**C**(8)), 32.1, 34.0, 35.1 (3xCH_2), 40.0 (**C**(5)), 87.7 (**C**(1)), 145.0 (**C**(3)); *m/z* (ES, +ve) 267 (10), 266 (MH^+, 100%).

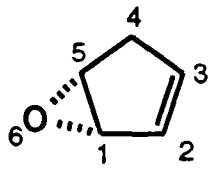
rel-(1*R*, 12*R*)-Bicyclo[10.2.1]pentadec-13-en-3-one oxime 286[189]



To a solution of the macrocycle **205** (4mg, 18μmol) and NaOAc (2.2mg, 27μmol) in MeOH (0.5ml) was added $NH_2OH.HCl$ (2mg, 29μmol). After 6h the reaction mixture was diluted with water (5ml) and extracted with DCM (3x5ml). The combined organic components were washed with brine (5ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (10:1, petrol:ether) to give the title oximes **286** (3.5mg, 82%) as a mixture of oils. R_f (1:1, petrol:ether) 0.45, 0.34; $\nu_{max.}$ (thin film) 3400 (br s), 2926 (s), 2854 (s), 1633 (w), 1444 (w), 1128 (sh m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.10-1.79 (14H, m), 1.86-1.91 (1H, m), 1.96 (1H, dt, *J* 13.5, 8.8, **H**$(15)_b$), 2.13-2.21 (1H, m, **H**$(4)_a$), 2.32 (1H, dd, *J* 12.5, 7.9, **H**$(2)_a$), 2.39 (1H, ddd, *J* 14.4, 10.8, 3.6, **H**$(4)_b$), 2.53-2.56 (1H, m, **H**(12)),

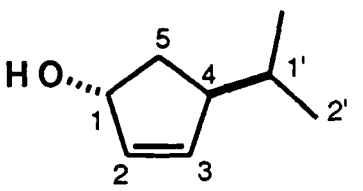
2.84 (1H, dd, *J* 12.5, 3.8, **H**(2)$_b$), 3.09-3.14 (1H, m, **H**(1)), 5.73-5.76 (2H, m, **H**(13), **H**(14)); δ_C (125MHz, $CDCl_3$) 22.3, 22.7, 24.2, 25.7, 26.0, 26.5, 31.8, 31.9, 32.8, 34.1 (10x**C**H_2), 41.9 (**C**(12)), 45.1 (**C**(1)), 134.1 (**C**(14)), 135.9 (**C**(13)), 156.8 (**C**(3)); *m/z* (C.I., NH_3) 236 (MH^+, 10), 220 (MNH_4^+-NH_2OH, 100%); Accurate Mass: Found 236.2014, $C_{15}H_{26}NO$ (MH^+) requires 236.201439.

6-Oxabicyclo[3.1.0]hex-2-ene 217[201]



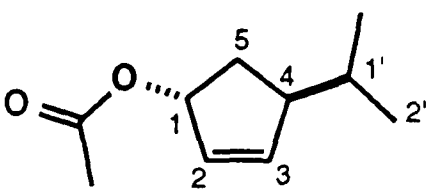
To a cooled (0°C) vigorously stirred suspension of anhydrous Na_2CO_3 (47.1g, 379mmol) in DCM (200ml) was added cyclopentadiene **75** (20ml, 303mmol) followed by a solution of anhydrous NaOAc (0.88g, 11mmol) in AcOOH (30ml, 36% solution in AcOH, 152mmol) added over a period of 30mins. After 2h activated charcoal (microspatula head) was added and the mixture stirred vigorously for a further 15mins. The slurry was filtered and the residue washed with DCM (50ml). Subsequent distillation of the combined filtrates (RT, water pump, unwanted distillate collected at -78°C) to remove the most volatile components left the title epoxide **217** (12.5g of a 1.3:1 mixture with DCM: 7.1g, 60%) as the residue. A small sample was distilled on a Kugelrohr apparatus (RT, high vacum) for characterisation. $\nu_{max.}$ (thin film) 3409 (br), 2959 (s), 1730 (s), 1650 (s), 1361 (s), 1245 (s), 1052 (s), 1024 (s), 849 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.30-2.45 (1H, m, **H**(4)$_a$), 2.50-2.70 (1H, m, **H**(4)$_b$), 3.73-3.83 (2H, m, **H**(1), **H**(5)), 5.85-6.15 (2H, m, **H**(2), **H**(3)); *m/z* (C.I., NH_3) 100 (MNH_4^+, 65), 83 (MH^+, 80), 82 (MNH_4^+-H_2O, 100), 71 (12), 56 (18), 54 (91), 53 (34%).

trans-4-(1'-Methylethyl)-2-cyclopenten-1-ol 291



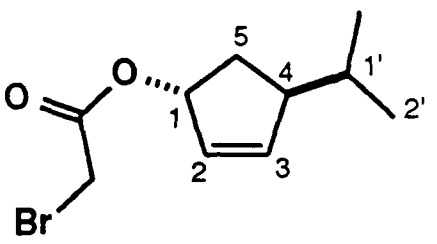
To a cooled (-40°C), vigorously stirred, suspension of anhydrous CuCN (9.9g, 111mmol) in ether (230ml) was added dropwise isopropyl magnesium chloride (51ml, 2M solution in ether, 102mmol). After 1h at -40°C the solution was cooled to -78°C and a solution of epoxide **217** (7.0g, 85mmol) in ether (20ml) added dropwise. After 5h the reaction mixture was diluted with sat. aq. NH_4Cl (50ml) and separated. The ether layer was washed with water (100ml) and brine (100ml) and concentrated *in vacuo* (with care, to avoid loss of the product) to give the alcohol **291** (8.5g, 79%) as a volatile oil. A small sample was purified by flash column chromatography (6:1, petrol:ether) for characterisation. R_f (1:1, petrol:ether) 0.21; $\nu_{max.}$ (thin film) 3387 (br s), 3052 (m), 2959 (s), 2872 (s), 1615 (w), 1468 (m), 1385 (m), 1368 (m), 1331 (w), 1268 (w), 1111 (w), 1026 (m), 849 (m), 837 (w), 731 (w), 709 (w), 678 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.7, C**H**$_3$), 0.90 (3H, d, *J* 6.7, C**H**$_3$), 1.52 (1H, oct, *J* 6.7, **H**(1')), 1.81 (1H, ddd, *J* 14.1, 7.7, 2.9, **H**$(5)_a$), 1.88 (1H, ddd, *J* 14.1, 7.0, 5.4, **H**$(5)_b$), 2.72 (1H, dddt, *J* 7.7, 7.0, 6.7, 2.2, **H**(4)), 4.84 (1H, dt, *J* 4.6, 2.2, **H**(1)), 5.86 (1H, dt, *J* 5.5, 2.2, **H**(2)), 5.97 (1H, dd, *J* 5.5, 2.2, **H**(3)); δ_C (125MHz, $CDCl_3$) 20.2, 20.4 (2x**C**H_3), 32.3 (**C**(1')), 38.0 (**C**(5)), 51.3 (**C**(4)), 77.3 (**C**(1)), 133.2 (**C**(2)), 138.6 (**C**(3)); *m/z* (C.I., NH_3) 109 (MH^+-H_2O, 100), 93 (45), 91 (20%); Accurate Mass: Found 109.1017, C_8H_{13} (MH^+-H_2O) requires 109.101725.

trans-1-Acetoxy-4-(1'-methylethyl)cyclopent-2-ene 292



To a solution of alcohol **291** (0.49g, 3.9mmol) in DCM (10ml) was added successively triethylamine (0.81ml, 5.83mmol) and acetyl chloride (0.41ml, 5.83mmol). After 7h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x15ml). The combined organic layers were washed with water (10ml) and brine (15ml), concentrated and purified by flash column chromatography (50:1, petrol:ether) to give the desired acetate **292** (0.4g, 61%) as an oil. R_f (1:1, petrol:ether) 0.64; $\nu_{max.}$ (thin film) 3057 (w), 2960 (s), 2873 (m), 1736 (s), 1618 (w), 1467 (m), 1437 (w), 1366 (s), 1244 (s), 1195 (m), 1109 (w), 1071 (w), 1020 (s), 972 (m), 910 (w), 849 (w), 793 (m), 753 (w), 608 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.7, C**H**$_3$), 0.91 (3H, d, *J* 6.7, C**H**$_3$), 1.55 (1H, oct, *J* 6.7, **H**(1')), 1.88-1.95 (2H, m, **H**(5)$_2$), 2.02 (3H, s, C**H**$_3$), 2.71 (1H, qt, *J* 6.7, 2.2, **H**(4)), 5.67 (1H, dt, *J* 7.3, 2.2, **H**(1)), 5.83 (1H, dt, *J* 5.5, 2.2, **H**(2)), 6.08 (1H, dd, *J* 5.5, 2.2, **H**(3)); δ_C (50.3MHz, $CDCl_3$) 20.0, 20.2 (2xC**H**$_3$), 21.1 (CO**C**H$_3$), 32.0 (**C**(1')), 34.3 (**C**(5)), 51.3 (**C**(4)), 80.3 (**C**(1)), 129.4 (**C**(2)), 141.1 (**C**(3)), 171.3 (**C**=O); *m/z* (C.I., NH_3) 109 (MH^+-AcOH, 100), 93 (25), 91 (10%); Accurate Mass: Found 109.1017, C_8H_{13} (MH^+-AcOH) requires 109.101725.

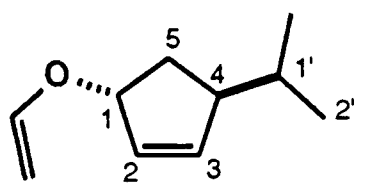
***trans*-1-(Bromoacetoxy)-4-(1'-methylethyl)cyclopent-2-ene 293**



To a solution of alcohol **291** (0.1g, 0.79mmol), bromoacetic acid (0.11g, 0.79mmol) and DMAP (10mg, 0.08mmol) in THF (1ml) was added dropwise a solution of DCC (0.18g, 0.87mmol) in THF (1ml). After 15h the reaction mixture was filtered and the DCU residue washed with ether (2x5ml). The combined organic filtrates were washed with 1M aq. NaOH (5ml), water (5ml) and brine (5ml) then concentrated and purified by flash column

chromatography (50:1, petrol:ether) to give the desired bromoacetate **293** (0.14g, 72%) as an oil. R_f (1:1, petrol:ether) 0.63; $\nu_{max.}$ (thin film) 3059 (w), 2959 (s), 2872 (m), 1734 (s), 1654 (w), 1618 (w), 1467 (w), 1421 (w), 1369 (w), 1336 (w), 1280 (s), 1165 (m), 1108 (m), 962 (w), 668 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.7, CH_3), 0.90 (3H, d, *J* 6.7, CH_3), 1.55 (1H, oct, *J* 6.7, **H**(1')), 1.88-1.99 (2H, m, **H**$(5)_2$), 2.73 (1H, qt, *J* 7.0, 2.2, **H**(4)), 3.79 (2H, s, CH_2Br), 5.72 (1H, dt, *J* 6.9, 2.2, **H**(1)), 5.84 (1H, dt, *J* 5.6, 2.2, **H**(2)), 6.13 (1H, dd, *J* 5.6, 2.2, **H**(3)); δ_C (125MHz, $CDCl_3$) 20.1, 20.3 (2xCH_3), 26.2 (CH_2Br), 32.0 (**C**(1')), 34.1 (**C**(5)), 51.3 (**C**(4)), 82.5 (**C**(1)), 128.4 (C(2)), 142.0 (**C**(3)), 167.1 (**C**=O); *m/z* (C.I., NH_3) 266 ($M(^{81}Br)NH_4^+$, 92), 264 ($M(^{79}Br)NH_4^+$, 90), 217 (100), 205 (75), 203 (80), 199 (52%).

trans-1-(Ethenyloxy)-4-(1'-methylethyl)cyclopent-2-ene 295

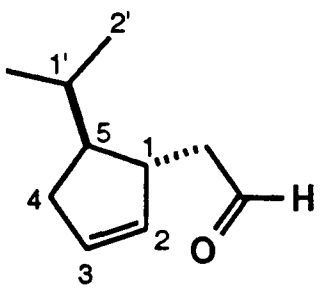


A solution of alcohol **291** (0.35g, 2.8mmol) and $Hg(OAc)_2$ (90mg, 0.28mmol) in EVE (25ml) was stirred at RT. After 27h the reaction mixture was concentrated *in vacuo* to remove the excess EVE. The residue was then dissolved in ether (5ml) and filtered through a short silica pad which was then washed with additional ether (2x10ml). The combined organic filtrate was concentrated to give the desired allyl vinylether **295** (0.40g, 93%) as an oil which was not further purified. R_f (1:1, petrol:ether) 0.67; $\nu_{max.}$ (thin film) 2959 (s), 2873 (s), 1634 (m), 1612 (m), 1467 (w), 1368 (m), 1317 (w), 1245 (m), 1037 (m), 819 (w), 756 (w), 678 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.5, CH_3), 0.91 (3H, d, *J* 6.5, CH_3), 1.50-2.00 (3H, m, **H**(1'), **H**$(5)_2$), 2.60-2.80 (1H, m, **H**(4)), 4.02 (1H, dd, *J* 7.0, 1.5, OCH=CH_aH_b), 4.25 (1H, dd, *J* 14.5, 1.5, OCH=CH_aH_b), 4.94-4.99 (1H, m, **H**(1)), 5.89 (1H, ddd, *J* 6.0, 3.5, 2.0, **H**(2)), 6.10 (1H, dd, *J* 6.0, 2.0, **H**(3)), 6.42 (1H, dd, *J* 14.5, 7.0, OC**H**=CH_2); δ_C (50.3MHz, $CDCl_3$) 20.0, 20.2 (2xCH_3), 32.1 (**C**(1')), 34.1

(**C**(5)), 51.3 (**C**(4)), 83.0 (**C**(1)), 87.5 (OCH=CH_2), 129.5 (**C**(2)), 140.1 (**C**(3)), 150.4 (OCH=CH_2); *m/z* (C.I., NH_3) 109 (MH^+-MeCHO, 100%).

trans-5-(1'-Methylethyl)cyclopent-2-ene-1-acetaldehyde 294

Method 1



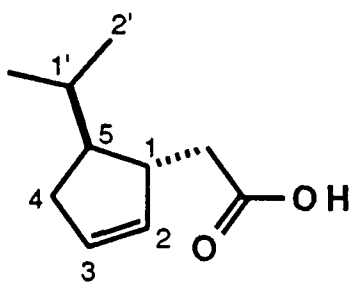
A solution of alcohol **291** (50mg, 0.4mmol) and $Hg(OAc)_2$ (13mg, 0.04mmol) in BVE (0.5ml) was heated at 180°C in a sealed tube. After 17h the reaction mixture was concentrated *in vacuo* to remove the excess BVE and the residue purified by flash column chromatography (50:1, petrol:ether) to give the desired aldehyde **294** (35mg, 60%) as an oil. R_f (1:1, petrol:ether) 0.56; $\nu_{max.}$ (thin film) 3054 (w), 2958 (s), 2932 (s), 2872 (s), 1723 (s), 1620 (w), 1466 (m), 1386 (m), 1368 (m), 1339 (w), 1242 (m), 1129 (s), 1059 (s), 932 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.5, C**H**$_3$), 0.88 (3H, d, *J* 6.5, C**H**$_3$), 1.60-1.76 (2H, m, **H**(1'), **H**(5)), 2.00-2.14 (1H, m, **H**$(4)_a$), 2.25-2.50 (1H, m, **H**$(4)_b$), 2.39 (1H, ddd, *J* 16.5, 8.0, 2.0, C**H**$_a$H$_b$CHO), 2.54 (1H, ddd, *J* 16.5, 5.5, 2.0, CH$_a$**H**$_b$CHO), 2.85-2.91 (1H, m, **H**(1)), 5.56-5.60 (1H, m, **H**(2)), 5.64-5.69 (1H, m, **H**(3)), 9.77 (1H, t, *J* 2.0, C**H**O); δ_C (50.3MHz, $CDCl_3$) 19.3, 20.7 (2x**C**H_3), 31.8 (**C**(1')), 35.2 (**C**(4)), 43.3 (**C**(5)), 49.8 (**C**(1)), 50.4 (**C**H_2CHO), 130.7 (**C**(2)), 132.5 (**C**(3)), 202.5 (**C**HO); *m/z* (C.I., NH_3) 170 (MNH_4^+, 30), 152 (MNH_4^+-H_2O, 15), 109 (MH^+-MeCHO, 50), 108 (100), 93 (20), 91 (11), 81 (30), 67 (11%); Accurate Mass: Found 170.1540, $C_{10}H_{20}NO$ (MNH_4^+) requires 170.154489.

Method 2

A solution of allyl vinyl ether **295** (0.3g, 2.0mmol) in toluene (3ml) was heated at 180°C in a sealed tube. After 17h the reaction mixture was concentrated *in*

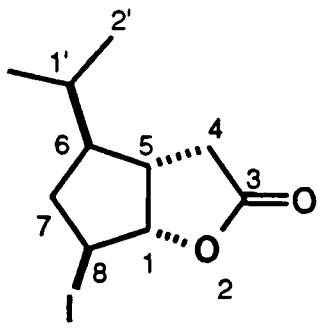
vacuo and purified by flash column chromatography (10:1, petrol:ether) to give the aldehyde **294** (0.17g, 57%) as an oil. The data for this compound were identical to that described above.

trans-5-(1'-Methylethyl)cyclopent-2-ene-1-acetic acid 290



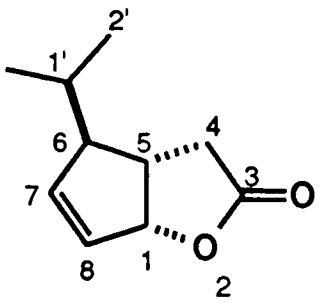
To a solution of aldehyde **294** (60mg, 0.39mmol) in acetone (2ml) was added Jones' reagent (0.39ml, ~2M in aq. H_2SO_4, 0.78mmol). After 15mins MeOH was added dropwise until a green colour persisted. The reaction mixture was diluted with 1M aq. HCl (10ml), extracted with ether (2x10ml) and the combined ether layers washed with sat. aq. $NaHCO_3$ (10ml). The aqueous layer was acidified by dropwise addition of conc. HCl until the pH fell below 7.0 and extracted with ether (2x10ml). The combined ether portions were washed with brine (10ml), dried ($MgSO_4$) and concentrated to give the title acid **290** (55mg, 83%) as an oil. R_f (1:1, petrol:ether) 0.30; $\nu_{max.}$ (thin film) 3307 (w), 2959 (m), 1708 (s), 1451 (w), 1268 (w), 1160 (w), 1097 (w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.5, C**H**$_3$), 0.90 (3H, d, *J* 6.5, C**H**$_3$), 1.61-1.78 (2H, m, **H**(1'), **H**(5)), 2.02-2.13 (1H, m, **H**$(4)_a$), 2.27 (1H, dd, *J* 15.0, 9.0, C**H**$_a$H$_b$CO$_2$H), 2.40-2.50 (1H, m, **H**$(4)_b$), 2.48 (1H, dd, *J* 15.0, 5.5, CH$_a$**H**$_b$CO$_2$H), 2.75-2.83 (1H, m, **H**(1)), 5.65-5.70 (2H, m, **H**(2), **H**(3)); δ_C (50.3MHz, $CDCl_3$) 19.3, 20.6 (2x**C**H$_3$), 31.8 (**C**(1')), 35.2 (**C**(4)), 40.8 (**C**(5)), 45.4 (**C**(1)), 49.6 (**C**H$_2$CO$_2$H), 130.6 (**C**(2)), 132.8 (**C**(3)), 178.9 (**C**O$_2$H); *m/z* (C.I., NH_3) 247 (18), 222 (25), 205 (35), 189 (15), 186 (MNH_4^+, 100), 168 (11), 109 (MH^+-AcOH, 70), 108 (70), 93 (20), 81 (13), 80 (70), 79 (19%); Accurate Mass: Found 186.1494, $C_{10}H_{20}NO_2$ (MNH_4^+) requires 186.149404.

rel-(1*S*, 5*S*, 6*S*, 8*S*)-7-Iodo-6-(1'-methylethyl)-2-oxabicyclo[3.3.0]octan-3-one 296



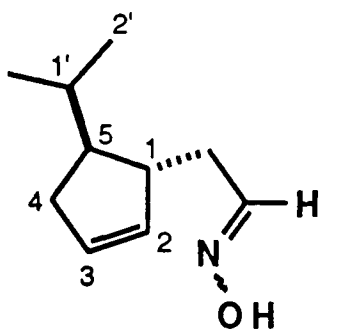
To a vigorously stirred solution of the acid **290** (1.02g, 6.1mmol) in water (30ml) was added $KHCO_3$ (3.7g, 36.4mmol) followed by KI (6.2g, 36.4mmol) and, after 5mins, I_2 (3.13g, 12.1mmol) and ether (15ml). After 13h conc. HCl was added dropwise until the pH fell below 7.0 at which point the mixture was diluted with ether (30ml) and the organic layer separated. The combined ether portions were washed with sat. aq. $Na_2S_2O_3$ (5ml), water (20ml) and brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (5:1, petrol:DCM) afforded the iodo-lactone **296** (1.70g, 95%) as colourless plate crystals. m.p. (DCM/pentane) 41-44°C; R_f (1:1, petrol:ether) 0.36 (uv active); $\nu_{max.}$ (KBr) 2959 (m), 1780 (s), 1469 (s), 1368 (s), 1161 (m), 1057 (m), 895 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.6, C**H**$_3$), 0.95 (3H, d, *J* 6.7, C**H**$_3$), 1.48 (1H, dddd, *J* 10.8, 8.6, 8.6, 6.5, **H**(6)), 1.60-1.67 (1H, m, **H**(1')), 1.87 (1H, dt, *J* 13.3, 11.0, **H**(7)$_a$), 2.42 (1H, dd, *J* 18.4, 3.6, **H**(4)$_a$), 2.57 (1H, ddd, *J* 13.3, 6.5, 6.5, **H**(7)$_b$), 2.63 (1H, dddd, *J* 9.9, 8.6, 8.6, 3.6, **H**(5)), 2.82 (1H, dd, *J* 18.4, 10.0, **H**(4)$_b$), 4.05 (1H, ddd, *J* 11.0, 6.5, 5.2, **H**(8)), 5.09 (1H, dd, *J* 8.4, 5.2, **H**(1)); δ_C (125MHz, $CDCl_3$) 20.7, 21.4 (2x**C**H$_3$), 22.9 (**C**(8)), 32.6 (**C**(1')), 35.8 (**C**(7)), 42.2 (**C**(6)), 42.7 (**C**(5)), 54.2 (**C**(4)), 93.7 (**C**(1)), 176.0 (**C**(3)); *m/z* (C.I., NH_3) 312 (MNH_4^+, 100), 184 (MNH_4^+-HI, 10), 167 (MH^+-HI, 20%); Accurate Mass: Found 312.0466, $C_{10}H_{19}INO_2$ (MNH_4^+) requires 312.046579.

rel-(1*R*, 5*S*, 6*R*)-6-(1'-Methylethyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one 288



To a solution of the iodo-lactone **296** (1.2g, 4.1mmol) in benzene (40ml) was added DBU (0.92ml, 6.1mmol) and the mixture heated at reflux. After 4h the reaction mixture was diluted with 1M aq. HCl (20ml) and extracted with ether (2x15ml). The combined organic portions were washed with brine (20ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (1:1, petrol:ether) to give the alkenyl-lactone **288** (0.66g, 98%) as an oil. R_f (1:1, petrol:ether) 0.32; $\nu_{max.}$ (thin film) 2959 (m), 2873 (w), 1775 (s), 1642 (w), 1466 (w), 1368 (w), 1342 (w), 1168 (m), 1028 (m), 977 (w), 749 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.88 (2x3H, d, *J* 6.7, 2xCH_3), 1.66 (1H, sept, *J* 6.7, **H**(1')), 2.34 (1H, dd, *J* 17.7, 4.8, $\mathbf{H}(4)_a$), 2.45 (1H, ddd, *J* 6.7, 5.1, 2.0, **H**(6)), 2.75 (1H, dddd, *J* 10.5, 7.3, 5.1, 4.5, **H**(5)), 2.82 (1H, dd, *J* 17.7, 10.5, $\mathbf{H}(4)_b$), 5.46 (1H, dt, *J* 7.3, 2.0, **H**(1)), 5.88 (1H, dt, *J* 5.8, 2.0, **H**(8)), 6.04 (1H, dd, *J* 5.8, 2.0, **H**(7)); δ_C (125MHz, $CDCl_3$) 20.0, 20.1 (2xCH_3), 32.0 (**C**(1')), 35.9 (**C**(6)), 39.4 (**C**(4)), 60.4 (**C**(5)), 89.4 (**C**(1)), 129.1 (**C**(8)), 140.2 (**C**(7)), 177.7 (**C**(3)); *m/z* (C.I., NH_3) 184 (MNH_4^+, 25), 168 (45), 167 (MH^+, 100), 124 (15), 108 (11), 107 (40), 95 (12), 82 (28), 80 (18), 79 (50), 78 (19%); Accurate Mass: Found 167.1072, $C_{10}H_{15}O_2$ (MH^+) requires 167.107205.

***Syn-* and *anti-trans*-5-(1'-Methylethyl)cyclopent-2-ene-1-acetaldehyde oxime 298, 299**

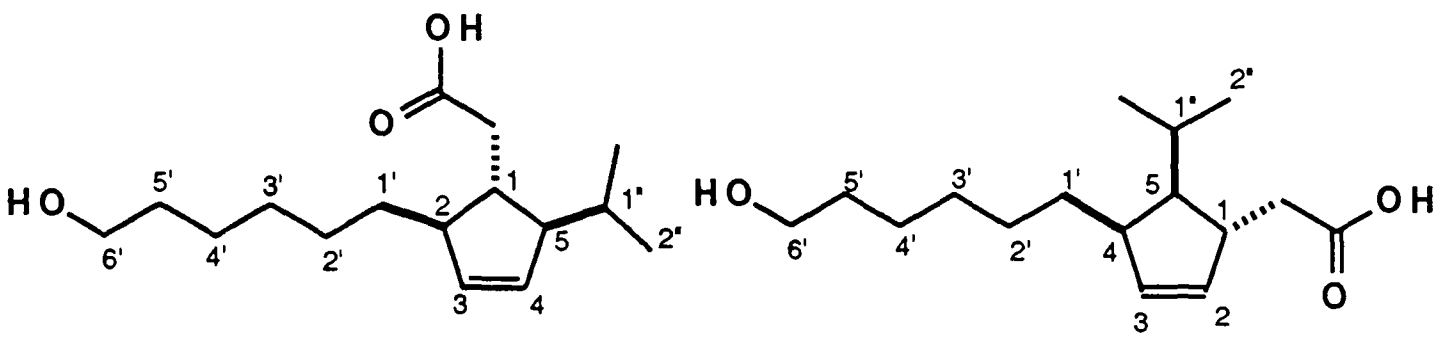


265

To a solution of aldehyde **294** (0.5g, 3.29mmol) and NaOAc (0.3g, 3.62mmol) in MeOH (5ml) was added $NH_2OH.HCl$ (0.25g, 3.62mmol) in one portion. After 15h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x10ml). The combined organic extracts were washed with water (5ml) and brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (10:1, petrol:ether) to give the oximes (ratio 2:1) **298, 299** (505mg, 92%) as oils. Major isomer: R_f (1:1, petrol:ether) 0.45; $\nu_{max.}$ (thin film) 3370 (br s), 3051 (w), 2957 (s), 1651 (w), 1466 (m), 1386 (w), 1368 (m), 935 (w), 723 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.7, C**H**$_3$), 0.90 (3H, d, *J* 6.7, C**H**$_3$), 1.64 (1H, oct, *J* 6.7, **H**(1')), 1.75 (1H, dq, *J* 9.0, 5.9, **H**(5)), 2.09 (1H, dddd, *J* 17.0, 5.9, 5.9, 2.2, **H**$(4)_a$), 2.20 (1H, ddd, *J* 14.4, 7.1, 7.1, C**H**$_a$H$_b$CHNOH), 2.36 (1H, dt, *J* 14.4, 5.8, CH$_a$**H**$_b$CHNOH), 2.41-2.51 (1H, m, **H**$(4)_b$), 2.62-2.69 (1H, m, **H**(1)), 5.58 (1H, dddd, *J* 8.0, 8.0, 3.4, 2.2, **H**(2)), 5.70 (1H, dddd, *J* 8.0, 8.0, 4.5, 2.2, **H**(3)), 7.44 (1H, t, *J* 6.4, C**H**NOH), 8.40 (1H, br s, NO**H**); δ_C (125MHz, $CDCl_3$) 19.5, 20.6 (2xC**H**$_3$), 32.0 (**C**(1')), 35.5 (**C**(4)), 35.7 (**C**H$_2$CHNOH), 46.8 (**C**(5)), 49.2 (**C**(1)), 130.8 (**C**(2)), 132.6 (**C**(3)), 151.2 (**C**HNOH); *m/z* (C.I., NH_3) 153 (10), 152 (MNH_4^+-NH_2OH, 100), 109 (MH^+-MeCHNOH, 30), 108 (32%). Minor isomer: R_f (1:1, petrol:ether) 0.37; $\nu_{max.}$ (thin film) 3257 (br s), 3051 (w), 2958 (s), 2872 (m), 1659 (w), 1466 (m), 1386 (m), 1368 (m), 935 (w), 722 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.7, C**H**$_3$), 0.91 (3H, d, *J* 6.7, C**H**$_3$), 1.64 (1H, oct, *J* 6.7, **H**(1')), 1.75 (1H, dddd, *J* 11.7, 8.8, 8.8, 5.9, **H**(5)), 2.09 (1H, dddd, *J* 17.0, 8.8, 4.4, 2.2, **H**$(4)_a$), 2.20 (1H, ddd, *J* 14.4, 7.1, 7.1, C**H**$_a$H$_b$CHNOH), 2.36 (1H, dt, *J* 14.4, 5.9, CH$_a$**H**$_b$CHNOH), 2.41-2.51 (1H, m, **H**$(4)_b$), 2.62-2.70 (1H, m, **H**(1)), 5.58 (1H, dddd, *J* 8.5, 8.5, 4.4, 2.2, **H**(2)), 5.69 (1H, dddd, *J* 8.5, 8.5, 4.5, 2.2, **H**(3)), 6.79 (1H, t, *J* 5.4, C**H**NOH), 8.92 (1H, br s, NO**H**); δ_C (125MHz, $CDCl_3$) 19.6, 20.6 (2xC**H**$_3$), 32.1 (**C**(1')), 35.6 (**C**(4)), 35.8 (**C**H$_2$CHNOH), 46.2 (**C**(5)), 49.7 (**C**(1)), 130.8 (**C**(2)), 132.9 (**C**(3)), 151.4 (**C**HNOH); *m/z* (C.I., NH_3) 153 (11), 152 (MNH_4^+-NH_2OH,

100), 109 (MH^+-MeCHNOH, 27), 108 (30%); Accurate Mass: Found 168.1388, $C_{10}H_{18}NO$ (MH^+) requires 168.138839.

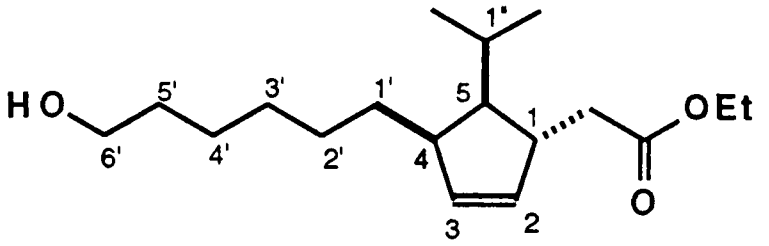
rel-(1_R_, 4_R_, 5_R_)-4-(6'-Hydroxyhexyl)-5-(1''-methylethyl)cyclopent-2-ene-1-acetic acid 301 and _rel_-(1_S_, 2_R_, 5_S_)-2-(6'-Hydroxyhexyl)-5-(1''-methylethyl)cyclopent-3-ene-1-acetic acid 302



To a cooled (-78°C) suspension of iodo-hexanol **199** (0.27g, 1.20mmol) in ether (5ml) was added dropwise *n*-butyllithium (0.9ml, 1.4M in hexanes, 1.30mmol) and, after 15mins, *t*-butyllithium (1.6ml, 1.6M in pentane, 2.50mmol) followed by, after a further 15mins, a solution of $CuBr.SMe_2$ (0.27g, 1.30mmol) in Me_2S (5ml). The mixture was warmed to -20°C and stirred vigorously. After 20mins the dark blue solution was cooled to -78°C and a solution of the alkenyl-lactone **288** (80mg, 0.48mmol) in ether (1ml) added dropwise. After 15h the reaction mixture was diluted with ether (10ml) and extracted with sat. aq. $NaHCO_3$ (3x5ml). The combined aqueous portions were acidified by the dropwise addition of conc. HCl until the pH fell below 7.0 and then extracted with ether (4x5ml). The combined organic extracts were washed with brine (10ml), dried ($MgSO_4$) then concentrated and purified by flash column chromatography (5:1, petrol:EtOAc) to give an inseparable mixture (ratio **301**:**302**, 5.8:1) of the title hydroxy acids **301** and **302** (102mg, 79%) as oils. The major acid **301** formed white crystals and could be partially separated. Minor product **302**: R_f (EtOAc) 0.24; δ_H (500MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.7, CH_3), 0.94 (3H, d, *J* 6.7, CH_3), 1.23-1.41 (8H, m), 1.50-1.60 (3H, m, **H**(1''), **H**(5')$_2$), 1.91-1.98 (1H, m, **H**(1)), 2.10-2.15 (1H, m, **H**(5)), 2.30-2.40 (2H, m, **H**(4), $CH_aH_bCO_2H$), 2.40-2.50 (1H, m,

$CH_aH_bCO_2H$), 3.65 (2H, t, *J* 6.6, **H**(6')$_2$), 5.61 (1H, dt, *J* 5.9, 1.8, **H**(2)), 5.64 (1H, dt, *J* 5.9, 2.0, **H**(3)). Major Product **301**: m.p. (EtOAc/petrol) 38-40°C; R_f (EtOAc) 0.24; $\nu_{max.}$ (thin film) 3374 (br s), 2929 (s), 2856 (m), 1708 (s), 1463 (m), 1368 (m), 1261 (w), 1160 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.6, C**H**$_3$), 0.93 (3H, d, *J* 6.6, C**H**$_3$), 1.23-1.41 (8H, m), 1.45-1.53 (2H, m), 1.54-1.63 (2H, m), 1.81-1.87 (1H, m, **H**(1")), 2.19 (1H, dd, *J* 15.4, 9.6, C**H**$_a$H$_b$CO$_2$H), 2.67 (1H, dd, *J* 15.4, 4.8, CH$_a$**H**$_b$CO$_2$H), 2.64-2.71 (1H, m, **H**(4)), 2.84-2.89 (1H, m, **H**(1)), 3.65 (2H, t, *J* 6.6, **H**(6')$_2$), 5.67 (1H, dt, *J* 5.8, 1.5, **H**(2)), 5.83 (1H, dt, *J* 5.8, 2.1, **H**(3)); δ_C (125MHz, $CDCl_3$) 21.3, 22.7 (2x**C**H$_3$), 25.7 28.2, 29.8, 30.1, 32.7 (5x**C**H$_2$), 27.6 (**C**(1")), 40.0 (**C**H$_2$CO$_2$H), 43.2 (**C**(5)), 46.6 (**C**(4)), 53.4 (**C**(1)), 63.0 (**C**(6')), 133.1 (**C**(2)), 135.6 (**C**(3)), 178.5 (CO$_2$H); *m/z* (ES, -ve) 267 (M-H$^+$, 100%); Found: C, 70.86; H, 10.26%; $C_{16}H_{28}O_3$; requires C, 71.6; H, 10.52%.

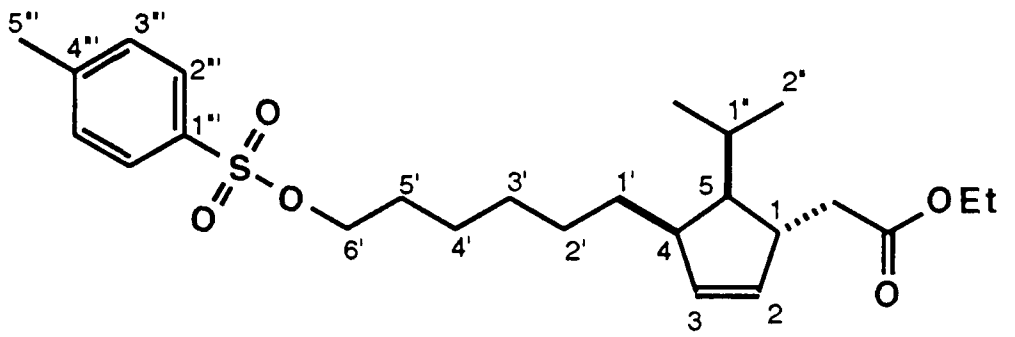
Ethyl *rel*-(1*R*, 4*R*, 5*R*)-4-(6'-hydroxyhexyl)-5-(1"-methylethyl)cyclopent-2-ene-1-acetate 303



To a solution of the acid **301** (25mg, 0.093mmol) in EtOH (1ml) was added conc. H_2SO_4 (one drop). After 15h the reaction mixture was concentrated and purified by flash column chromatography (1:1, petrol:ether) to afford the ester **303** (27mg, 96%) as a colourless oil. R_f (1:1, petrol:ether) 0.27; $\nu_{max.}$ (thin film) 3050 (w), 2931 (s), 2858 (m), 1735 (s), 1465 (m), 1387 (w), 1370 (m), 1343 (w), 1304 (w), 1246 (m), 1161 (s), 1035 (m), 744 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.7, C**H**$_3$), 0.90 (3H, d, *J* 6.7, C**H**$_3$), 1.21-1.44 (8H, m), 1.24 (3H, t, *J* 7.1, OCH$_2$C**H**$_3$), 1.45-1.49 (1H, m), 1.50-1.60 (2H, m), 1.81 (1H, oct, *J* 6.7, **H**(1")), 2.13 (1H, dd, *J* 15.0, 9.6, C**H**$_a$H$_b$CO$_2$Et), 2.57 (1H, dd, *J* 15.0, 5.1, CH$_a$**H**$_b$CO$_2$Et), 2.64 (1H, dddd, *J* 10.0, 7.7, 4.7, 2.1, **H**(4)), 2.83 (1H, dddd, *J* 9.3, 6.9, 5.0, 2.0, **H**(1)),

3.61 (2H, t, *J* 6.6, **H**(6')$_2$), 4.11 (2H, q, *J* 7.1, OC**H**$_2$CH$_3$), 5.61 (1H, dt, *J* 5.8, 1.7, **H**(2)), 5.79 (1H, dt, *J* 5.8, 2.1, **H**(3)); δ_C (125MHz, $CDCl_3$) 14.2 (OCH$_2$**C**H$_3$), 21.1, 22.6 (2x**C**H$_3$), 25.7 28.2, 29.7, 29.9, 32.7 (5x**C**H$_2$), 27.5 (**C**(1")), 40.3 (**C**H$_2$CO$_2$H), 43.3 (**C**(5)), 46.6 (**C**(4)), 53.3 (**C**(1)), 60.1 (O**C**H$_2$CH$_3$), 62.9 (**C**(6')), 133.3 (**C**(2)), 135.2 (**C**(3)), 173.1 (**C**O$_2$Et); *m/z* (C.I., NH_3) 314 (MNH_4^+, 10), 297 (MH^+, 100), 209 (MH^+-EtOAc, 25), 208 (MNH_4^+-EtOAc-H_2O, 25), 195 (15), 122 (15), 107 (20%); Accurate Mass: Found 314.2695, $C_{18}H_{36}NO_3$ (MNH_4^+) requires 314.269519.

Ethyl *rel*-(1*R*, 4*R*, 5*R*)-4-(6'-*para*-toluenesulponyloxyhexyl)-5-(1"-methylethyl) cyclopent-2-ene-1-acetate 304

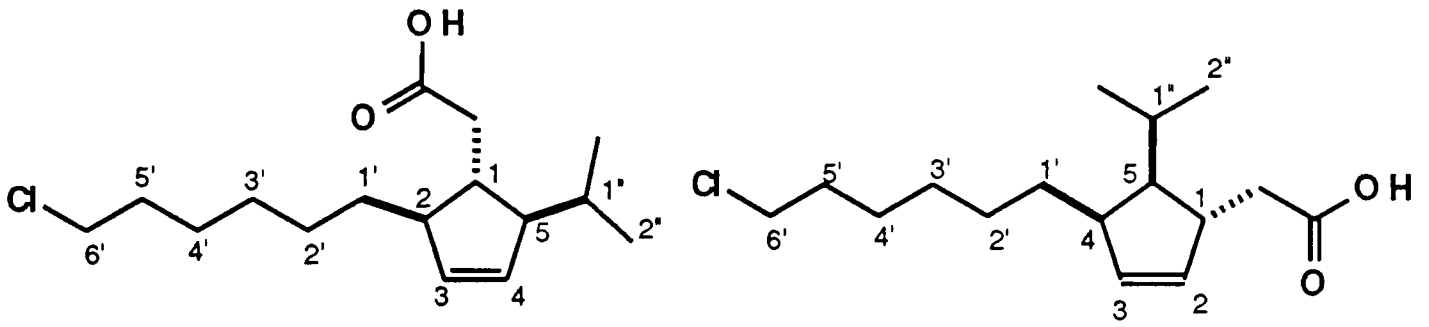


To a solution of alcohol **303** (25mg, 0.084mmol) in pyridine (1ml) was added TsCl (18mg, 0.092mmol). After 15h the reaction mixture was diluted with ether (15ml), washed successively with 1M aq. HCl (2x10ml), sat. aq. $CuSO_4$ (5ml), water (5ml) and brine (5ml), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (10:1, petrol:ether) afforded the title compound **304** (32mg, 85%) as an orange oil. R_f (1:1, petrol:ether) 0.50 (uv active); $\nu_{max.}$ (thin film) 2930 (s), 2858 (m), 1732 (s), 1463 (m), 1361 (m), 1249 (w), 1189 (m), 1178 (s), 1098 (w), 1035 (w), 962 (w), 816 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.9, C**H**$_3$), 0.92 (3H, d, *J* 6.6, **CH**$_3$), 1.20-1.52 (8H, m), 1.27 (3H, t, *J* 7.1, OCH$_2$C**H**$_3$), 1.57-1.70 (3H, m), 1.78-1.85 (1H, m, **H**(1")), 2.15 (1H, dd, *J* 15.0, 9.3, C**H**$_a$H$_b$CO$_2$Et), 2.46 (3H, s, **CH**(5''')$_3$), 2.59 (1H, dd, *J* 15.0, 5.1, CH$_a$**H**$_b$CO$_2$Et), 2.62-2.67 (1H, m, **H**(4)), 2.83-2.88 (1H, m, **H**(1)), 4.03 (2H, t, *J* 6.5, **H**(6')$_2$), 4.14 (2H, q, *J* 7.1, OC**H**$_2$CH$_3$), 5.64 (1H, br s, **H**(2)), 5.78 (1H, dt, *J* 5.7, 2.0, **H**(3)), 7.35

(2H, d, *J* 8.2, 2x**H**(3''')), 7.80 (2H, d, *J* 8.2, 2x**H**(2''')); δ_C (125MHz, $CDCl_3$) 14.3 ($OCH_2\mathbf{C}H_3$), 21.2, 21.6 (2x$\mathbf{C}H_3$), 22.7 (**C**(5''')), 25.3 28.0, 28.8, 29.3, 29.9 (5x$\mathbf{C}H_2$), 27.6 (**C**(1'')), 40.3 ($\mathbf{C}H_2CO_2H$), 43.4 (**C**(5)), 46.7 (**C**(4)), 53.4 (**C**(1)), 60.2 ($O\mathbf{C}H_2CH_3$), 70.6 (**C**(6')), 127.9 (2x**C**(3''')), 129.8 (2x**C**(2''')), 133.3 (**C**(4''')), 133.5 (**C**(2)), 135.1 (**C**(3)), 144.6 (**C**(1''')), 173.1 ($\mathbf{C}O_2Et$); *m/z* (A.P.C.I., +ve) 487 (13), 466 (30), 465 (100), 451 (MH^+, 55), 449 (30), 437 (18), 419 (55), 405 (MH^+-EtOH, 60), 403 (31), 377 (20), 363 (MH^+-EtOAc, 40%); Accurate Mass: Found 451.2510, $C_{25}H_{39}O_5S$ (MH^+) requires 451.251820.

***rel*-(1*R*, 4*R*, 5*R*)-4-(6'-Chlorohexyl)-5-(1''-methylethyl)cyclopent-2-ene-1-acetic acid 305 and *rel*-(1*S*, 2*R*, 5*S*)-2-(6'-Chlorohexyl)-5-(1''-methylethyl)cyclopent-3-ene-1-acetic acid 306**

Method 1



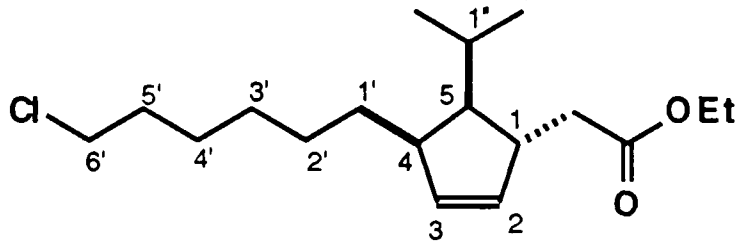
To a cooled (-78°C) solution of chloro-iodohexane **253** (2.0g, 8.10mmol) in ether (30ml) was added dropwise *t*-butyllithium (11.4ml, 1.5M in pentane, 17.0mmol) and, after 15mins, a solution of $CuBr.SMe_2$ (1.7g, 8.27mmol) in Me_2S (30ml). The mixture was warmed to -20°C and stirred vigorously. After 20mins the dark blue solution was cooled to -78°C and a solution of the alkenyl-lactone **288** (0.33g, 1.98mmol) in ether (2ml) added dropwise. After 15h the reaction mixture was diluted with 1M aq. HCl (30ml) and extracted with ether (20ml). The combined organic portions were washed with brine (30ml), dried ($MgSO_4$) then concentrated and purified by flash column chromatography (8:1, petrol:ether) to give a mixture (ratio **306**:**305**, 1:4) of the title acids **305** and **306** (0.42g, 74%) as oils. Major (S_N2') product **305**: R_f (1:1, petrol:ether) 0.30; $\nu_{max.}$

(thin film) 3400 (br w), 3050 (w), 2930 (s), 2856 (s), 1708 (s), 1464 (w), 1387 (w), 1367 (w), 1278 (w), 1169 (w), 1038 (w), 741 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.7, C**H**$_3$), 0.94 (3H, d, *J* 6.6, C**H**$_3$), 1.22-1.37 (6H, m), 1.38-1.56 (2H, m), 1.57-1.64 (1H, m, **H**(5)), 1.74-1.80 (2H, m, **H**(5')$_2$), 1.82-1.87 (1H, m, **H**(1")), 2.15-2.22 (1H, m, C**H**$_a$H$_b$CO$_2$H), 2.67 (1H, dd, *J* 15.0, 4.4, CH$_a$**H**$_b$CO$_2$H), 2.66-2.69 (1H, m, **H**(4)), 2.86-2.87 (1H, m, **H**(1)), 3.54 (2H, t, *J* 6.8, **H**(6')2), 5.68 (1H, br d, *J* 5.7, **H**(2)), 5.83 (1H, dt, *J* 5.7, 2.1, **H**(3)); δ_C (125MHz, $CDCl_3$) 21.2, 22.7 (2x**C**H$_3$), 26.9, 28.0, 29.2, 30.0, 32.6 (5x**C**H$_2$), 27.6 (**C**(1")), 40.0 (**C**H$_2$CO$_2$H), 43.2 (**C**(5)), 45.1 (**C**(6')), 46.7 (**C**(4)), 53.4 (**C**(1)), 133.1 (**C**(2)), 135.5 (**C**(3)), 179.3 (**C**O$_2$H); *m/z* (C.I., NH_3) 306 (M(^{37}Cl)NH_4^+, 25), 304 (M(^{35}Cl)NH_4^+, 55), 241 (33), 227 (M(^{35}Cl)H^+-AcOH, 100), 207 (12), 185 (20), 149 (20), 123 (23), 109 (70), 58 (22%); Accurate Mass: Found 304.2043, $C_{16}H_{31}ClNO_2$ (MNH_4^+) requires 304.204331. Minor (S_N2) product **306**: R_f (1:1, petrol:ether) 0.42; $\nu_{max.}$ (thin film) 3050 (w), 2930 (s), 2858 (s), 1708 (s), 1465 (m), 1410 (m), 1367 (m), 1306 (m), 943 (w), 728 (w), 628 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.7, C**H**$_3$), 0.94 (3H, d, *J* 6.7, C**H**$_3$), 1.27-1.39 (6H, m), 1.39-1.49 (2H, m), 1.56 (1H, oct, *J* 6.7, **H**(1")), 1.74-1.82 (2H, m, **H**(5')$_2$), 1.95 (1H, dddd, *J* 7.5, 6.7, 4.5, 3.1, **H**(1)), 2.16 (1H, ddd, *J* 6.2, 4.6, 1.8, **H**(5)), 2.29-2.35 (1H, m, **H**(2)), 2.38 (1H, dd, *J* 14.7, 7.7, C**H**$_a$H$_b$CO$_2$H), 2.43 (1H, dd, *J* 14.7, 6.7, CH$_a$**H**$_b$CO$_2$H), 3.53 (2H, t, *J* 6.8, **H**(6')$_2$), 5.61 (1H, dt, *J* 5.9, 1.8, **H**(4)), 5.64 (1H, dt, *J* 5.9, 2.0, **H**(3)); δ_C (125MHz, $CDCl_3$) 19.7, 21.3 (2x**C**H$_3$), 26.8, 29.1, 32.4, 32.6, 36.4 (5x**C**H$_2$), 27.5 (**C**(1")), 41.1 (**C**H$_2$CO$_2$H), 43.1 (**C**(1)), 45.1 (**C**(6')), 52.3 (**C**(2)), 59.3 (**C**(5)), 133.2 (**C**(4)), 133.3 (**C**(3)), 179.1 (**C**O$_2$H); *m/z* (C.I., NH_3) 306 (M(^{37}Cl)NH_4^+, 40), 304 (M(^{35}Cl)NH_4^+, 100), 287 (M(^{35}Cl)H^+, 12), 245 (20), 243 (55), 226 (20), 185 (11), 183 (19), 167 (30), 122 (40), 107 (39), 93 (28), 91 (30), 79 (35%); Accurate Mass: Found 304.2043, $C_{16}H_{31}ClNO_2$ (MNH_4^+) requires 304.204331.

Method 2

To a cooled (-78°C) solution of chloro-iodohexane **253** (2.0g, 8.10mmol) in ether (30ml) was added dropwise *t*-butyllithium (11.4ml, 1.5M in pentane, 17.0mmol) and, after 15mins, a solution of $CuBr.SMe_2$ (1.0g, 4.90mmol) in Me_2S (20ml). The mixture was warmed to -20°C and stirred vigorously. After 20mins the dark blue solution was cooled to -78°C and a solution of the alkenyl-lactone **288** (0.54g, 3.20mmol) in ether (5ml) added dropwise. After 15h the reaction mixture was diluted with 1M aq. HCl (30ml) and extracted with ether (20ml). The combined organic fractions were washed with brine (30ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (8:1, petrol:ether) to give a mixture (ratio **306**:**305**, 4:1) of the title acids **305** and **306** (0.75g, 82%) as oils. The data for these two acids were identical to those described above.

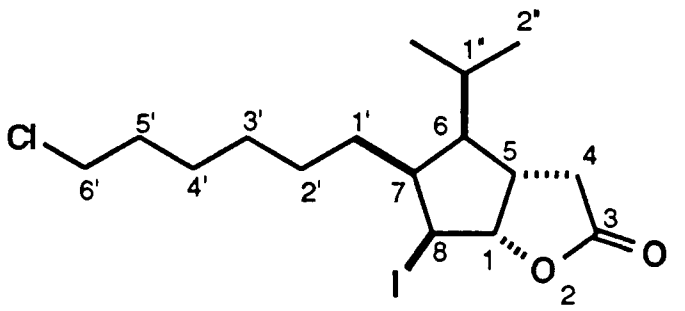
Ethyl *rel*-(1*R*, 4*R*, 5*R*)-4-(6'-chlorohexyl)-5-(1"-methylethyl)cyclopent-2-ene acetate 307



To a solution of the acid **305** (30mg, 0.11mmol) in EtOH (2ml) was added conc. HCl (one drop). After 15h the reaction mixture was concentrated and purified by flash column chromatography (5:1, petrol:ether) to afford the ester **307** (31mg, 94%) as a colourless oil. R_f (1:1, petrol:ether) 0.66; $\nu_{max.}$ (thin film) 3050 (w), 2932 (s), 2857 (s), 1734 (s), 1622 (w), 1465 (m), 1387 (m), 1369 (w), 1344 (m), 1304 (m), 1246 (m), 1160 (s), 1097 (m), 1035 (m), 944 (w), 855 (w), 743 (m), 652 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.9, CH_3), 0.90 (3H, d, *J* 6.6, CH_3), 1.23-1.36 (6H, m), 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.37-1.55 (2H, m), 1.57-1.67 (1H, m, **H**(5)), 1.72-1.78 (2H, m, $H(5')_2$), 1.79-1.85 (1H, m, **H**(1")), 2.13 (1H, dd, *J* 15.1, 9.5, $CH_aH_bCO_2Et$), 2.57 (1H, dd, *J* 15.1, 5.0, $CH_aH_bCO_2Et$), 2.65 (1H, dddd, *J* 10.0, 7.6, 5.0, 2.0, **H**(4)), 2.84 (1H, dddd, *J* 9.5, 6.9, 5.0, 2.0, **H**(1)), 3.52 (2H, t, *J* 6.8,

H(6')$_2$), 4.12 (2H, q, *J* 7.1, OC**H**$_2$CH$_3$), 5.63 (1H, dt, *J* 5.7, 2.0, **H**(2)), 5.79 (1H, dt, *J* 5.7, 2.0, **H**(3)); δ_C (125MHz, $CDCl_3$) 14.2 (OCH$_2$**C**H$_3$), 21.1, 22.6 (2x**C**H$_3$), 26.8 28.1, 29.2, 29.9, 32.6 (5x**C**H$_2$), 27.6 (**C**(1")), 40.3 (**C**H$_2$CO$_2$Et), 43.4 (**C**(5)), 45.0 (**C**(6')), 46.6 (**C**(4)), 53.3 (**C**(1)), 60.1 (O**C**H$_2$CH$_3$), 133.4 (**C**(2)), 135.1 (**C**(3)), 173.0 (**C**O$_2$Et); *m/z* (C.I., NH_3) 332 (M(^{35}Cl)NH_4^+, 12), 317 (M(^{37}Cl)H^+, 40), 315 (M(^{35}Cl)H^+, 100), 281 (28), 279 (MH^+-HCl, 50), 271 (11), 227 (M(^{35}Cl)H^+-EtOAc, 40), 226 (25), 195 (30), 122 (45), 107 (50), 93 (23), 79 (19%); Accurate Mass: Found 332.2356, $C_{18}H_{35}ClNO_2$ (MNH_4^+) requires 332.235631.

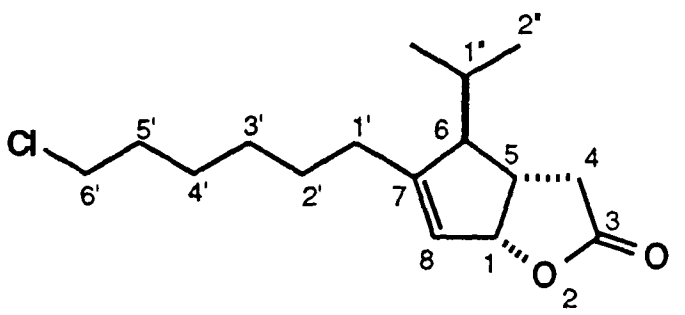
***rel*-(1*S*, 5*S*, 6*S*, 7*S*, 8*S*)-7-(6'-Chlorohexyl)-8-iodo-6-(1"-methylethyl)-2-oxabicyclo[3.3.0]octan-3-one 310**



To a vigorously stirred solution of the acid **305** (0.44g, 1.50mmol) in water (20ml) was added $KHCO_3$ (0.94g, 9.20mmol) followed by KI (1.56g, 9.20mmol) and then, after 5mins, I_2 (0.79g, 3.10mmol) and ether (10ml). After 13h conc. HCl was added dropwise until the pH fell below 7.0 at which point the mixture was diluted with ether (20ml) and the organic layer separated. The ether portion was washed with sat. aq. $Na_2S_2O_3$ (5ml), water (10ml) and brine (20ml), dried ($MgSO_4$) then concentrated *in vacuo*. Flash column chromatography (4:1, petrol:ether) afforded the iodo-lactone **310** (580mg, 92%) as a colourless oil. R_f (1:1, petrol:ether) 0.29 (uv active); $\nu_{max.}$ (thin film) 2933 (m), 2860 (w), 1780 (s), 1465 (w), 1417 (w), 1388 (w), 1368 (w), 1167 (m), 1057 (m), cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.7, C**H**$_3$), 0.97 (3H, d, *J* 6.5, C**H**$_3$), 1.32-1.41 (4H, m), 1.42-1.51 (4H, m), 1.54 (1H, dt, *J* 9.8, 5.8, **H**(6)), 1.73-1.81 (3H, m, **H**(5')$_2$, **H**(1")), 2.17-2.21 (1H, m, **H**(7)), 2.40 (1H, dd, *J* 18.7, 4.3, **H**(4)$_a$), 2.60 (1H, dddd, 10.5, 9.8, 9.2, 4.3, **H**(5)), 2.85 (1H, dd, *J* 18.7, 10.5, **H**(4)$_b$), 3.54 (2H, t, *J* 6.7, **H**(6')$_2$), 4.15 (1H, dd,

J 7.0, 6.1, **H**(8)), 5.02 (1H, dd, *J* 9.2, 7.3, **H**(1)); δ_C (125MHz, $CDCl_3$) 21.9, 22.2 (2x**C**H_3), 29.0, 29.0, 29.0, 29.6, 32.4 (5x**C**H_2), 26.5 (**C**(1")), 34.5 (**C**(8)), 36.3 (**C**(6)), 40.0 (**C**(4)), 45.0 (**C**(6')), 45.6 (**C**(7)), 56.8 (**C**(5)), 91.7 (**C**(1)), 176.6 (**C**(3)); *m/z* (A.P.C.I., +ve) 351 (11), 329 (25), 299 (30), 287 ($M(^{37}Cl)H^+$-HI, 45), 285 ($M(^{35}Cl)H^+$-HI, 100), 283 (22), 243 (12), 227 ($M(^{37}Cl)H^+$-AcOH-HI, 11), 225 ($M(^{35}Cl)H^+$-AcOH-HI, 38), 189 (MH^+-AcOH-HI-HCl, 15), 173 (89), 122 (11%); Accurate Mass: Found 285.1621, $C_{16}H_{26}ClO_2$ (MH^+-HI) requires 285.162132.

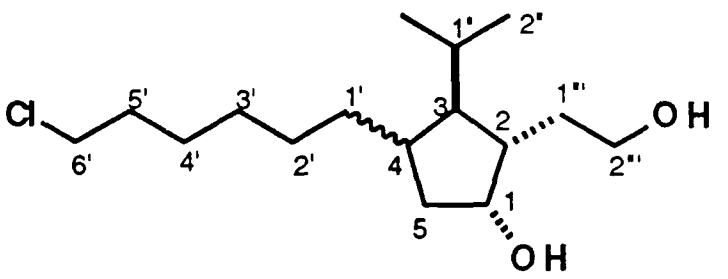
***rel*-(1*R*, 5*S*, 6*S*)-7-(6'-Chlorohexyl)-6-(1"-methylethyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one 308**



To a stirred solution of the iodo-lactone **310** (0.23g, 0.56mmol) in benzene (5ml) was added DBU (92µl, 0.61mmol) and the mixture heated at reflux. After 1.5h the reaction mixture was diluted with 1M aq. HCl (10ml) and extracted with ether (2x10ml). The combined organic portions were washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (3:1, petrol:ether) to give the alkenyl-lactone **308** (0.15g, 95%) as an oil. R_f (1:1, petrol:ether) 0.52; $\nu_{max.}$ (thin film) 2956 (s), 2931 (s), 2859 (s), 1772 (s), 1647 (w), 1419 (w), 1346 (w), 1170 (m), 1013 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.66 (3H, d, *J* 6.9, C**H**$_3$), 1.00 (3H, d, *J* 6.9, C**H**$_3$), 1.26-1.57 (6H, m), 1.76-1.81 (2H, m, **H**(5')$_2$), 1.94-1.99 (2H, m, **H**(1')$_2$), 2.05-2.12 (1H, m, **H**(1")), 2.30 (1H, dd, *J* 22.7, 10.5, **H**(4)$_a$), 2.48-2.50 (1H, m, **H**(6)), 2.79-2.85 (1H, m, **H**(5)), 2.82 (1H, dd, *J* 22.7, 10.5, **H**(4)$_b$), 3.55 (2H, t, *J* 6.6, **H**(6')$_2$), 5.42 (1H, dd, *J* 6.9, 1.7, **H**(1)), 5.56 (1H, t, *J* 1.7, **H**(8)); δ_C (50.3MHz, $CDCl_3$) 15.8, 21.2 (2x**C**H_3), 26.5, 27.8, 28.6, 28.9, 32.3 (5x**C**H_2), 26.7 (**C**(1")), 36.3, 36.4 (**C**(4), **C**(6)), 45.0 (**C**(6')), 61.0 (**C**(5)), 89.4 (**C**(1)), 123.0 (**C**(8)), 154.4 (**C**(7)), 177.8 (**C**(3)); *m/z* (C.I., NH_3) 304

($M(^{37}Cl)NH_4^+$, 10), 302 ($M(^{35}Cl)NH_4^+$, 30), 287 ($M(^{37}Cl)H^+$, 25), 285 ($M(^{35}Cl)H^+$, 80), 243 ($M(^{37}Cl)H^+$-CO_2, 30), 241 ($M(^{35}Cl)H^+$-CO_2, 100), 205 (15), 149 (20), 136 (20), 121 (19), 91 (12%); Accurate Mass: Found 285.1621, $C_{16}H_{26}ClO_2$ (MH^+) requires 285.162132.

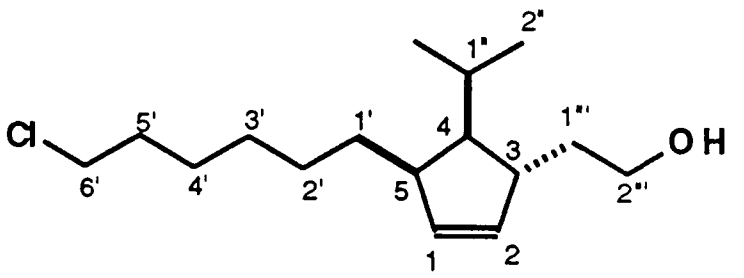
***rel*-(1*R*, 2*S*, 3*R*, 4*R*)- and *rel*-(1*R*, 2*S*, 3*R*, 4*S*)-4-(6'-Chlorohexyl)-2-(2'''-hydroxyethyl)-3-(1''-methylethyl)cyclopentan-1-ol 309**



To a solution of chloro-lactone **308** (50mg, 0.18mmol) in THF (5ml) was added dropwise BH_3.THF or $BH_3.SMe_2$ (0.18ml, 1.0M in THF, 0.18mmol), then, after 18h, 1M aq. NaOH (1ml) and, after a further 1h, conc. HCl (2 drops). After 1h the reaction mixture was diluted with water (10ml) and extracted with ether (20ml). The organic fraction was washed with brine (10ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:EtOAc) to give the title diols **309** (46mg, 91%) as a mixture (ratio 8:3) of oils. R_f (EtOAc) 0.46, 0.41; $\nu_{max.}$ (thin film) 3349 (br s), 2929 (s), 1476 (m), 1387 (w), 1363 (w), 1065 (m) cm^{-1}; major isomer: δ_H (500MHz, $CDCl_3$) 0.89-0.94 (6H, m, 2xCH_3), 1.23-1.60 (10H, m), 1.61-1.93 (7H, m), 1.97-2.00 (1H, m), 3.54 (2H, t, *J* 6.7, **H**(6')$_2$), 3.60-3.71 (2H, m, **H**(2''')$_2$), 3.83-3.91 (1H, m, **H**(1)); minor isomer: 0.89-0.94 (6H, m, 2xCH_3), 1.03-1.09 (1H, m), 1.23-1.60 (10H, m), 1.61-1.93 (6H, m), 2.16-2.20 (1H, m), 3.54 (2H, t, *J* 6.7, **H**(6')$_2$), 3.60-3.71 (2H, m, **H**(2''')$_2$), 3.93 (1H, dd, *J* 8.2, 3.8, **H**(1)); δ_C (125MHz, $CDCl_3$) 19.3/20.3, 20.9/21.0 (2xCH_3), 26.8 (**C**(1'')), 28.0/28.1, 29.2/29.8, 30.5/30.9, 32.6, 35.7/35.9, 37.3/37.7, 37.9/39.3 (7xCH_2), 39.7/40.6 (**C**(3)), 45.2 (**C**(6')), 50.0/50.5 (**C**(4)), 56.7/57.4 (**C**(2)), 62.0/62.8 (**C**(2''')), 77.7/77.8 (**C**(1)); *m/z* (A.P.C.I., +ve) 275 ($M(^{37}Cl)H^+$-H_2O, 10), 273 ($M(^{35}Cl)H^+$-H_2O, 30), 257 ($M(^{37}Cl)H^+$-$2H_2O$, 35), 255 ($M(^{35}Cl)H^+$-$2H_2O$,

100), 231 (10), 231 (10), 229 (45), 227 (10), 201 (12), 199 (40), 185 (20), 173 (15), 137 (38), 124 (16), 123 (51), 122 (96), 111 (32), 109 (50%); Accurate Mass: Found 273.1985, $C_{16}H_{30}ClO$ (MH^+-H_2O) requires 273.198517.

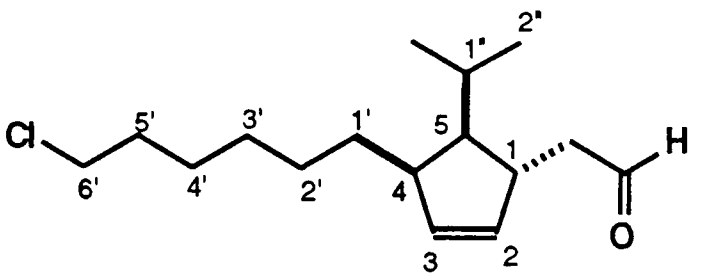
rel-(3_R_, 4_R_, 5_R_)-5-(6'-Chlorohexyl)-3-(2'''-hydroxyethyl)-4-(1''-methylethyl) cyclopentene 313



To a cooled (0°C) suspension of $LiAlH_4$ (17mg, 0.44mmol) in THF (3ml) was added dropwise a solution of acid **305** (50mg, 0.18mmol) in THF (1ml). After 15h sat. aq. potassium sodium tartrate (1ml) was added and the mixture stirred vigorously. After a further 1h the reaction mixture was diluted with sat. aq. potassium sodium tartrate (2ml) and ether (5ml) and the layers separated. The organic portion was washed with 1M aq. NaOH (2ml), water (5ml) and brine (5ml), dried ($MgSO_4$) then concentrated and purified by flash column chromatography (6:1, petrol:ether) to give the title alcohol **313** (35mg, 79%) as a colourless oil. R_f (1:1, petrol:ether) 0.33; $\nu_{max.}$ (thin film) 3333 (br s), 3047 (w), 2928 (s), 2856 (s), 1621 (w), 1464 (m), 1386 (m), 1367 (m), 1310 (m), 1174 (w), 1055 (m), 738 (m), 653 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.7, C**H**$_3$), 0.91 (3H, d, *J* 6.6, C**H**$_3$), 1.21-1.38 (6H, m), 1.39-1.59 (4H, m), 1.61-1.69 (1H, m, **H**(4)), 1.70-1.90 (3H, m, **H**(5')$_2$, **H**(1'')), 2.51 (1H, dddd, *J* 8.5, 6.5, 4.6, 2.0, **H**(5)), 2.65 (1H, dddd, *J* 10.0, 7.6, 4.8, 2.0, **H**(3)), 3.52 (2H, t, *J* 6.8, **H**(6')$_2$), 3.65-3.73 (2H, m, **H**(2''')$_2$), 5.67 (1H, dt, *J* 5.9, 2.0, **H**(2)), 5.77 (1H, dt, *J* 5.9, 2.0, **H**(1)); δ_C (125MHz, $CDCl_3$) 21.0, 22.7 (2x**C**H$_3$), 26.8, 28.2, 29.2, 29.9, 32.6 (5x**C**H$_2$), 27.6 (**C**(1'')), 38.3 (**C**(1''')), 43.2 (**C**(4)), 45.1 (**C**(6')), 46.6 (**C**(5)), 53.2 (**C**(3)), 61.8 (**C**(2''')), 133.7 (**C**(2)), 134.7 (**C**(1)); *m/z* (C.I., NH_3) 292 ($M(^{37}Cl)NH_4^+$, 40), 290 ($M(^{35}Cl)NH_4^+$, 80), 255 (12), 229 ($M(^{37}Cl)H^+$-$2H_2O$, 60), 227 ($M(^{35}Cl)H^+$-$2H_2O$,

100), 211 (19), 187 (30), 185 (80), 154 (20), 153 (65), 135 (40), 109 (100), 107 (52), 95 (45), 93 (85), 91 (41), 81 (62), 79 (40), 67 (28%); Accurate Mass: Found 290.2251, $C_{16}H_{33}ClNO$ (MNH_4^+) requires 290.2250661.

rel-(1*R*, 4*R*, 5*R*)-4-(6'-Chlorohexyl)-5-(1"-methylethyl)cyclopent-2-ene-1-acetaldehyde 311



A suspension of alcohol **313** (40mg, 0.15mmol), molecular sieves (0.15g, 4Å powdered) and PDC (77mg, 0.22mmol) in DCM (3ml) was stirred at RT. After 4h the solution was diluted with ether (5ml) and filtered through Celite®. The organic layer was washed with sat. aq. $CuSO_4$ (2ml), 1M aq. HCl (4ml) and brine (5ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the aldehyde **311** (35mg, 88%) as an oil. R_f (1:1, petrol:ether) 0.75; $\nu_{max.}$ (thin film) 3050 (w), 2931 (s), 2857 (s), 2716 (w), 1724 (s), 1465 (m), 1387 (m), 1367 (m), 1309 (w), 1174 (w), 1037 (w), 742 (w), 652 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.7, C**H**$_3$), 0.93 (3H, d, *J* 6.6, C**H**$_3$), 1.24-1.58 (8H, m), 1.60-1.64 (1H, m, **H**(5)), 1.74-1.79 (2H, m, **H**(5')$_2$), 1.80-1.87 (1H, m, **H**(1")), 2.35 (1H, ddd, *J* 16.8, 8.8, 2.4, C**H**$_a$H$_b$CHO), 2.65 (1H, dddd, *J* 10.1, 7.8, 4.4, 2.0, **H**(4)), 2.71 (1H, ddd, *J* 16.8, 4.5, 1.6, CH$_a$**H**$_b$CHO), 2.94 (1H, dddd, *J* 8.8, 6.7, 4.5, 2.0, **H**(1)), 3.53 (2H, t, *J* 6.8, **H**(6')$_2$), 5.62 (1H, dt, *J* 5.7, 2.0, **H**(2)), 5.83 (1H, dt, *J* 5.7, 2.0, **H**(3)), 9.79 (1H, dd, *J* 2.4, 1.6, C**H**O); δ_C (125MHz, $CDCl_3$) 21.2, 22.7 (2x**C**H$_3$) 26.8, 28.0, 29.2, 29.9, 32.6 (5xCH$_2$), 27.7 (**C**(1")), 41.0 (**C**H$_2$CHO), 45.0 (**C**(6')), 46.6 (**C**(5)), 49.7 (**C**(4)), 53.6 (**C**(1)), 132.9 (**C**(2)), 135.6 (**C**(3)), 202.5 (**C**HO); *m/z* (C.I., NH_3) 290 (M(^{37}Cl)NH_4^+, 20), 288 (M(^{35}Cl)NH_4^+, 60), 228 (15), 227 (M(^{35}Cl)H$^+$-MeCHO, 30), 226 (50), 122 (100), 109 (22), 107 (80), 93 (18), 81 (30%); Accurate Mass: Found 288.2094, $C_{16}H_{31}ClNO$ (MNH_4^+) requires 288.209416.

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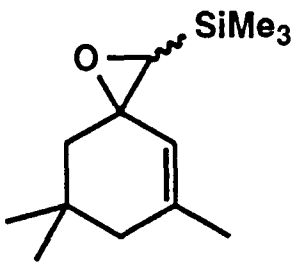
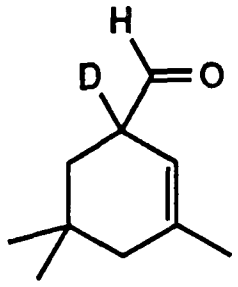
APPENDIX A

1. Epoxysilane 45 (Section 2.1.2., p24)

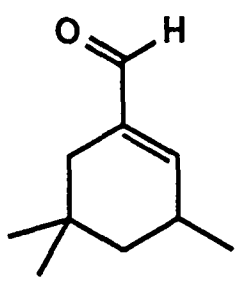


3:2 mixture of diastereomers. Major isomer, δ_H (200MHz, C_6D_6) 0.10 (9H, s, $Si(CH_3)_3$), 0.86 (3H, s), 1.05 (3H, s), 0.90-1.52 (4H, m), 2.05 (3H, d, *J* 0.5), 2.40 (1H, s), 5.03 (1H, br s); minor isomer, δ_H (200MHz, C_6D_6) 0.08 (9H, s, $Si(CH_3)_3$), 0.88 (3H, s), 0.92 (3H, s), 0.90-1.52 (4H, m), 2.05 (3H, d, *J* 0.5), 2.15 (1H, s), 5.23 (1H, br s).

2. Aldehyde 46 (Section 2.1.2., p24)

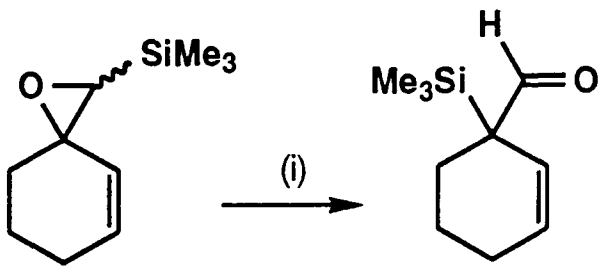


δ_H (200MHz, $CDCl_3$) 1.60 (3H, s), 1.50-1.75 (3H, m), 1.75 (3H, s), 2.15 (3H, s), 2.30-2.40 (1H, m), 5.70 (1H, br s), 9.58 (1H, s). This compound, on column chromatography, isomerised to give an α,β-unsaturated aldehyde.



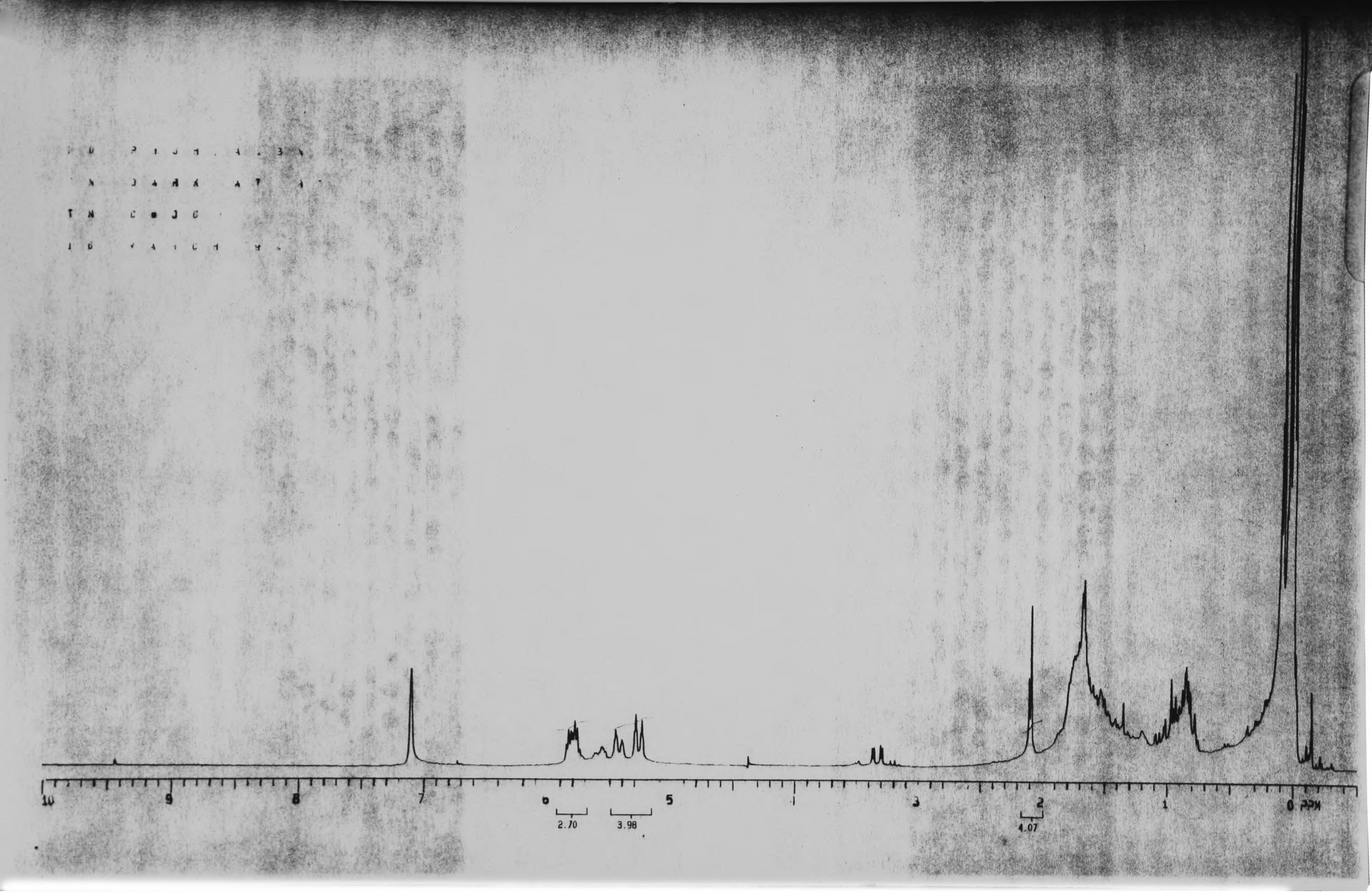
δ_H (200MHz, $CDCl_3$) 0.98 (3H, d, *J* 7.0), 1.50-1.70 (2H, m), 1.40 (3H, s), 1.75 (3H, s), 2.00-2.05 (1H, m), 2.08-2.10 (1H, m), 2.10-2.30 (1H, m), 6.65-6.70 (1H, m), 9.60 (1H, s).

APPENDIX B



The following ^1H NMR spectra associated with this study are included in the order:

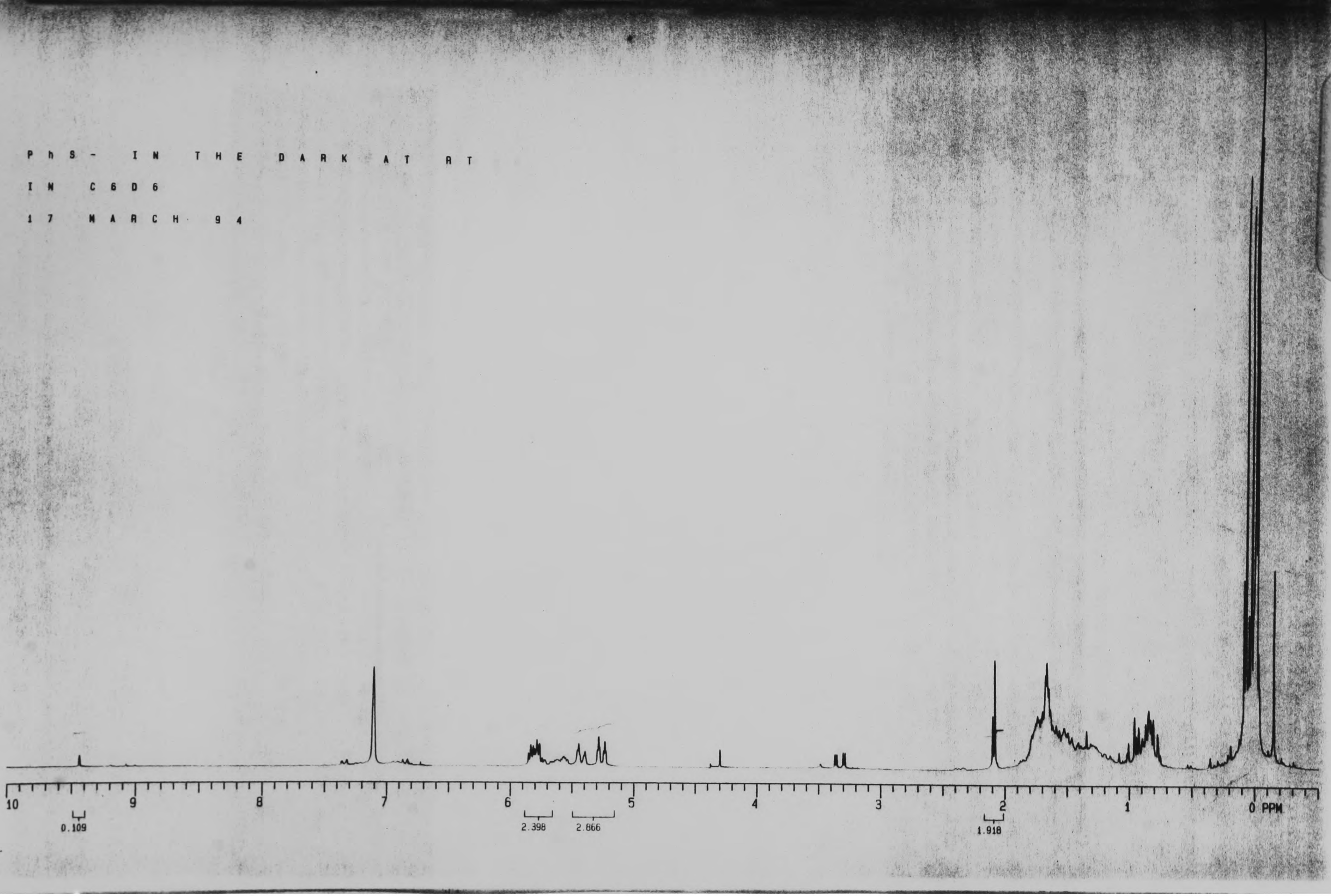
Conditions (i)
No additives, RT, 15h
0.1 eq. PhSNa, RT, 15h
0.1eq. PhSH, RT, 15h
0.1 eq. PhSH, 0.1 eq. AIBN, RT, 15h
0.1 eq. PhSSPh, 0.1 eq. AIBN, RT, 15h

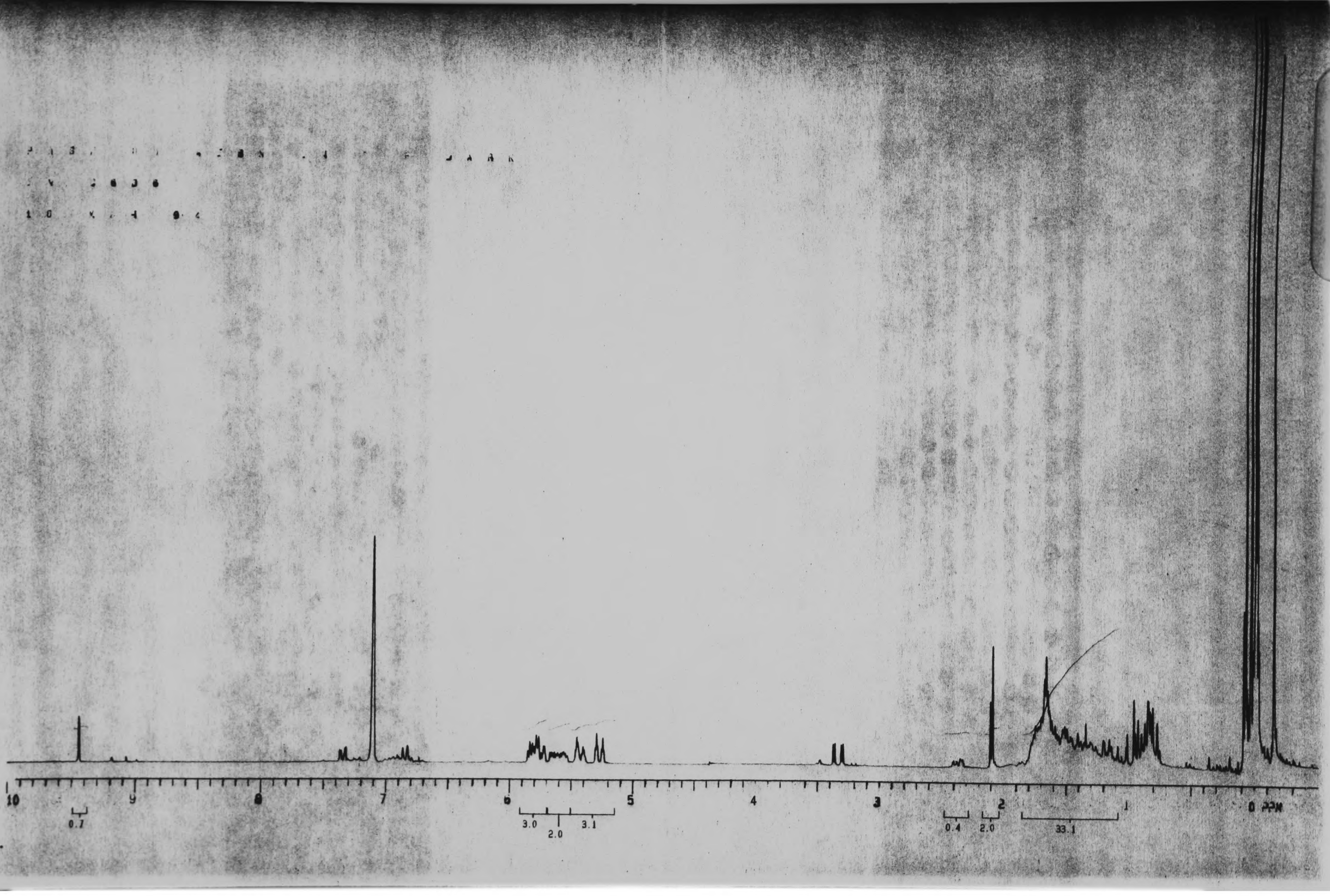

10
9
8
7
6
5
3
2
1
0 PPM
2.70
3.98
4.07

PhS- IN THE DARK AT RT

IN C6D6

17 MARCH 94




10
9
8
7
6
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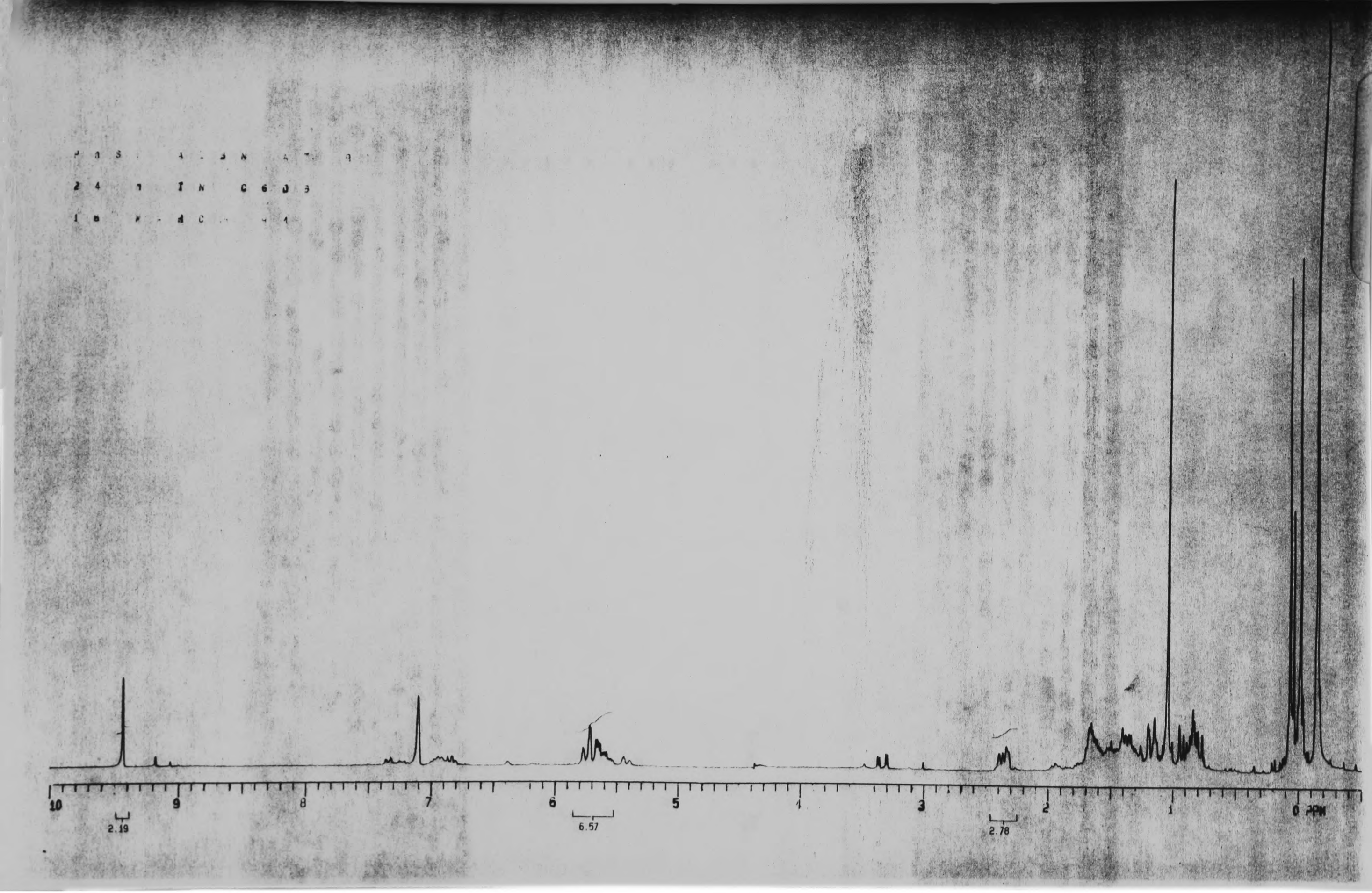
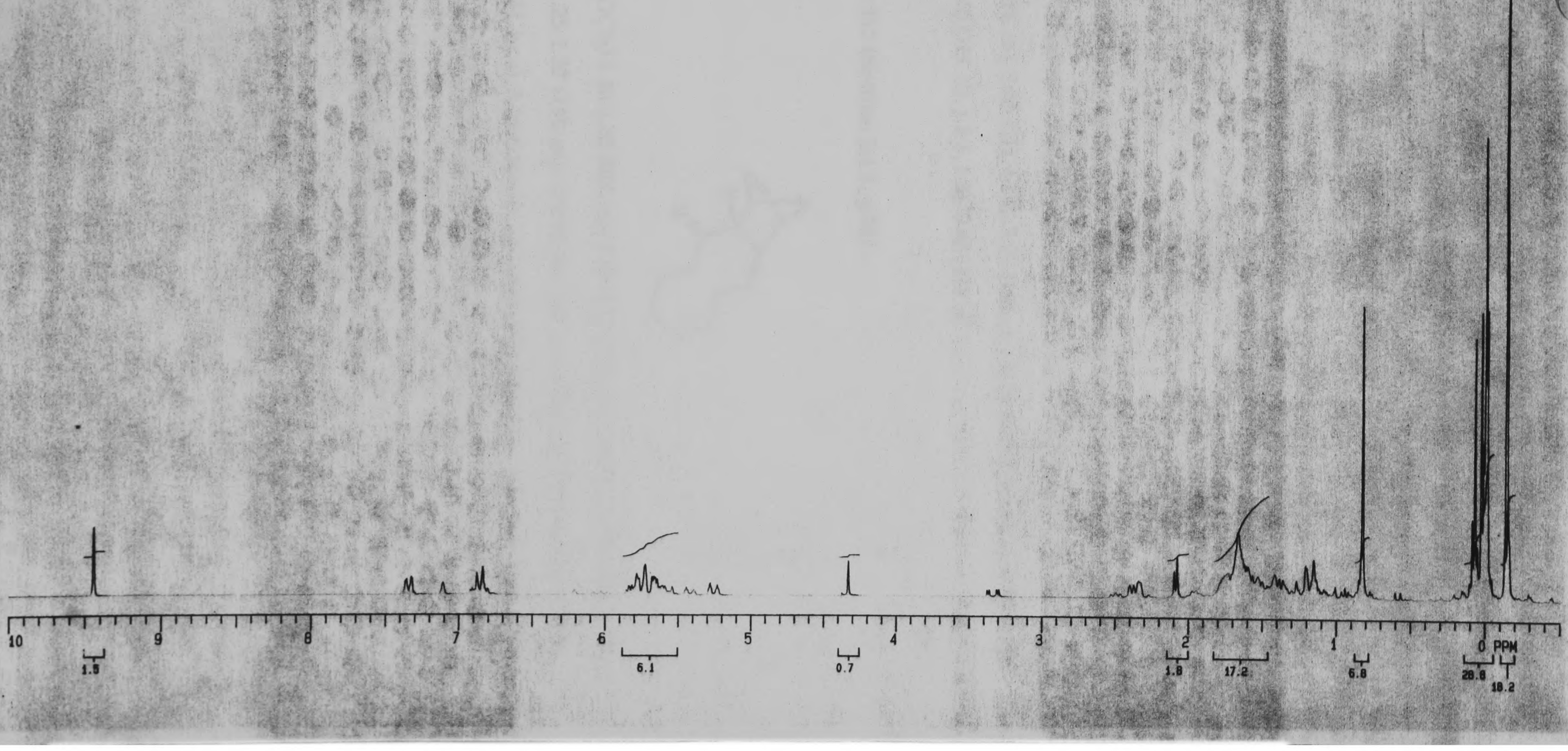
4
3
2
1
0 PPM
0.7
3.0
2.0
3.1
0.4
2.0
33.1


10
9
8
7
6
5
4
3
2
1
0 PPM
2.19
6.57
2.78

NMR EXPERIMENT WITH PhSSPh AND AIBN

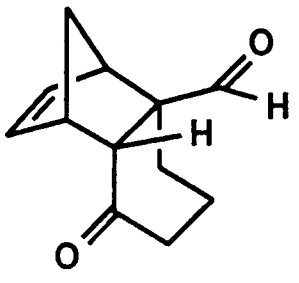
IN C6D6

11 NOV 93



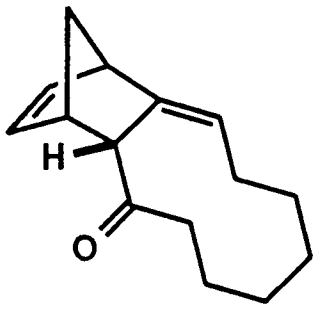
APPENDIX C

1. Cycloadduct 95 (Section 5.3.4., p93)



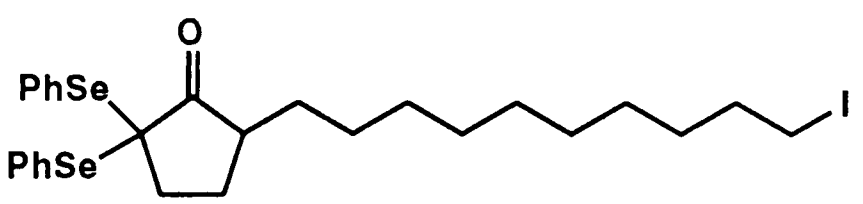
$\nu_{max.}$ (thin film) 2948 (s), 2874 (s), 1715 (s), 1695 (sh s), 1455 (s), 1326 (m), 1251 (m), 1193 (s), 1131 (s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.20-1.75 (4H, m), 1.75-1.82 (2H, m), 2.40-2.70 (2H, m), 2.95 (1H, br s), 3.25 (1H, d, *J* 8.0), 3.35 (1H, br s), 6.12 (1H, dt, *J* 5.5, 1.5), 6.45 (1H, dt, *J* 5.5, 1.5), 9.65 (1H, s).

2. Tricycle 117 (Section 5.4.1., p99)



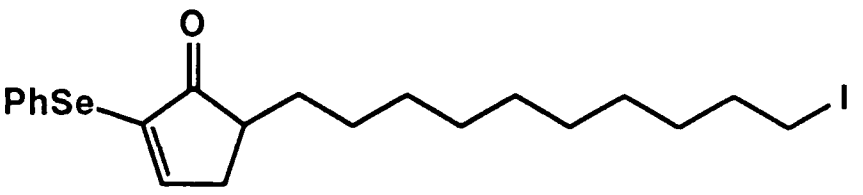
δ_H (500MHz, $CDCl_3$) 1.20-1.55 (8H, m), 1.68-1.75 (2H, m), 1.93-2.03 (1H, m), 2.15-2.20 (1H, m), 2.25-2.32 (1H, m), 2.52-2.56 (1H, m), 2.56-2.67 (1H, m), 2.65-2.71 (1H, m), 2.66 (1H, br s), 5.00-5.05 (1H, m), 5.68 (1H, dd, *J* 5.5, 1.5), 6.37 (1H, dd, *J* 5.5, 2.8); *m/z* (C.I., NH_3) 219 (12), 217 (MH^+, 100), 201 (20%).

3. Diselenide 163 (Section 6.3.2., p121)



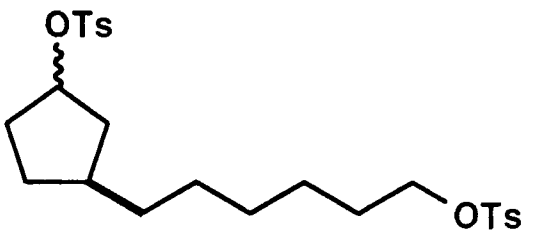
δ_H (200MHz, $CDCl_3$) 1.25-1.45 (14H, m), 1.65-1.80 (2H, m), 1.80-1.85 (2H, m), 2.00-2.10 (2H, m), 2.13-2.25 (3H, m), 3.20 (2H, t, *J* 7.0), 7.25-7.37 (6H, m), 7.59-7.63 (4H, m).

4. Selenoenone 164 (Section 6.3.2., p121)



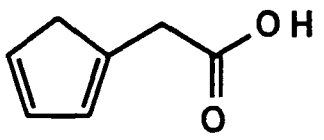
R_f (1:1, petrol:ether) 0.60 (uv active); $\nu_{max.}$ (thin film) 2922 (s), 2847 (s), 1688 (s), 1462 (w), 1269 (w), 1165 (w), 1064 (w), 810 (w), 741 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.20-1.40 (16H, m), 1.80-1.86 (2H, m), 2.30 (1H, dt, *J* 19.0, 3.0), 2.45-2.50 (1H, m), 2.80 (1H, ddd, *J* 19.0, 6.5, 3.0), 3.19 (2H, t, *J* 7.0), 7.08 (1H, t, *J* 3.0), 7.33-7.36 (3H, m), 7.60-7.61 (2H, m); δ_C (125MHz, $CDCl_3$) 7.31, 27.1, 28.5, 29.3, 29.3, 29.4, 29.5, 30.5, 31.4, 33.5, 35.8, 45.3, 126.5, 128.5, 129.5, 135.3, 138.6, 157.9, 208.0.

5. Ditosylate 190 (Section 6.3.3.3., p127)



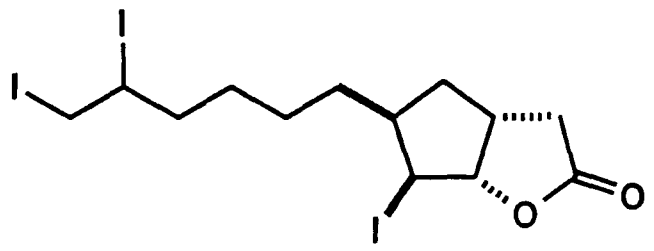
1:1 Mixture of diasteromers. R_f (1:1, petrol:ether) 0.40 (uv active); $\nu_{max.}$ (thin film) 2961 (s), 2932 (s), 2858 (m), 1599 (m), 1496 (w), 1464 (m), 1359 (s), 1307 (m), 1292 (w), 1189 (s), 1177 (s), 1120 (w), 1098 (s), 1055 (w), 1020 (m), 941 (s), 887 (s), 816 (s), 706 (m), 730 (m) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.10-1.62 (11H, m), 1.61-1.80 (4H, m), 1.90-2.15 (2H, m), 2.46 (6H, s), 4.03 (2H, t, *J* 6.5), 4.80-5.00 (1H, m) 7.35 (4H, d, *J* 7.0), 7.81 (4H, d, *J* 7.0); *m/z* (C.I., NH_3) 376 (100), 190 (20), 511 (20%).

6. Cyclopentadienyl acid 224 (Section 6.4.3., p139)



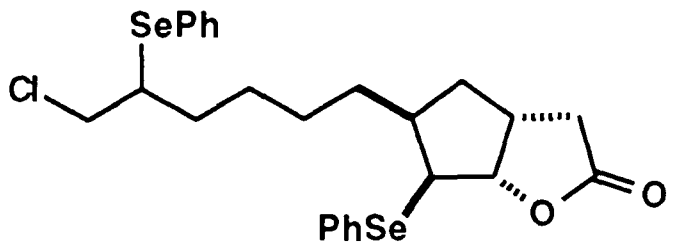
δ_H (200MHz, $CDCl_3$) 3.01-3.08 (2H, m), 3.45-3.50 (2H, m), 6.20-6.55 (3H, m).

7. Triiodide 228 (Section 6.4.4.1., p140)



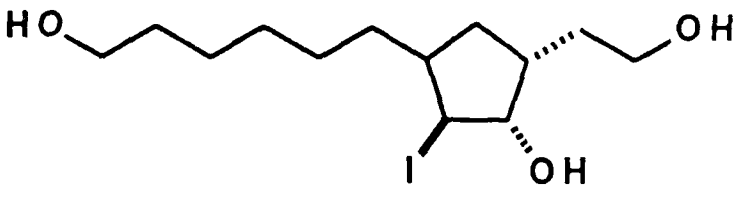
δ_H (200MHz, $CDCl_3$) 1.20-1.60 (8H, m), 1.75-1.95 (3H, m), 2.37 (1H, dd, *J* 18.0, 2.0), 2.89 (1H, dd, *J* 18.0, 10.5), 3.05-3.25 (1H, m), 3.63 (1H, dd, *J* 13.0, 11.0), 4.05 (1H, dd, *J* 13.0, 5.0), 4.20-4.40 (1H, m), 4.53 (1H, d, *J* 4.0), 5.30 (1H, d, *J* 6.0).

8. Diselenide 229 (Section 6.4.4.1., p140)



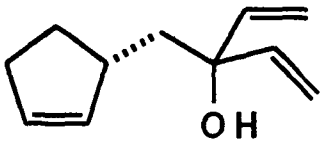
δ_H (200MHz, $CDCl_3$) 1.30-1.70 (7H, m), 1.75-1.95 (3H, m), 2.30-2.35 (1H, m), 2.33 (1H, dd, *J* 18.0, 2.5), 2.84 (1H, dd, *J* 18.0, 10.5), 3.10-3.20 (1H, m), 3.30 (1H, dd, *J* 13.0, 10.5), 3.55 (1H, dd, *J* 13.0, 4.5), 3.91 (1H, br d, *J* 5.0), 4.10-4.30 (1H, m), 4.93 (1H, d, *J* 6.0), 7.28-7.53 (6H, m), 7.53-7.61 (4H, m).

9. Triol 234 (Section 6.4.4.1., p141)



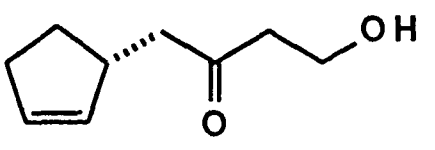
R_f (EtOAc) 0.15 (uv active).

10. Divinyl alcohol 237 (Section 6.4.4.3., p143)



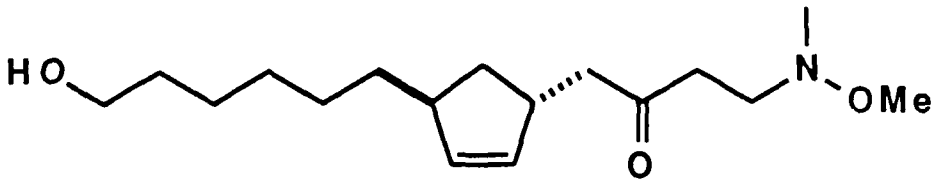
δ_H (200MHz, $CDCl_3$) 1.30-1.50 (2H, m), 1.65 (1H, dd, *J* 16.0, 5.0), 1.78 (1H, dd, *J* 16.0, 5.0), 2.00-2.40 (2H, m), 2.70-2.90 (1H, m), 5.15 (2H, dd, *J* 10.0, 2.0), 5.30 (2H, dd, *J* 17.0, 2.0), 5.70-5.80 (2H, m), 6.00 (2H, dd, *J* 17.0, 10.0).

11. Hydroxy-Ketone 238 (Section 6.4.4.3., p143)



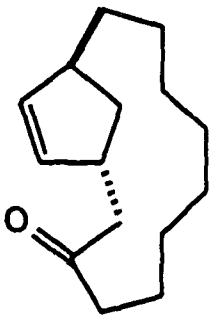
δ_H (200MHz, $CDCl_3$) 1.30-1.50 (2H, m), 2.00-2.50 (6H, m,), 2.95-3.20 (1H, m), 3.65 (2H, t, *J* 7.0), 5.60-5.70 (1H, m), 5.70-5.80 (1H, m).

12. Amino-Ketone 241 (Section 6.4.4.4., p144)



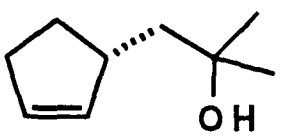
δ_H (200MHz, $CDCl_3$) 1.20-1.40 (8H, m), 1.50-1.65 (2H, m), 1.65-1.85 (2H, m), 2.25-2.70 (4H, m), 2.40 (3H, s), 2.85 (2H, t, *J* 8.0), 2.65-2.75 (1H, m), 3.10-3.20 (1H, m), 3.45 (3H, s), 3.65 (2H, t, *J* 7.0), 5.68-5.73 (2H, m).

13. *trans*-Macrocycle 260 (Section 6.4.4.7., p147)



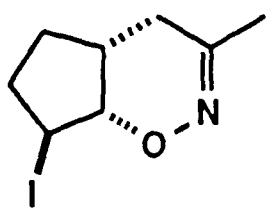
δ_H (200MHz, $CDCl_3$) 1.20-1.85 (16H, m), 2.20-2.55 (4H, m), 2.60-2.70 (1H, m), 3.05-3.15 (1H, m), 5.60-5.65 (1H, m), 5.68-5.73 (1H, m); *m/z* (C.I., NH_3) 238 (MNH_4^+, 25), 221 (MH^+, 100%).

14. Alcohol 280 (Section 6.4.5.7., p153)



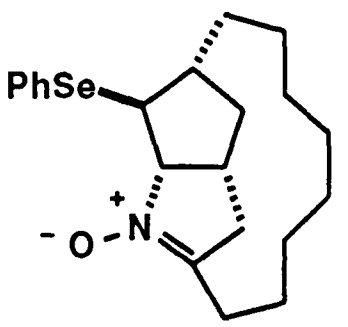
δ_H (200MHz, $CDCl_3$) 1.10 (6H, s), 1.30-1.50 (2H, m), 1.60-180 (2H, m), 2.10-2.35 (2H, m), 2.70-2.90 (1H, m), 5.60-5.70 (1H, m), 5.70-5.80 (1H, m).

15. Iodooxazine 283 (Section 6.4.5.7., p153)



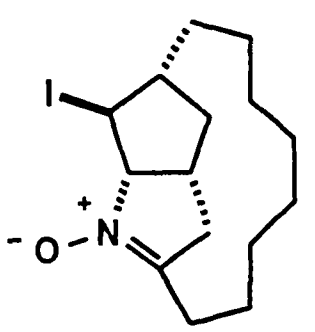
δ_H (200MHz, $CDCl_3$) 1.20-1.50 (2H, m), 1.90-2.20 (2H, m), 1.98 (3H, s), 2.35 (1H, dd, *J* 18.0, 10.0), 2.50-2.60 (1H, m), 2.70-2.80 (1H, m), 4.21 (1H, d, *J* 6.0), 4.25-4.40 (1H, m).

16. Seleno-tricycle 284 (Section 6.4.5.8., p154)



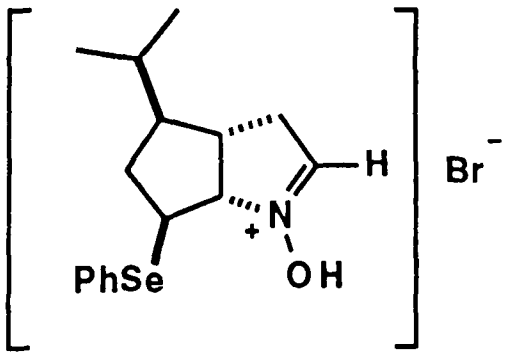
m/z (A.P.C.I., +ve) 394 (M(^{82}Se)H$^+$, 12), 393 (M(^{81}Se)H$^+$, 15), 392 (M(^{80}Se)H$^+$, 100), 390 (M(^{78}Se)H$^+$, 50), 388 (M(^{76}Se)H$^+$, 12), 236 (35), 234 (MH$^+$-PhSeH, 20%); Accurate Mass: Found 392.1493, $C_{21}H_{30}NOSe$ (MH$^+$) requires 392.149259.

17. Iodo-tricycle 285 (Section 6.4.5.8., p154)



m/z (A.P.C.I., +ve) 362 (MH$^+$, 100), 350 (40), 303 (15), 236 (40), 234 (MH$^+$-HI, 85), 219 (55), 181 (20), 173 (35), 171 (30), 150 (55%).

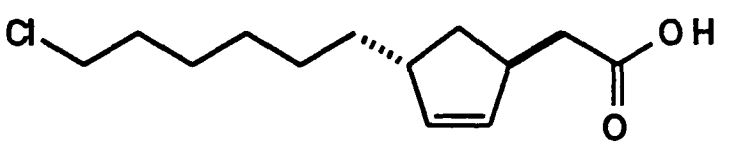
18. Seleno nitrone 300 (Section 6.5.3., p159)



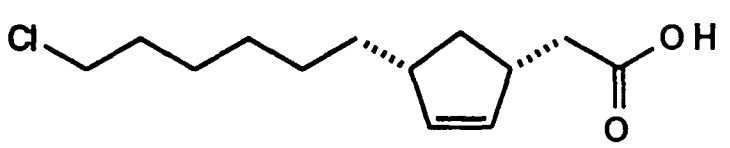
δ_H (200MHz, $CDCl_3$) 0.80-0.95 (6H, m), 1.70-2.30 (5H, m), 2.50-2.60 (1H, m), 2.65-2.80 (1H, m), 4.20-4.40 (1H, m), 4.65 (1H, dd, *J* 16.0, 8.0), 7.20-7.35 (3H, m), 7.55-7.70 (2H, m), 9.80 (1H, br s).

APPENDIX D

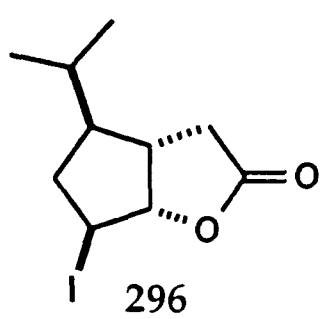
The n.O.e. spectra for the following compounds are included in the order:



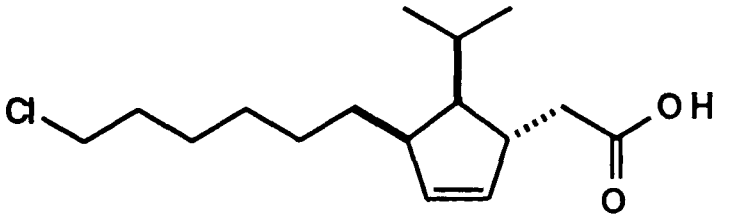
254



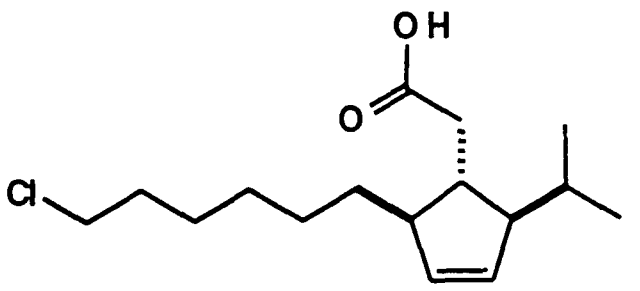
266



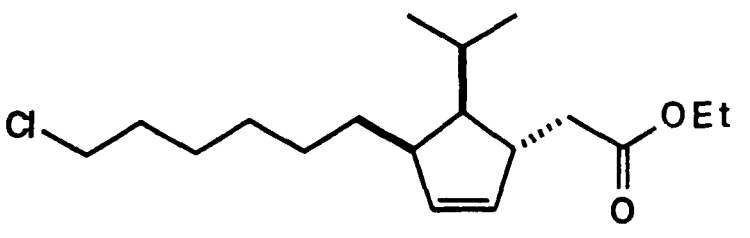
296



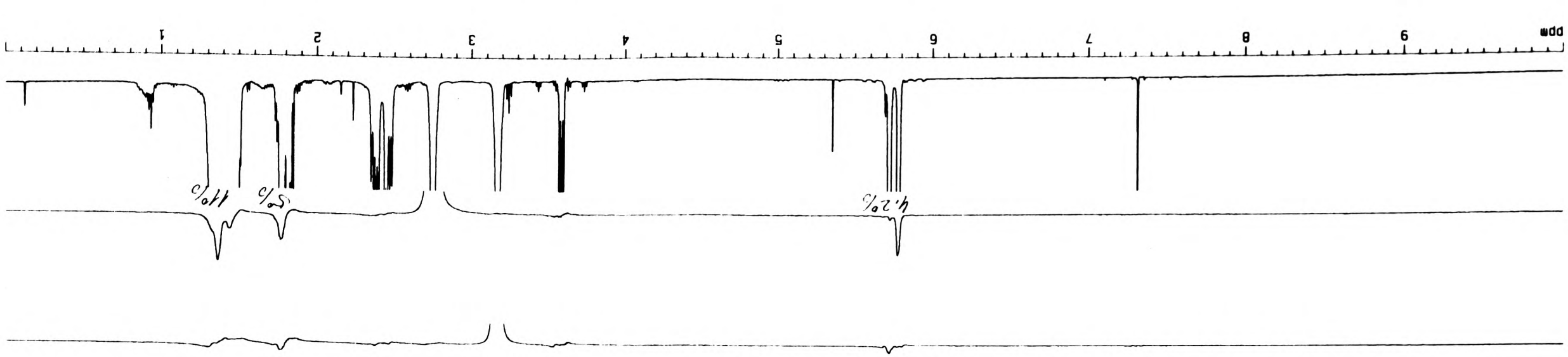
305



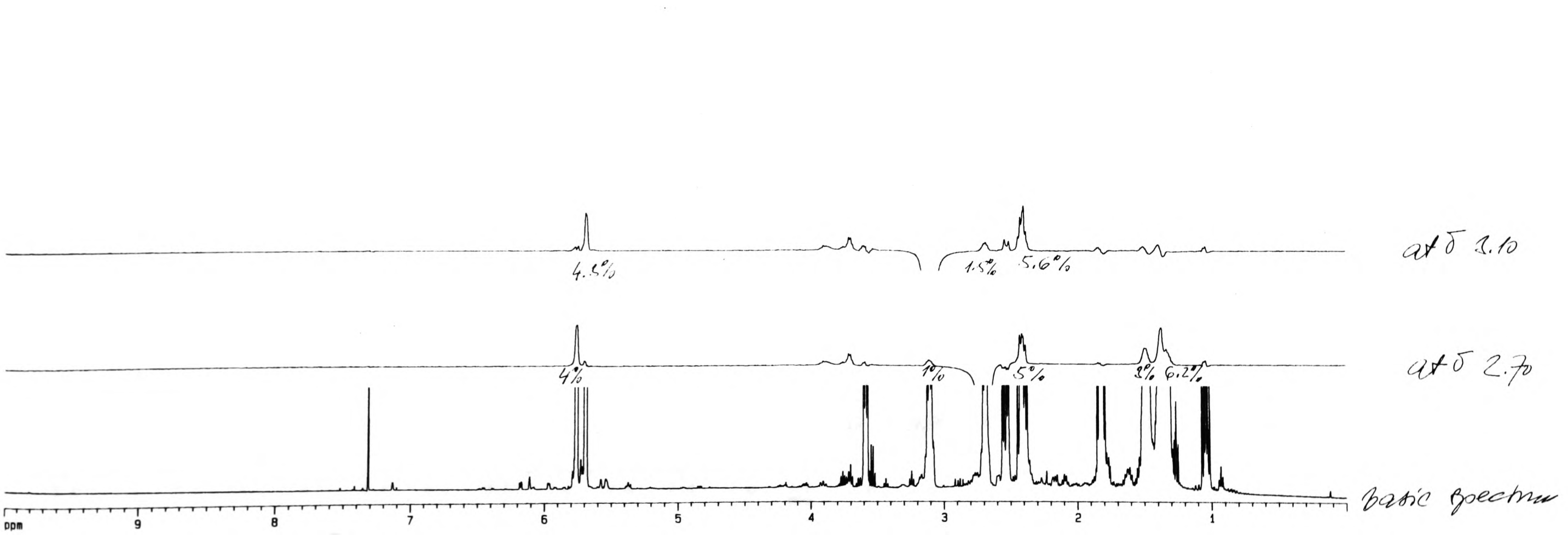
306

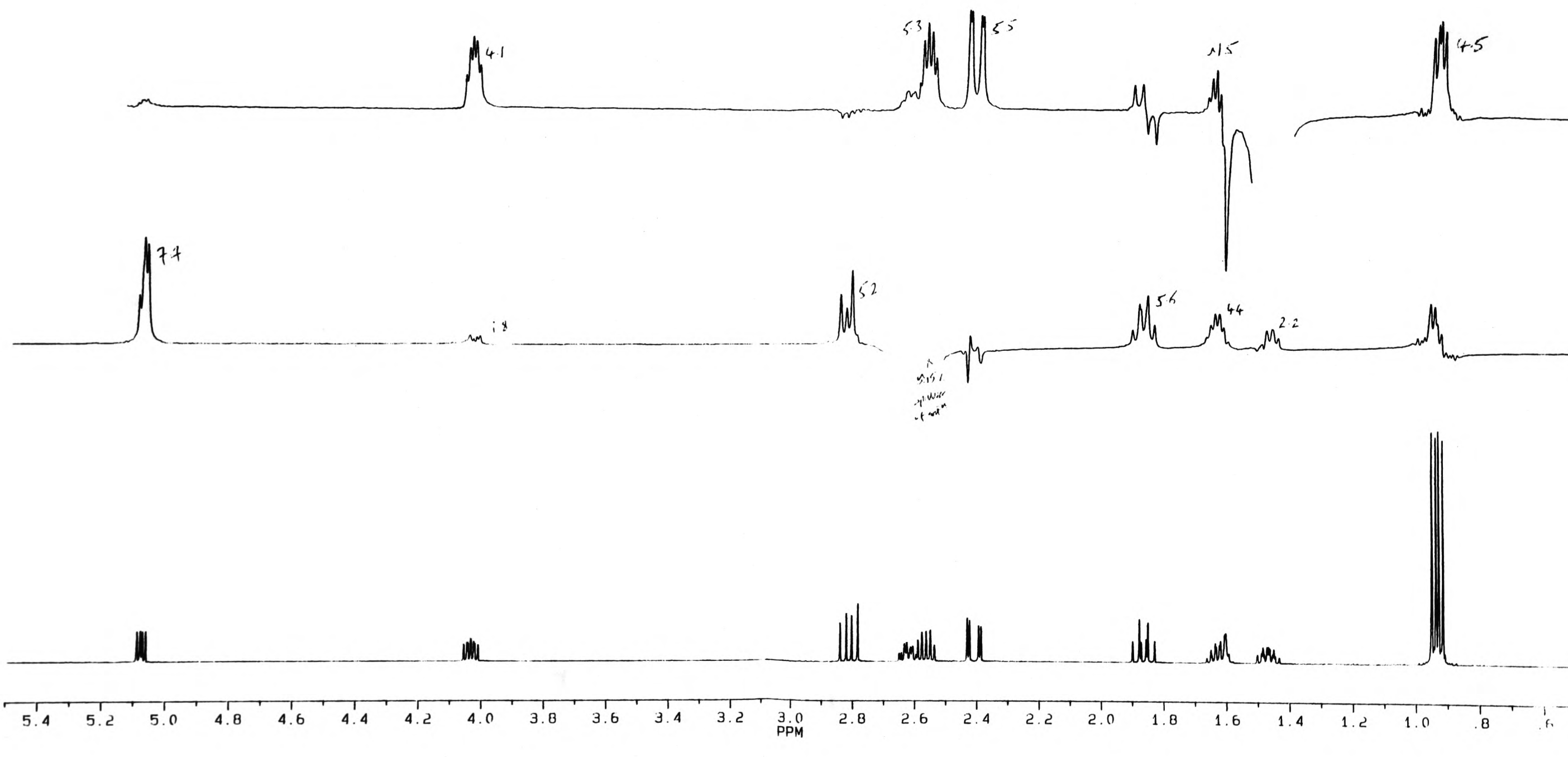


307

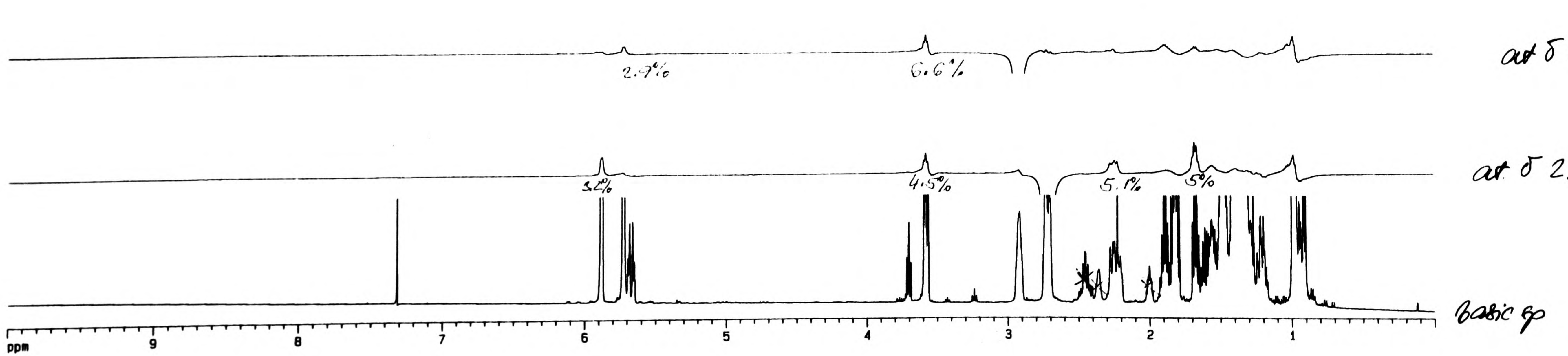

ppm
9
8
7
6
5
4
3
2
1
4.20%
17%
27%

Jeremy Burrows
6th July
EMR
106




4.1
5.3
5.5
1.5
4.5
7.7
1.8
5.2
5.6
4.4
2.2
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
PPM

Jeremy
Burrows
2nd June 9E
E.I.



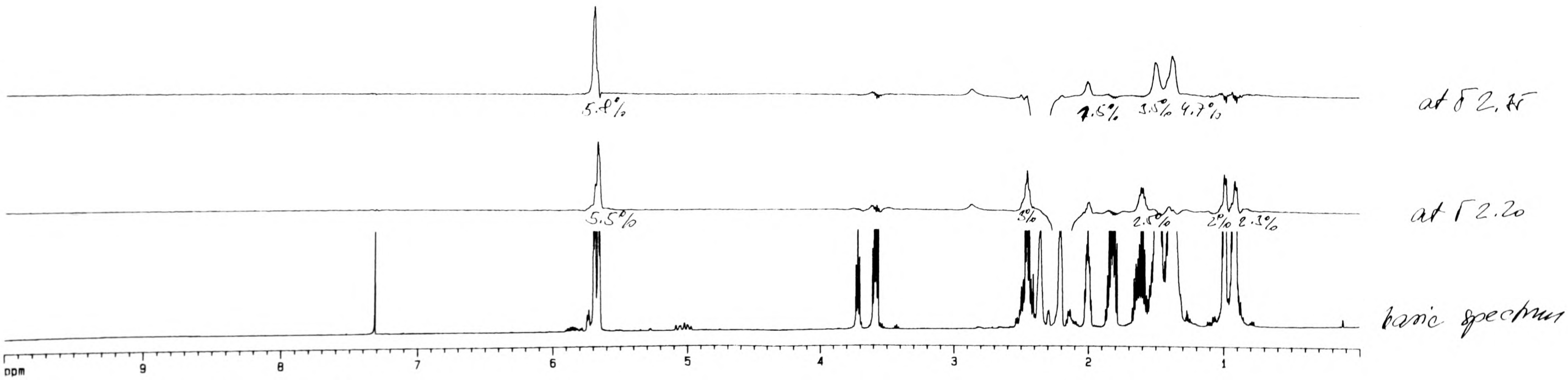
4992

Jeremy Burrows

3rd June 96

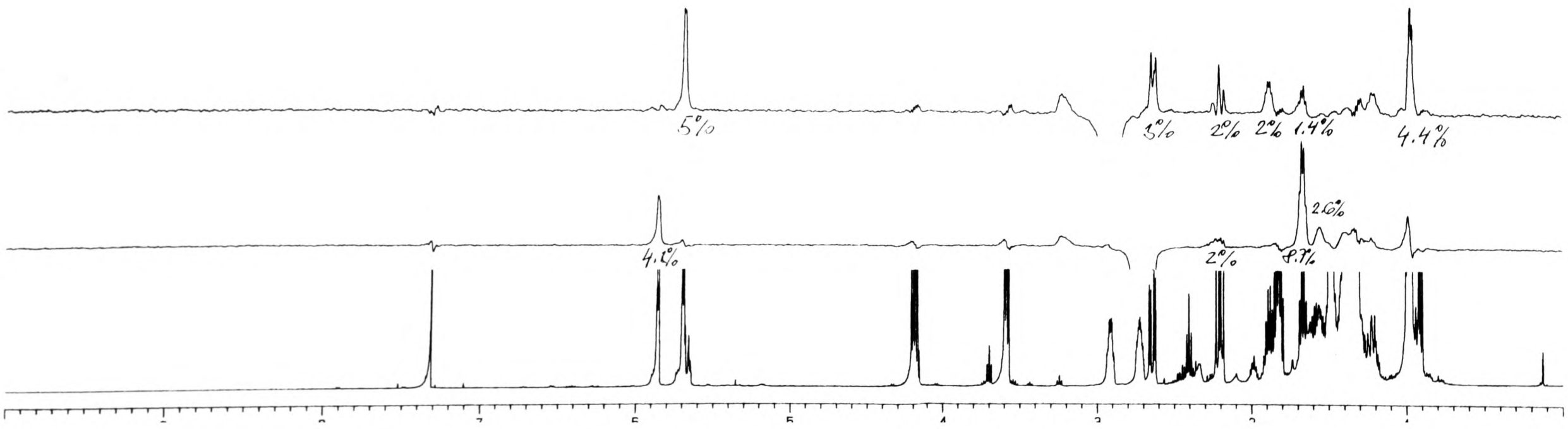
EHdg

NOE

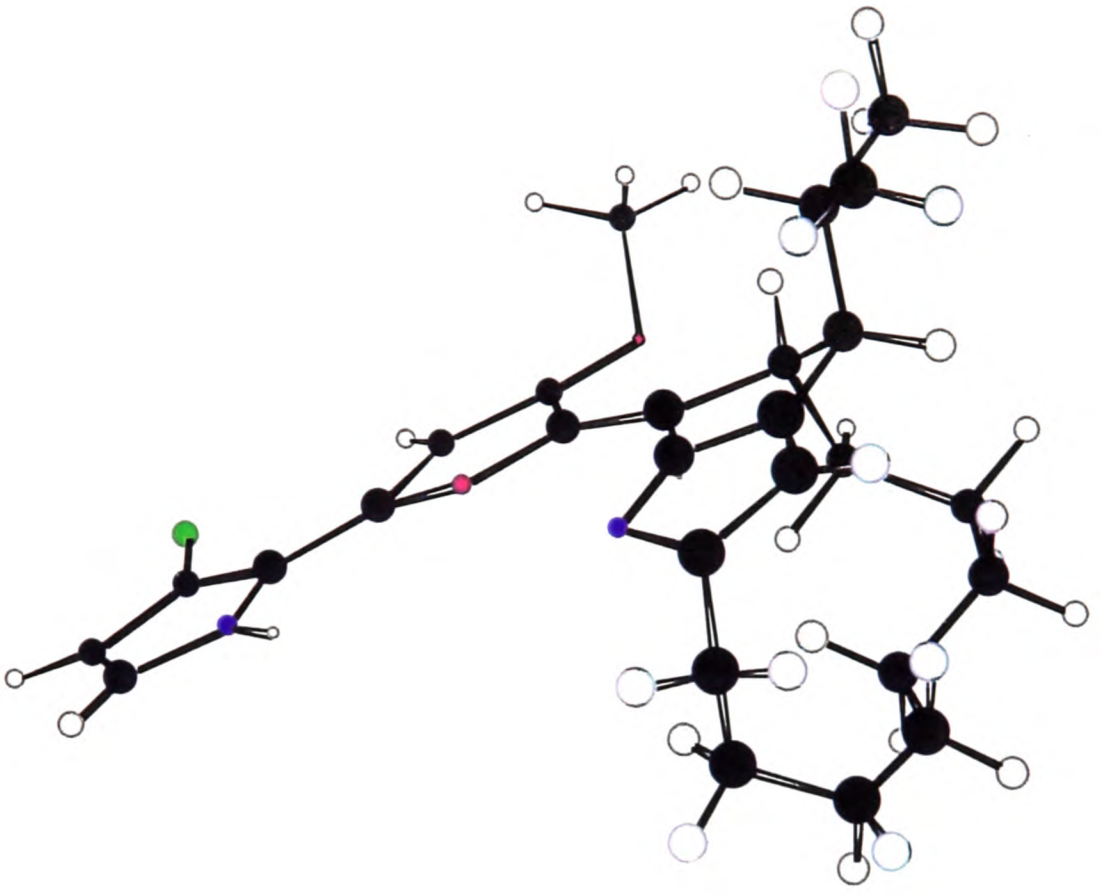


4947

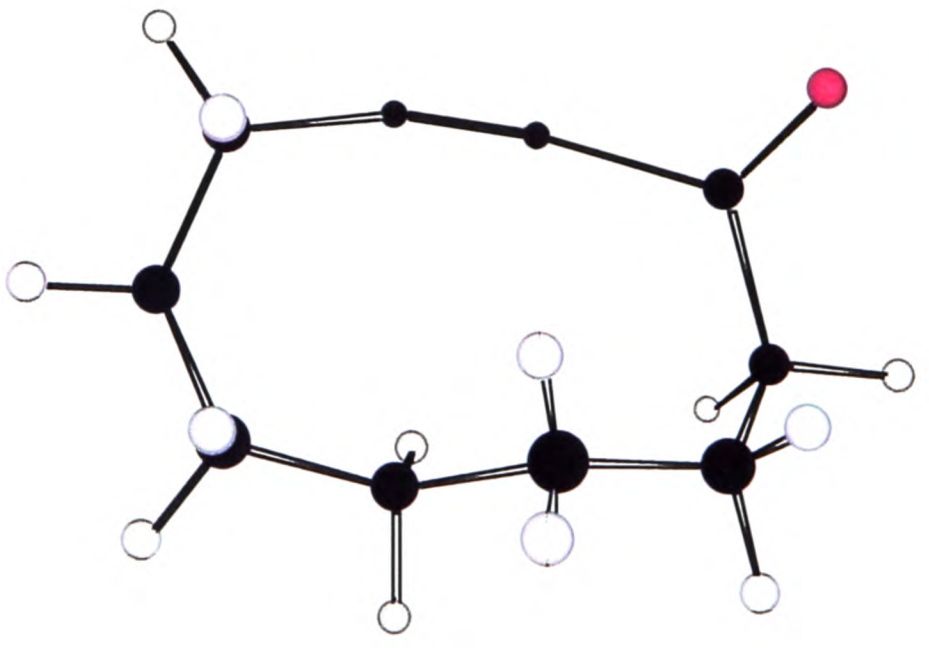
NOE



APPENDIX E



Roseophilin **1**



Cyclodec-2-yn-1-one **98**