ABSTRACT

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RING EXPANSION REACTION *VIA* HOMOLYTIC PATHWAYS

The preparation of carbocyclic medium rings by two electron processes is reviewed with particular reference to the synthesis of natural products. The formation of medium rings by oxidative and homolytic methods is also reviewed.

The synthesis and behaviour of both *cis*- and *trans*- ring expansion precursors is described. The 1,4-addition of tributylstannyl lithium to a range of cyclic α,β–unsaturated ketones was performed and procedures found whereby the so-formed enolates could be alkylated with a variety of electrophiles. Using these procedures a range of *trans*- ring expansion precursors were obtained in moderate to good yield. By the 1,4-addition of tributylstannyl lithium to 2-(ω-phenylselenoalkyl)-cyclohexenones, followed by enolate quenching with either water or methyl iodide, a range of *cis*- ring expansion precursors were produced. Homolytic ring expansion by either one, three, or four carbon atoms was shown to be possible, producing, respectively, seven, nine, or ten membered functionalised cycloalkenones in high yield except in cases where intramolecular reductive elimination was also possible.

Attempts to extend this methodology to the synthesis of exomethylene cycloalkanones is described. The 3-tributylstannyl-3-(ω-phenylselenoalkyl)-cyclohex-2-enone precursors were found not to be successful substrates for ring expansion. The regiospecific alkylation of 2-(tributylstannylmethyl)-cyclohexanone with 1-chloro-4-iodo-butane, followed by conversion of the chloride moiety to iodide led to a precursor which, on exposure to homolysis conditions, fragmented to produce the desired exomethylene cyclodecanone in high yield.

Work directed towards the synthesis of medium ring cycloalkynones is described. Procedures were developed whereby 2-alkylated cyclohexan-1,3-dione derivatives could be obtained cleanly and in excellent yield on a large scale. The conversion of these derivatives to potential cycloalkynone precursors is described. It is shown that the products obtained after exposure of these precursors to homolysis conditions could, in principle, be derived from the putative cycloalkynones and mechanisms are suggested to explain the formation of these compounds.

The homolytic ring expansion reaction was also performed on a substrate possessing an acyl radical precursor in the hope that a medium ring 1,2-dione would be produced. The synthesis of this substrate and its behaviour towards ring expansion is described. It is shown that, again, radical reaction was successful (to the medium ring dione) however subsequent reactions of this product led to the isolation and characterisation of a number of compounds .

Attempts to extend this methodology to the synthesis of the natural products curdione and neocurdione is also described. Model reactions with 2,6-dimethylcyclohex-2-enone as the 1,4-addition precursor and 1,4-di-iodobutane as the electrophile led to a ring expansion substrate which fragmented to two ring contracted isomeric compounds in addition to the ring expanded material. Approaches to the preparation of suitable electrophiles for the natural product synthesis are described and their proposed use in subsequent conversion to curdione and neocurdione given.

RING EXPANSION REACTION *VIA* HOMOLYTIC PATHWAYS

A thesis submitted to the
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by

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ABBREVIATIONS

Ac	Acetyl
AIBN	Azo-*bis*-isobutyronitrile
aq.	Aqueous
Ar	Aromatic
Bu, ^{n}Bu	Butyl
^{t}Bu	*tert*-Butyl
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DCM	Dichloromethane
DMAP	4-*N*,*N*-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulphoxide
EE	Ethoxyethyl
equiv.	Equivalent(s)
Et	Ethyl
Hz	Hertz
HMPA	Hexamethylphosphoric triamide
i.r.	Infra-red
LDA	Lithium di-isopropylamide
LTA	Lead tetra-acetate
mCPBA	*meta*-Chloroperbenzoic acid

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CHAPTER I
INTRODUCTION

I.1 Occurrence and synthesis of carbocyclic medium rings.

The construction of carbocyclic medium rings, which for the purposes of this discussion include systems with eight to ten ring carbon atoms, is of immense importance in preparative organic chemistry as a result of the wide occurrence of natural products containing such structures[1]. These compounds possess a wide range of biological properties which renders their synthesis, on a reasonable scale, of great importance.

The particular problems associated with medium ring systems, such as transannular reactions and unfavourable entropic factors on attempted synthesis by cyclisation, limits the use of classical ring construction procedures[2]. For this reason synthetic transformations which convert readily available normal ring precursors (five to seven membered) directly into medium rings by an expansion process[3] are of particular importance. A brief survey of a number of recent natural product syntheses, in which the ring systems are produced by this type of methodology, will serve to illustrate the most widely used reactions in this area.

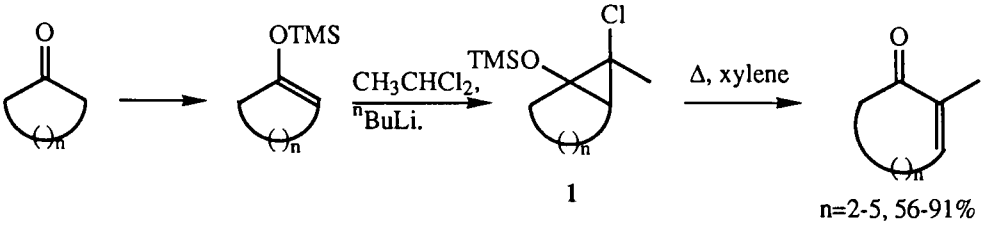
I.2 Synthesis of carbocyclic medium rings <u>via</u> two electron processes.

I.2.1 Preparation of eight membered carbocycles.

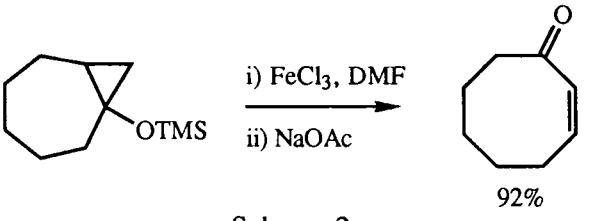
Beginning with one carbon ring expansion reactions, a number of procedures exist which offer alternatives to the classical Tiffeneau-Demjanov process[4]. For example, Conia[5] has developed a flexible route in which fused n,3-bicyclic alkanol derivatives **1**, produced by the addition of chloromethyl carbene to trimethylsilyl enol ethers of cyclic ketones, undergo thermal rearrangement to 2-methylcycloalk-2-enones in reasonable yield (Scheme 1).

A similar method has been employed by Saegusa[6] in which five to twelve membered cycloalkanone derivatives were subjected to oxidative conditions ($FeCl_3$, DMF) to produce ring expanded 3-chlorocycloalkanones which subsequently eliminate hydrogen chloride, in the presence of sodium acetate, to provide cycloalk-2-enones, the

transformation from the seven to the eight membered ring proceeding in excellent yield (Scheme 2).

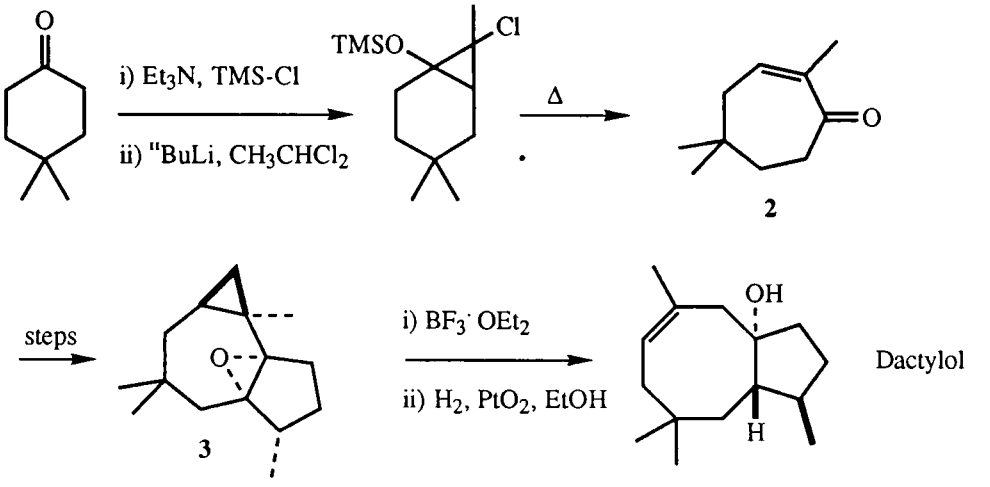


Scheme 1



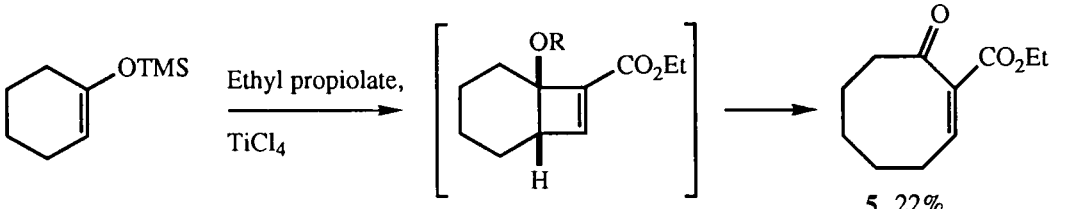
Scheme 2

Paquette has employed two one carbon ring expansion reactions in his formal total synthesis of dactylol[7], an irregular isoprenoid sesquiterpene alcohol originally isolated in 1978[8]. The first ring expansion step employed the Saegusa protocol, *vide supra*, to provide the seven membered compound **2**. This was elaborated in a number of steps to epoxide **3** which had been reported[9] to be converted to dactylol in two steps (Scheme 3).



Scheme 3

Trimethylsilyl enol ethers were also employed as starting materials in a ring expansion reaction by Untch[10]. This procedure, which increased the ring size by two carbon atoms, has been applied to the general synthesis of rings in addition to those containing eight members. In this case the Lewis acid catalysed reaction of trimethylsilyloxycyclohexene with ethyl propiolate afforded the bicyclic cyclobutene derivative **4** which spontaneously fragmented, under the reaction conditions, to the cyclooctenone **5** although the yield was not impressive (Scheme 4).

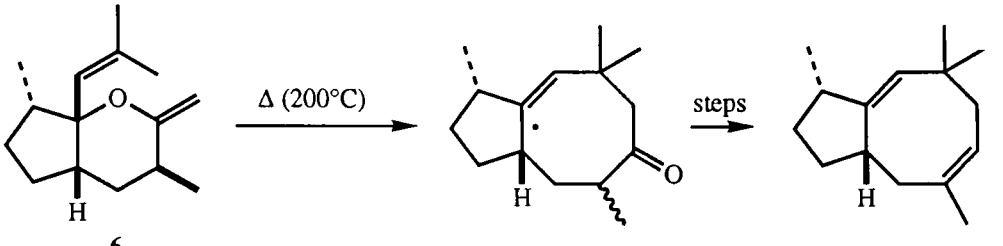


4, R=H, TMS

5, 22%

Scheme 4

A number of pericyclic rearrangements have been published which may also be viewed as two carbon ring expansions. For example, Paquette[11] has employed an efficient alicyclic Claisen rearrangement of the enol ether **6**. This fused 5,8-bicyclic system was then elaborated in a number of steps to precapnelladiene[12], a compound isolated from the soft coral *Capnella imbricata* (Scheme 5).



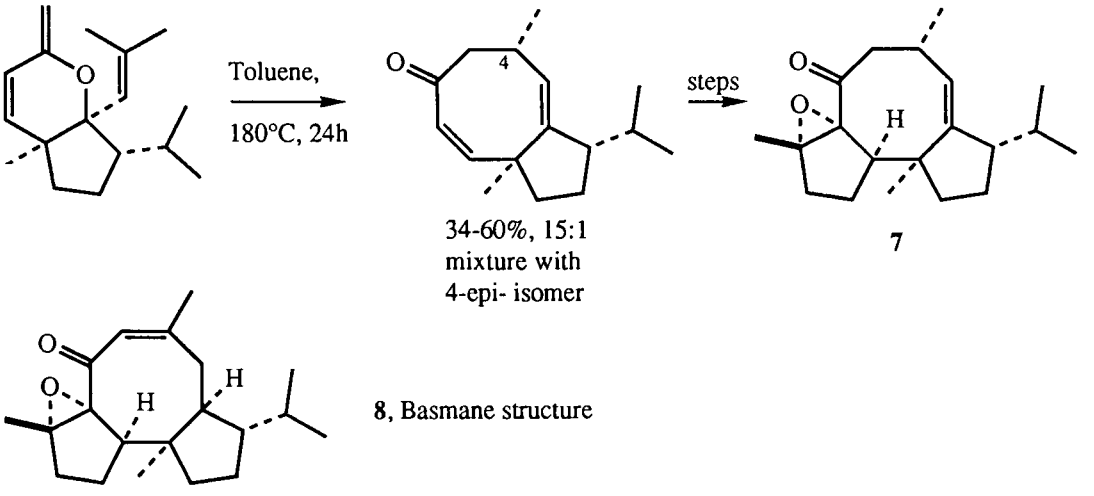
6

87%

Precapnelladiene

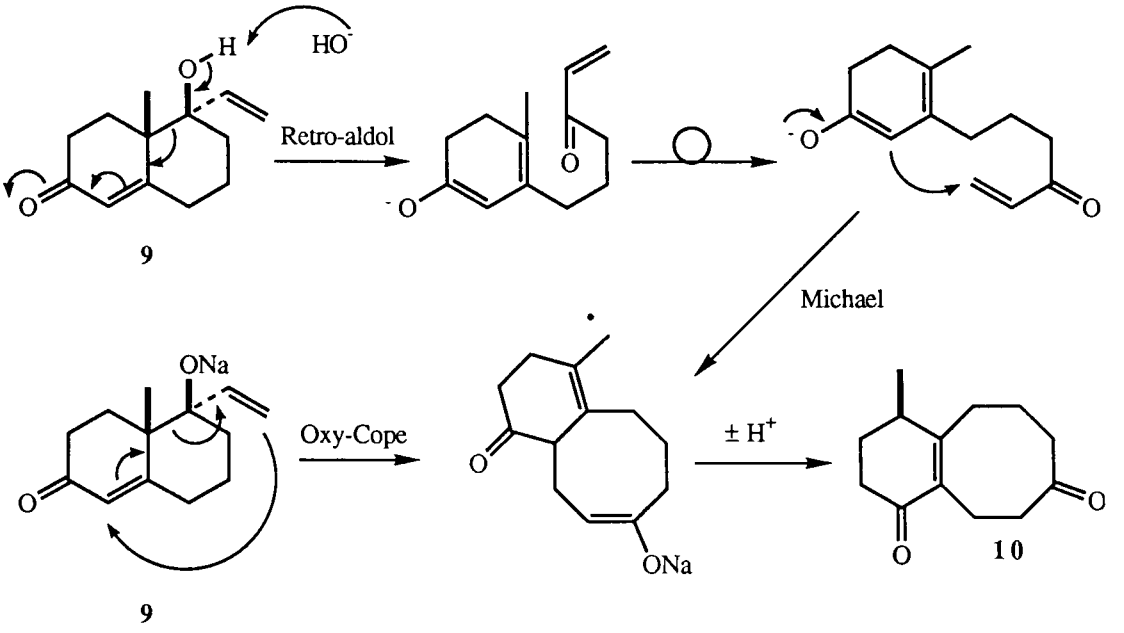
Scheme 5

More recently Paquette has applied this type of strategy to the synthesis of the basmane[13] precursor **7**. It was proposed to transform this precursor to compound **8**, a product isolated from Greek tobacco leaves[14] (Scheme 6).



Scheme 6

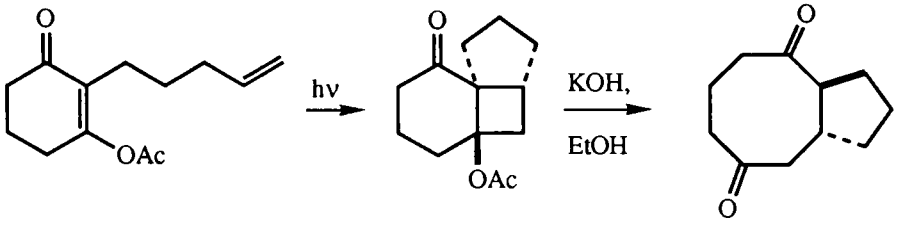
The first literature report of the anionic variation of the recently reviewed[15] oxy-Cope reaction was that of the fused bicyclic diene **9** to the 6,8-ring system **10** although the nature of the mechanism was not fully understood at this time[16]. A later report by the same author[17] has suggested two pathways by which this two carbon expansion may be rationalised, involving either an oxy-Cope reaction or a retro-aldol-Michael addition process as depicted in Scheme 7.



Scheme 7

This work pre-dated the observation of Evans[18] that potassium alkoxides exhibit dramatically enhanced rates of rearrangement compared with the corresponding alcohols.

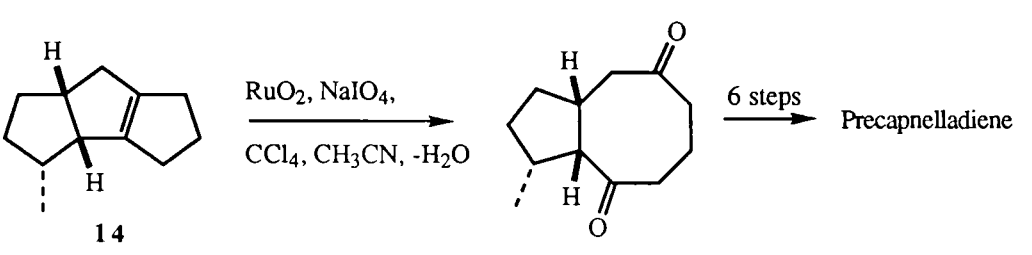
Pattenden[19] has employed a cycloaddition-fragmentation approach to a number of substituted diones. For example, the [2+2] cycloaddition of enol acetate **11** afforded tricycle **12** in quantitative yield. This compound was reported to undergo Grob fragmentation[20] to dione **13** in 78% yield (Scheme 8). This two step procedure was originally reported by DeMayo[21] and has been employed in a synthetic approach to the taxane diterpenes[22].



11 **12**, quant. **13**, 78%

Scheme 8

Three carbon ring expansion reactions are rather less commonly used although oxidative cleavage of fused bicyclic compounds does provide such an entry into medium ring structures if one of the rings in the precursor is five membered. This approach is exemplified by the work of Mehta[23] in which precapnelladiene, *vide supra,* was prepared in order to confirm its stereochemistry which had been correctly predicted by Pattenden[24]. Oxidative cleavage of tricyclic alkene **14** with ruthenium dioxide and sodium periodate (= RuO_4) led to the natural product precursor in high yield. This approach is given in Scheme 9.



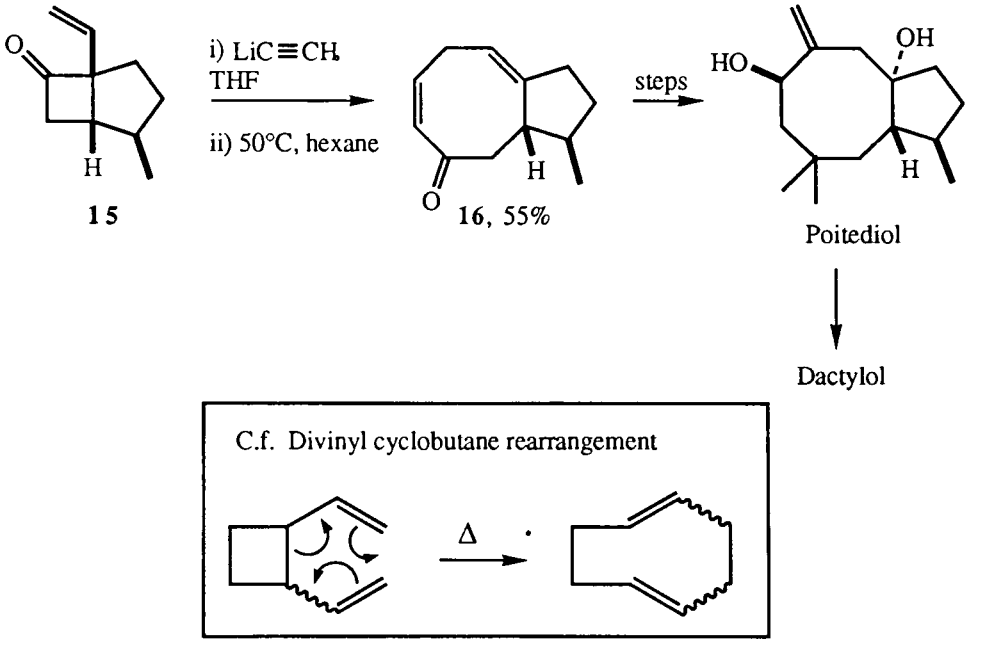
14

Scheme 9

Four carbon expansion to medium rings constitutes the most widely used procedure in this area of natural product synthesis. The so-called divinyl cyclobutane rearrangement[25] (Scheme 10), and variants thereof, is essentially a Cope rearrangement in

which the C-C bond linking the two vinyl units forms part of a cyclobutane ring (c.f. divinyl cyclopropane rearrangement[26]) and many versions of these two interrelated processes have been employed. Danheiser[27] has used such an approach to simple cyclooctadiene systems although little use of this protocol has been made in natural product synthesis.

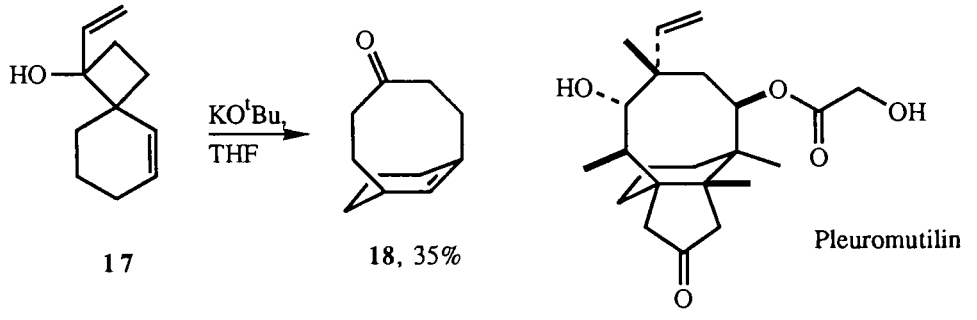
Gadwood provided the first syntheses of dactylol[28], epipoitediol[29], and poitediol[28,29] using this approach which was based on his earlier model work directed towards a general solution to the problem of cyclooctenone synthesis[30] (which has been more recently updated[31]). 1,2-addition of lithium acetylide to the cyclobutanone **15** resulted in an anionic oxy-Cope system which, on warming in hexane, provided dienone **16** in reasonable yield. This material was transformed in a number of steps to poitediol, a marine sesquiterpene[32], which was subsequently converted to dactylol (Scheme 10).



Scheme 10

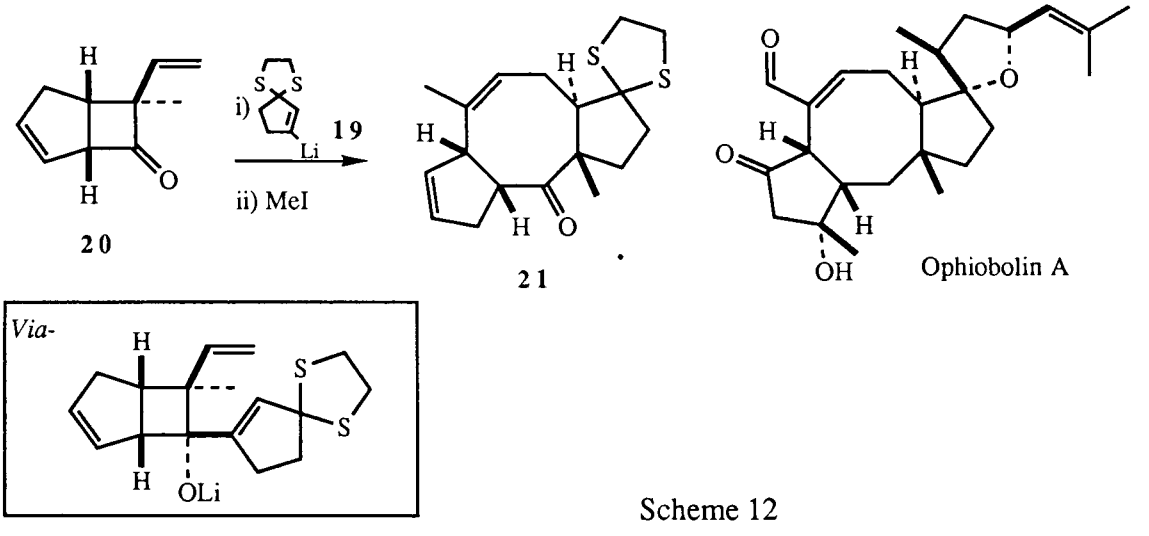
Kahn[33] has employed a similar reaction in his approach towards the synthesis of the antibiotic pleuromutilin. The allylic spiro-cycloalkanol **17** was treated with potassium ^{t}butoxide in THF to provide a moderate yield of bicyclic ketone **18** *via* the oxy-Cope pathway. As shown in Scheme 11 the structural convergence of this material with pleuromutilin is evident, however, the compatibility of the reaction with the highly

increased structural complexity which would exist in a potential pleuromutilin synthesis has yet to be investigated.



Scheme 11

Paquette has been active in this area, for example, providing a novel approach to the ophiobolin skeleton[34]. Addition of the 3-lithiocyclopent-2-enone equivalent **19**[35] to vinyl cyclobutanone derivative **20** resulted in clean ring expansion to the tricyclic nucleus **21** during which the intermediate enolate was alkylated on carbon with methyl iodide (Scheme 12). Ophiobolin A is of particular interest since the elucidation by Nozoe[36] of its structure and absolute configuration constituted the first definitive characterisation of a naturally occurring sesterterpene.

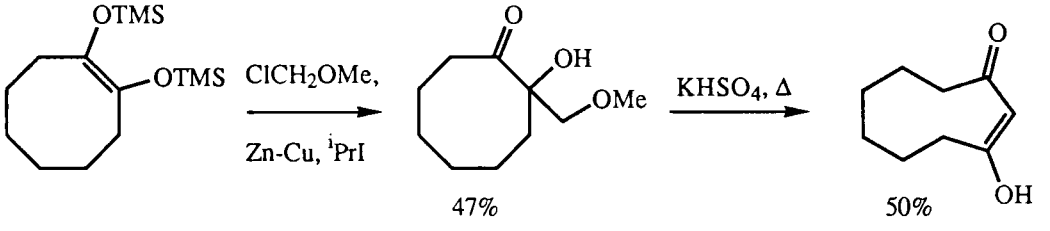


Scheme 12

1.2.2 Preparation of nine membered carbocycles.

The study of synthetic routes to nine membered rings is less well developed since the occurrence of this ring size in natural product chemistry is not widespread. However,

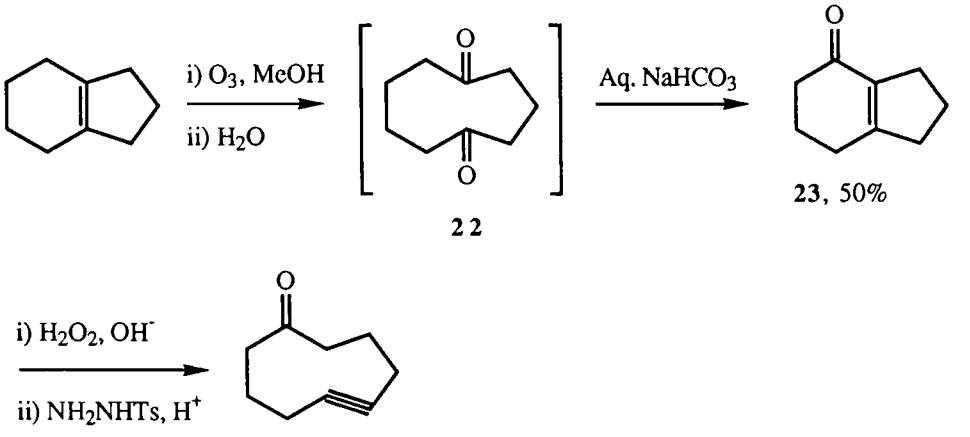
in addition to the general methods discussed in Section I.2, a number of such procedures have been reported. Again, various protocols exist for the one carbon expansion to nine membered rings but the reduced availability of simple cyclooctanone derivatives renders this route less attractive. Shono[37], however, has developed a general procedure for the preparation of cycloalkan-1,3-diones of five to nine members. The cyclic precursors were produced by a modified acyloin reaction[38] and the resulting bis-trimethylsilyl-oxycycloalkenes alkylated with (chloromethyl)methyl ether in the presence of Zn-Cu reagents (the mechanism of this reaction is not fully understood[39]). The so-formed α-hydroxy ketone derivatives were reported to undergo 1,2-migration of the acyl group, with concomitent loss of methanol, in the presence of an acid catalyst to provide the ring expanded dione derivatives in moderate yield as depicted in Scheme 13.



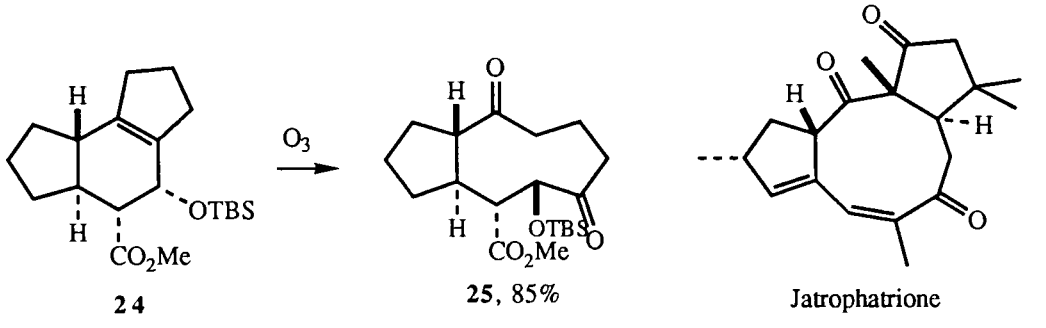
Scheme 13

The oxidative cleavage of a fused bicyclic system has also been used to provide a three carbon expansion to nine membered rings. This procedure was utilised by Lange[40] in the first synthesis of cyclonon-5-ynone (c.f. Section II.3.3). The oxidative cleavage step provided dione **22** which was immediately subjected to intramolecular aldol condensation (aq. $NaHCO_3$) to yield bicyclic enone **23**. This enone was transformed to the alkynone by the classical Eschenmoser fragmentation[41] as shown (Scheme 14).

A similar oxidation was used by Kozikowski[42] in an approach towards the synthesis of diterpenes. Compound **24**, prepared by intramolecular Diels-Alder reaction[43], produced dione **25** in 85% yield after ozonolysis. This compound bore a number of structural features common to those of jatrophatrione[44] and projected work was to involve application of this chemistry to the synthesis of this natural product (Scheme 15).

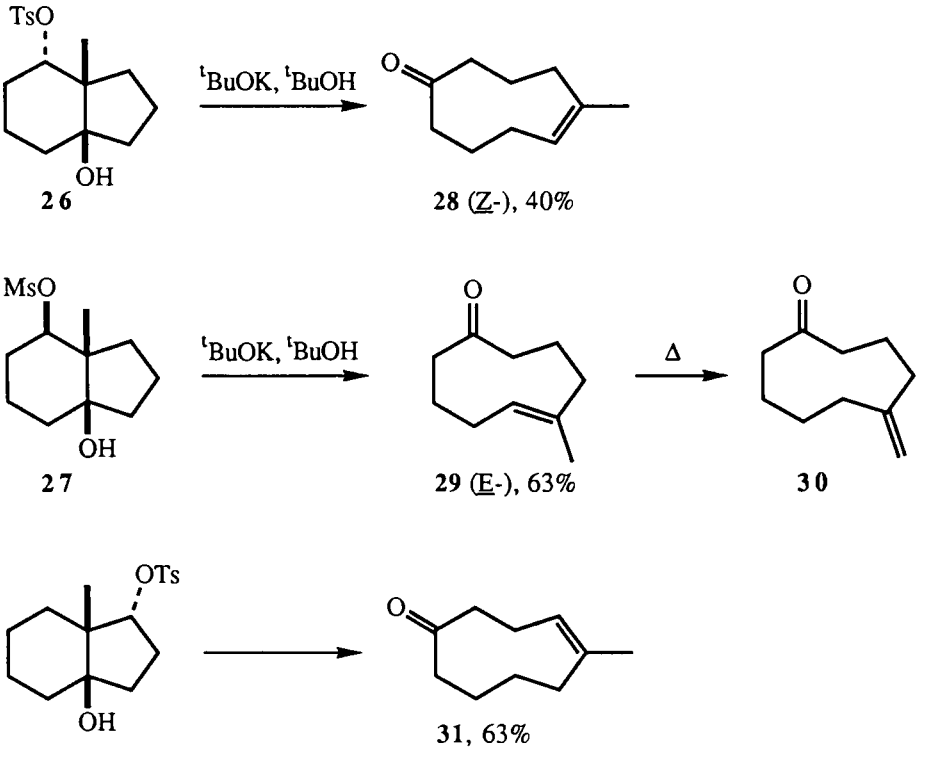


Scheme 14



Scheme 15

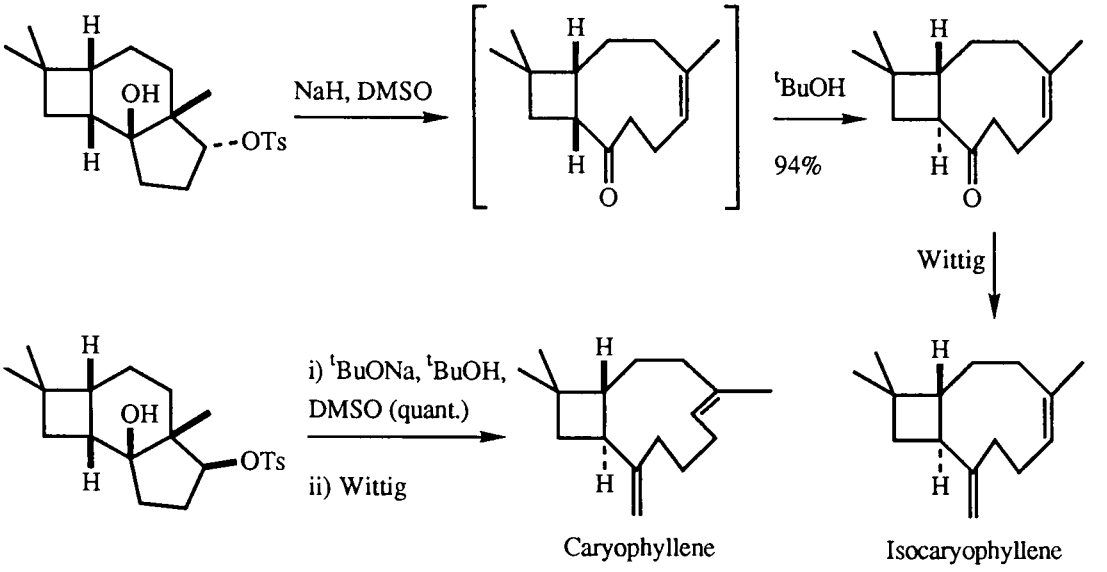
In a further model study for the synthesis of jatrophatrione, Caine[45], employed the so-called Wharton fragmentation[46], a derivative of the general Grob fragmentation, *vide supra,* to provide a number of cyclononenone derivatives with specific olefin geometry. The hydroxy sulphonates **26** and **27**, on exposure to base-induced fragmentation, provided the nine membered cycloalkenones **28** and **29**, respectively, in reasonable yield. It was also found that the strained E- isomer **29** underwent thermal isomerisation to the exomethylene derivative **30**[45]. This work was complementary to the work of Dev[47] in which the corresponding 4-alkenone **31** was prepared (Scheme 16).



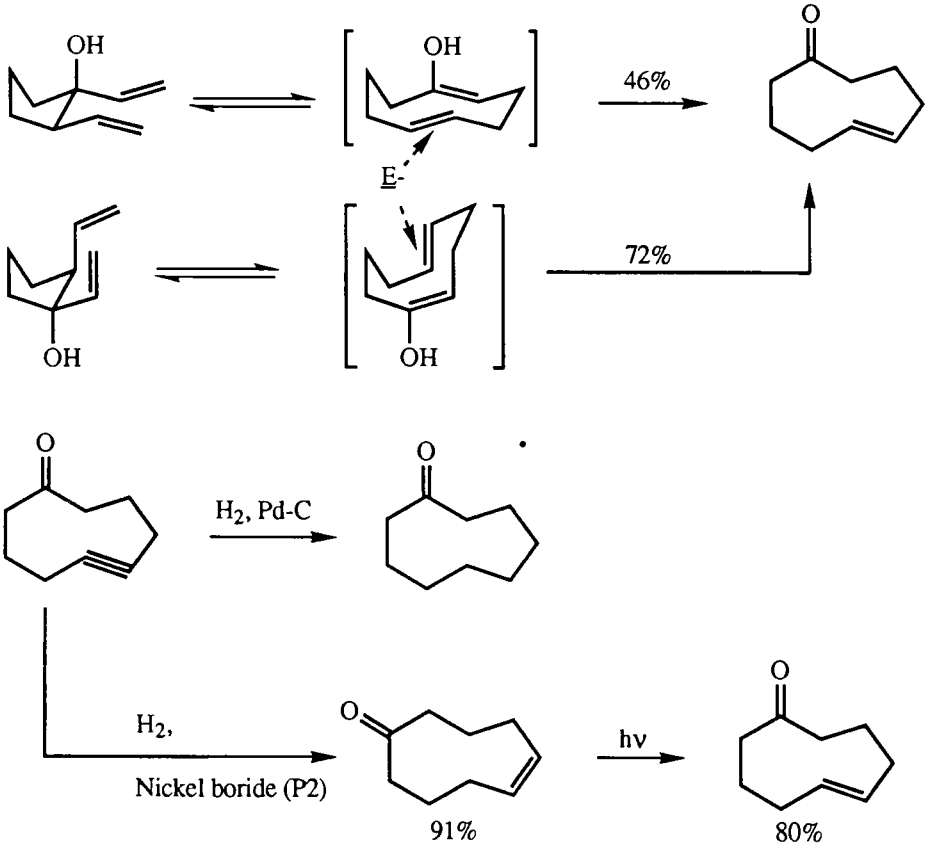
Scheme 16

Corey[48] used this type of fragmentation in his early syntheses of caryophyllene and isocaryophyllene. The fused 4,9-ring system had, up to that time, eluded a number of groups in attempts to prepare these compounds due to their propensity for rearrangement[49]. Corey's procedure produced the desired ring system towards the end of the synthesis thus circumventing such problems (Scheme 17).

The four carbon ring expansion to nine membered rings has also been achieved by oxy-Cope reaction, this time of divinyl cyclopentanone derivatives. For example, simple cyclononenones were prepared by Kato *et al.*[50] in such a manner; both *cis*- and *trans*-divinyl compounds producing the E- isomer after ring expansion (Scheme 18). This material was reported to be identical in all respects to that obtained by Lange and Hall[40] who studied the reduction of cyclonon-5-ynone under various conditions as a means of confirming its synthesis.

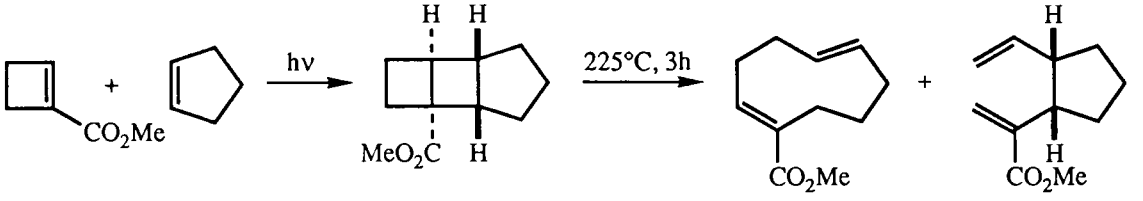


Scheme 17



Scheme 18

Wender[51] has developed a two step procedure which results in overall four carbon expansion from cyclopentene in a process akin to that of Untch[10]. Photochemical [2+2] cycloaddition with cyclobutene derivative **32** produced fused tricycle **33** in 67% yield. On heating, this compound afforded the desired ring expanded diene **34** and the divinyl cyclopentane derivative **35** in a ratio of 2:1 and a combined yield of 90%. Compound **35** could, in principle, arise from either Cope rearrangement of diene **34** or alternative fragmentation of the tricyclic compound **33**; it was found that subjecting pure diene **35** to the rearrangement conditions reproduced the 2:1 mixture of **34** and **35** indicating thermodynamically controlled product formation by the former pathway (Scheme 19).



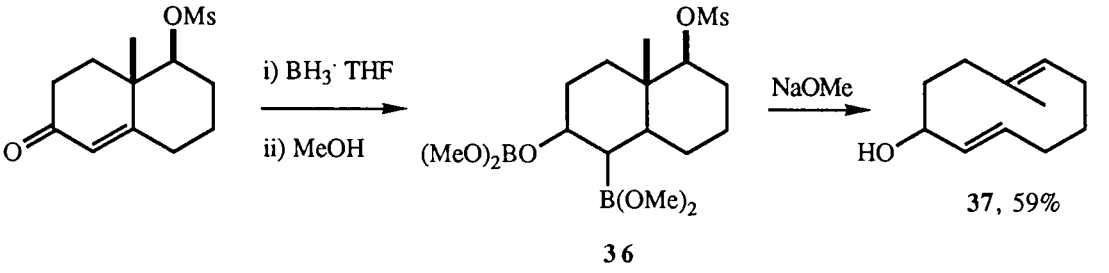
32 **33**, 67% **34** **35**

Scheme 19

I.2.3 Preparation of ten membered carbocycles.

Interest in the chemistry of cyclodecanone derivatives has been much more widespread since the occurrence of natural products based on this structure is extensive. A number of important fragmentation and rearrangement reactions have been developed specifically with these compounds in mind; much of this chemistry has also been applied to compounds with rings not containing ten members in general expansion procedures, some of which have been discussed, *vide supra*.

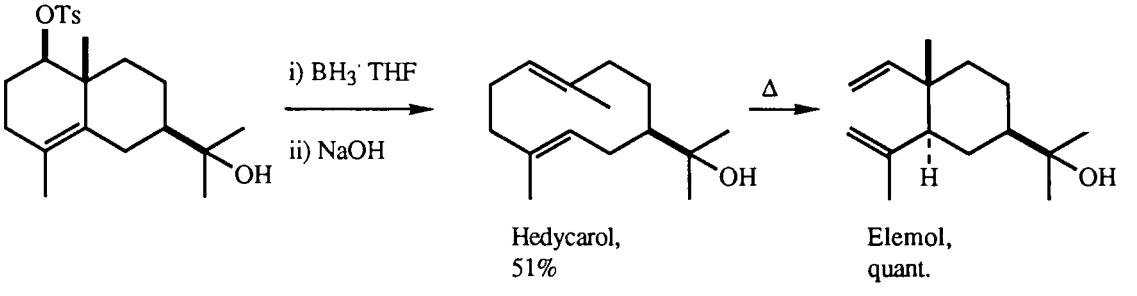
Marshall has developed a route to cyclodecadiene systems using a hydroboration, rearrangement sequence[52]. The initially formed borane **36**, on treatment with methoxide ion, underwent stereospecific 1,4-fragmentation to the dienol **37** in good yield (Scheme 20).



36

Scheme 20

Wharton[53] went on to use this methodology in a synthesis of hedycarol, a biogenetically important sesquiterpene. This mild method of fragmentation was chosen since it was known[54] that hedycarol was thermally unstable with respect to the ring contracted isomer elemol, arising from the reverse Cope rearrangement, having a half life for the transformation of approximately 3h at 100°C (Scheme 21).

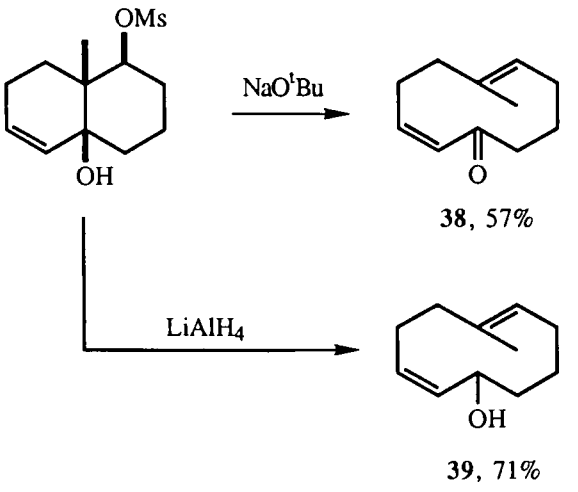


Hedycarol, 51%

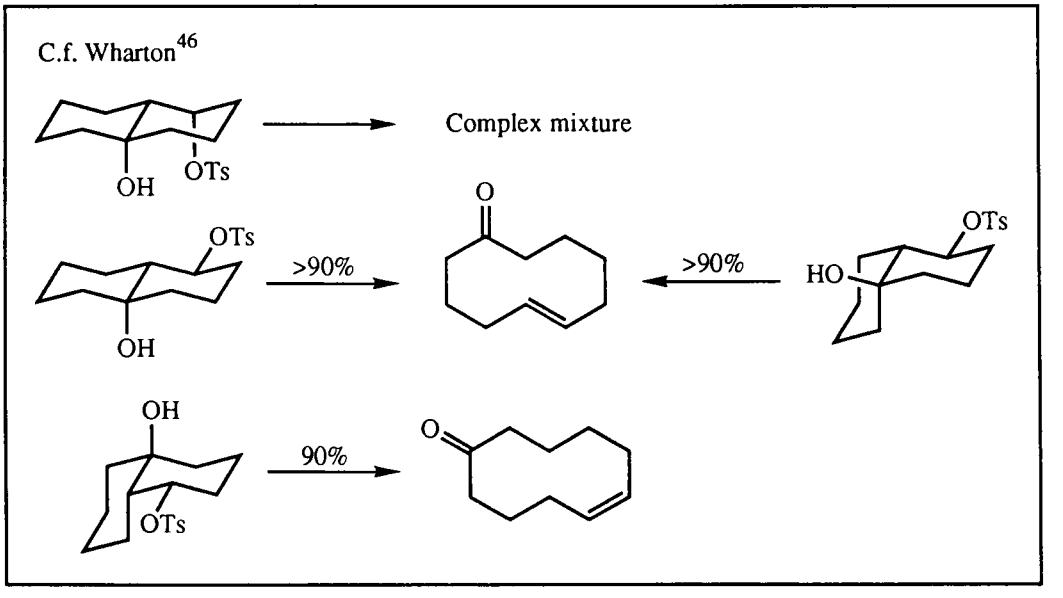
Elemol, quant.

Scheme 21

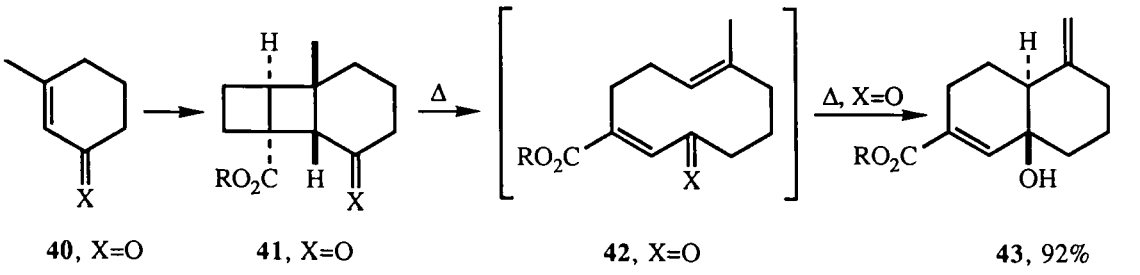
In a related procedure[55], a range of cyclodecadienols were prepared in order to access hydroazulenes stereoselectively. This method relied on the earlier fragmentation developed by Wharton[46] but modified in such a way that either the ketone **38** or the alcohol **39** were obtained directly as shown in Scheme 22. These compounds were elaborated to various hydroazulene derivatives by cyclisation of the allylic cations arising from loss of RO^- from the molecules.



Scheme 22



Problems with ring contracting Cope rearrangement of the 1,5-diene systems produced in these reactions, such as the conversion of hedycarol to elemol discussed above, have led to a number of procedures to be developed in which the first-formed dienes undergo subsequent reaction to a desired product. For example Wender[56] applied a four carbon ring expansion reaction of the enone **40** to the synthesis of calameon, a decalinol derivative. Pyrolysis of the photoadduct **41** afforded the ring expanded material **42** which was not isolated (although spectroscopic analysis of the crude material, before completion of the reaction, indicated its intermediacy) but allowed to be converted by intramolecular ene reaction to the decalinol **43** in 92% yield as shown in Scheme 23.



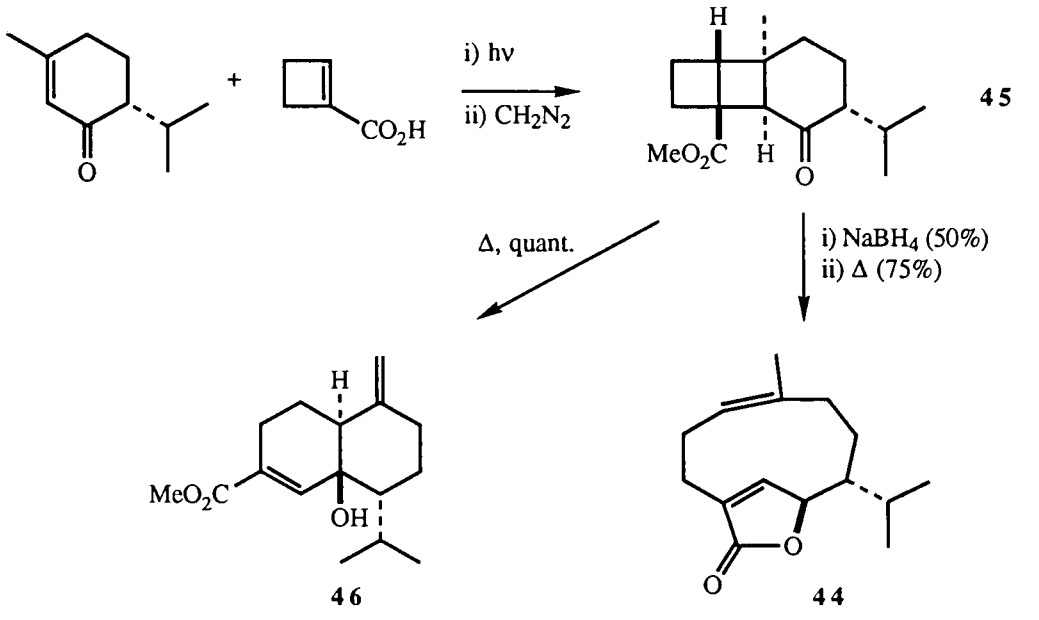
40, X=O **41**, X=O **42**, X=O **43**, 92%

Scheme 23

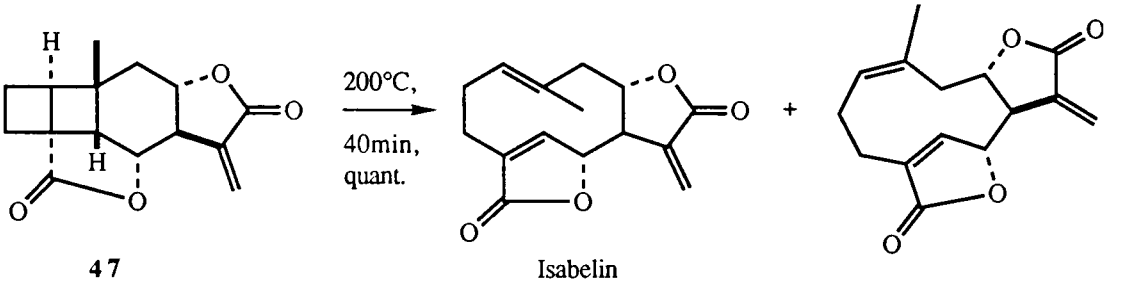
The particular geometry of the medium ring produced in this reaction, i.e. E,Z-, presumably has major bearing on the subsequent reaction of this compound since alternative ring contracting Cope rearrangement is also feasible. Application of this route to related compounds (X=CH_2, CHOMe etc.) was also carried out with similar results.

The fragmentation reaction of 4,4,6-fused tricyclic systems (c.f. Dauben[57]) has been employed in the synthesis of germacranolide derivatives. Lange[58] applied methodology very similar to that of Wender to provide compound **44** possessing the germacranolide skeleton. By variation of the substrate applied to thermal rearrangement either the ring expansion or intramolecular ene product was isolated. Thus heating ketone **45** resulted in a quantitative yield of the decalinol derivative **46**, however, the corresponding alcohol (which cyclised to the lactone) afforded solely the cyclodecadiene product **44** as depicted in Scheme 24.

The germacranolide isabelin has been prepared by Wender[59] using identical methodology, however, two compounds were obtained from the pyrolysis of tricycle **47**. The postulated explanation for the observation of both compounds was that the presence of the methylene lactone moiety has a considerable influence on the relative energies for the pro-E,E- (boatlike) and pro-E,Z- (chairlike) transition states required for fragmentation since such product mixtures were not obtained in similar reactions of substrates devoid of this structural unit[51,56]. This result is summarised in Scheme 25.

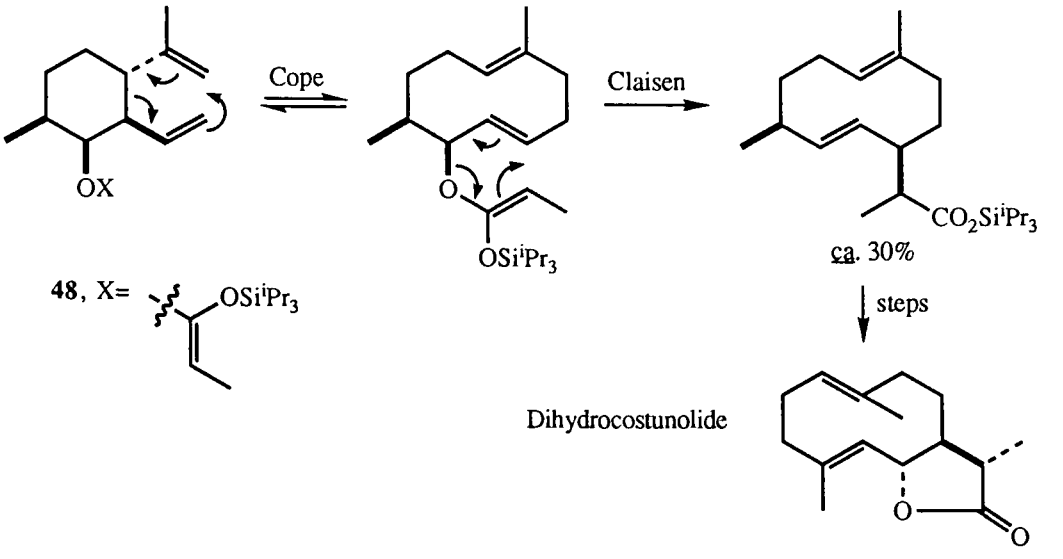


Scheme 24



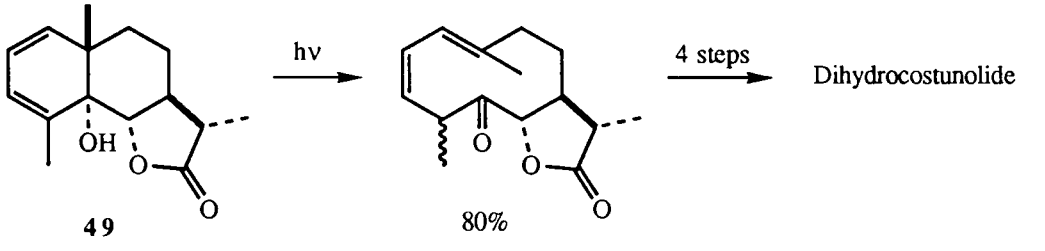
Scheme 25

Raucher[60] has employed a tandem Cope-Claisen method such that reversible Cope rearrangement ceased to present a problem as the initially formed medium rings were essentially irreversibly converted to the observed products by the Ireland ester-enolate Claisen rearrangement[61]. Although model work did not provide conclusive results[62] use of the tri-isopropylsilyl ether **48** afforded a 30% yield of the medium ring diene as explained in Scheme 26. This material was subsequently transformed to the germacrane sesquiterpene dihydrocostunolide[63].



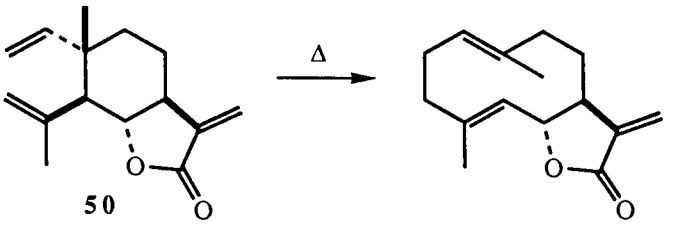
Scheme 26

Although out of place in a section on two electron ring expansions it is of interest to compare this synthesis of dihydrocostunolide with that of Fujimoto[64]. Photochemical fragmentation of dienol **49** (Scheme 27) provided an advanced intermediate which was transformed to the natural product in four further steps. This photochemical approach was based on earlier work by Corey[65] in which the same natural product was synthesised.



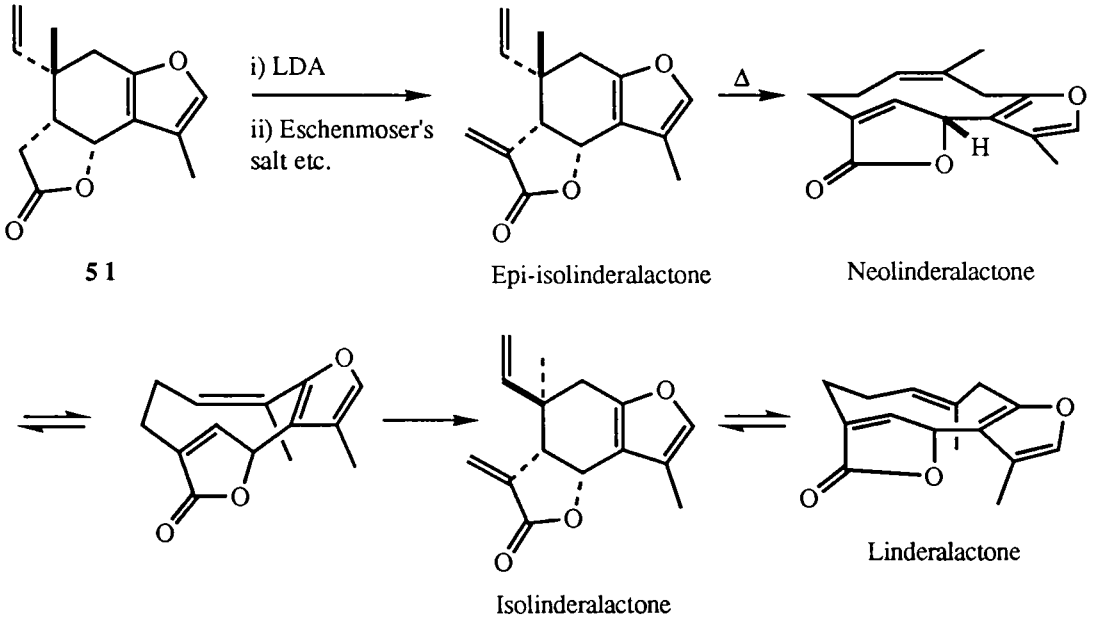
Scheme 27

The related germacrane, costunolide, was synthesised by Grieco *via* Cope rearrangement of substrate **50**; once again, an equilibrating mixture was reached with the natural product being isolated in only 20% yield with a 42% recovery of starting material[66] (Scheme 28).



Scheme 28

An equilibrating Cope system was also obtained in work by Magnus in which the synthetic compound **51** was α-methylenated to epi-isolinderalactone[67]. On heating, the Cope product neolinderalactone eventually became converted to an equilibrium mixture of isolinderalactone and linderalactone as depicted in Scheme 29.

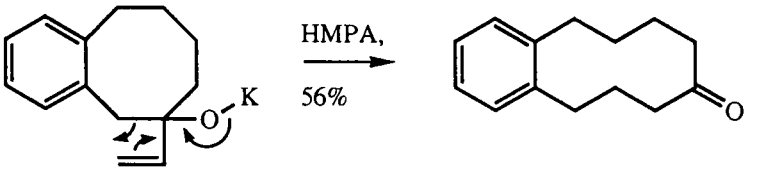


Scheme 29

Thies' approach[68] to ten membered ring ketones involved the [1,3]-sigmatropic shift of the benzo-cyclooctanone compound **52** in a two carbon ring expansion procedure (Scheme 30). This type of anion accelerated "[1,3]-shift"* is closely related to the extremely widely used anionic version of the oxy-Cope procedure (see references cited

* An alternative two step process may also be invoked involving ejection of a benzyl carbanion followed by re-addition to the so-formed α,β–unsaturated ketone.

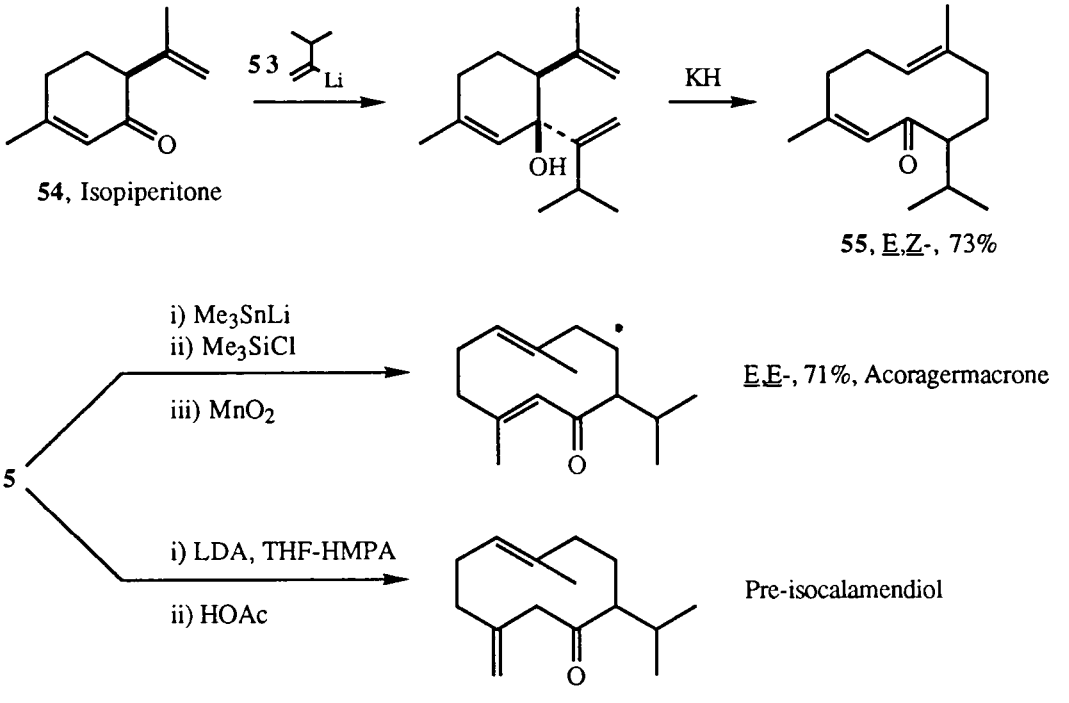
above[15,18]) of which acetylenic versions have been reported[69]. A particularly popular synthetic target using this procedure has been periplanone B, the major sex pheremone of the American cockroach *Periplaneta americana*[70].



52

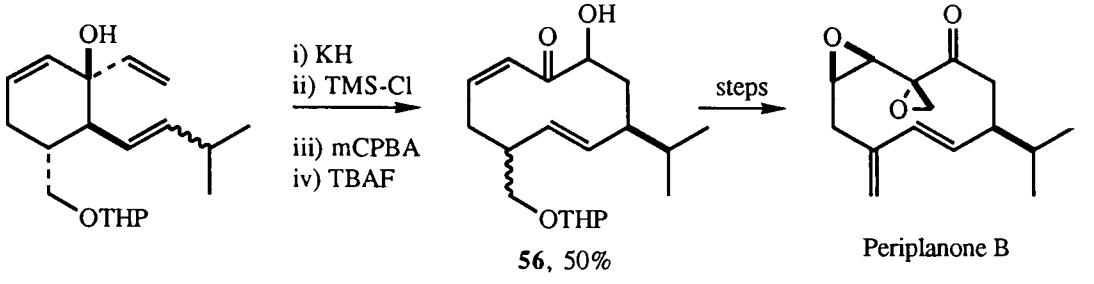
Scheme 30

Still's approach[71] to this compound involved the addition of the vinyl lithium **53** to ketone **54** followed by the production and rearrangement of the potassium alkoxide which afforded the E,Z- diene **55**. This material was isomerised to the E/E- diene acoragermacrone and the exomethylene compound pre-isocalamendiol by the procedures depicted in Scheme 31. This method was used to furnish similar dienes which were elaborated to periplanone B in a separate report[72].



Scheme 31

Hauptmann used a similar approach to that of Still but trapped the initially formed potassium enolate, resulting from rearrangement of the alkoxide, with trimethylsilyl chloride. The resulting trimethylsilyl enol ether was oxidised with *m*-chloroperbenzoic acid and the silyl group removed with tetrabutylammonium fluoride resulting in the production of α-hydroxyketone **56** in 50% overall yield. This intermediate was elaborated in a number of steps to periplanone B[73] (Scheme 32).



56, 50%

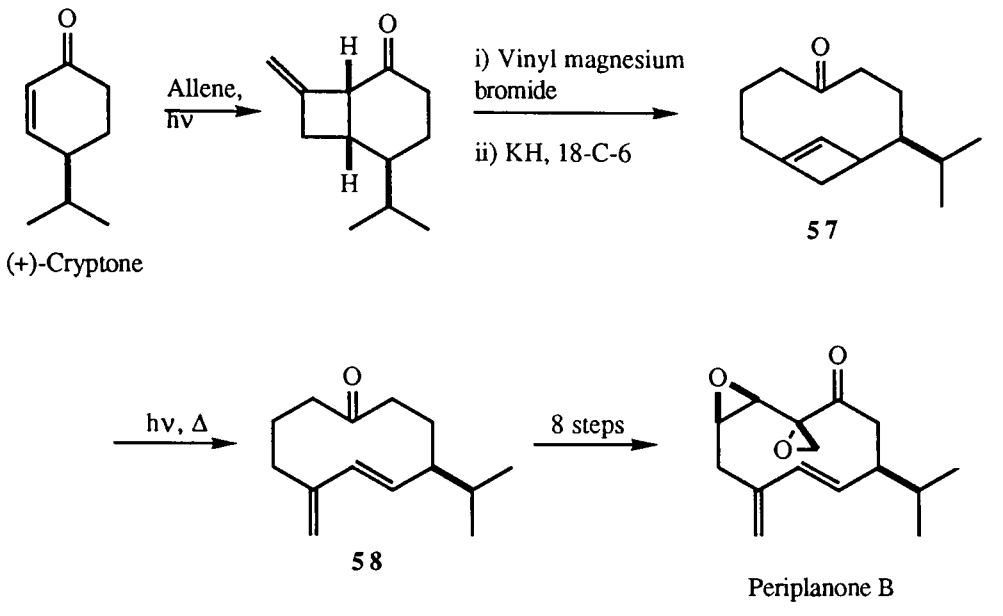
Periplanone B

Scheme 32

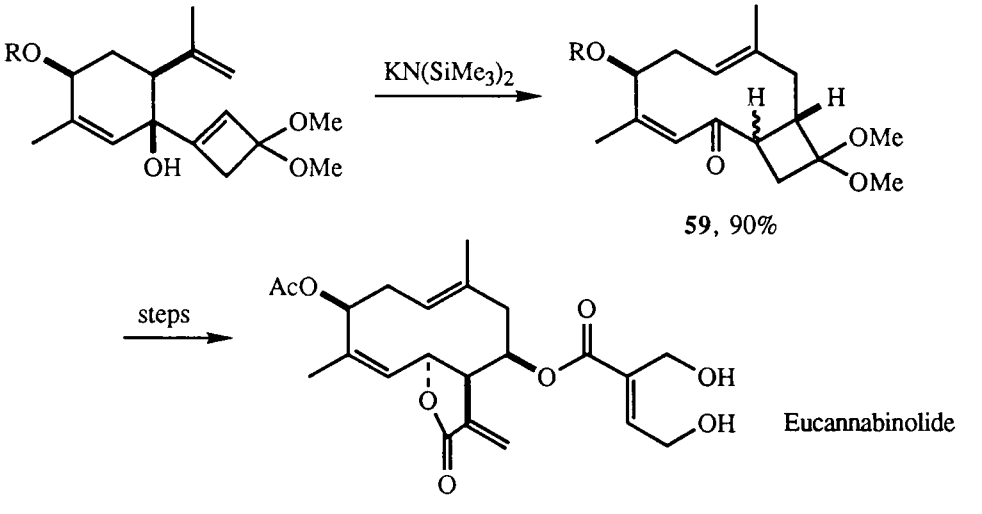
Schreiber has developed an alternative oxy-Cope approach to this structural type[74], the synthesis to periplanone B beginning with the [2+2] cycloaddition of allene to (+)-cryptone[75]. Addition of vinyl magnesium bromide to this photo-adduct and production of the potassium alkoxide resulted in spontaneous ring expansion to bridged bicyclic compound **57** which was decomposed to diene **58**. The completed synthesis of the natural product required eight further steps and relied on the particular conformation of the medium ring to direct stereoselective epoxidation[76] (Scheme 33).

An alternative approach to periplanone B was recently described by DeClerq[77].

Anion oxy-Cope reactions have found further application in the preparation of germacranolides as exemplified by the preparation of the cytotoxin eucannabinolide by Still[78]. One vinyl component in the diene precursor was chosen as a masked cyclobutenone function such that ring expansion of this material resulted in the formation of the fused bicyclic compound **59** in high yield (90%). This material was converted to the natural product by a number of standard transformations (Scheme 34).

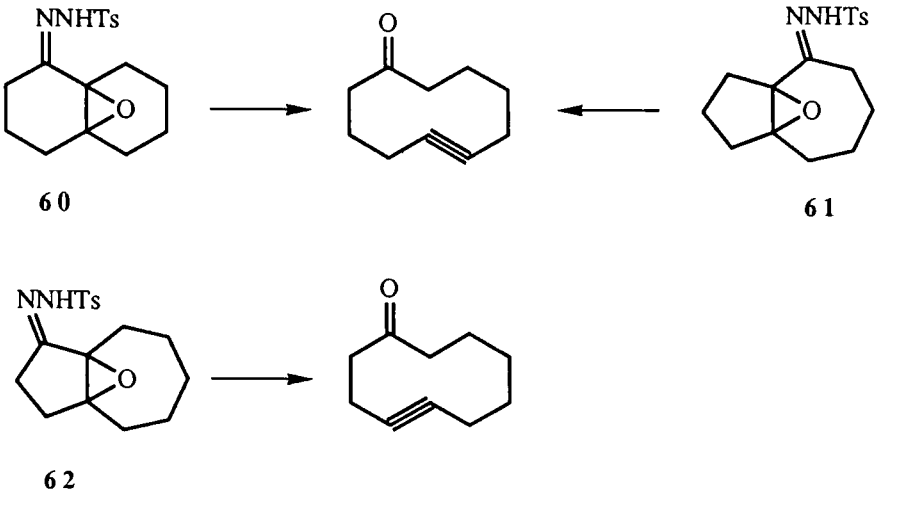


Scheme 33



Scheme 34

Although not directly used in natural product synthesis, the Eschenmoser fragmentation (see also Section I.3) has been employed to prepare a number of simple cyclodecynone derivatives, the location of the triple bond relative to the carbonyl group resulting from both the location of the tosyl hydrazone function, and from the ring sizes in the bicyclic precursors. Thus reaction of the α,β-epoxy tosyl hydrazones **60** and **61** resulted in formation of cyclodec-5-ynone under standard conditions[41,79]. Alternatively, situation of the tosyl hydrazone function on the five membered ring (i.e. **62**) enabled fragmentation to produce cyclodec-4-ynone in high yield[80] as shown in Scheme 35.



60 61 62

Scheme 35

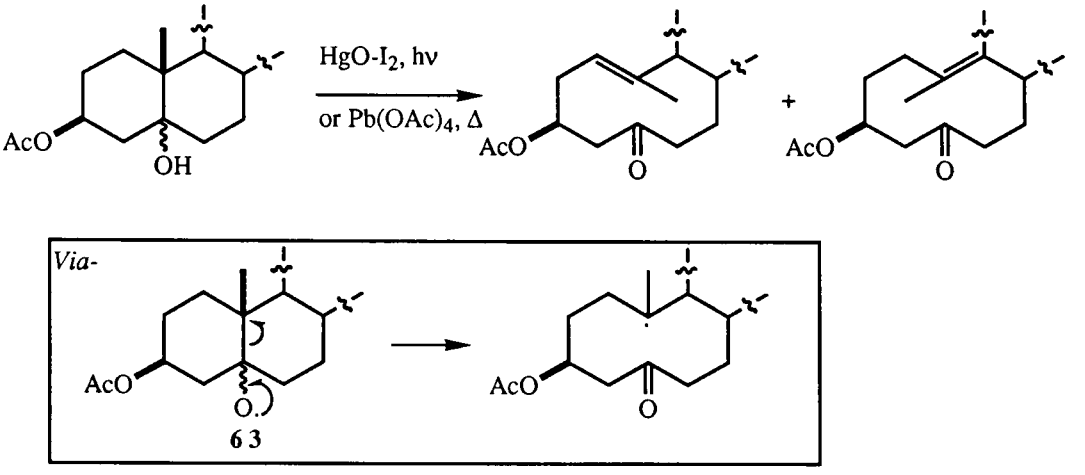
I.3 Synthesis of medium ring ketones and lactones <u>via</u> one electron processes.

I.3.1 Homolytic cleavage of bicycloalkanols to provide ring expanded products.

This survey of synthetic methods to natural products containing medium ring carbocyclic structures has been provided to illustrate the power of ring expansion chemistry in providing relatively complex frameworks in one synthetic step. The photochemical fragmentation procedure reported by Fujimoto[64] to provide dihydrocostunolide, discussed above (Section I.2.3), based on the early work of Corey[65] is of particular importance since this suggests the possibility of applying homolytic methods to the synthesis of medium rings. The application of free radical chemistry to the generation of organic structures has been comprehensively reviewed by a number of authors (Curran[81], Ramaiah[82], and Giese[83], amongst others[84]) and the particular advantages of homolytic methods over two electron transformations, in terms of selectivity and functional group compatibilty, need not be reiterated here.

Although, at the time of Corey's report[65] photofission of 1,3-cyclohexadiene systems was a well documented process[85], this transformation proceeded by $\pi \rightarrow \pi^*$ activation and no general (and mild) method of ring expansion could be easily extrapolated from this work. However, at about the same time, Mihailovic *et al.* reported the preparation of new steroidal derivatives containing a ten membered ring portion *via* lead

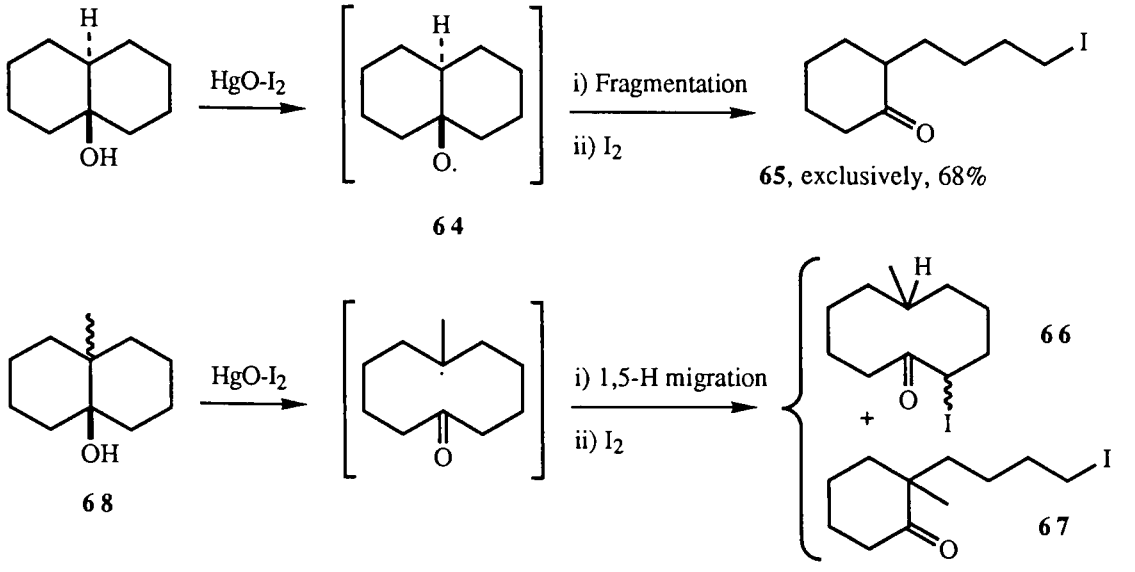
tetra-acetate (LTA) induced oxidative cleavage of 5-hydroxy steroids[86]. A similar conversion was simultaneously reported by Akhtar[87] in which the hydroxy steroids were fragmented with mercuric iodide and iodine to generate hypoiodites which rapidly decomposed homolytically, in the presence of light, to the observed ring expanded products. The intermediate decalinoxy radical **63** was postulated in both cases (Scheme 36).



Scheme 36

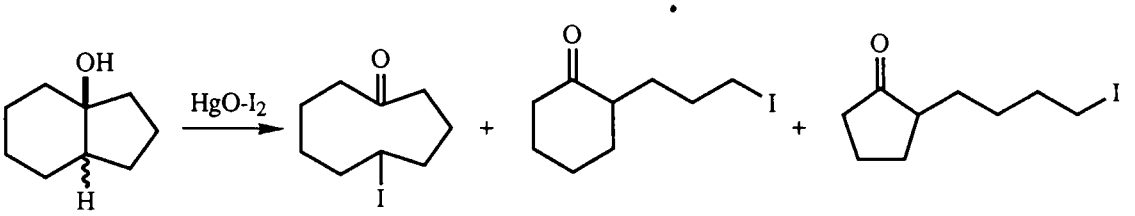
Little use of this method was, however, employed outside the field of 5,10-seco-steroids for the preparation of medium rings in general until the scope of the reaction was explored by Macdonald[88]. Generation of the decalinoxy radical **64** from decalinol ($HgO-I_2$) resulted in reaction solely to the 4'-iodobutyl ketone **65** in 68% yield. This reaction stood in contrast with the pioneering work of Criegee[89] and Holmquist[90] in which, respectively, the perbenzoates and hydroperoxides prepared from decalinol decomposed to products derived from exclusive cleavage of the ring junction bond. This dichotomous behaviour was postulated to be a consequence of the difference between the precise electronic character of the alkoxy oxygen in the transition state for rearrangement in the three separate cases.

Interestingly, alkyl substitution at the ring junction was found to have a dramatic effect on the course of the fragmentation process. For example a 94:6 mixture of ketones **66** and **67** were obtained from the methyl derivative **68**. These results are summarised in Scheme 37.



Scheme 37

This work was extended to include unsaturation in the precursor[88] and to study the cleavage of hydrindanoxy (and related) radicals[91]. In this latter system, there exists three modes of breakdown, i.e. initial cleavage of (i) the ring junction bond, (ii) the six membered ring, or (iii) the five membered ring. Studies by Greene[92] and Walling[93], combined with the results of earlier work by Beckwith, *vide infra,* indicated the relative rates of these three processes ($k_{i\text{-}iii}$) to be in the order $k_i > k_{iii} > k_{ii}$. Indeed, it was found that heating hydrindanol **69** in carbon tetrachloride in the presence of the HgO-I_2 system resulted in a product distribution which was in loose agreement with this prediction, the clearest results coming from fragmentation of the *cis*- bicyclic isomer (Scheme 38).

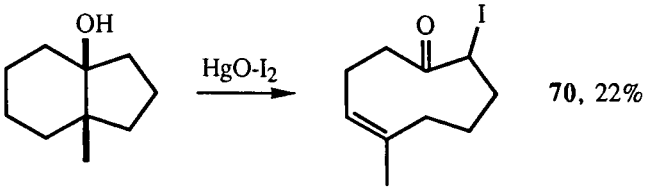


69a, H_α (*trans*-)	16%	17%	10%
69b, H_β (*cis*-)	36%	15%	18%

Scheme 38

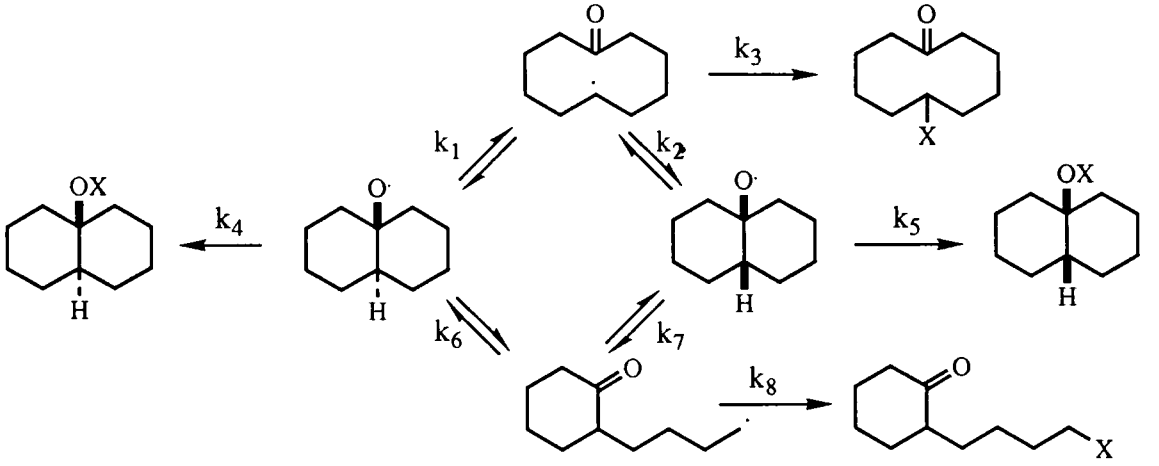
Once more, alkyl substitution of the ring junction affected the outcome of the reaction with only the ring expanded product **70** being observed as depicted in Scheme 39.

Unfortunately the low yield (22%) of this product, which was suggested to arise from halogenation of the enol tautomer of the medium ring ketone, throws the validity of a mechanistic interpretation of these results into considerable doubt.



Scheme 39

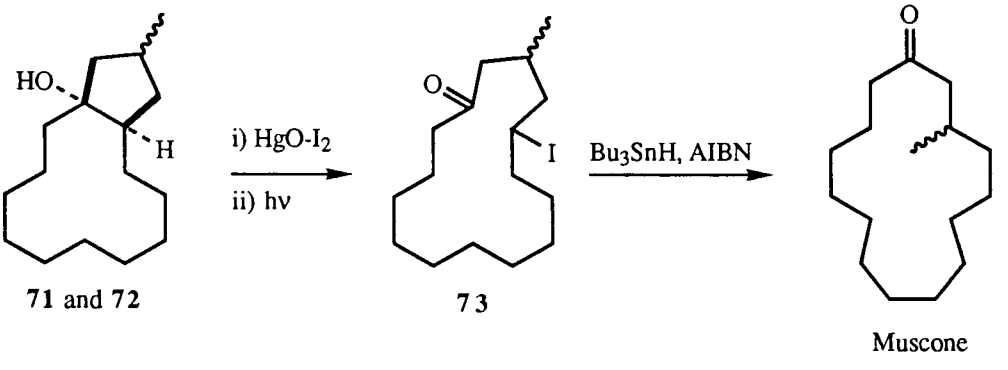
Fortunately Beckwith[94] undertook a rather more systematic course of study in which both *cis-* and *trans-* decalinol derivatives were fragmented under a wide variety of conditions in order to probe the dependence of the product ratio on the specific conditions used to generate the alkoxy radical. Indeed these results were found to indicate that product ratios were not only dependent on the competition between the trapping of intermediate radicals and their interconversion, but on the concentration and nature of the trapping agent. The conclusions drawn from this work were that fission of the ring junction bond, to generate the cyclodecanone radical, is a rapid and reversible process but that fission to the butyl cyclohexanone radical is relatively slow and essentially irreversible. These results were presented as a series of competing equilibria (Scheme 40).



Scheme 40

These conclusions suggested that under appropriate conditions a homolytic fragmentation reaction of this sort could be synthetically viable. Suginome has exploited

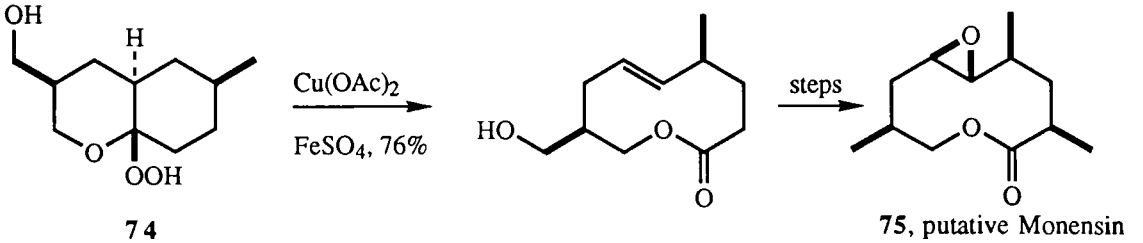
the aforementioned $HgO\text{-}I_2$-hν conditions to effect a number of such transformations[95]. Representative of this work was the preparation of muscone[95a] from the trimethylsilyl enol ether of cyclododecanone. This was transformed in six steps to the diastereomeric mixture of bicyclic alcohols **71** and **72** which, on exposure to the oxidative conditions, resulted in an effective three carbon ring expansion to iodide **73**. This iodide was reduced directly to the racemic natural product with tributyltin hydride and AIBN. Interestingly no bicyclic alcohols were reproduced during this reduction (Scheme 41).



71 and **72** **73** Muscone

Scheme 41

Schreiber has employed an alternative fragmentation procedure which involved the oxidative cleavage of bicyclic peroxy ketals[96] to medium ring lactones. The oxidative system of cupric acetate and ferrous sulphate was used to effect this conversion, the mechanism suggested to be homolytic by analogy with related hydroperoxide decompositions[97]. Thus, in a route directed towards the synthesis of ionophore sub-units[98], hydroperoxide **74** afforded macrolide **75** which was envisaged to be a monensin precursor (Scheme 42).

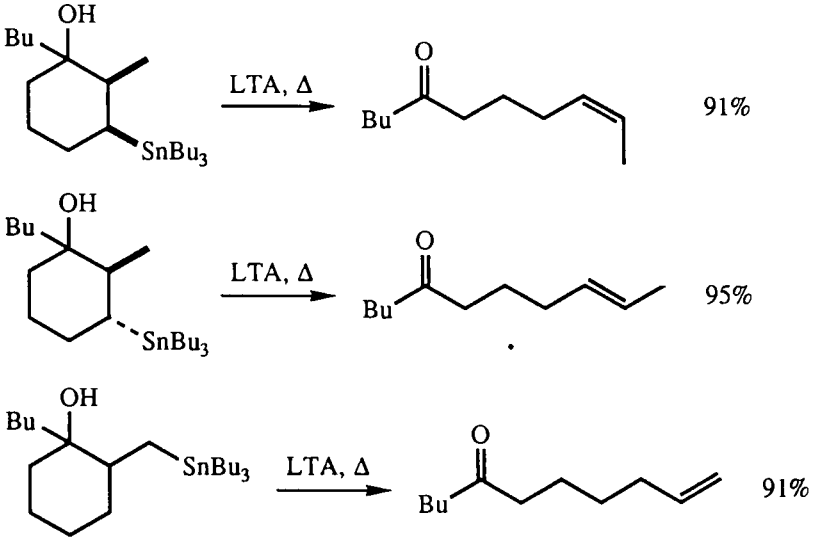


74 **75**, putative Monensin precursor

Scheme 42

I.3.2 Oxidative cleavage of γ-stannyl alcohols.

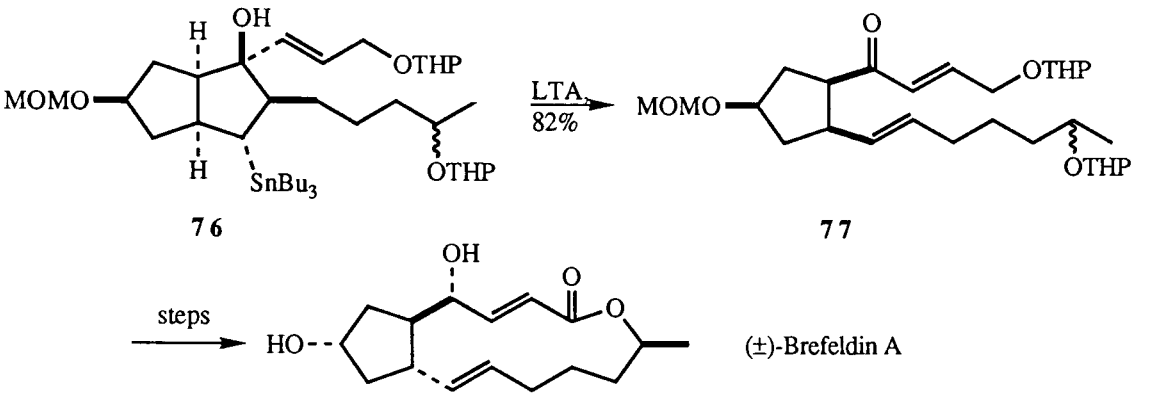
Although the review of radical methods in organic chemistry by Ramaiah[82] included a section on the β-scission reaction, little mention was made of an important development in this area which has transformed the nature of the homolytic fragmentation process. The introduction of a one electron leaving group, in such a position that a putative ring expanded radical intermediate may fragment to produce an alkene, enables the ejected species to continue the radical chain process such that the problem of selectively trapping only the desired ring expanded radical is avoided. The development in recent years of organotin chemistry[99] suggested the choice of $Bu_3Sn\cdot$ as the one electron leaving group to researchers such as Isoe[100] who used γ-stannyl alcohols derived from cyclopentenone and cyclohexenone in a LTA-induced oxidative fragmentation. This procedure represented a one electron alternative to the classical 1,4(Grob)-fragmentation[20,101]. Model work in this field indicated that stereochemical information in the starting alcohol was effectively retained in the product suggesting a concerted and *anti-* elimination as shown in Scheme 43.



Scheme 43

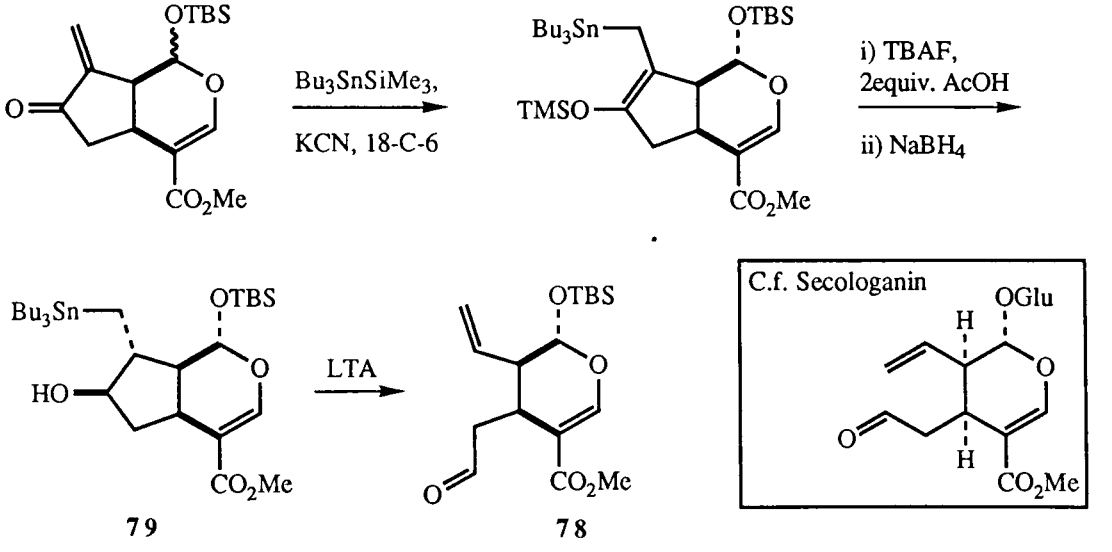
This new type of fragmentation was applied as the key step to a synthesis of (±)-brefeldin A[102] which possesses wide ranging biological activity. Fragmentation of bicyclic alcohol **76**, under the conditions reported above, afforded cyclopentane derivative **77**

which bore obvious sructural resemblance to the natural product (Scheme 44). The full synthesis of this compound was reported in a separate article[103].



Scheme 44

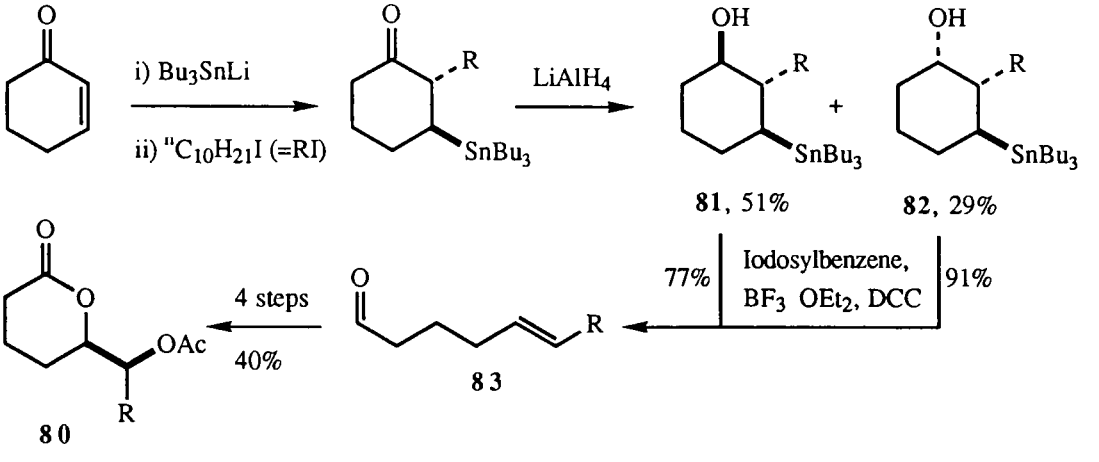
Later work by Isoe[104] employed the same methodology to the synthesis of (-)-secologanin-aglucone-*O*-silyl ether **78**. 1,4-addition of the tributylstannanyl group was effected with tributylstannyl trimethylsilane in the presence of potassium cyanide and the crown ether 18-C-6 in THF[105]. This enol ether was elaborated to bicyclic γ-stannyl alcohol **79**, subsequent oxidative fragmentation providing the secologanin derivative **78** in 82% yield as shown in Scheme 45.



Scheme 45

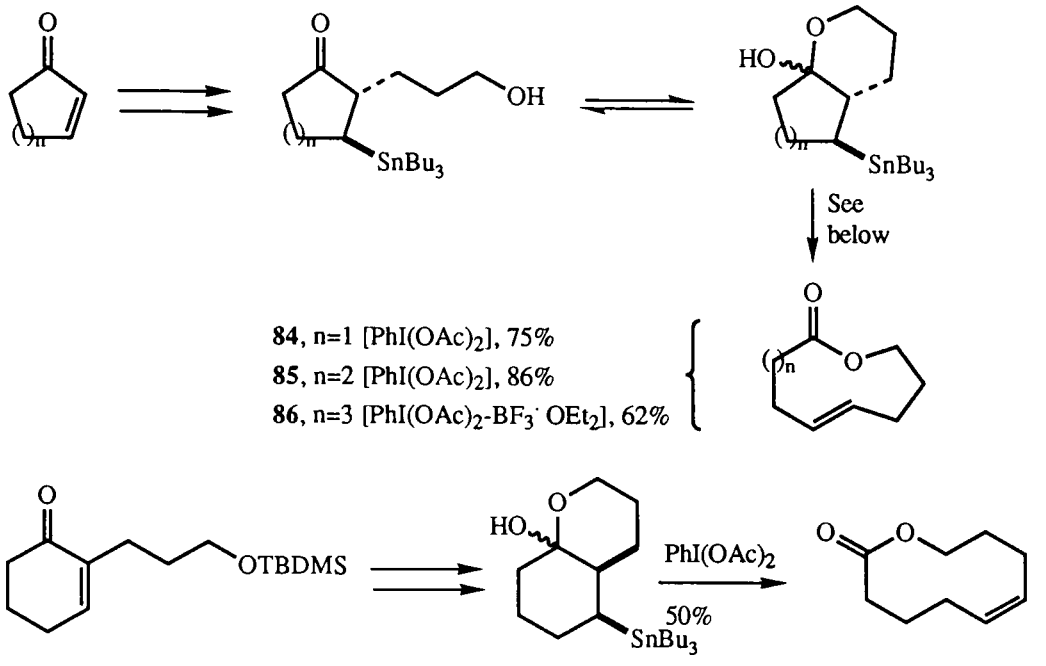
Ochiai published almost identical work at the same time as the report of Isoe. In this work the same type of fragmentation reaction was reported but alternative oxidation

conditions (namely iodosylbenzene/boron trifluoride etherate/DCC in dichloromethane) were used to effect the reaction. Results were comparable but the isolated yields of fragmented products were slightly lower[106]. However the same author applied this chemistry to the synthesis of *erythro*-6-acetoxyhexadecan-5-olide **80**, the major component of a mosquito oviposition pheremone[107]. The first stage of the synthesis[108] involved the 1,4-addition of tributylstannyl lithium to cyclohexenone followed by direct alkylation of the so-formed enolate with ^{n}decyl iodide. The resulting *trans*- ketone was reduced with lithium aluminium hydride to provide a separable mixture of alcohols **81** and **82**. These were independently fragmented to the *trans*- enone **83** which was converted to the pheremone in four steps (Scheme 46). This work was fully detailed in a later publication[109] in which further applications of this method were reported and which included a discussion of the mechanistic aspects of the process.



Scheme 46

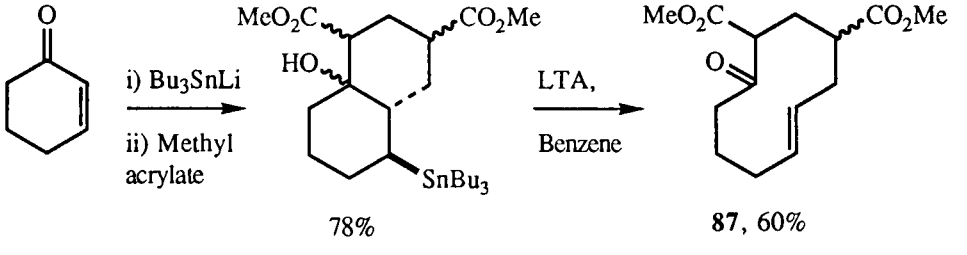
The first report of such a fragmentation resulting in overall ring expansion also arose from this group[110] as a method for the construction of medium ring lactones with stereospecifically controlled olefin formation. Once again, 1,4-addition of tributylstannyl lithium followed by enolate alkylation with 1-iodo-3-^{t}butyldimethylsilyloxypropane, ketone reduction, and alcohol deprotection, resulted in the formation of the *trans*- fragmentation precursors. Use of the milder oxidising reagent diacetoxyiodobenzene[111] resulted in clean fragmentation to lactones **84** to **86** as shown in Scheme 47. The preparation and fragmentation of the *cis*- substrate is also given in this Scheme.



Scheme 47

This work compares with the work of Suarez[112] in which macrolide syntheses were reported based on model studies directed towards the production of alkoxy[113] and aminyl[114] radicals using diacetoxyiodobenzene and iodine in a similar manner.

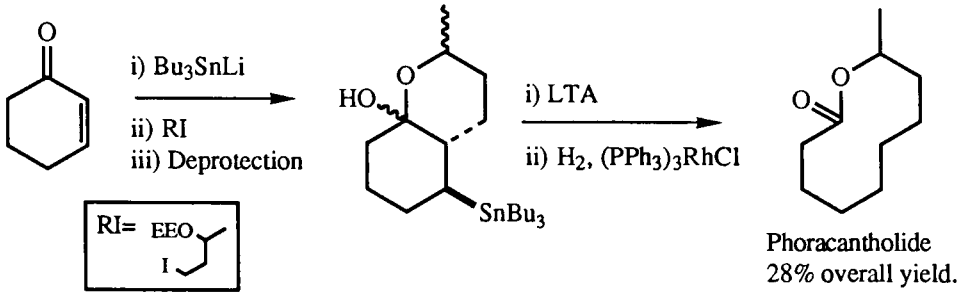
Posner's ongoing interest in multicomponent annulation[115] has led to his involvement in medium ring ketone and lactone synthesis by oxidative fragmentations of γ-stannyl alcohols in a similar manner to that reported by Ochiai. The first such report from this group[116] concerned the synthesis of the functionalised ketone **87** in high yield from cyclohexenone in two steps (Scheme 48).



Scheme 48

This rapid elaboration of readily available precursors to relatively complex medium ring systems was used in a synthesis of phoracantholide which occurs naturally as an insect

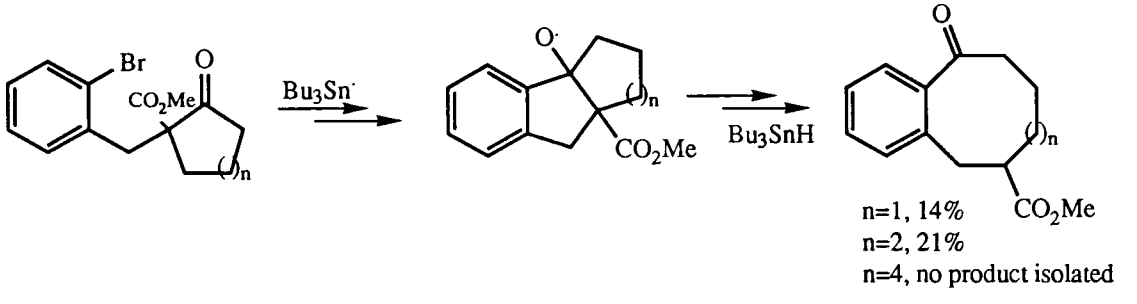
secretion (Scheme 49). Further examples of this work have been reported more recently[117].



Scheme 49

1.3.3 In situ formation and fragmentation of bicyclic alkoxy radicals.

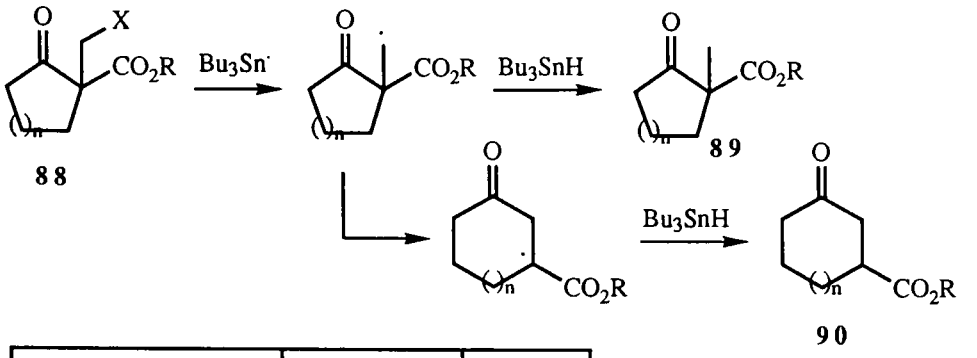
In a separate study Beckwith has produced bicyclic alkoxy radicals *in situ* by the intramolecular addition of an alkyl or aryl radical onto a carbonyl group. It was postulated that the suitable placement of a carboxyalkyl function would stabilise the ring expanded radical thus favouring its production on thermodynamic grounds. Scheme 50 indicates the first example of such a process[118].



Scheme 50

Unfortunately, this reaction could not be generalised due to problems of competitive ring contraction and/or reduction, either by 1,5-hydrogen atom abstraction or by direct reaction with tributyltin hydride.

A more successful procedure was obtained if the alkyl chain was limited to one carbon in a ring expansion protocol which paralleled the results of Widdowson[119]. This procedure was used to prepare normal and medium rings in reasonable yield[120] from the β-keto ester progenitors **88** (Table 1).



			Ratio (89:90) in crude	Isolated yield (%)
n=1	X=SePh	R=Et	2:98	88%
	X=I		0:100	82%
n=2	X=SePh	R=Me	15:85	5, 48%
	X=I		18:82	15, 76%
n=3	X=I		7:93	5, 90%
n=4	X=SePh		22:78	16, 73%
	X=I		17:83	10, 75%

Table 1

These results indicated the feasibility of a homolytic one carbon ring expansion, concurrent work by Dowd[121] confirming the observations. However the articles by Dowd described the extension of such a process to encompass three and four carbon ring expansion by a similar protocol. Alkylation of cyclopentyl and cyclohexyl β-keto esters with dihaloalkanes (n=2, 3, 4) resulted in radical precursors which, under conditions of high dilution (5 mmolar), underwent fragmentation as summarised in Table 2.

This set of results reinforced the postulate that the primary radical attacked the carbonyl group rather than the alternative scenario of cleavage to an acyl radical followed by re-addition of this acyl radical in a 1,4-mode since this would only be possible for the one carbon series (Scheme 51).

Recently Dowd has been able to extend this methodology to the synthesis of medium ring heterocycles in an analogous manner[122] although results were variable.

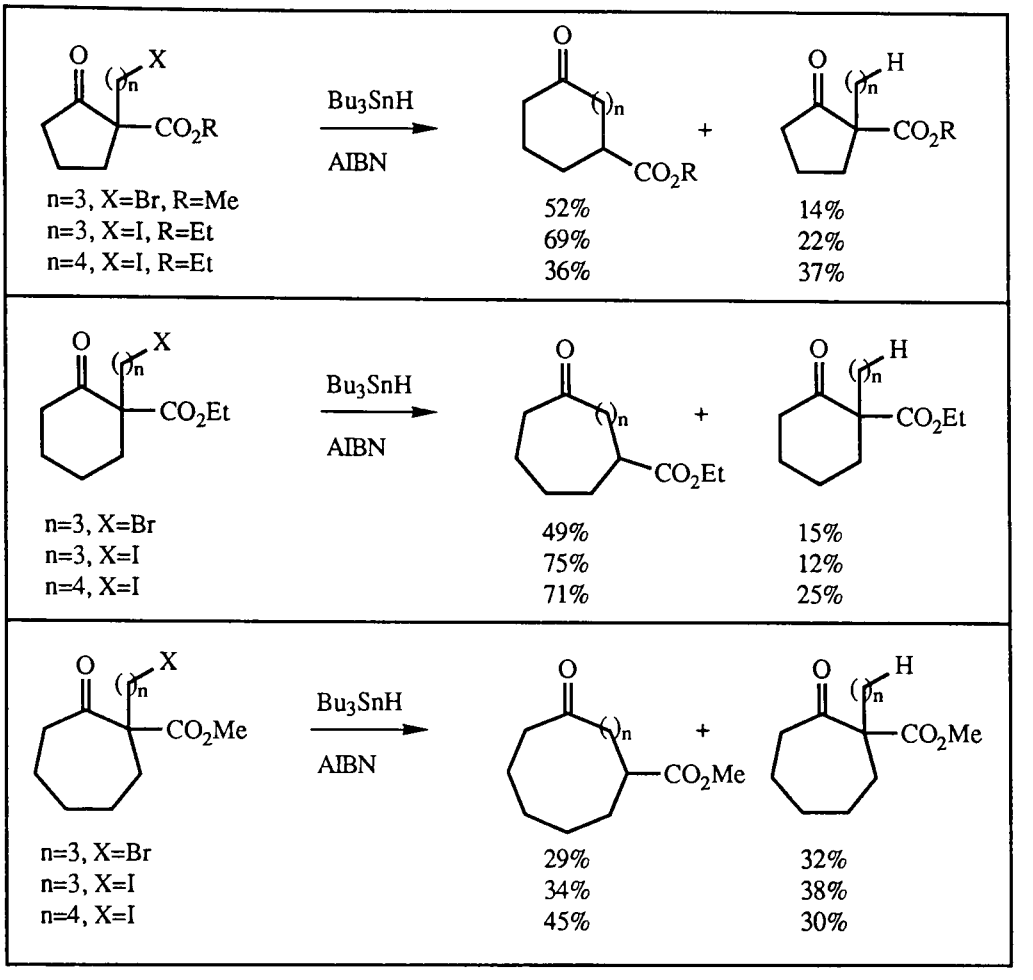
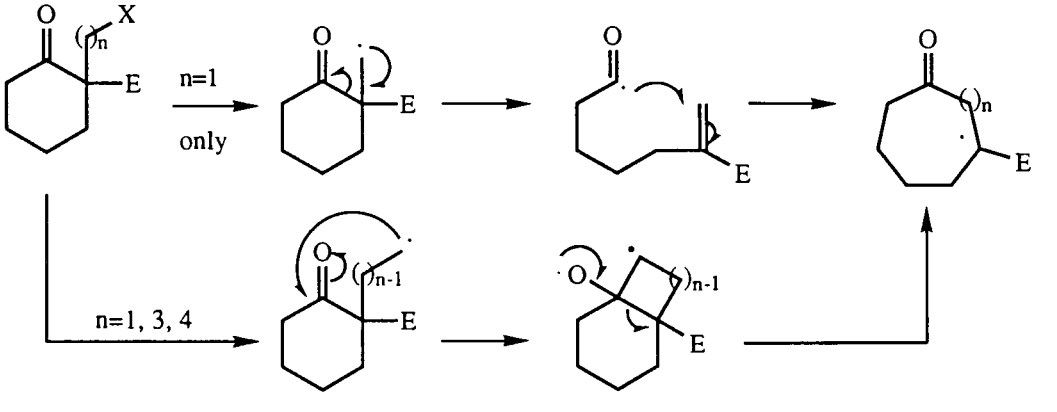


Table 2



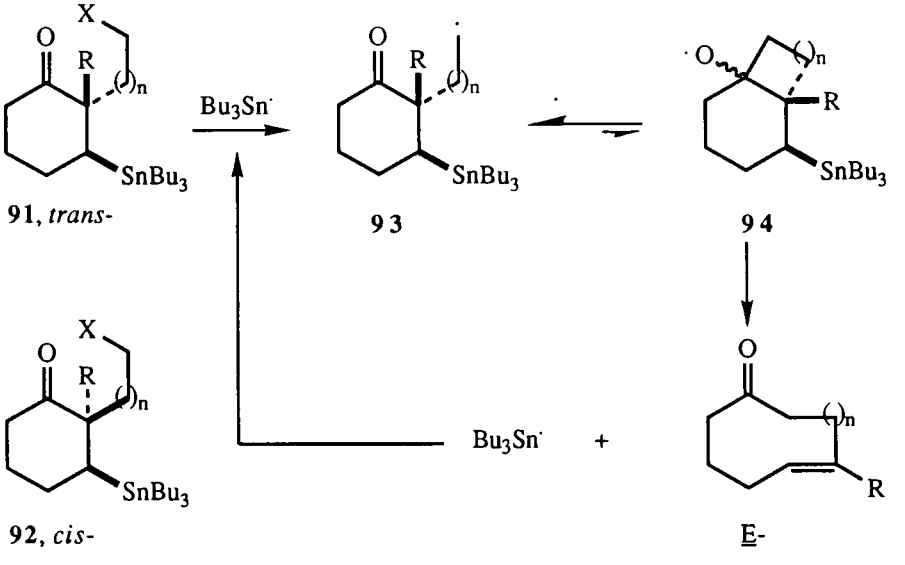
Scheme 51

I.4 Summary and proposed work.

We have seen that a number of diverse procedures exist for the preparation of natural products *via* conventional two electron pathways. However, each reaction may usually be used only for ring expansion by a specific number of carbon atoms unless

unusual structural features are included in the precursors. This lack of generality has been partially overcome by the homolytic procedures of Dowd and Beckwith described above although the stoichiometric requirement of tributyltin hydride in these reactions results in significant amounts of direct reduction at the expense of ring expansion, particularly in the more demanding cases.

The oxidative processes involving γ-stannyl alcohols suggest a means of tailoring the Dowd/Beckwith system in such a way that only a catalytic quantity of tributyltin hydride is required (to initiate the reaction). Thus, these features were combined and the substrates **91** and **92** identified as potential ring expansion precursors. On treatment with tributylstannyl radical (generated from AIBN and tributyltin hydride) the so-formed primary radical **93** is expected to add to the carbonyl group intramolecularly (c.f. Dowd/Beckwith) resulting in an equilibrating mixture of intermediate alkoxy radical **94** and primary radical **93**. Although the work of Beckwith and Macdonald suggest that this alkoxy radical **94** will be present in only low concentration, the merely catalytic requirement of tributyltin hydride should result in little or no direct reduction especially if high dilution conditions are deployed. The alkoxy radical **94**, once formed however, is expected to rapidly eject $Bu_3Sn\cdot$ (c.f. the work of Ochiai and Isoe), in a concerted fashion, to provide ring expanded cycloalkenones with double bond geometry derived from the configuration of the radical precursors (Scheme 52).



Scheme 52

It is therefore proposed, during the course of this project, to prepare suitable precursors of the general type described above and to study their behaviour towards homolysis. It is hoped that this procedure, if successful, may be developed to a generalised intramolecular addition-1,4-fragmentation reaction applicable to a range of precursors such that alternative ring systems become accessible. Once the methodology for such processes has been fully elucidated it is hoped to verify the synthetic applications of the reaction by attempting the preparation of natural products possessing structural features amenable to the proposed transformation.

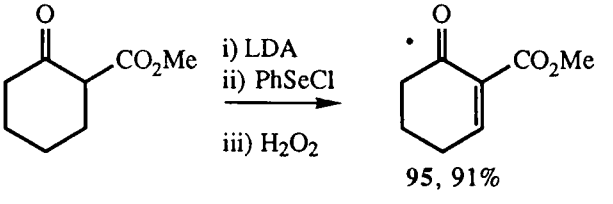
CHAPTER II
RESULTS AND DISCUSSION

II.1 Preparation of seven, nine, and ten membered cycloalkenones.

II.1.1 Preparation of trans- substrates for ring expansion.

A suitable approach to the *trans*- substrates (Scheme 52, Chapter I) appeared to be *via* 1,4-addition of R_3SnLi to an α,β-unsaturated cyclic ketone followed by direct alkylation of the so-formed enolate with appropriately functionalised halides. It was hoped that this reaction would proceed stereospecifically to result in a *trans*- disposition of the trialkylstannyl group and the radical-carrying side chain. At the outset of this work we were aware of the work of Still[123] and Dowd[121], in which this type of chemistry had been used in a synthesis of *cis*-jasmone (although later investigation revealed the procedures of Isoe and Ochiai, *vide supra*). Early studies were therefore directed towards verifying some of this work and attempting to extend the methodology to the specific transformation required.

In the light of the work of Beckwith[120] and Dowd[121] it seemed most appropriate to study 1,4-addition-alkylation procedures using 2-carbomethoxycyclohex-2-enone **95** as the starting material since the presence of the ester function was thought to be necessary to promote the ring expansion. The enone **95** was produced according to the literature as shown in Scheme 53 displaying data which was in agreement with that reported[124].

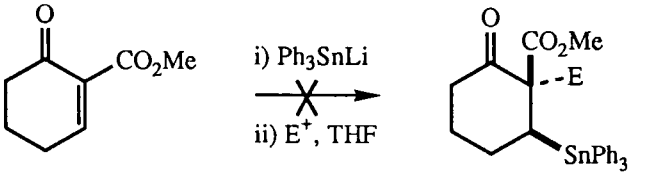


95, 91%

Scheme 53

Initially triphenyltin hydride was used as the stannyl anion source since this was rather easier to handle than tributyltin hydride, being a solid which possessed reasonable stability in air and would hopefully yield crystalline product. It was found that 1,4-addition

of Ph_3SnLi to the enone **95** was a rapid and efficient process at -78°C, however, subsequent alkylation of the so-formed enolate in THF alone was not viable. During a number of attempted alkylations with 1,4-di-iodobutane re-elimination of the stannyl function (either as Ph_3Sn^- or $Ph_3Sn\cdot$) appeared to compete to the exclusion of enolate alkylation. Only with very reactive electrophiles such as methyl iodide and benzyl bromide was alkylation observed but in very low yield. This work is summarised in Scheme 54.



Scheme 54

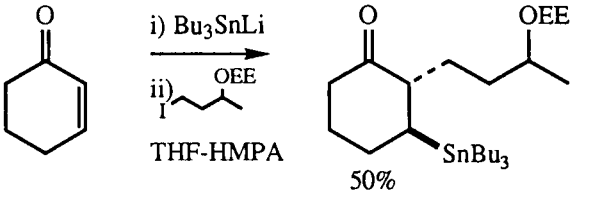
At this stage it was decided to identify those factors which could be altered in order to maximise the reactivity of the system towards enolate alkylation:

(i) Changing R_3Sn- such that a less stabilised leaving group is present,

(ii) Replacing the 2-carboxymethyl group for one which would maximise enolate reactivity, i.e. H, alkyl, and,

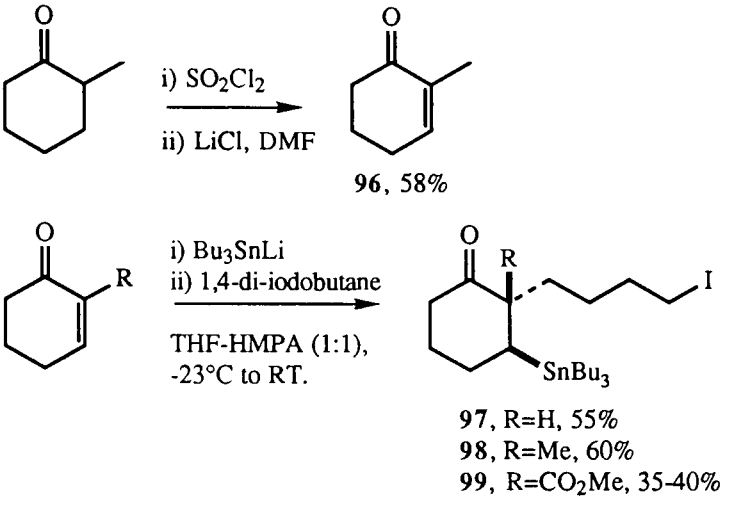
(iii) Replacing the solvent or introducing a co-solvent in order to enhance the reactivity of the enolate.

These considerations were embodied in a synthesis of (±)-phoracantholide, communicated by Posner[117a], in which the 1,4-addition-alkylation sequence shown in Scheme 55 was reported (see also Section I.3.2).



Scheme 55

The conditions for this reaction were based on work by Ochiai[110] and involved the use of Bu_3SnLi and a solvent mixture of THF and HMPA (≈1:1) with an alkylation temperature of -20°C. Application of these conditions enabled the production of a number of the desired substrates using 1,4-di-iodobutane in the alkylation. The enone **96** was produced as shown in Scheme 56 according to a literature procedure[125]. The first successful addition-alkylation reactions are also detailed.

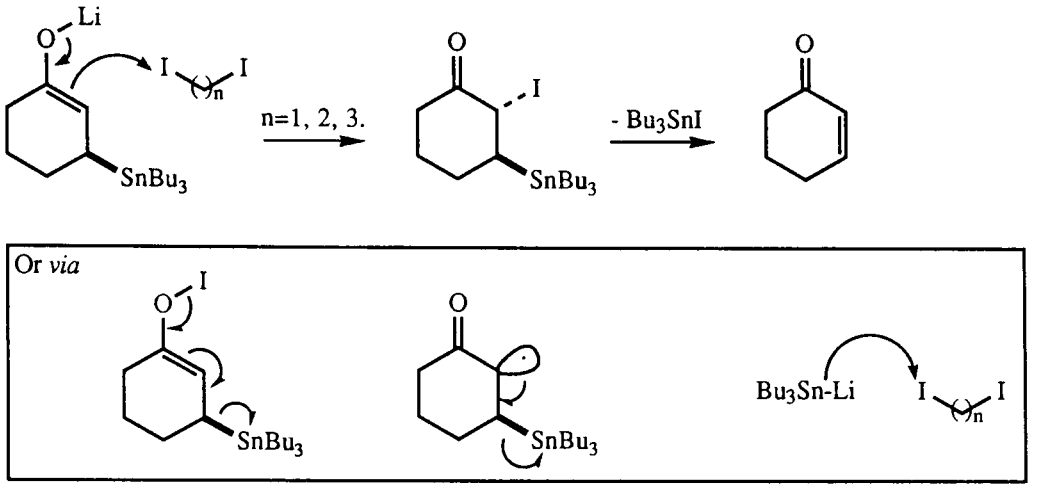


Scheme 56

The products were identified by the presence of the $\underline{Bu_3}Sn$- and $\underline{CH_2}I$ resonances in their ^1H n.m.r. spectra, and by mass spectral data which clearly indicated the correct molecular masses. T.l.c. analysis indicated only one isomer in the case of **97** and **98**, however, with compound **99** the crude ^1H n.m.r. spectrum exhibited a number of $CO_2\underline{Me}$ resonances indicating the likelihood of competing *O*-alkylation and production of the *cis*- substrate. These impurities were removed by careful chromatography and account for the reduced yield of this compound.

Unfortunately, attempts to alkylate the enolates, derived from cyclohex-2-enone, with di-iodomethane, 1,2-di-iodoethane, and 1,3-di-iodopropane met with failure, resulting in recovered starting materials and/or decomposition products. In these examples the intermediate enolate may react preferentially at the halide atom resulting in the ejection of a neutral hydrocarbon and I^- as shown in Scheme 57. Alternatively, *O*-alkylation followed

by homolytic decomposition, or reaction of stannyl anion with the halide in an equilibrium process, represent plausible explanations. In any case tributyltin iodide was always produced so at this stage side chains with one to three carbon atoms were not accessible.



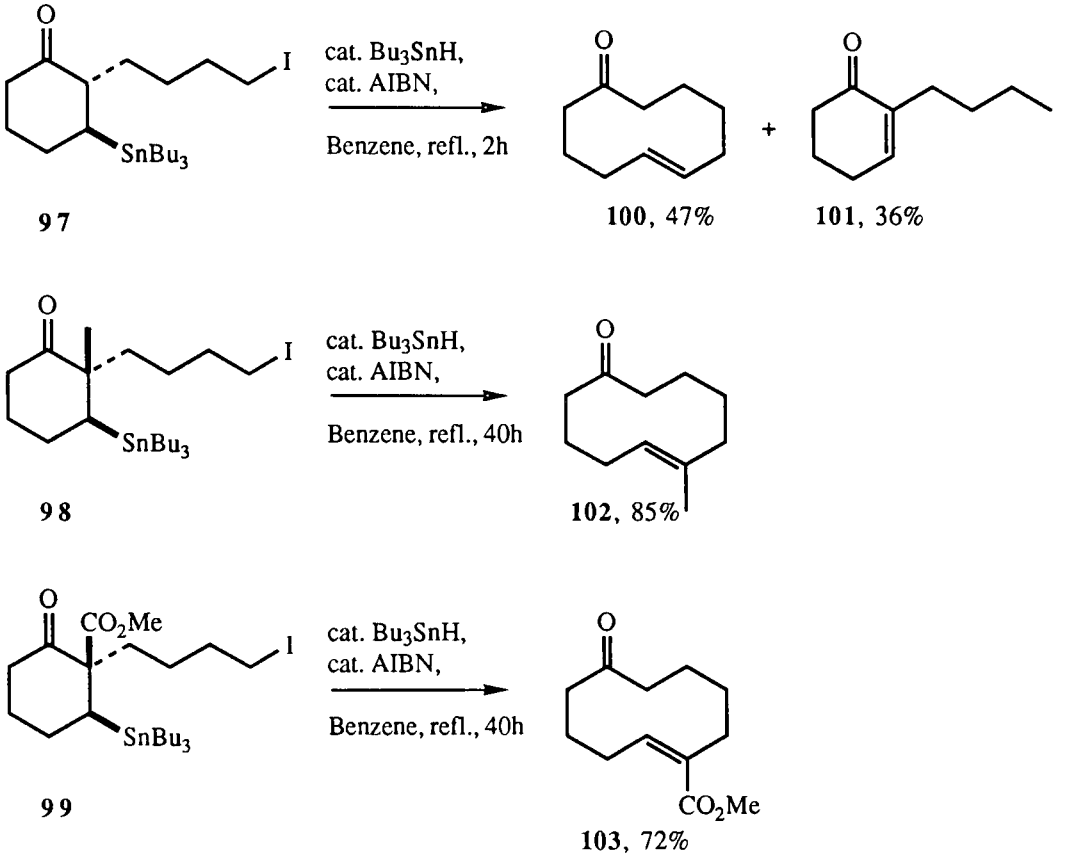
Scheme 57

II.1.2 Trial four carbon ring expansions.

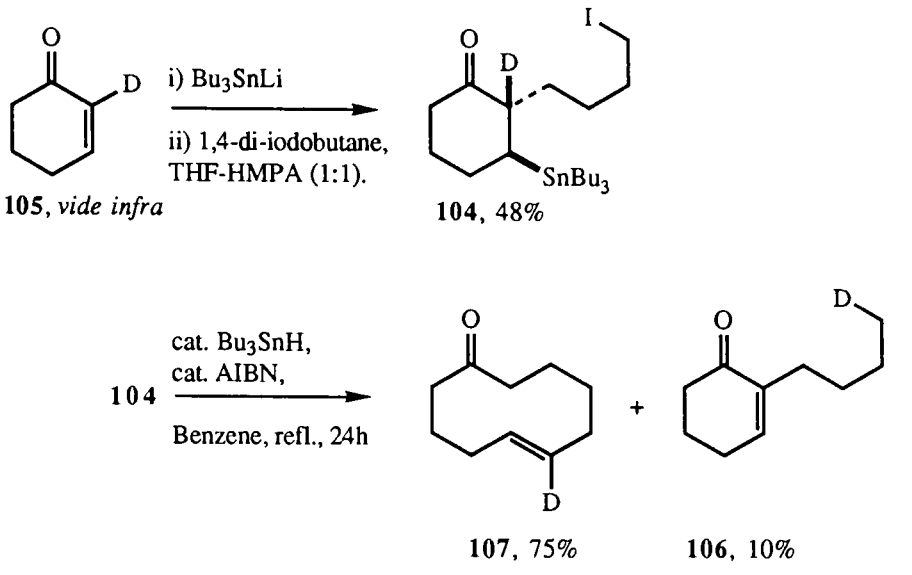
With three *trans*- substrates in hand their reactivity under conditions known to promote homolytic processes was studied. Following the protocol used by Dowd[121] the substrates were dissolved in benzene to produce a 5mM solution and the mixtures degassed. Catalytic quantities of AIBN and tributyltin hydride were added to initiate the reactions and the mixtures heated at reflux until the starting materials were consumed (t.l.c.). The products were isolated by chromatography and in each case it was found that ring expansion was possible as detailed in Scheme 58.

The compounds **100**[86b], **101**[126], and **102**[127] had been previously reported and their spectroscopic data was found to be in agreement with that described. The structure of **103** was confirmed by ^{1}H n.m.r. (δ 5.59, 1H, t, *J* 9.0Hz, CH=), i.r. ($\nu_{max.}$ 1680-1750cm^{-1}), and mass spectral data (211, MH$^+$, 100%). All of these compounds had characteristic odours which provided a good indicator for the success (or otherwise) of subsequent radical reactions.

The competing production of the enone **101** was not foreseen; in order to obtain information as to its formation the 2-deutero- substrate **104** was prepared (from **105**) and its behaviour towards ring expansion conditions studied. The radical reaction was found to be complete after 24h at reflux affording a mixture of the eliminated compound **106** and the ring-expanded material **107** (Scheme 59).

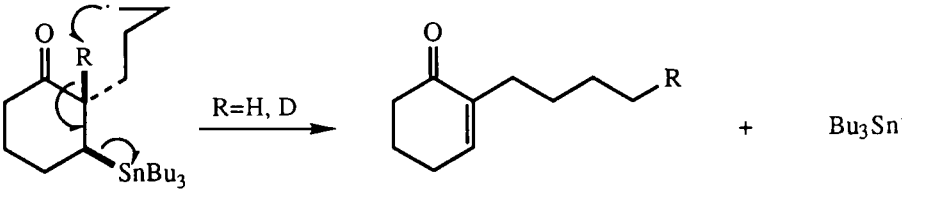


Scheme 58



Scheme 59

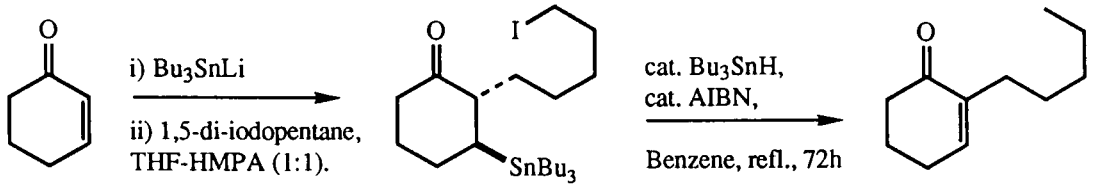
The structures of the products were assigned by comparison of their spectroscopic data with that obtained for **100** and **101** above and by ^{13}C and ^{2}H n.m.r. spectroscopy (δ 0.82 and 5.32, the integrations implying an ≈1:8 ratio of compounds **106**:**107** in accordance with the ^{1}H n.m.r. spectrum). This information indicated complete transferral of the deuterium atom to the radical centre during the reductive elimination process. Support for an intramolecular process came from an experiment in which the radical reaction of the substrate **97** was run at a concentration of 50mM resulting in no perceptible alteration of the ratio of ring expanded to reductively eliminated material. Were the reductive elimination process intermolecular it would be expected that an increase in reaction concentration would favour the production of compound **101** over the ring expansion product **100**.



Scheme 60

II.1.3 Extension to side chains other than C_4.

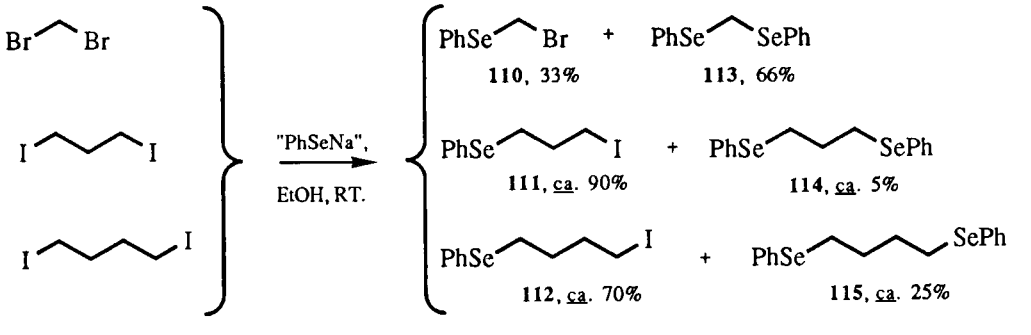
In addition to 1,4-di-iodobutane the alkylation was successful with 1,5-di-iodopentane although the yield of the product **108** was lowered (39%). Unfortunately, no ring expansion to an eleven membered carbocycle was observed, solely intramolecular reductive elimination to give 2-pentyl-cyclohex-2-enone **109** which exhibited spectroscopic data in agreement with that reported[126a] (Scheme 61).



108, 39% **109**, 86%

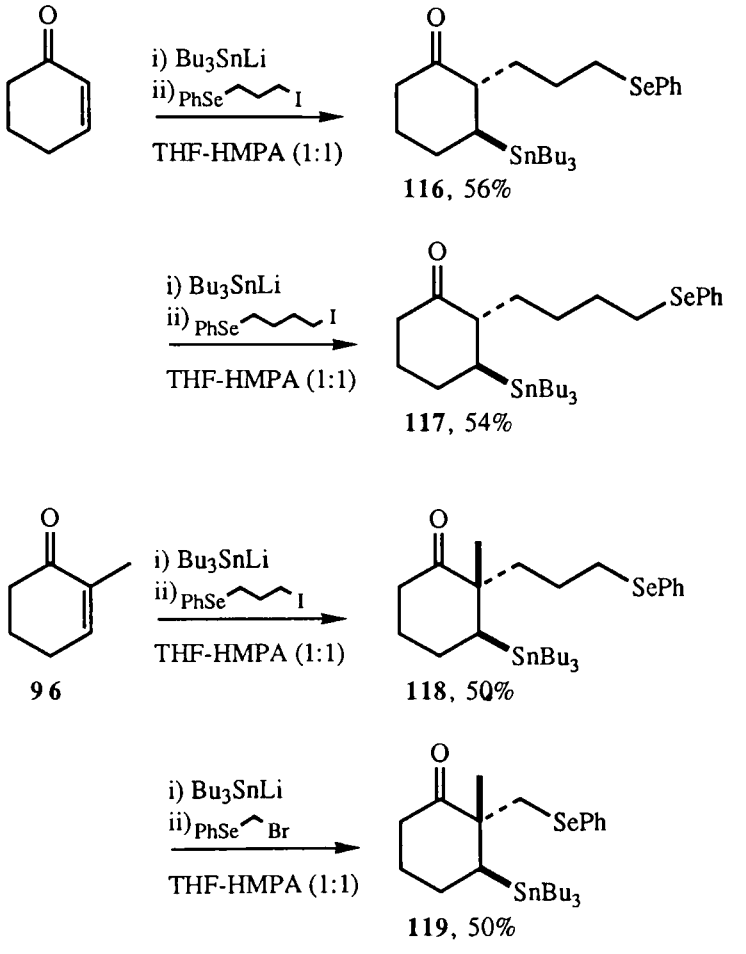
Scheme 61

In order to access substrates possessing shorter side chains phenylseleno-haloalkanes were prepared as electrophiles since it was known that a) the PhSe- function serves as a convenient radical precursor[128] resulting in the formation of $Bu_3SnSePh$ which is easily removed by chromatography and b) $PhSe^-$ is a relatively poor two-electron leaving group (compared with iodide) therefore minimising the occurrence of such processes as those suggested in Scheme 57 above. Electrophiles **110** - **112** were readily prepared by the reaction of diphenyl diselenide/sodium borohydride[129] with a selection of dihalides as detailed below (Scheme 62), accompanied by varying amounts of the diselenides, even when large excesses of the dihalides were used.



Scheme 62

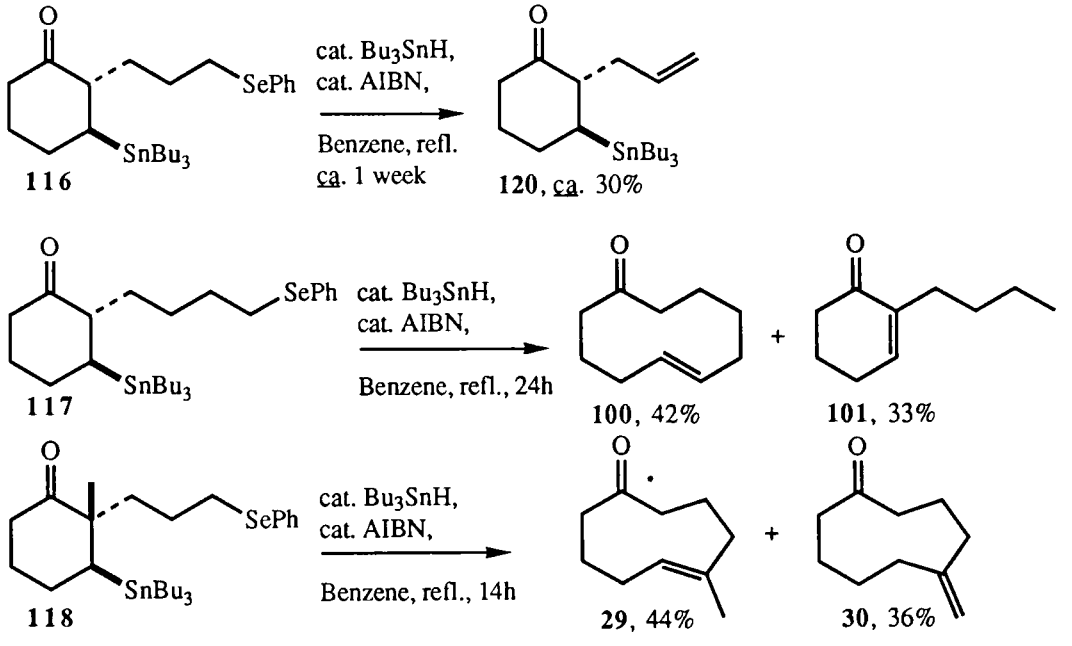
All compounds showed the expected spectroscopic data. These electrophiles could be employed successfully in 1,4-addition-alkylation reactions to yield the *trans*- substrates **116 - 119** in reasonable yield. The reaction of the electrophile **110** with the enolate derived from cyclohex-2-enone was very low yielding and that with 2-carbomethoxycyclohex-2-enone **95** failed completely. These results are summarised in Scheme 63. The mass spectra for each of these compounds showed molecular ions with isotope peaks precisely in accord with the calculated abundances. ^{1}H n.m.r. and i.r. spectral data as well as microanalysis confirmed the expected structures.



Scheme 63

The phenylseleno- function is known[130] to be rather less reactive towards radical formation than is the iodine atom (under normal conditions) and it was found that these

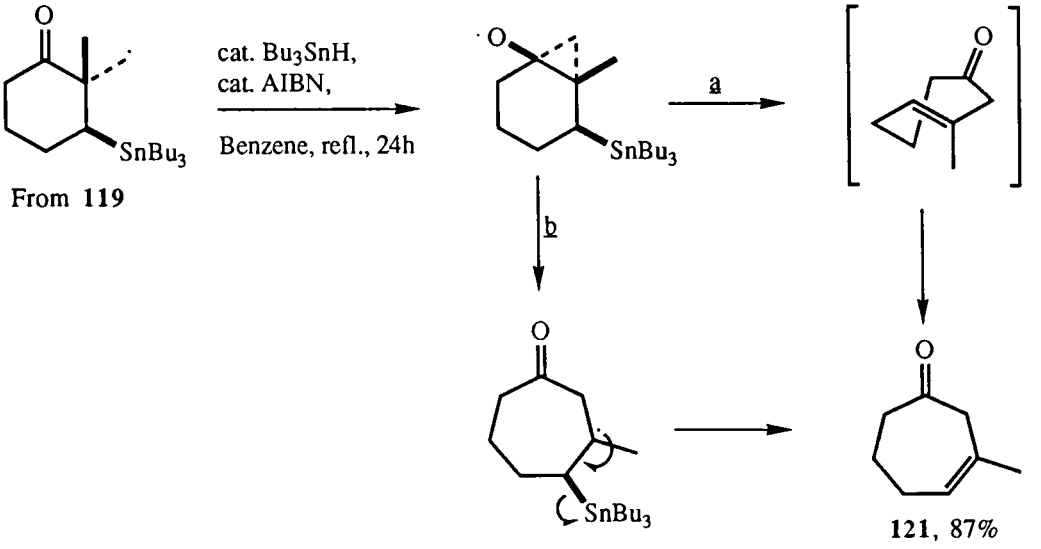
substrates generally required longer reaction times in order for the reactions to reach completion. In the case of the substrate **116** no ring expansion or reductive elimination was observed, the only isolable product **120** being that arising from the elimination of the selenide function and this only after prolonged reaction times. No succesful explanation has been proposed as to the complete failure of this reaction (*vide infra*). The substrate **117** provided a comparison with compound **97**; again the two products were formed in approximately the same ratio however the reaction required 24h to go to completion. The first successful example of a three carbon ring expansion to a nine membered ring was that of substrate **118** giving initially the E-cyclononen-one **29** which is known[45] to undergo thermal isomerisation to the exomethylene isomer **30** in order to relieve ring strain (Section I.2.2). On repetition of this reaction, using a longer reaction time, the product isolated was exclusively the exomethylene isomer **30**. The results of the radical reactions of the selenides **116-118** are summarised in Scheme 64.



Scheme 64

The substrate **119** underwent one carbon ring expansion to the Z-cycloheptenone **121**[131a]. Clearly, this is to be expected since E-cycloheptenes are only known as transient

intermediates and have been proposed to be involved in a number of photochemical reactions[131b]. In this case, even if the E- compound were produced, it would not survive the thermal conditions used for radical generation however, an alternative stepwise mechanism may also be invoked which does not require the involvement of strained intermediates and cannot be ruled out (Scheme 65). It is interesting to note that the double bond in this product does not move into conjugation with the carbonyl, as might have been expected, which serves as an indicator of the mildness of the ring expansion reaction.

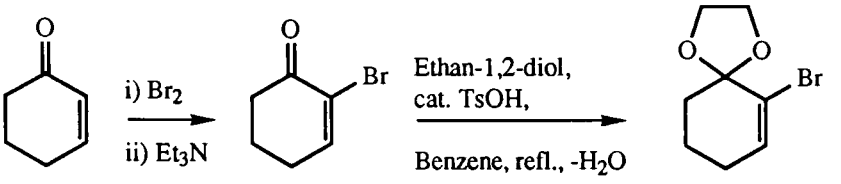


Scheme 65

II.1.4 Access to cis- substrates and their behaviour under radical conditions.

In order to complete this area of the project and provide a suitable comparison with the work described above, it was proposed to prepare a number of *cis*- substrates in the hope that *cis*- cycloalkenones would be produced. This represented a slightly more challenging task since the obvious approach requires cyclohex-2-enones substituted at the 2- position with a radical carrying side chain. It was then proposed that 1,4-addition of the stannyl anion would give rise to an enolate which could be protonated or alkylated *trans*- to the bulky stannyl substituent thus resulting in a *cis*- disposition of the tin function and the side chain[110]. The most general method for the preparation of such compounds was that of Smith[132a] in which the bromoketal **122** may be metallated with butyl lithium then alkylated

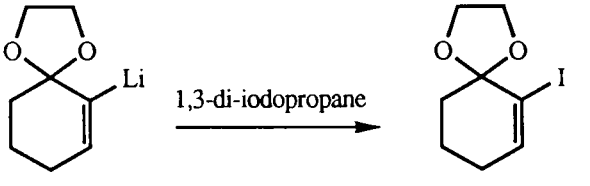
with a variety of electrophiles; hydrolysis of the resulting ketals was reported to furnish the enones. The requisite bromoketal **122** was prepared according to the literature[132b] in three steps from cyclohex-2-enone as shown (Scheme 66). Both the ketone **123** and the ketal **122** had identical spectroscopic data to that reported.



123, 81% **122**, 98%

Scheme 66

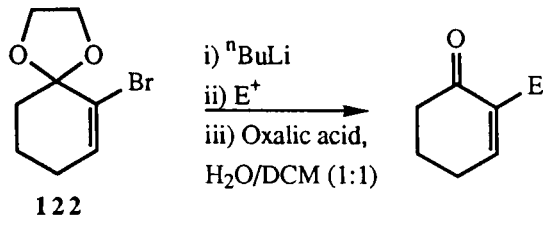
Attempts to alkylate the lithio- species **124** with 1,3-di-iodopropane failed for the reasons discussed above (Section II.1.1); in this case it was possible to isolate the initially formed product, the iodoketal **125** (Scheme 67).



124 **125**, 95%

Scheme 67

Characteristic of this compound were the mass spectrum (267, MH^+, 100%) and the ^1H n.m.r. spectrum (δ 6.70, 1H, t, *J* 4.0Hz, C<u>H</u>=). In all other cases the alkylations were successful resulting in ketals **126-129** in high yield. Application of acid hydrolysis conditions to these ketals effected the clean removal of the protecting group to yield the enones **105, 130-132**. In each case the enones had characteristic i.r. data ($\nu_{max.}$ 1670-1680, C=C-C=O) and the resonance in the ^1H n.m.r. spectrum due to the olefinic proton moved significantly downfield (<u>ca</u>. δ 6.70). A summary of these results is given in Table 3.



122

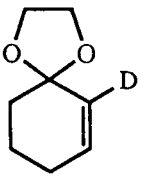
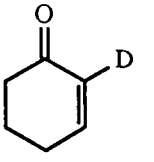
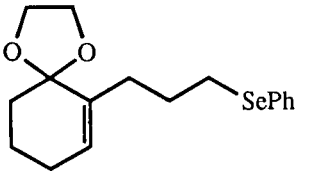
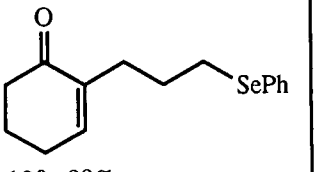
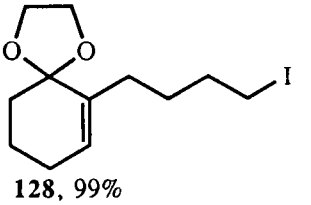
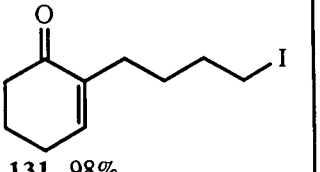
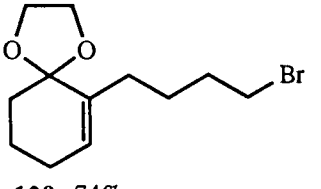
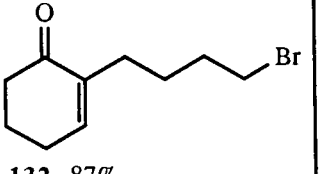
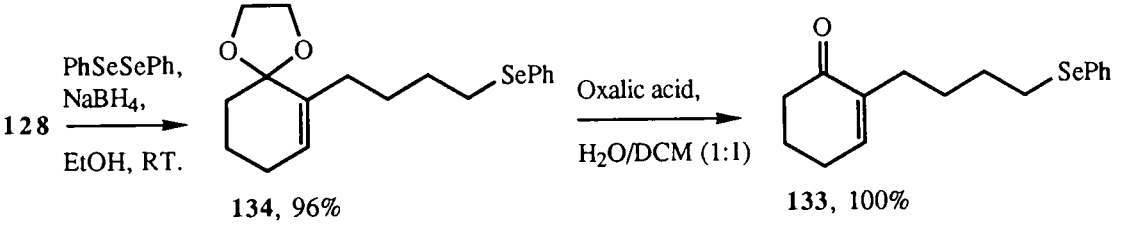
Electrophile	Alkylation product	Hydrolysis product
D_2O	 **126**, 87%	 **105**, 95%
1-Iodo-3-phenylseleno-propane **111**	 **127**, 69%	 **130**, 98%
1,4-Di-iodobutane	 **128**, 99%	 **131**, 98%
1,4-Dibromobutane	 **129**, 74%	 **132**, 87%

Table 3

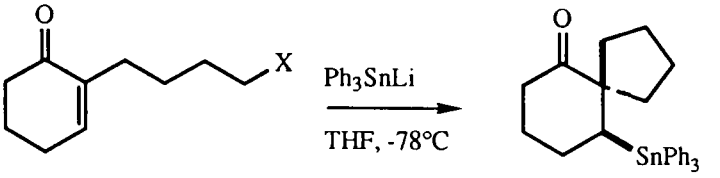
The final substrate **133** was produced from the ketal **134** as shown in Scheme 68.



134, 96% **133**, 100%

Scheme 68

The reaction of triphenylstannyl lithium with the enone **131** resulted in rapid intramolecular alkylation of the enolate at -78°C to give the spiro- compound shown (Scheme 69). This material (identified on the basis of ^{1}H and ^{13}C n.m.r. and mass spectral data) was also obtained in the reaction of triphenylstannyl lithium with the enone **129**, although in rather lower yield.



129, X=Br
131, X=I

135, 92% (X=I)
variable (X=Br)

Scheme 69

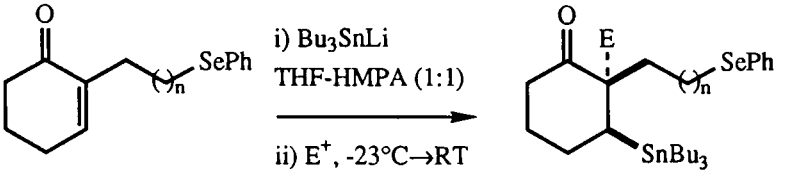
The two 2-phenylselenoalkylcyclohex-2-enones **130** and **133** were, however, useful substrates since 1,4-addition could be effected albeit at a higher temperature (-23°C) for 2h in the presence of HMPA as co-solvent. The resultant enolates could then be quenched (water, deuterium oxide, or methyl iodide) to give the *cis*- compounds **136-141** shown (Table 4). The spectroscopic data of each of these compounds was very similar to those of the corresponding *trans*- analogues, however, two pieces of evidence were particularly characteristic:

(i) $^{3}J_{Sn\text{-}C}$ satellites in the carbonyl resonance of the ^{13}C n.m.r. spectra were generally smaller than the corresponding values for the *trans*- substrates (see experimental section) and were in agreement with those values reported for similar systems[110,133].

(ii) In the case of substrates **138** and **141**, the singlets due to $C\underline{H}_3$- in the ^{1}H n.m.r. spectra were shifted significantly compared to the corresponding signals in the spectra of the *trans*- cases.

"*trans*- 3"	**118**	1.05
"*cis*- 3"	**141**	0.96
"*trans*- 4"	**98**	1.13
"*cis*- 4"	**138**	1.00 (a signal at 1.08 indicated the presence of the *trans*- isomer, ≈10%).

It can be seen from Table 4 that the attempted preparation of the *cis*- 2-carbomethoxy derivative failed due to exclusive *O*-alkylation to give enol carbonate **139**. Although the use of Mander's reagent[134] is known to circumvent this problem the use of this protocol has not been attempted.



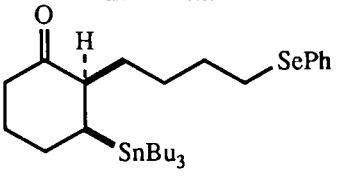
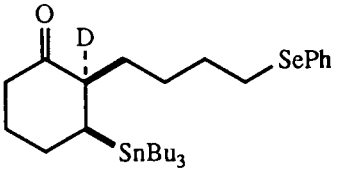
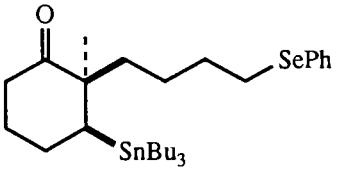
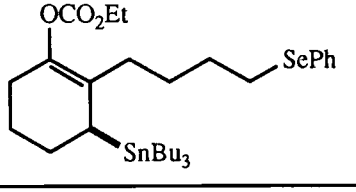
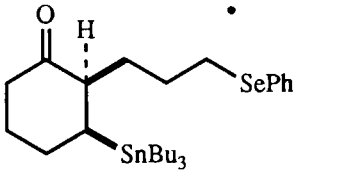
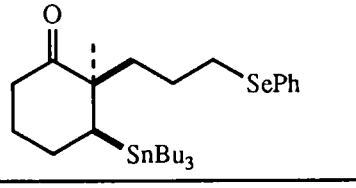
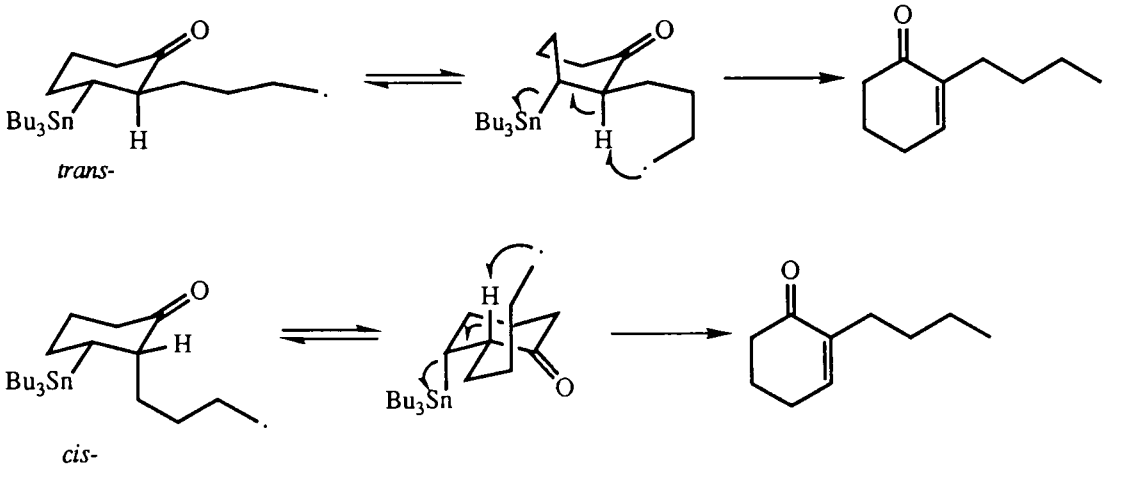
Electrophile	n	Product	No., Yield
H_2O	4		**136**, 51%
D_2O	4		**137**, 62%
MeI	4		**138**, 60%
EtOCOCl	4		**139**, 52%
H_2O	3		**140**, 60%
MeI	3		**141**, 74%

Table 4

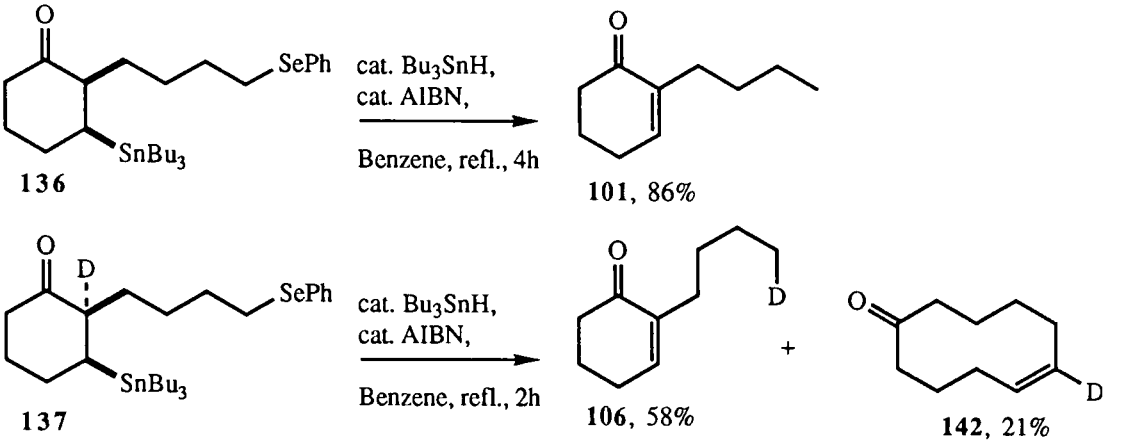
These *cis*- compounds were subjected to the radical conditions which were found to induce ring expansion (or otherwise) in the *trans*- series. From compound **136** only the eliminated product **101** was obtained which acts as a comparison with the result of radical reaction of *trans*- analogue **97** in which a significant proportion of ring expanded material was also observed. A plausible explanation for this observation is the relative ease with which *cis*- compound **136** can attain a *trans*- diaxial arrangement of H- and Bu_3Sn- required for the most rapid intramolecular reductive elimination. In the *trans*- case this arrangement is impossible however *syn*- elimination is facilitated if a boat conformation is adopted such that only one bulky group occupies a disfavoured axial position (Scheme 70).



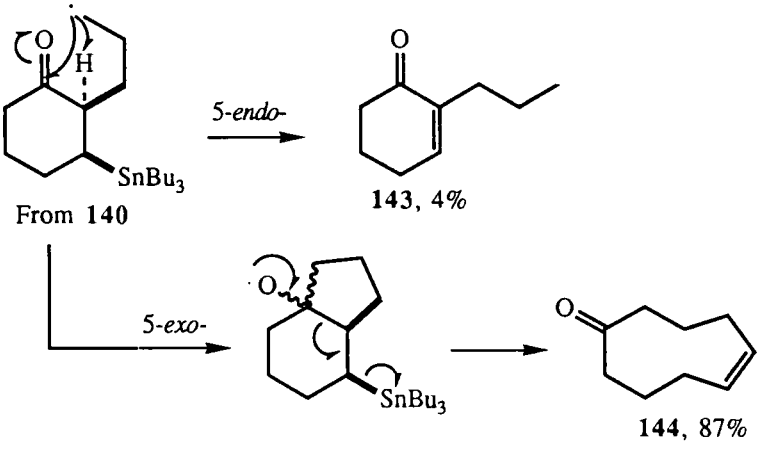
Scheme 70

An isotope effect also exists in this case as evidenced by the formation of the ring expanded product **142** in addition to isomer **106** albeit in low yield. These two results are summarised below (Scheme 71).

Interestingly, the three carbon ring expansion of substrate **140** proceeded very efficiently resulting in only a small proportion of the eliminated compound **143**. This result agrees with Baldwin's rules[135] in that it constitutes a further example of a preference for the 5-*exo*- over the 5-*endo*- mode of reaction (Scheme 72) (c.f. homologue **136** in which 6-*exo*- and 6-*endo*- compete).

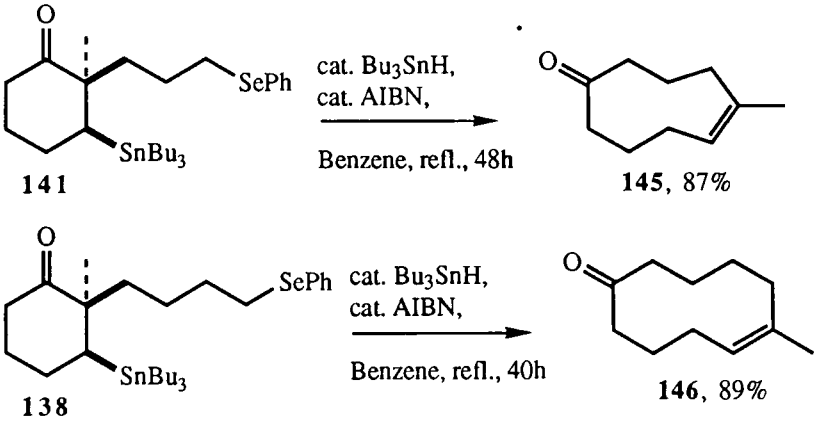


Scheme 71



Scheme 72

In the case of substrates **141** and **138** these considerations cease to be relevant; ring expansion was found to occur in high isolated yield (Scheme 73).

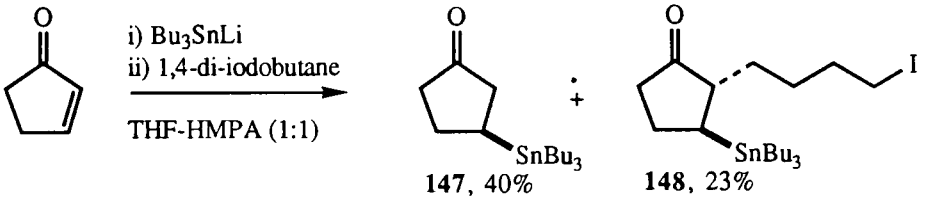


Scheme 73

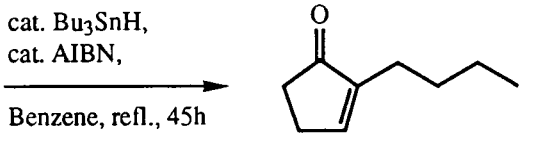
In all of these cases, the ring expanded products had been previously reported; the spectral data of each product was in agreement with the literature values[136]. These results[137] indicate the feasibility of one, three, and four carbon ring expansion reactions of cyclohexanone derivatives giving seven, nine, and ten membered rings, respectively, with retention of stereochemical integrity. Further studies were proposed to extend the methodology to different starting ring sizes, alternative fragmentation pathways, and its application to natural product synthesis (Section I.4).

II.1.5 Extension to starting ring sizes other than six membered.

The 1,4-addition/alkylation reaction with cyclopent-2-enone was also attempted. With 1,4-di-iodobutane as the electrophile alkylation did not proceed to completion, a significant yield of 3-tributylstannylcyclopentanone **147** being isolated (40%) in addition to the required compound **148**. Once more the product **148** was identified both on the basis of ^{1}H n.m.r. (δ 3.19, 2H, t, C$\underline{H_2}$I) and mass specrometry (428, M^+-I·, 100%). This material was subjected to the usual ring expansion conditions, however, after a reaction time of 45h only the reductively eliminated product **149** was obtained in 87% yield (Scheme 74). This result may reflect the lowered reactivity of five-membered ketones towards nucleophilic attack (compared with cyclohexanones) due to the increased s-character of the carbonyl group, its relatively hindered nature, and the eclipsing interactions of the C-O bond with adjacent hydrogen atoms which would occur on addition[138].



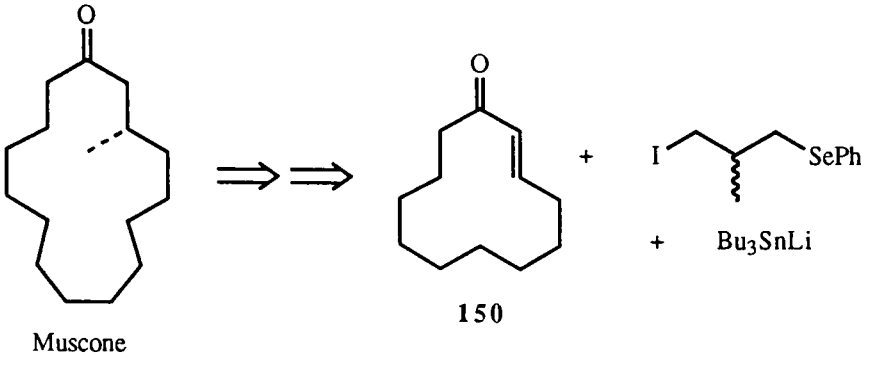
147, 40% **148**, 23%



149, 87%

Scheme 74

With rings larger than six-membered, it was proposed that it could in principle be possible to access such molecules as muscone[139] (see also Section I.3.2). In this case the fifteen membered ring in the natural product disconnects to the readily available cyclododec-2-enone **150** and a suitable three-carbon side chain as illustrated in Scheme 75.

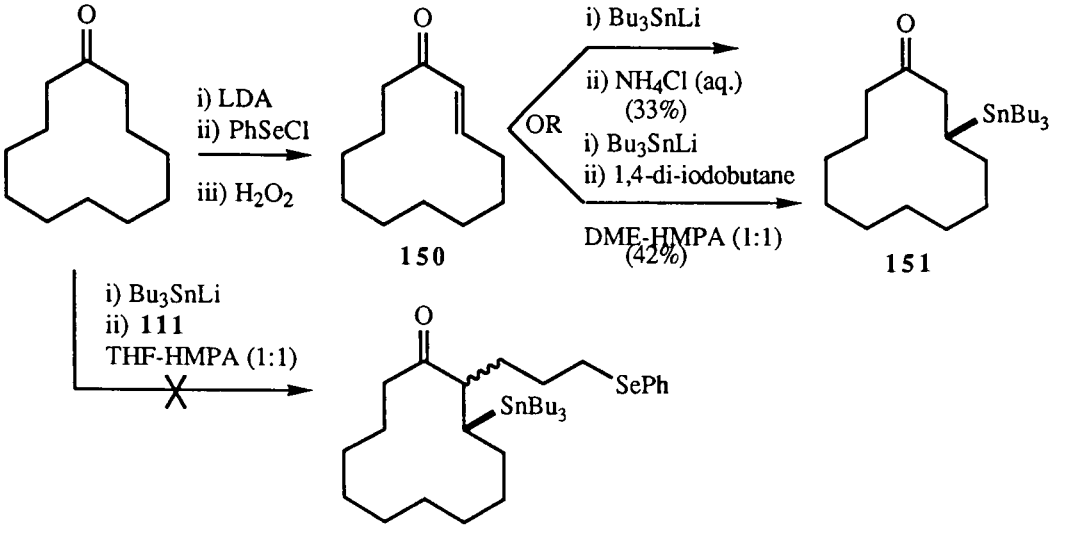


Scheme 75

The success of this proposal requires 1,4-addition of Bu_3Sn^- to cyclododec-2-enone **150** followed by alkylation of the resultant enolate, a procedure which had not been previously reported. Cyclododec-2-enone **150** was prepared by the procedure of Reich[140,124] and subjected to the standard addition-alkylation conditions using 1-iodo-3-phenylseleno-propane **111** as the electrophile in a model for the natural product synthesis. No tin-containing products derived from 1,4-addition could be isolated under these conditions, however, it was found that switching the solvent to DME and protonating the enolate gave 3-tributylstannylcyclododecanone **151** in moderate yield (33%). Using a mixture of DME and HMPA as the solvent and a 1,4-addition time of 1h at -23°C it was attempted to alkylate the enolate with 1,4-di-iodobutane; work-up and chromatography led only to the isolation of the stannane **151** but in improved yield (42%). These results are summarised in Scheme 76.

The decreased reactivity of this system towards both 1,4-addition of Bu_3Sn^- and enolate alkylation is suggested to be a result of the increased fluxionality of the ring resulting in highly sterically hindered reaction centres. Concurrent work in our group by Singh with seven membered enones has also presented problems and although alkylation

was possible yields were generally reduced in comparison with the six membered ring series[141].

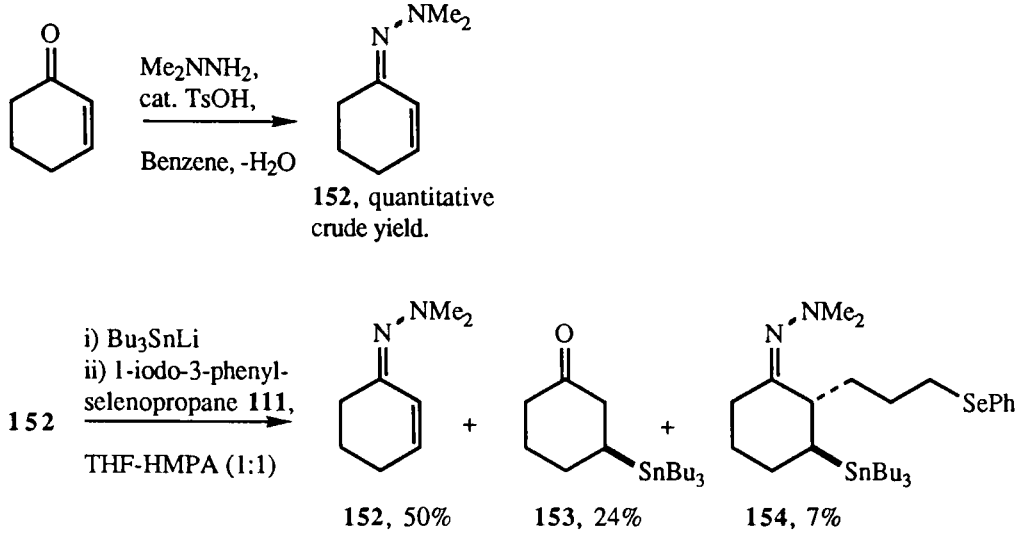


Scheme 76

A recent report[142] detailed the increased reactivity of α,β–unsaturated hydrazones both to 1,4-addition of Me_3SiLi and subsequent metallo-enamine alkylation. It was proposed that a similar effect may be observed in analogous tin chemistry and that the reactivity of the twelve membered ring system could be boosted to a useful degree by the preparation of the hydrazone. Unfortunately, model work on the six membered ring system failed to produce encouraging results; the hydrazone **152**, prepared by the method of Corey and Enders[143], was subjected to the addition-alkylation conditions found to work with cyclohex-2-enone (and which were analogous to those reported by Hudrlik[142]) with 1-iodo-3-phenylselenopropane **111** as the electrophile. The reaction was not clean; flash chromatography of the crude product afforded starting material **152** (50%), 3-tributyl-stannylcyclohexanone **153**[144] (24%), and only a low yield (7%) of the requisite compound **154** (Scheme 77).

Since the model work had produced discouraging results, the prospects of extending this methodology to twelve membered rings appeared bleak so further work

towards a synthesis of muscone was abandoned and all subsequent work was confined to derivatives of cyclohexanone.

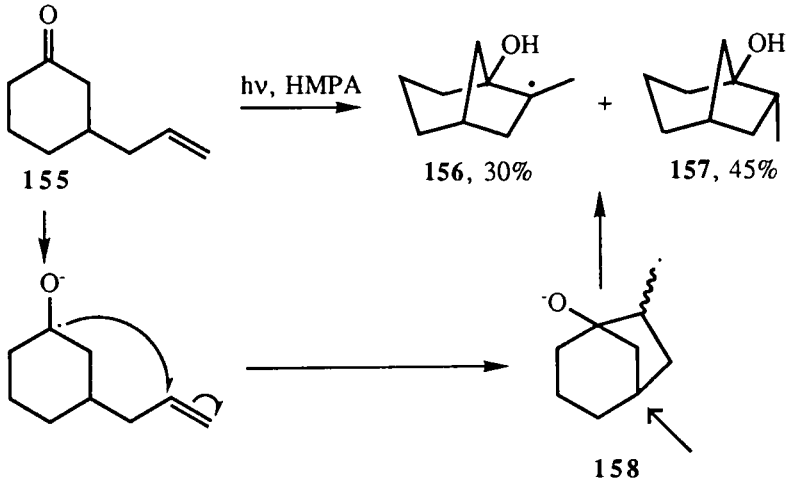


Scheme 77

II.2 Approaches to the synthesis of exomethylene cycloalkanones.

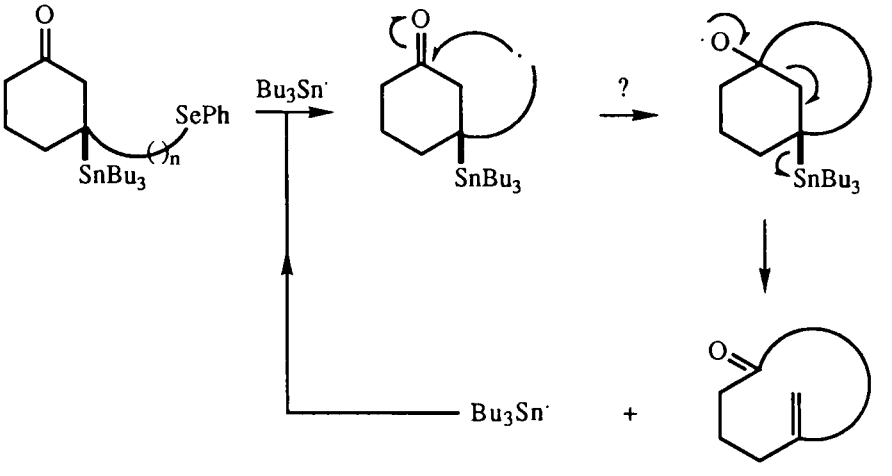
II.2.1 From 3,3-difunctionalised cyclohexanone derivatives.

A recent review by Mattay[145] included the photochemical conversion of 3-allylcyclohexanone **155** to the two isomeric bicyclic alcohols **156** and **157** shown in Scheme 78 for which a pathway involving electron transfer to the carbonyl group is suggested.



Scheme 78

In this reaction the intermediate alkoxy anion **158** is expected to be produced and it was envisaged that a suitably positioned tributylstannyl group (marked by →) could encourage collapse of an analogous alkoxyl radical to produce exomethylene cycloalkanones (Scheme 79). Once more the ejected $Bu_3Sn\cdot$ radical should allow a chain process, catalytic in tributyltin hydride, such that a radical precursor (e.g. PhSe-) could be used rather than less controllable photochemically induced electron transfer reactions.

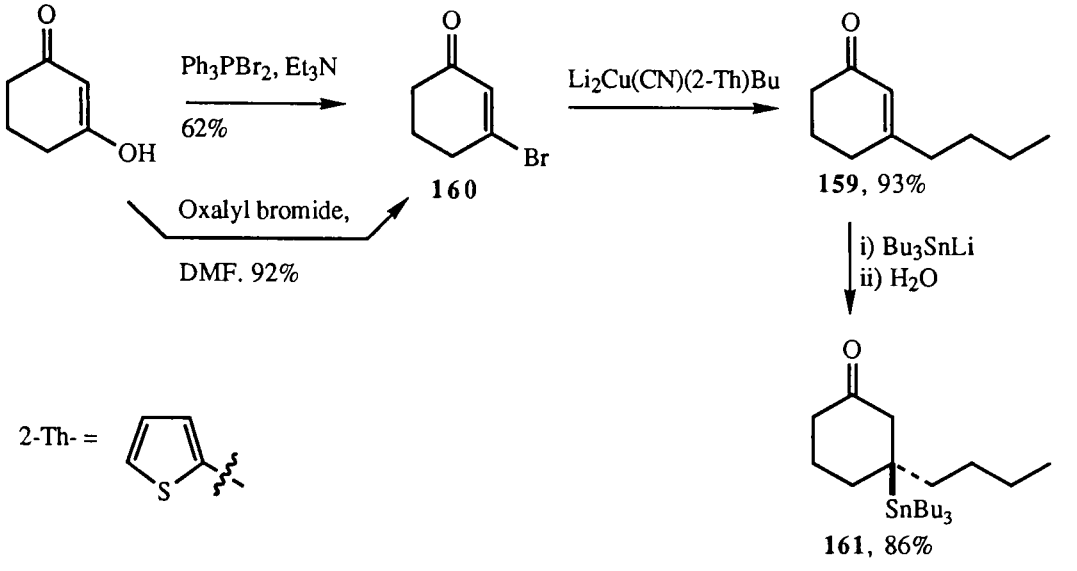


Scheme 79

The 3-tributylstannyl-3-phenylselenoalkylcyclohexanones would be expected to be prepared by 1,4-addition of Bu_3Sn^- to a 3-phenylselenoalkylcyclohex-2-enone, for which little literature precedent existed at the stage that this work was in progress. For this reason 3-butylcyclohex-2-enone **159** was prepared in two steps from cyclohexane-1,3-dione initially using the procedure of Piers[146] for the bromination reaction (later preparations of this compound utilised the recent procedure of Mewshaw[147] which gave much increased yields) and Lipshutz[148] for the addition-elimination reaction. The product **159** was produced from the bromide **160** in high yield (93%) exhibiting specroscopic data in full agreement with that reported for this compound[149].

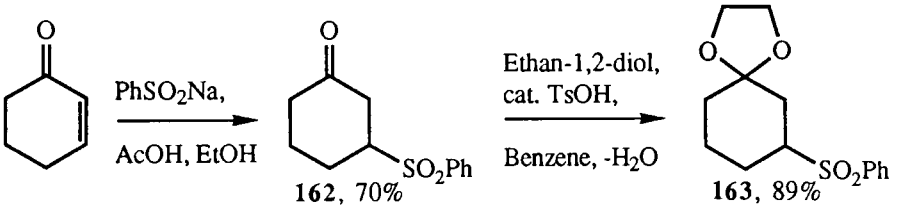
With a simple 3-substituted cyclohex-2-enone in hand 1,4-addition was attempted at -78°C for 2.5h followed by quenching with water at room temperature. The requisite stannane **161** was isolated in 86% yield showing a saturated C=O absorbtion in the i.r.

spectrum (1715cm^{-1}), correct mass spectral data (387, M^{+}-^{n}Bu·, ^{120}Sn, 67%) and ^{1}H n.m.r. in agreement with that expected. This model work is summarised in Scheme 80.



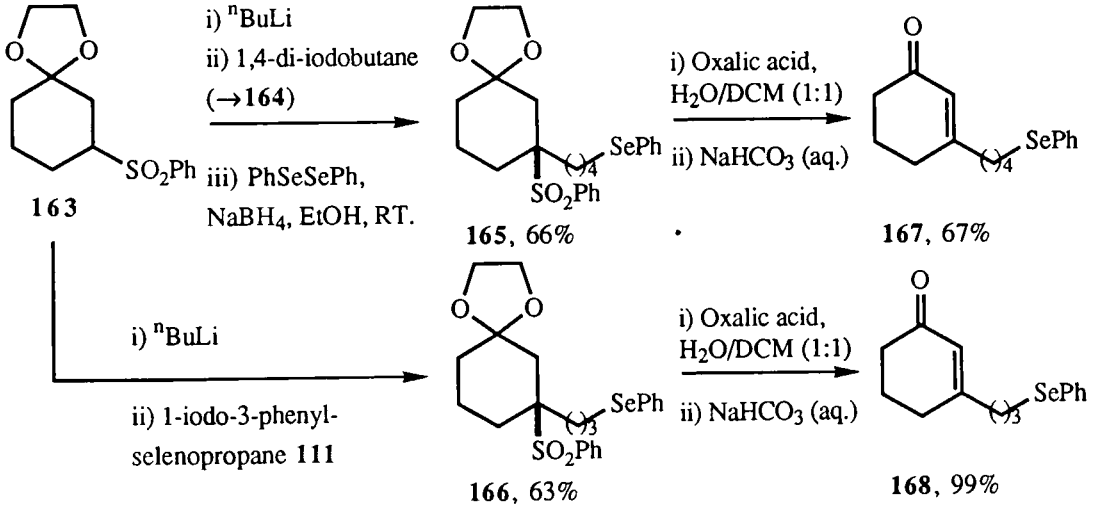
Scheme 80

Since this type of chemistry was shown to be feasible, the radical precursors (Scheme 79) with n=3 and 4 were prepared. An alternative access to the intermediate cyclohexenones was favoured since it was believed that putative lithio-alkylselenides ($Li(CH_2)_nSePh$) required in projected cuprate reactions may not be stable entities, especially since C-Se bond cleavage has been shown to occur in the presence of certain organolithiums[150]. The procedure of Dolby[151], in which the carbonyl-protected sulphone **163** is used as a 3-lithiocyclohex-2-enone equivalent, allowed the generality required to access a number of substrates. The ketal sulphone **163** was prepared in two steps from cyclohex-2-enone and exhibited spectroscopic properties in close agreement with the literature values[151] (Scheme 81).

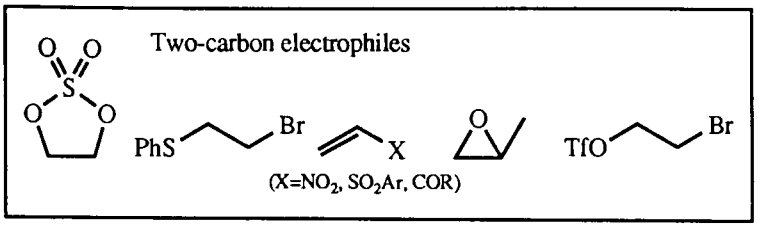


Scheme 81

Although from the above report[145], it would seem preferable to alkylate initially with a two-carbon unit, this was known to be problematical due to competing ethylene elimination although exceptions known to be reliable two-carbon electrophiles[152] are given in Scheme 82. For this reason initial work was restricted to the preparation of three- and four-carbon side chains since the appropriate electrophiles were in hand. The sulphone **163** was deprotonated with ^{n}BuLi, in the presence of an indicator to allow the formation of the anion to be monitored, and alkylated with either 1-iodo-3-phenylselenopropane **111** or 1,4-di-iodobutane to give the products as viscous gums which were extremely difficult to purify completely. The iodide **164** was converted to the selenide **165** by the standard procedure and the selenides **165** and **166** subjected to sequential acidic hydrolysis of the ketal function and basic elimination of the phenylsulphonyl group to form the cyclohex-2-enones **167** and **168**. These products were mobile oils and could be readily purified by chromatography exhibiting i.r. spectra (1670cm^{-1}, α,β-unsaturated C=O) and ^{1}H n.m.r. spectra (δ 5.87, 1H, C<u>H</u>=, δ 2.91, 2H, t, C<u>H</u>$_2$SePh) which were particularly characteristic. The moderate yield of the enone **167** probably reflects an accumulation of impurities in the ketal **165**. This work is summarised in Scheme 82.

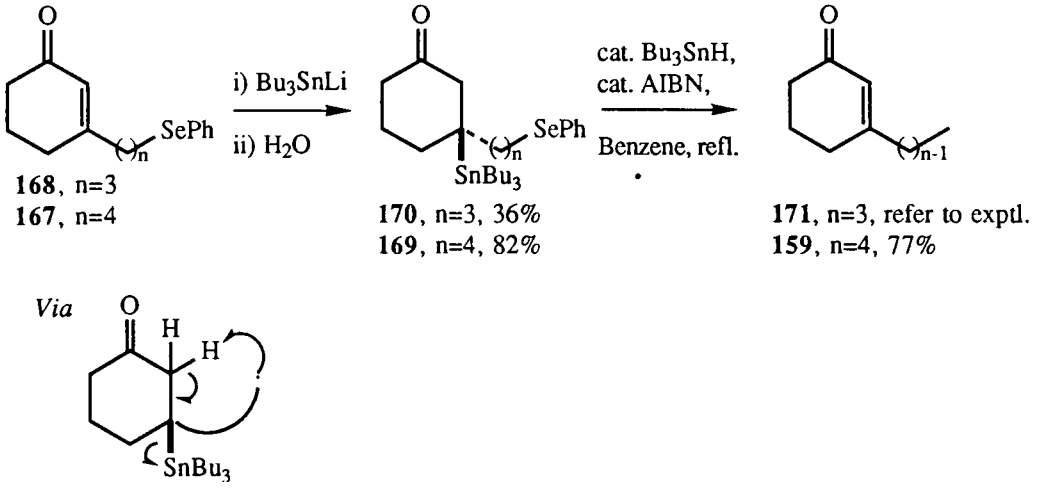


Scheme 82



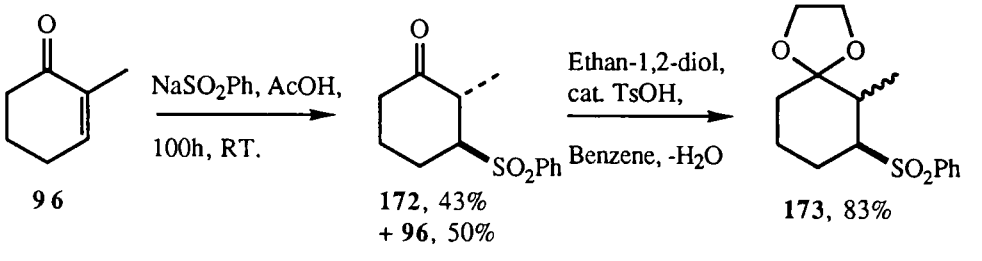
Scheme 82 (contd.)

With the enone **167**, 1,4-addition of Bu_3Sn^- once more occurred in high yield; the product **169** gave a mass spectrum (601, MH^+, 23%) having isotope peaks in the molecular ion cluster in excellent agreement with the calculated values for this molecular formula and exhibited the expected i.r. and ^1H n.m.r. spectroscopic properties. Although 1,4-addition to enone **168** was also successful, the yield of the product **170** was much reduced (36%), possibly a reflection of the slightly more sterically crowded nature of the starting enone. Both of these stannanes were subjected to conditions previously found to induce radical reaction, however, in neither case were the desired ring expanded products observed, the substrate **169** producing 3-butylcyclohex-2-enone **159** (77%) which was identical to material produced previously (*vide supra*). The stannane **170** afforded only 3-propylcycohex-2-enone **171**[153] contaminated with 2,3-dicyano-2,3-dimethylbutane (arising from recombination of isobutyronitrile radical). A summary of this work is given Scheme 83.



Scheme 83

In order to prevent hydrogen atom abstraction from the 2-position of the ketone the sequence was repeated beginning with 2-methylcyclohex-2-enone **96** with the objective of methylating the enolate, produced from 1,4-addition of Bu_3Sn^-, to fully block the 2-position. The analogous sulphone **173** was more difficult to prepare than the sulphone **163** since the initial reaction of sodium phenylsulphinate with the enone **96** was a far less efficient process. Neat acetic acid as the solvent and an extended reaction time (100h) were required to reach a synthetically useful equilibrium which, even then, resulted in a 50% recovery of starting material **96**. The ketone **172** was shown by ^1H n.m.r. to have a *trans*- configuration of the Me- and $PhSO_2$- groups ($J_{H(2)H(3)}$ 12Hz), however, on preparation of the ketal **173** doubling of certain peaks in the ^1H n.m.r. spectrum indicated a mixture of diastereomers (Scheme 84).



96

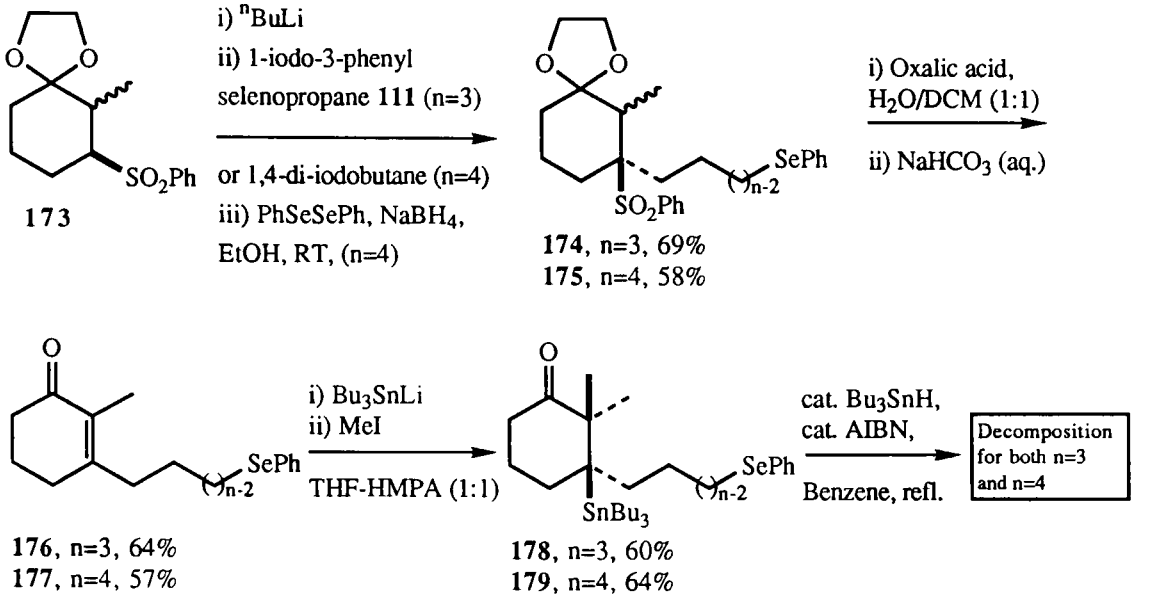
172, 43%
+ **96**, 50%

173, 83%

Scheme 84

This sulphone was alkylated with 1-iodo-3-phenylselenopropane **111** and 1,4-di-iodobutane as before to give products consisting of diastereomeric mixtures which were extremely closely running on t.l.c. and separation was not attempted. Deprotection of the ketals and elimination of the sulphone groups afforded the enones **176** and **177** in moderate yield; both enones gave an absorbtion in the i.r. spectrum corresponding to an α,β-unsaturated ketone (1665cm^{-1}) and showed resonances in their ^1H n.m.r. spectra indicative of the vinyl $C\underline{H}_3$- grouping (**176**: δ 1.87. **177**: δ 1.75). Both enones were subjected to 1,4-addition of Bu_3Sn^- (1h, -78°C) and the resulting enolates quenched with an excess of methyl iodide in the presence of HMPA. The products were isolated in a pure form by chromatography, giving the expected spectroscopic properties; for **178** ^1H n.m.r. (δ 1.01 and 1.12, 2x$C\underline{H}_3$-), for **179** ^1H n.m.r. (δ 1.03 and 1.14, 2x$C\underline{H}_3$-).

Unfortunately exposure of these substrates to ring expansion conditions led to no useful reaction. Prolonged heating of the substrates in benzene, with regular additions of AIBN and tributyltin hydride, resulted in eventual decomposition to unidentifiable material (Scheme 85).

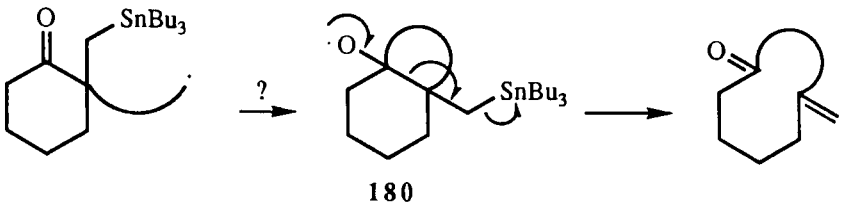


Scheme 85

It was presumed that the presence of the two methyl groups rendered the carbonyl group sterically inaccessible to attack by the radical-carrying side chain so an alternative approach was sought.

II.2.2 From 2,2-difunctionalised cyclohexanone derivatives.

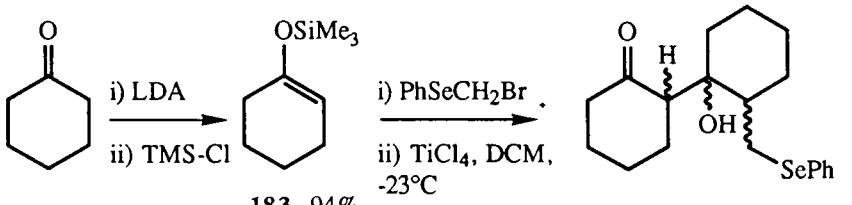
An alternative arrangement of radical-carrying side-chain and β-stannyl ketone was also envisaged to allow access to exomethylene cycloalkanones (Scheme 86). The proposed ring expansion process would proceed *via* a fused bicyclic alkoxyl radical **180** rather than the previously proposed bridged bicyclic analogue described in Scheme 79 and was expected to be a more facile process.



180

Scheme 86

By analogy to the work in Section II.1 the precursor could become available through 1,4-addition-alkylation reaction of 2-methylenecyclohexanone **181**. Although this enone has been prepared using the classical Mannich procedure, *vide infra*, the so-formed product is always accompanied by varying amounts of dimeric material so it was proposed to extend the work of Paterson and Fleming[154], in which 2-(phenylthiomethyl)-cycloalkanones and lactones were prepared by Lewis acid catalysed reaction of cyclic trimethylsilyl enol ethers and phenylthiomethylchloride, to the selenium analogue in the hope that the so-formed 2-(phenylselenomethyl)-cyclohexanone **182**[155] could be decomposed to the enone under very mild conditions. Unfortunately, use of the protocol of Fleming[154] with bromo-phenylselenomethane **110** and 1-trimethylsilyloxycyclohexene **183** never resulted in the requisite ketone **182** but always produced, in varying proportions depending on exact conditions, the compounds **184** and **185** arising from reaction of the ketone **182** with the enol ether in a Lewis acid catalysed aldol reaction for which a representative case is shown (Scheme 87).



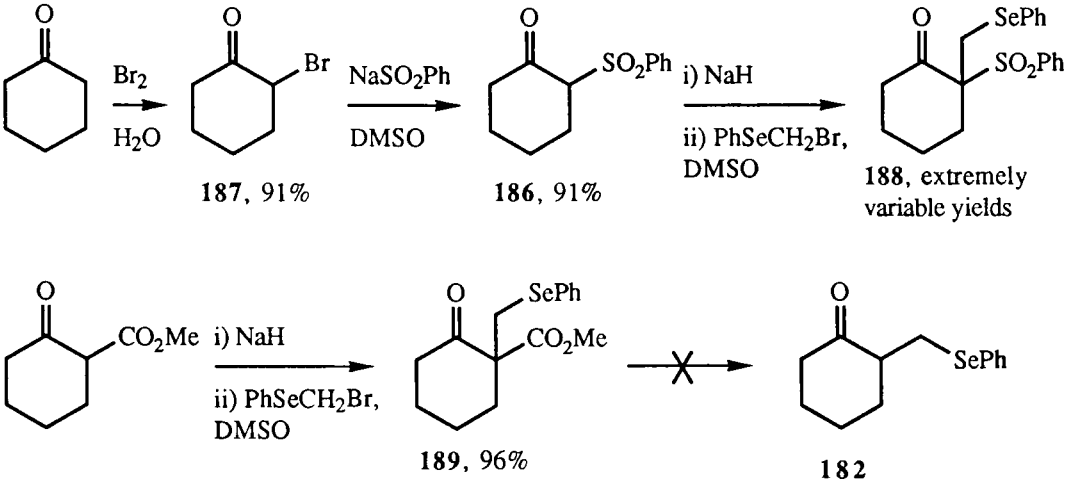
183, 94%

184 (39%), **185** (18%).
Diastereomeric mixture.

Scheme 87

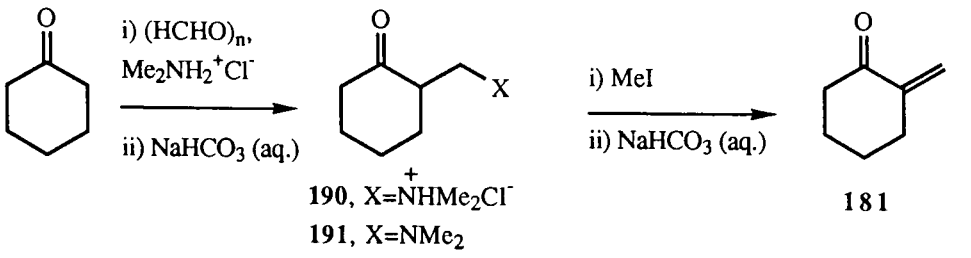
Alternatively a 2-phenylselenomethyl group may be introduced *via* direct alkylation of an activated cyclohexanone. 2-Phenylsulphonylcyclohexanone **186**[156] was produced from 2-bromocyclohexanone **187**[157] and its alkylation with bromo-phenylselenomethane

110 attempted. A variety of conditions were tried however the only success was had with sodium hydride/DMSO as the base; even under these conditions yields of compound **188** were extremely variable and generally low, the alkylating agent seemingly prone to alternative reactions in this system. Using 2-carbomethoxycyclohexanone, alkylation was found to be extremely efficient to yield the selenide **189** in 96% yield. The $C\underline{H}_2SePh$ protons were easily identifiable in the ^1H n.m.r. spectrum (δ 3.18 and 3.33, 2H, ABq, *J* 13Hz) and the mass spectrum confirmed the molecular composition (327, MH^+, ^{80}Se, 100%). Unfortunately, this material could not be cleanly decarboxylated to the requisite ketone **182**, providing decomposition products instead, so this approach, too, was abandoned. (Scheme 88).



Scheme 88

Since alternatives to the classical Mannich procedure were not forthcoming the literature protocol[158] was followed to produce the extremely labile enone **181** as shown in Scheme 89. This material was readily identified by its i.r. (1725 and 1695cm^{-1}) and ^1H n.m.r. spectra (δ 5.13 and 5.82, 2H, $C\underline{H}_2$=) but was found to be unstable at room temperature, rapidly dimerising on isolation.



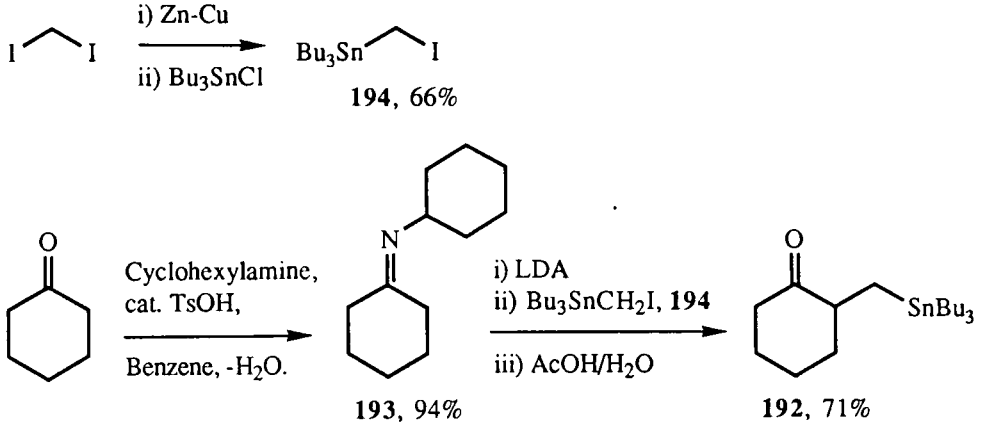
190, X=$\overset{+}{N}HMe_2Cl^-$
191, X=NMe_2

181

Scheme 89

Although the enone **181** was always prepared immediately prior to use and stored refrigerated, this instability proved problematic since all attempts to effect 1,4-addition of Bu_3Sn^- afforded extremely low yields of stannylated compounds; large amounts of dimerised enone and polymeric material generally being observed, In no case was it possible to effect <u>any</u> alkylation of the enolate with 1,4-di-iodobutane so no radical precursors could be accessed from this enone.

Work by Isoe[100] included the preparation and subsequent reaction of 2-tributylstannylmethylcyclohexanone **192**. It was therefore proposed that conditions might be found in which this ketone could be alkylated specifically at the more hindered α-position to produce the desired substrates. Following a modified literature procedure[159] the ketone **192** was prepared in 71% yield from the imine **193**[160] and the iodide **194**[161] both of which were prepared as detailed in Scheme 90.



194, 66%

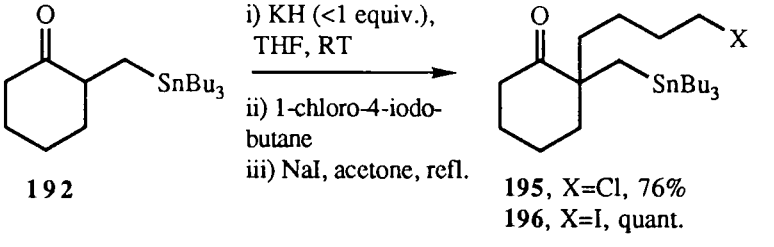
193, 94%

192, 71%

Scheme 90

The ketone **192**, a colourless oil, was identified on the basis of its i.r. (1710cm^{-1}, C=O), its ^{1}H n.m.r. (2.20-2.70, 3H, m, C<u>H</u>$_2$COC<u>H</u>R-) and its mass spectra (345, M$^+$-^{n}Bu·, ^{120}Sn, 100%) and was easily prepared on a large scale.

Although a number of procedures exist for the regiospecific formation and alkylation of enolates at the more hindered position[162] one of the most successful is that due to Negishi[163] in which potassium hydride is used as the base in the presence of triethyl borane. It was found that the Lewis acidic nature of the borane was sufficient to induce decomposition of the stannane **192** and little or no requisite product was isolated in a number of attempts. Fortunately simply dispensing with the borane, i.e. using potassium hydride alone (<1 equiv.) in THF at room temperature with an equilibration period of 1h, resulted in an enolate system which could be alkylated exclusively at the more hindered position. Thus, with 1-chloro-4-iodobutane as the alkylating agent the requisite precursor **196** could be produced after simple Finkelstein reaction[164] to convert the chloride to the more reactive iodide (Scheme 91).

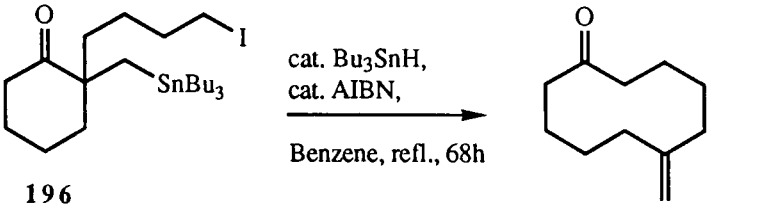


192

195, X=Cl, 76%
196, X=I, quant.

Scheme 91

The intermediate chloride **195** was shown to be solely the desired regioisomer by (i) t.l.c. and (ii) ^{1}H n.m.r. which showed a clean 2H multiplet at δ 2.33-2.45 corresponding to C<u>H</u>$_2$CO-; no evidence of the alternative regioisomer was observed in the crude product. The iodide **196** was subjected to radical reaction conditions and was found to undergo a clean reaction to a single product. The process was very slow, however, and after 68h at reflux starting material **196** (27%) was recovered along with the desired 6-methylene-cyclodecanone **197** (Scheme 92). This compound has been reported previously[165] and the literature data corresponded to that obtained for material prepared by this new method.

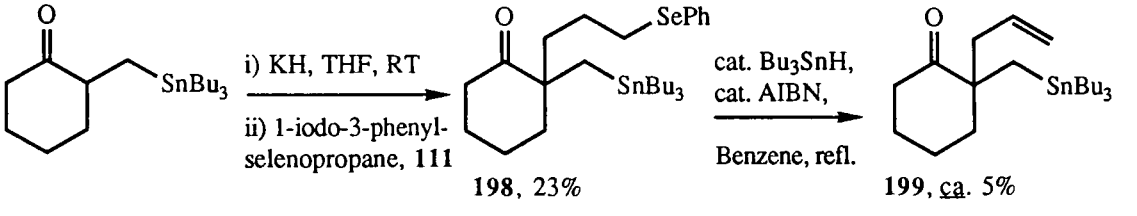


196

197, 56%
[77% based on
recovered 196 (27%)]

Scheme 92

Application of this protocol to a three-carbon ring expansion was, however, far less successful. Although alkylation of the ketone **192** with 1-iodo-3-phenylselenopropane **111** did proceed, the isolated yield of the selenide **198** was surprisingly low (23%), much unreacted or protonated starting material being recovered. The material obtained from this reaction was not found to undergo useful reaction under the radical conditions previously employed and this alkylation was never repeated and therefore remains unoptimised. After a reaction period of ca. 1 week the phenylseleno group began to eliminate and on chromatography of the crude residue no ring expanded products could be observed, only starting material **198** and the allyl derivative **199** in very low yield (Scheme 93).



198, 23%

199, ca. 5%

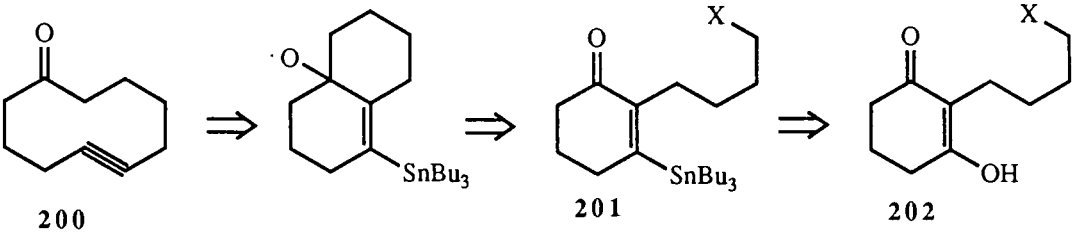
Scheme 93

This result did not bode well for a general ring expansion process so attention was turned towards the preparation of medium ring compounds containing a triple bond, *vide infra*.

II.3 Approaches to the synthesis of medium rings containing C-C triple bonds.

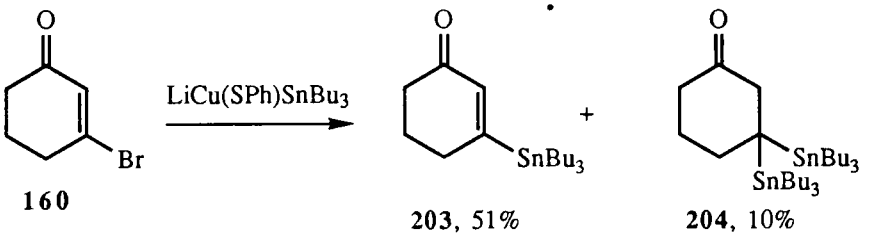
II.3.1 Attempts to alkylate cyclohexane-1,3-dione at the 2-position.

For a ring expansion process to produce molecules containing a C-C triple bond, such as cyclodec-5-ynone **200** (c.f. Section I.2), the requirement is for a substrate **201** of the type shown, i.e. possessing a cyclohexenone system; this can be disconnected to a 2-alkylated cyclohexane-1,3-dione derivative **202** (Scheme 94).



Scheme 94

Piers[166] has established procedures for the preparation of 3-trialkylstannylcyclohex-2-enones from cyclohexane-1,3-dione and it was decided to test this chemistry with tributylstannyl reagents before embarking on synthetic routes to substrates such as **202**. The bromo-enone **160** (*vide supra*) was treated with the cuprate $Bu_3SnCu(SPh)Li$[166b] since Bu_3SnLi itself, by analogy with Me_3SnLi, would be expected to give competing bis-stannylation. In the event a small amount of the distannane **204** was isolated but was readily separated from the required product by chromatography (Scheme 95).



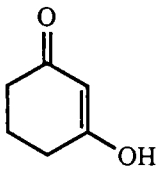
Scheme 95

The desired product **203** was identified by comparison of its spectroscopic data with that of the known[166b] trimethylstannyl analogue, displaying expected i.r. (1675cm^{-1}, α,β-

unsaturated C=O), ^{1}H n.m.r. (δ 6.26, 1H, t, C<u>H</u>=), and mass spectra (329, $M^{+-n}Bu\cdot$, ^{120}Sn, 92%). The distannane **204** showed a sharp singlet in the ^{1}H n.m.r. spectrum at δ 2.76 corresponding to C(2)<u>H</u>$_2$-; this resonance displayed ^{119}Sn and ^{117}Sn isotopomer satellites of 48 and 68Hz.

Since it was evident from this work that 3-tributylstannylcyclohex-2-enones were easily prepared, attention was turned to the synthesis of 1,3-diones possessing radical-precursor carrying side chains at the 2-position. Attempts to directly alkylate cyclohexane-1,3-dione with functionalised electrophiles produced results in agreement with previous literature precedent[167]. To summarise a large amount of work, it was found that use of standard protocols for 1,3-dione alkylation failed to produce usable substrates, reactions yielding either starting material, complex product mixtures, decomposition products, compounds derived from *O*-alkylation, and/or rearranged material. Although it was reported by Bittner[168] that alkylation with ω-hydroxy-1-iodoalkanes was possible, albeit in moderate yield, in our hands it was found that this methodology did not present a viable and reproducible synthetic procedure. A representative selection of alkylation attempts is given in Scheme 96. Clearly this approach was undesirable so alternatives had to be investigated.

It is known[170] that *C*-alkylation of cyclohexane-1,3-dione with allyl bromide is feasible since the initially formed *O*-alkylation product undergoes spontaneous rearrangement to the more stable *C*-alkylation product (Scheme 97). This reaction was repeated in the hope that 2-allylcyclohexane-1,3-dione **205** could be manipulated to a radical precursor by functionalisation of the allyl double bond. Conversion of this material to the bromide **206** by the method of Piers[146] proceeded in good yield (78%), the product displaying spectroscopic properties in accord with the literature[171]. Once more, use of $Bu_3SnCu(SPh)Li$ to convert the bromide to the stannane proved successful; although the reaction did not run entirely to completion, starting bromo-enone **206** was easily recovered and no <u>bis</u>-stannane was observed (Scheme 97).



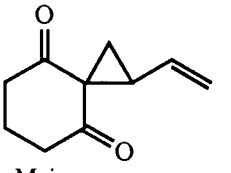
KOH/H_2O, 0°C,
Bromobutane
→ Recovered starting material

KOH/H_2O, Cu, 100°C,
1-iodo-4-propanol
→ No isolable products

K_2CO_3/DMSO,
1-iodo-4-propanol
→ Complex product mixture

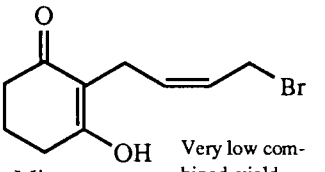
i) NaH/DMSO
ii) 1-iodo-4-propanol
→ Starting material plus a mixture of unidentified side-products

K_2CO_3/DMSO,
Z-1,4-dibromobut-2-ene
→



Major

+

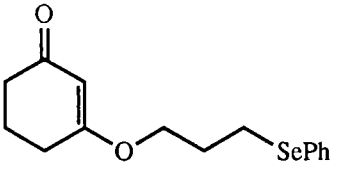


Minor

Very low combined yield.

$KOH/MeOH/H_2O$,
1-iodo-3-phenylseleno-propane **111**
→ Recovered starting material and unidentified compounds

K_2CO_3/DMSO,
1-iodo-3-phenylseleno-propane **111**
→

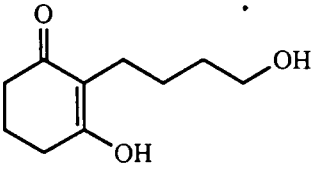


See ref. 169, 65%

KOH/H_2O, Cu-bronze,
E-1,4-dibromobut-2-ene
→ No isolable products

K_2CO_3, no solvent,
1,4-di-iodobutane
→ Complex mixture containing starting material

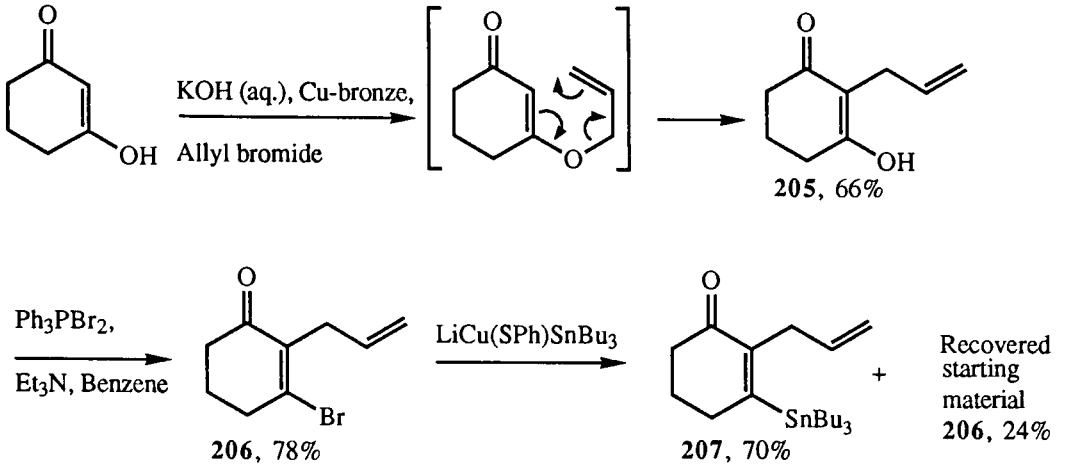
$KO^tBu/^tBuOH$,
1-iodo-4-propanol
→



<10%, (unstable)

Product mixture also consisted of *O*-alkylated and/or cyclised material

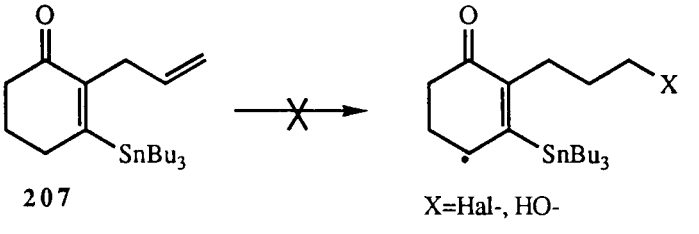
Scheme 96



Scheme 97

The stannane **207** was characterised by ^{1}H n.m.r. (δ 4.89–5.05, 2H, m, and 5.74-5.91, 1H, m, allyl), i.r. (1675cm^{-1}), and mass spectrometry (369, M$^+$-^{n}Bu·, ^{120}Sn, 100%), being a colourless oil which possessed long term stability if stored under argon at -20°C.

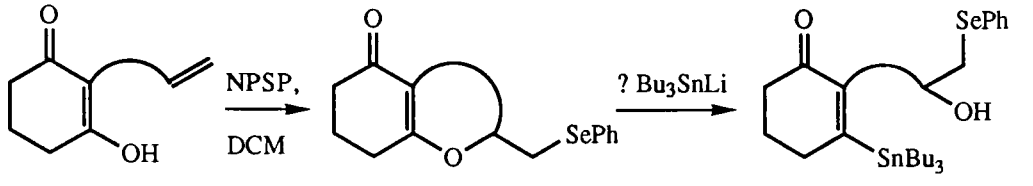
Unfortunately, all attempts to selectively functionalise the allyl C=C bond at the terminal position using borane chemistry[172] were dogged with products arising from Sn-C cleavage since, although hydroboration appeared successful, the oxidative conditions required for converting the C-B bond to useful functionality (e.g., KI/chloramine-T, I_2/NaOMe, H_2O_2/OH$^-$ etc.) were not compatible with the vinyl stannane moiety (Scheme 98).



Scheme 98

In the light of the sensitivity of the vinyl stannane function, and the fact that this synthesis resulted in only one side-chain length, alternatives were sought which could provide a more general solution to the problem of the preparation of 2-alkylated cyclohexane-1,3-diones.

Work by Ley[173] has illustrated the preparation of bicyclic compounds by the treatment of 2-(ω-alkenyl)-cyclohexane-1,3-diones with NPSP. It was hoped that treatment of such a bicyclic compound with Bu_3Sn^- would result in an addition-elimination reaction to produce compounds of the type **208** which would possess all the features required for this proposed route to medium ring alkynones (Scheme 99).

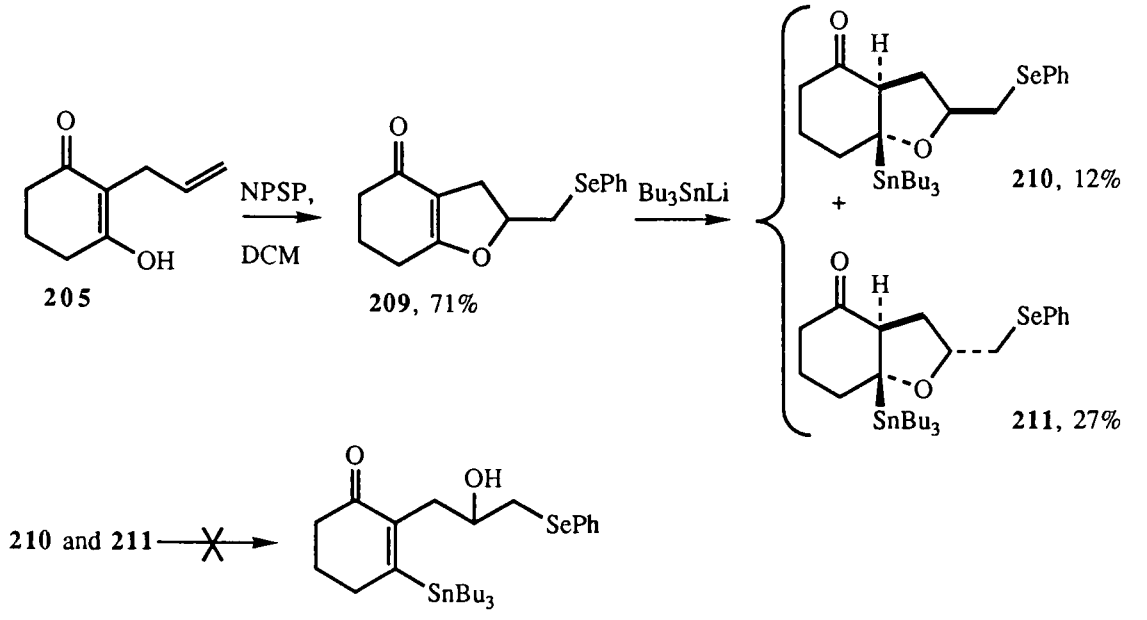


208

Scheme 99

Treatment of the dione **205** with NPSP in dichloromethane at -78°C resulted in a rapid seleno-cyclisation to the benzofuranone derivative **209** which was identified by comparison of its spectroscopic data with those of related compounds[173]. Tributylstannyl lithium was quenched at -23°C with a solution of this enone in THF; unfortunately, although 1,4-addition did proceed, elimination of RO^- failed to occur and two separable products **210** and **211** were isolated. Attempts to increase the reaction temperature to try to force elimination resulted in apparent re-elimination of the stannyl group, a large amount of starting material being recovered. The products **210** and **211** are thought to arise from *trans*- addition-protonation of Bu_3Sn^- to either face of the enone **209**, the phenylselenomethyl group exerting a small steric bias to one face. These products displayed the expected spectroscopic data, e.g., for **211** (major): ^1H n.m.r. (2.95 and 3.16, 2H, $C\underline{H}_2SePh$, 3.94-4.09, 1H, $C\underline{H}(OR)$-), i.r. (1710cm^{-1}), mass spectrum (599, MH^+, ^{120}Sn, 35%); the minor isomer **210** showed a shifted $C\underline{H}(OR)$- resonance in the ^1H n.m.r. spectrum (δ 4.32-4.47), other data being very similar to that obtained from the compound **211**. Further work to fully characterise these compounds was not carried out since it proved impossible to induce clean elimination of the alkoxide under a number of basic conditions (e.g., KO^{t}Bu/^{t}BuOH reflux, DBU/benzene reflux) which rendered this

material redundant for elaboration to radical precursors of the desired type. These results are detailed in Scheme 100.

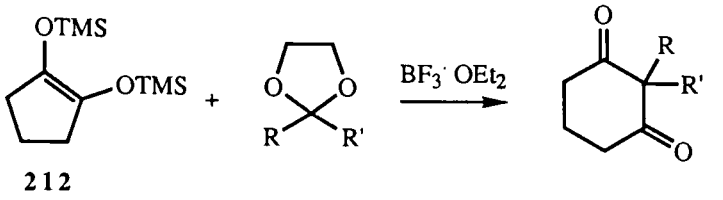


Scheme 100

Since all attempts to functionalise the dione **205** also met with failure, a rather different approach was required.

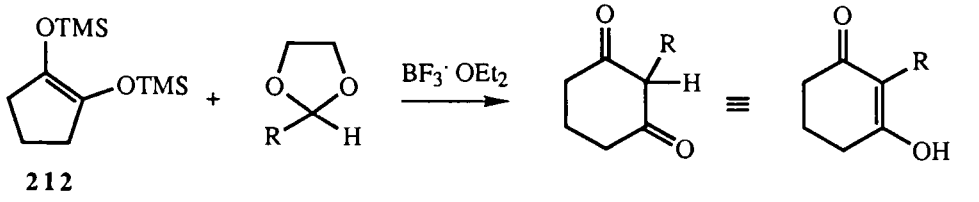
A recent literature report[174] described a one step procedure in which bis-trimethylsilyloxycyclopentene **212** was treated with a number of ketals in the presence of boron trifluoride to produce 2,2-disubstituted cyclohexane-1,3-dione derivatives. Although there exist literature precedents to the contrary[175] it was proposed to explore this chemistry using acetals in place of ketals in the hope that 2-monosubstituted cyclohexane-1,3-dione derivatives would be produced. The justification for this proposal was that previous failures to observe ring expansion using acetals was a result of the two step procedure previously used and that the new conditions [$BF_3 \cdot OEt_2$ as opposed to i) $BF_3 \cdot OEt_2$ ii) *p*-TsOH, benzene, reflux] might be amenable to the desired transformation (Scheme 101).

Known:



212

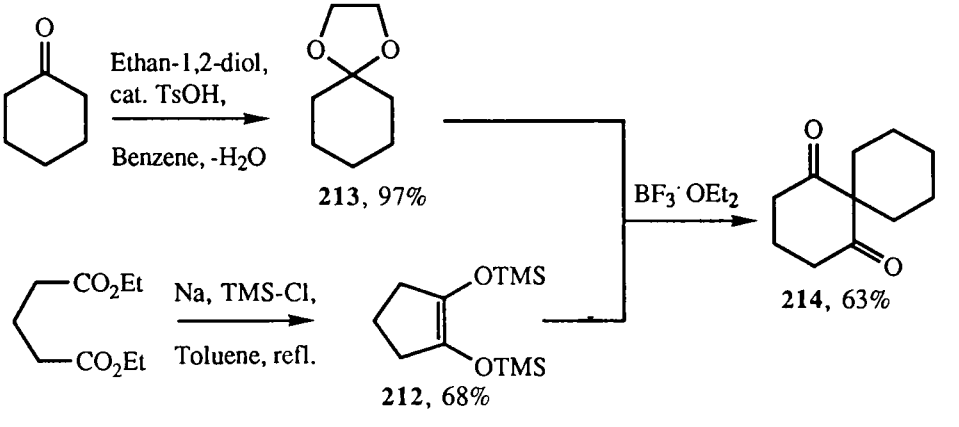
Proposed:



212

Scheme 101

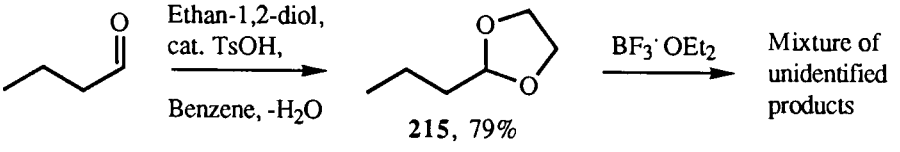
To establish the reaction conditions and to check the validity of the above work the ethylene ketal of cyclohexanone **213**[176] was prepared and its reaction with bis-trimethyl-silyloxycyclopentene **212** in the presence of $BF_3{\cdot}OEt_2$ was repeated as shown in Scheme 102. The reaction was successful, producing the expected spiro-diketone **214**[174] in good yield; this material was easily identified by ^1H n.m.r. (δ 2.69, 4H, t, 2xCH_2CO-) and i.r. spectroscopy (1730 and 1695cm^{-1}).



Scheme 102

It was then attempted to extend this methodology using initially a simple acetal as a model; for this reason 2-propyl-1,3-dioxolane **215**[177] was prepared and its behaviour to this reaction studied. The reaction was performed a number of times in an analogous fashion to that used for the ketal **213** above; in all cases the crude ^1H n.m.r. spectra were

identical but were seen not to arise from the desired six membered dione and were therefore not isolated (Scheme 103). For this reason this approach, too, had to be abandoned.



Scheme 103

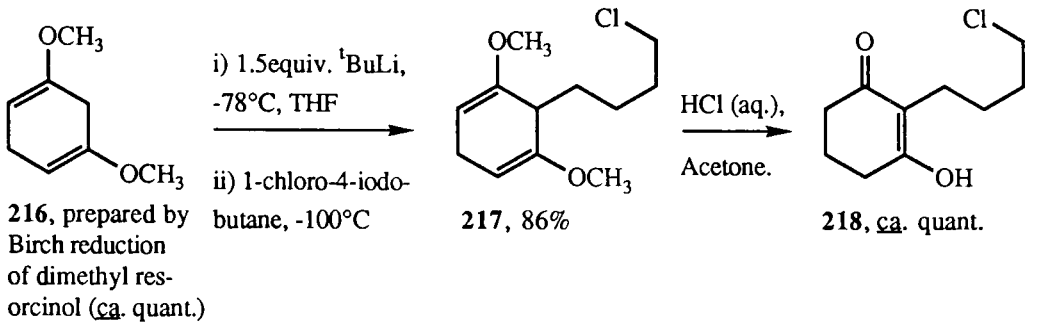
At no time was any of the desired cyclohexane-1,3-dione produced so this approach had to be discarded.

II.3.2 Alkylation of a cyclohexane-1,3-dione equivalent.

An extensive perusal of the literature revealed a general, direct method for the preparation of some simple 2-alkylated cyclohexane-1,3-diones. This involved the preparation of a masked dione, 2,4-dimethoxycyclohexa-1,4-diene **216**[178], its alkylation, and subsequent hydrolysis. This compound was prepared on a large scale (72mmol) by Birch reduction of dimethyl resorcinol in almost quantitative yield. Initial attempts to alkylate this diene followed the protocol of Piers[178] (1 equiv. ^{t}BuLi, THF-HMPA, -78°C) and with 1,4-di-iodobutane as electrophile resulted in poor yields. The HMPA present appeared to aid aromatisation of the starting material **216** and enhanced the production of di-alkylated products. Fortunately the use of an excess of ^{t}BuLi (1.5 equiv.), a lower temperature for the alkylation (-100°C), and omission of HMPA from the solvent mixture, combined with the use of 1-chloro-4-iodobutane resulted in an extremely clean alkylation, the desired product **217** being isolated in 86% yield. The product, a colourless oil, was readily identified on the basis of its ^{1}H n.m.r. [(δ 3.52 (2H, t, C<u>H</u>$_2$Cl), 3.56 (6H, s, 2xC<u>H</u>$_3$O-), 4.74 (2H, t, 2xC<u>H</u>=)] and mass spectra (229, MH$^+$, ^{35}Cl, 100%).

The procedure described by Piers[178] for the hydrolysis of this <u>bis</u>-enol ether was followed exactly and it was found that if the solvent (acetone) and the hydrochloric acid used in the reaction were deoxygenated prior to use a much cleaner reaction ensued, less aromatic by-products being isolated. Thus, exposure of the enol ether **217** to the literature

conditions resulted in rapid production of 2-(4'-chlorobutyl)-cyclohexane-1,3-dione **218**, a pale yellow solid [i.r. (3600-2500cm^{-1}, OH; 1760-1630cm^{-1}, C=O), ^{1}H n.m.r. (δ 2.48, 4H, t, 2x$C\underline{H}_2CO$-; 3.54, 2H, t, $C\underline{H}_2Cl$)]. This material was far more stable than the corresponding iodide (prepared during establishment of the alkylation conditions), which rapidly decomposed at room temperature, thus Finkelstein reaction was carried out at a later stage (Scheme 104).



216, prepared by Birch reduction of dimethyl resorcinol (ca. quant.)

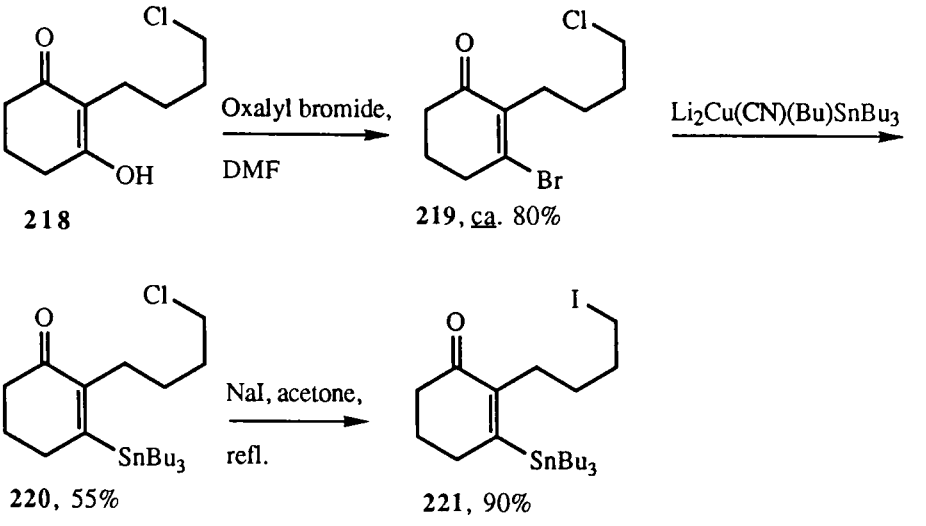
217, 86%

218, ca. quant.

Scheme 104

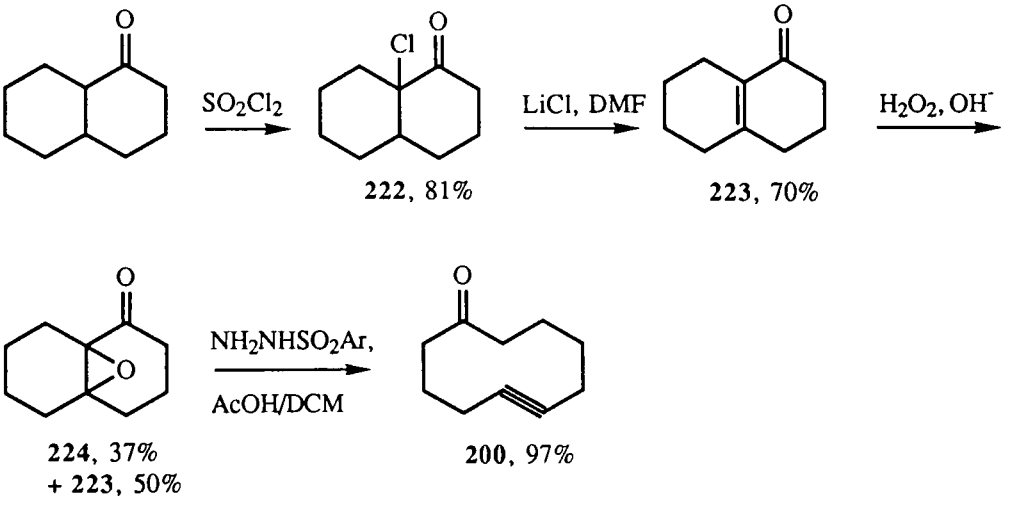
The dione **218** was converted to the vinyl bromide **219**; using the Piers[146] protocol low yields (30-40%) were generally obtained however use of the Vilsmeier reagent derived from *N,N*-dimethyl formamide and oxalyl bromide gave good (75-85%) yields of the bromo-enone **219** which was identified by comparison of its spectroscopic data with that of the bromo-enone **160**.

Recently Lipshutz[179] reported the use of a novel mixed stannyl cuprate, derived from $Li_2Cu(CN)Bu_2$ (2 equiv.) and tributyltin hydride, which was shown to deliver the tributylstannyl group to such systems as the enone **160** very cleanly and which was straightforward to employ in practice (Scheme 105). The vinyl stannane **220** was obtained using this reagent in 55% yield, the crude ^{1}H n.m.r. spectrum indicating some remaining starting material **219** (10-15%) which accounted for the lower than expected yield. This material, again identified by comparison of its spectroscopic data with that obtained for the stannane **203**, was converted to the iodide by heating in a saturated solution of sodium iodide in acetone giving the radical precursor **221** in 90% yield (Scheme 105).



Scheme 105

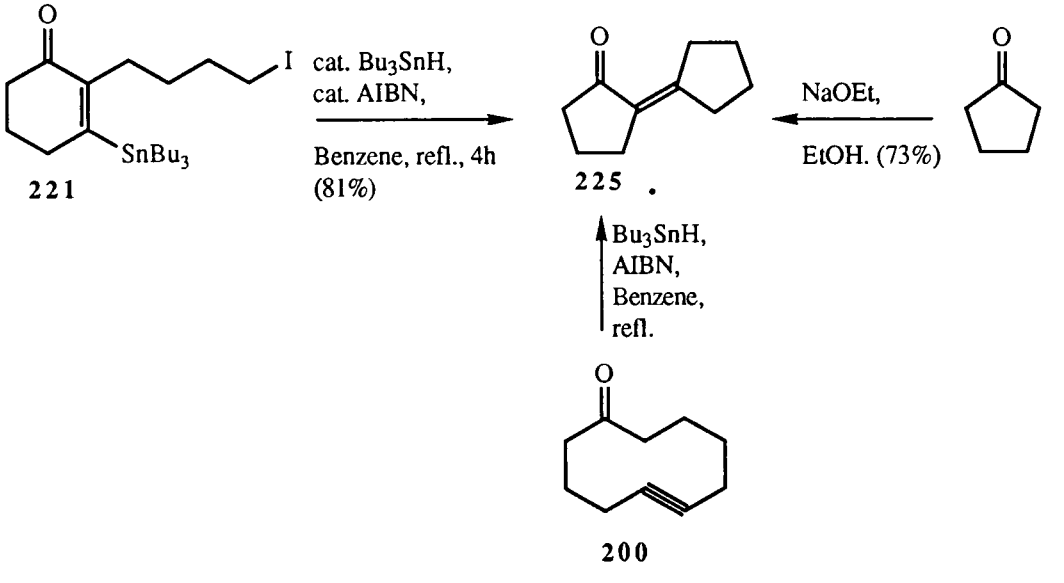
Exposure of this material to ring expansion conditions led to rapid reaction (4h) to a single product which was initially thought to be the desired alkynone **200**. The literature data[41b,180] for this compound was not, however, entirely consistent with this compound but was not of sufficient quality to allow us to discount our initial assignment. For this reason genuine cyclodec-5-ynone **200** was prepared by a modified version of the route used by Eschenmoser *et al.*[41,79] in order that direct comparisons could be made. This route is summarised in Scheme 106.



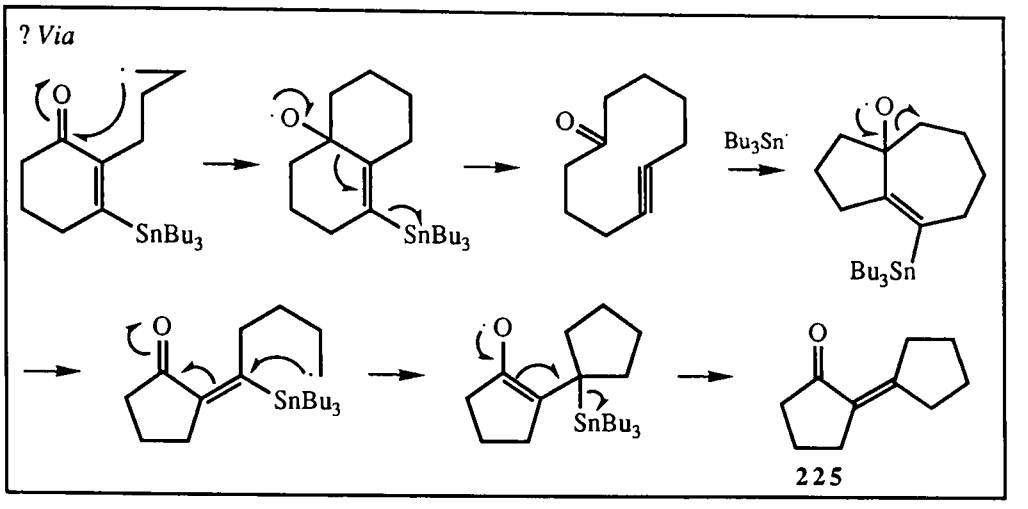
Scheme 106

The spectroscopic properties of this genuine material showed distinct differences to that obtained from the compound produced by radical reaction of the stannane **221** as did those of the bicyclic enone **223** which we had envisaged might be formed by isomerisation of the alkynone or by an alternative radical process. The data of the compound derived from the radical reaction were then re-examined; the i.r. spectrum showed two bands of similar intensity at 1710cm^{-1} and 1640cm^{-1} suggestive of an α,β–unsaturated five-membered ring ketone; the ^{13}C n.m.r. spectrum confirmed this [δ 127.94, 158.73 (C=C); 207.78 (C=O)]. Furthermore, the ^{1}H n.m.r. spectrum indicated the C=C bond to be fully substituted and the only compound which fitted all this data was 2-cyclopentylidenecyclopentanone **225**. To confirm this assignment, genuine material was prepared by the method of Plesek[181] and, indeed, this possessed identical spectroscopic properties.

It was suggested that this product could arise by isomerisation of initially-formed cyclodec-5-ynone **200** under the conditions of the radical reaction by re-addition of $Bu_3Sn\cdot$ to produce a fused 5,7-bicyclic ring system which subsequently fragments as shown in Scheme 107. Some evidence for this proposal came from the observation that exposure of genuine cyclodec-5-ynone **200** to radical conditions resulted in the formation of the ketone **225**.

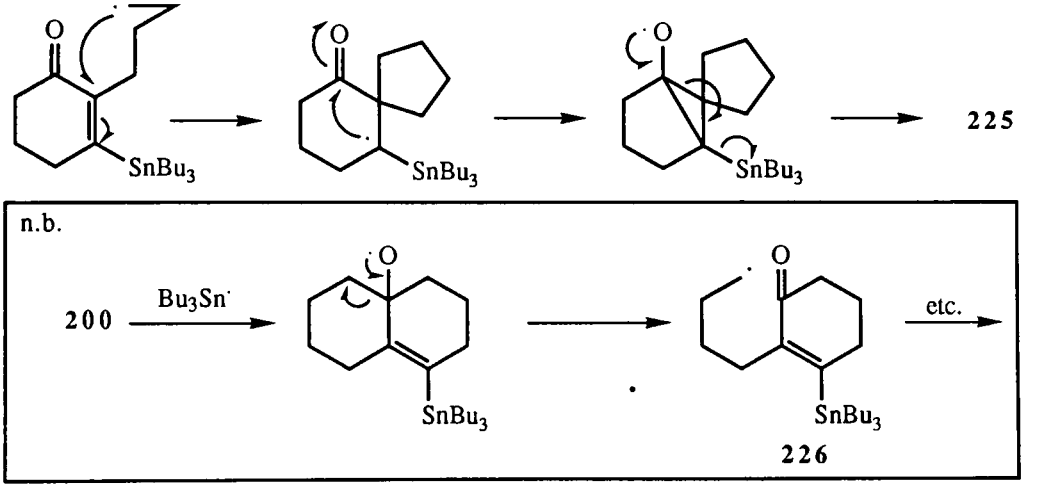


Scheme 107



Scheme 107 (contd.)

An alternative pathway has also been suggested which is detailed in Scheme 108. This mechanism is not precluded by the observed isomerisation of the alkynone **200**. The radical **226** could, in principle, be re-formed by attack of $Bu_3Sn\cdot$ at the C-C triple bond in a similar manner as in Scheme 107 except to produce a 6,6-fused bicyclic system which can further break down.



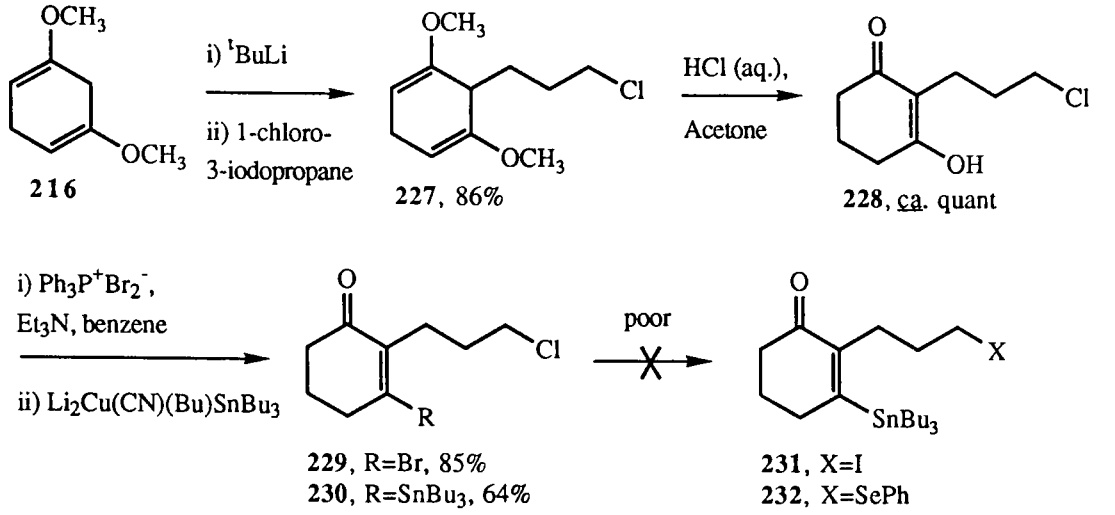
Scheme 108

Whichever mechanism operates in the above case it was thought to be of interest to prepare the three-carbon side-chain homologue and to compare its reactivity to radical conditions with those of the stannane **221** above.

II.3.3 Preparation of three carbon side chain substrates.

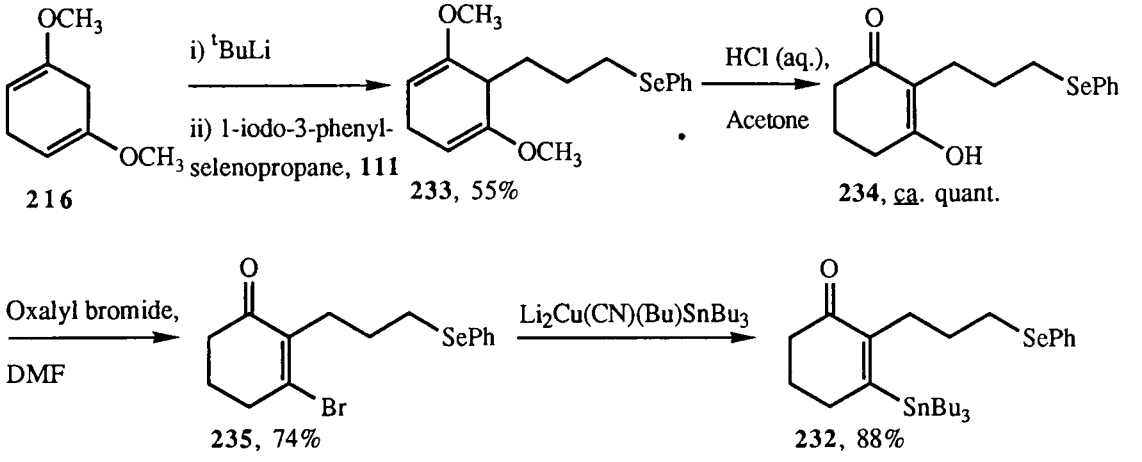
The synthetic sequence was followed, in an analogous manner to that used for the preparation of the chloride **220**, this time beginning with alkylation of the diene **216** with 1-chloro-3-iodo-propane to produce the three-carbon side chain. The product **227** was obtained in excellent yield (86%) and showed spectroscopic data directly comparable with those of the homologue **217**, the mass spectrum confirming its constitution (217, MH^+, ^{35}Cl, 100%). This diene was hydrolysed as before to give the dione **228** in quantitative crude yield. In this case the method of Piers[146] for the bromination proceeded efficiently to furnish bromo-enone **229** in 85% yield. Once again, the ^1H n.m.r. and i.r. spectra resembled closely those of compound **219**, the mass spectrum showing the expected protonated molecular ion (253, MH^+, $^{81}Br^{35}Cl$, 79%). Finally, conversion of bromo-enone **229** to vinyl-stannane **230** followed the same conditions as those employed for the preparation of stannane **220** to produce the requisite compound **230** in 64% yield with 15% recovery of starting material.

Rather surprisingly, the chloride **230** could not be cleanly converted to the corresponding iodide **231** since use of the previously successful conditions (5 equiv. NaI, acetone, reflux) resulted in exceptionally slow conversion (ca. 10% after 5 days) with Sn-C bond cleavage occurring after long reaction periods. Running this reaction in the dark to minimise iodine formation and hence Sn-C cleavage effected little improvement. Use of potassium iodide supported on alumina, reported by Clark[182] to be a highly reactive form of iodide ion, effected little conversion to the iodide **231**, Sn-C bond cleavage being the major reaction pathway. The most successful results were obtained by absorbing neat chloride **230** onto an excess of solid sodium iodide then sonicating the mixture in the dark; this procedure resulted in ca. 50% conversion to the iodide **231** after 12h (^1H n.m.r.). The isolated chloride/iodide mixture was then subjected to the same conditions and a further conversion to the iodide was observed however, this process clearly did not represent a viable synthetic procedure for the preparation of the iodide **231** in a pure form so attention was switched to the selenide **232**. This area of work is summarised below (Scheme 109).



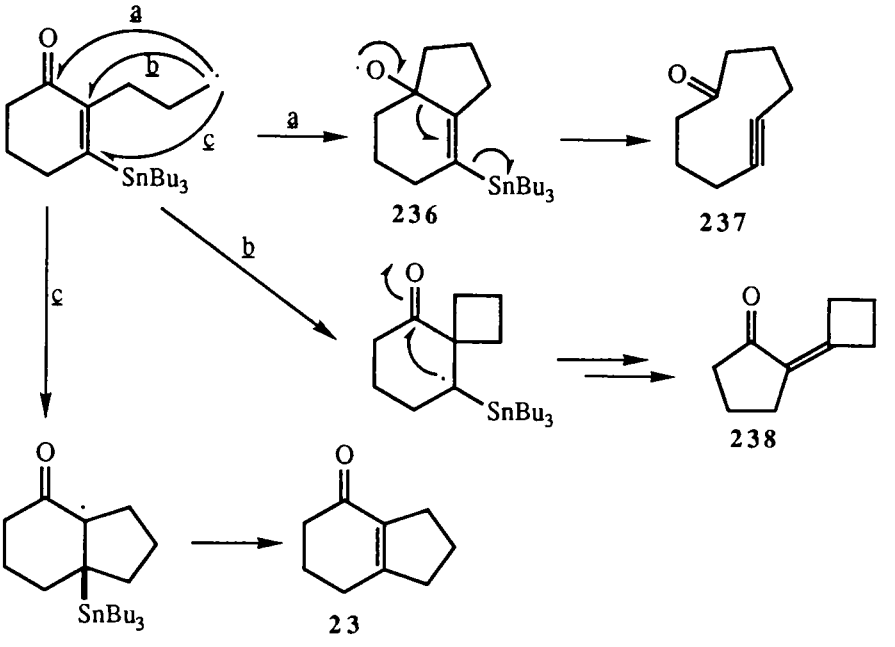
Scheme 109

The extremely low reactivity of the 3'-chloro group to nucleophilic substitution was further exemplified by its reaction with sodium phenyl selenide (generated from diphenyl diselenide and sodium borohydride in ethanol)[129] in which only trace amounts of the corresponding selenide **232**, *vide infra,* were observed by ^{1}H n.m.r. analysis. It was decided at this point that the sequence would be repeated beginning with alkylation of the diene **216** using 1-iodo-3-phenylselenopropane **111** such that any substitution problems would be circumvented. The synthesis of selenide **232** proceeded with no difficulties, all intermediates showing expected spectroscopic data directly comparable to those of the chloride series (Scheme 110).



Scheme 110

The projected radical reaction of substrate **232** to the cycloalkynone requires initial addition of the 1° radical to the carbonyl group in a 5-*exo*- fashion (pathway a); molecular models indicate this approach to be feasible and although the transition state for such addition is rather strained, this strain is released on attainment of suggested intermediate alkoxy radical **236**. Alternative reaction pathways b and c involve respectively 4-*exo*-trig and 5-*endo*-trig processes so it was with considerable anticipation that selenide **232** was subjected to the ring expansion conditions (Scheme 111).

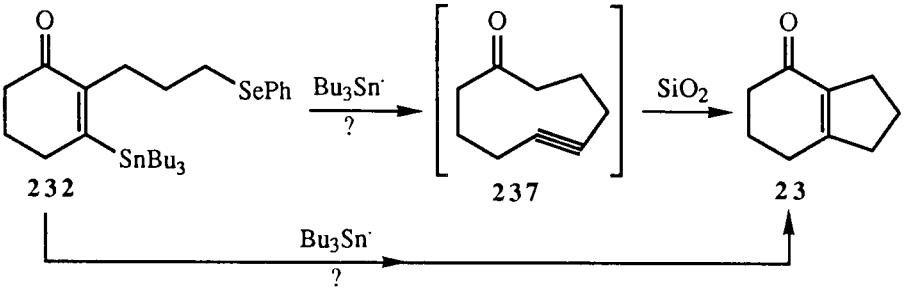


Scheme 111

In the event, a 90h reaction period resulted in complete consumption of the starting material **232**, t.l.c. analysis indicating a single product spot. The first time the reaction was run the residue was directly chromatographed on silica and the isolated product identified as the indanone derivative **23** (Section I.2.2). This known compound had i.r., ^{1}H n.m.r., and mass spectral data in accord with the literature[40]. An alternative report[183] also detailed the ^{13}C n.m.r. spectrum of this compound and a very close agreement was observed.

Although, initially, it appeared that pathway c was operating, comparison of the crude ^{1}H n.m.r. spectrum with that of the isolated material **23** indicated significant

discrepancies in the form and chemical shift of the resonances above δ 2.0 p.p.m. In the light of the known isomerisation of cyclonon-5-ynone **237** to the indanone derivative **23** on alumina and silica[40], it is suggested that the alkynone **237** is produced by the radical reaction but is not isolable by conventional chromatography. In two further runs of this reaction, the same crude ^{1}H n.m.r.* spectrum was observed but attempts to distil the product directly from the residue (at reduced pressure) were unsuccessful due to the high concentration of selenium and tin containing species; that material which did distil contained a significant amount of the indanone derivative **23** so the postulated involvement of alkynone **237** cannot be readily substantiated (Scheme 112).



Scheme 112

In any event, this procedure does not represent a practical synthetic alternative to existing procedures for such compounds[40,79,80,180] so no further work in this area was undertaken.

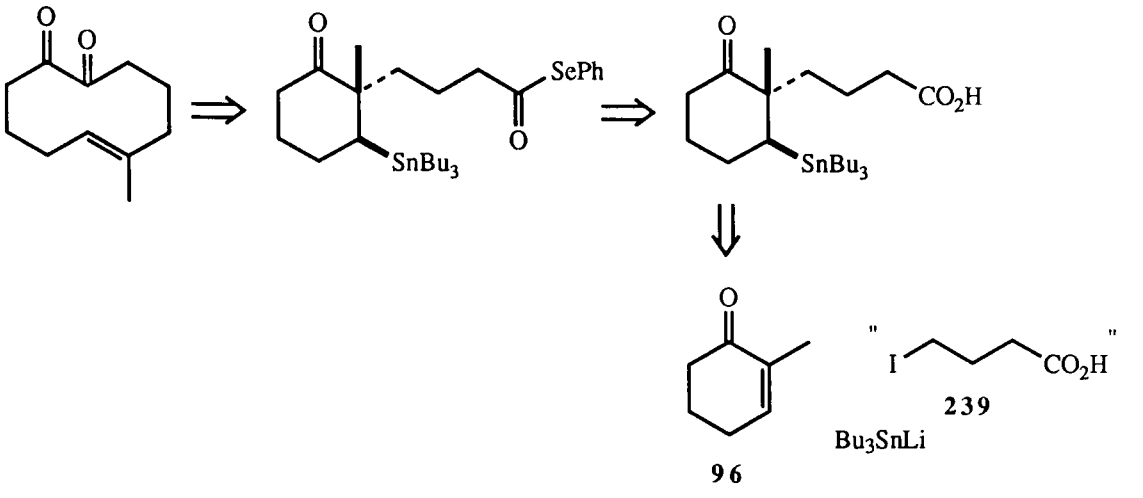
II.4 The use of acyl radicals in ring expansion reactions.

II.4.1 The synthesis of a four-carbon ring expansion precursor.

The synthesis of medium ring 1,2-diones by a ring expansion process has not to our knowledge been reported. This fact, coupled with the increasing use of acyl radical equivalents in organic synthesis[184] suggested a procedure whereby an acyl radical precursor could be used in a ring expansion process of the type described in Section II.1.

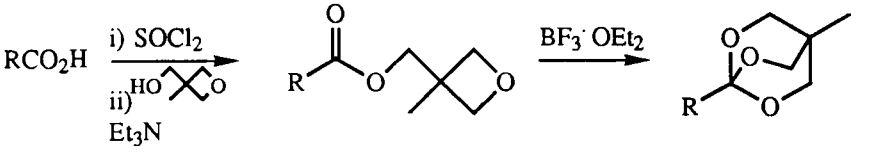
* ^{13}C n.m.r. spectroscopy of the crude material was inconclusive due to the relatively low concentration of product in the residue resulting in resonances being lost to the background.

The proposed strategy rested on the known conversion of carboxylic acids to acyl selenides[185], which are the most flexible acyl radical equivalents yet devised, and is summarised in Scheme 113.



Scheme 113

The desired iodocarboxylic acid **239** would have to be used in a protected form if it is to function successfully as an alkylating agent. Corey[186] has described the general conversion of carboxylic acids to cyclic orthoesters by the two-step methodology shown in Scheme 114.



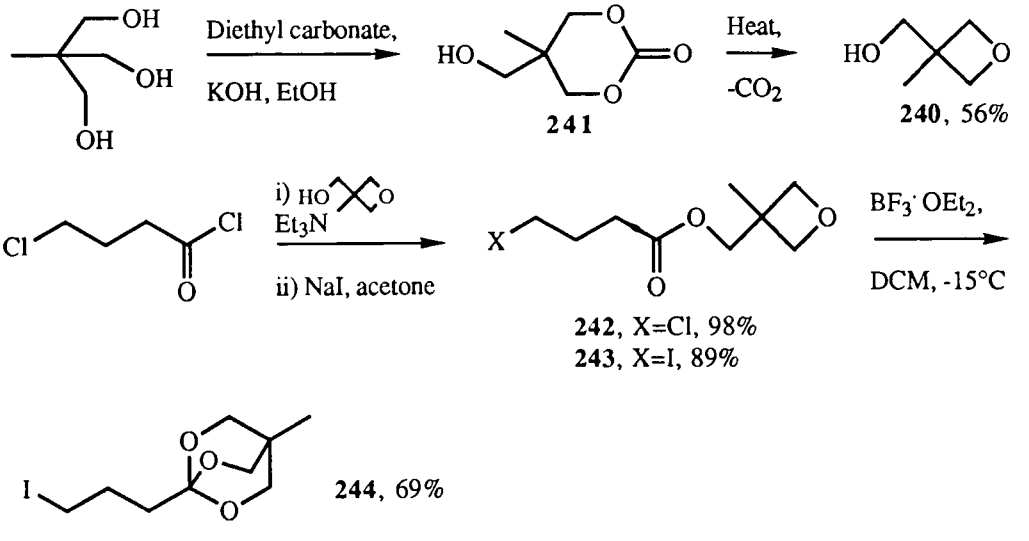
Scheme 114

Such orthoesters are inert to nucleophilic species such as enolates and organolithium reagents, under normal conditions, and may be readily deprotected to the free acids under mild hydrolysis.

The oxetanyl alcohol **240** was prepared in 56% yield, according to the literature[186], by treatment of tris-(hydroxymethyl)-ethane with diethyl carbonate under alkaline conditions followed by thermal decarboxylation of intermediate **241**. 4-Chlorobutyryl

chloride was then treated with this alcohol in the presence of triethylamine to produce the desired ester **242** in 98% yield. I.r. (1740cm^{-1}, CO_2R) and ^1H n.m.r. data (δ 3.63, 2H, t, $C\underline{H}_2Cl$; 4.21, 2H, s, $C\underline{H}_2O$-) for this compound were as expected. Chloride **242** was converted to iodide **243** by Finkelstein reaction, the product **243** being obtained in 89% yield as a colourless oil; ^1H n.m.r. (δ 3.27, 2H, t, $C\underline{H}_2I$) and mass spectra (299, MH^+, 100%) provided confirmation of the success of this reaction.

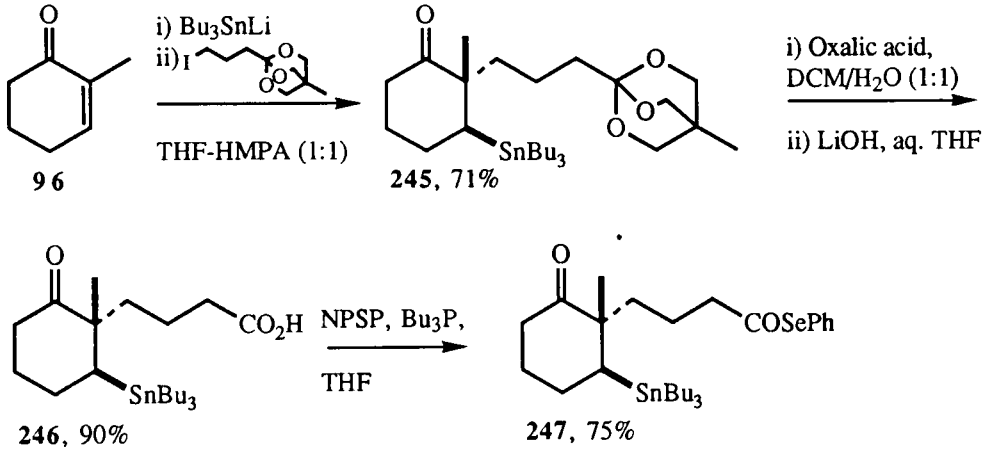
The isomerisation conditions ($BF_3{\cdot}OEt_2$) had to be carefully controlled. A mixture of the ester **243** and boron trifluoride etherate in dichloromethane was stirred at -15°C for 48h; attempts to increase the reaction rate by raising the temperature resulted in a trimeric compound as judged by examination of the integral ratios in the ^1H n.m.r. spectrum. However, if the above conditions were employed and the reaction quenched with triethylamine at -15°C, successful preparation of the orthoester was possible, the product **244** being obtained in 69% yield after chromatography on deactivated silica. The main diagnostic features in the ^1H n.m.r. spectrum of this compound were the shift of the $C\underline{H}_3$- resonance to δ 0.79 p.p.m. (from δ 1.35 p.p.m.) and the appearance of a sharp 6H singlet at δ 3.88 p.p.m. corresponding to the $C\underline{H}_2O$- protons in the bicyclic system. The preparation of this electrophile is detailed in Scheme 115.



Scheme 115

Gratifyingly, 1,4-addition-alkylation using tributylstannyl lithium, 2-methylcyclohex-2-enone **96** and electrophile **244** led to the formation of stannane **245** in 71% yield. This compound possessed the expected data, the ^{1}H n.m.r. spectrum indicating the orthoester function to be intact and the presence of a sharp singlet at δ 1.08 p.p.m. (2-C<u>H</u>$_3$-) indicating a discrete regioisomer. The orthoester protection was removed by a two-step procedure in which the putative diol, produced from mild acidic hydrolysis, was not isolated but subjected directly to saponification. The carboxylic acid **246** was isolated in 90% yield, requiring no purification at this stage. The i.r. spectrum clearly indicated the presence of the acid and the ^{1}H n.m.r. spectrum showed an absence of peaks associated with the orthoester, a signal at δ 2.23-2.52 (4H, m) corresponding to C<u>H</u>$_2$CO- and C<u>H</u>$_2$CO$_2$H.

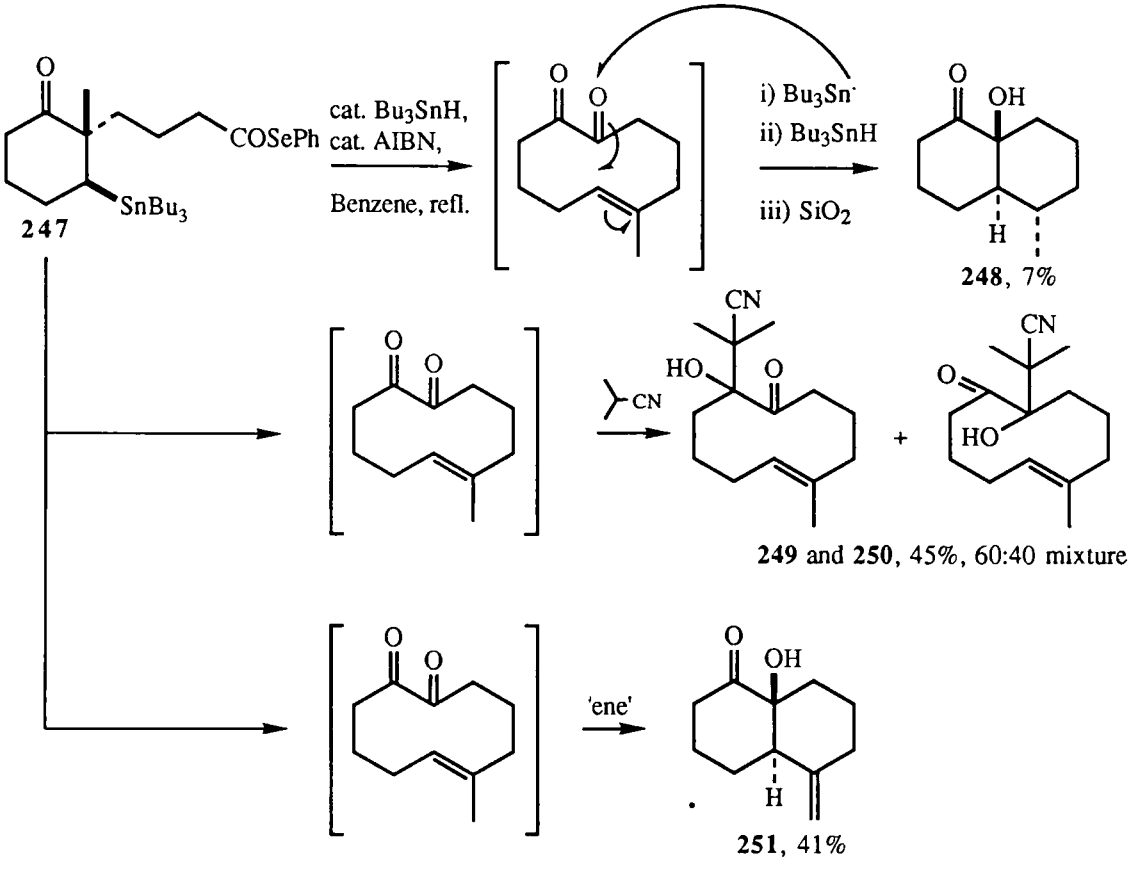
The procedure of Nicolaou[187], to convert the acid to the acyl selenide, proceeded efficiently although two equivalents of NPSP and tributyl phosphine were required in order to consume all the starting material. The product **247** was obtained in 75% yield after chromatography. Two bands in the i.r. spectrum (1730cm^{-1}, COSePh; 1705cm^{-1}, C=O) and a new resonance in the ^{1}H n.m.r. spectrum (δ 2.71, 2H, t, C<u>H</u>$_2$COSePh) confirmed the assigned structure (Scheme 116).



Scheme 116

II.4.2 Radical reaction of acyl selenide **247**.

Exposure of the acyl selenide **247** to the usual conditions required for radical reaction resulted in consumption of the starting material within 16h during which time a total of 0.4 equivalents of AIBN were added to maintain reaction. T.l.c. analysis of the crude material and the ^1H n.m.r. spectrum indicated a number of products which were separated by careful and repeated chromatography and corresponded to four components all of which could be derived from the desired 1,2-dione. Scheme 117 summarises this reaction and includes suggested pathways for the formation of the products.



Scheme 117

Clearly, the dione system possesses enhanced reactivity over the alkenone **102** which did not suffer any of these fates. The AIBN adducts **249** and **250** were inseparable, the ^{13}C n.m.r. spectrum showing doubling of all peaks, the ^1H n.m.r.

spectrum of the mixture was only partially resolved at 500 MHz with resonances at δ 1.66 ($C\underline{H}_3C$=), 4.37 (3° O$\underline{H}$) & 5.12 ($C\underline{H}$=) and δ 1.68 ($C\underline{H}_3C$=), 4.42 (3° O$\underline{H}$) & 5.17 ($C\underline{H}$=) being particularly characteristic. The i.r. (3550-3380cm^{-1}, OH; 2230cm^{-1}, CN) and mass spectra (267, MNH_4^+, 14%) confirmed the structural assignment. The compounds **251** and **248** possessed grossly similar ^{1}H n.m.r. spectra, the latter not showing resonances at δ 4.80 and 5.01 ($C\underline{H}_2$=) but a doublet at δ 1.14 ($C\underline{H}_3CHRR'$). ^{13}C, i.r., and mass spectra were all in agreement with the assigned structures. The production of compound **251** by intramolecular ene reaction is directly comparable to the work of Wender[56] described in Chapter I (Section I.2.3).

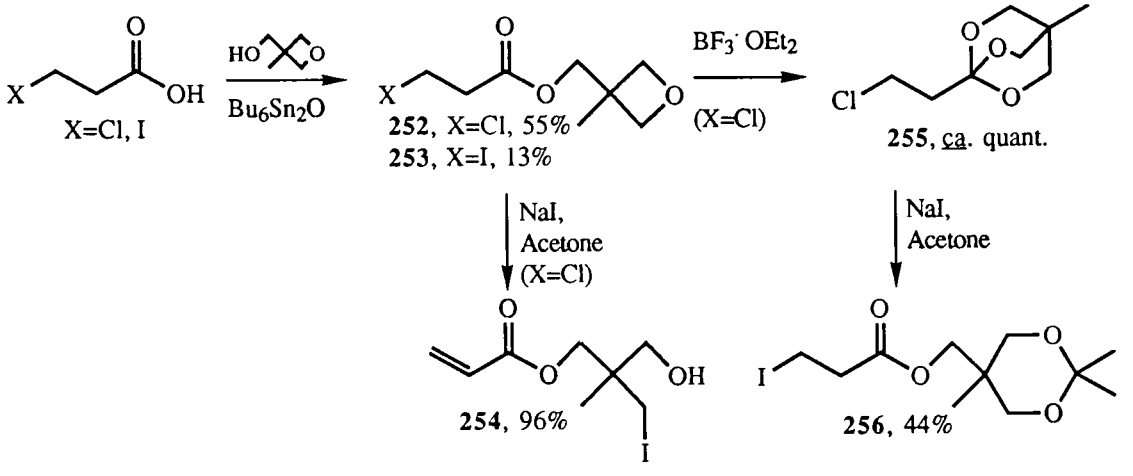
This reaction was repeated a number of times and although product distributions were variable, depending on the exact scale and hence reaction time and quantity of AIBN used, all four products were always observed. To place this rather unusual reaction into context, it was decided to embark on the synthesis of the three-carbon homologue to see if the nine-membered ring dione would behave in a similar manner. As it turned out, this proved to be a difficult problem which was never solved, *vide infra.*

II.4.3 Attempted preparation of a three carbon ring expansion precursor.

The preparation of a three-carbon chain analogue to the iodide **244** required, as the first stage, the preparation of the chloro-ester **252** which, due to the propensity for the β-chloro group to eliminate, was not possible utilising conventional methods, namely: RCO_2H + R'OH (DCC/DMAP) and RCOCl + R'OH (Et_3N). Fortunately, the desired chloro-ester **252** was produced in 55% yield by the use of the neutral reagent bis-tributylstannyl oxide as the esterification catalyst[188]. I.r. (1740cm^{-1}, CO_2R), ^{1}H n.m.r. (3.80, 2H, t, $C\underline{H}_2Cl$; 4.25, 2H, s, $C\underline{H}_2O$-), and mass spectral data (193, MH^+, ^{35}Cl, 46%) were all as expected. This compound could not, however, be converted to the corresponding iodide **253**, the eliminated and ring-opened compound **254** being obtained instead after heating with sodium iodide in acetone. This material was identified by ^{1}H n.m.r. (δ 3.25, 2H, s, $C\underline{H}_2I$; 4.18, 2H, s, $C\underline{H}_2O$-) and mass spectrometry (302, MNH_4^+, 14%). Fortunately the chloro-ester **252** underwent clean isomerisation to the orthoester

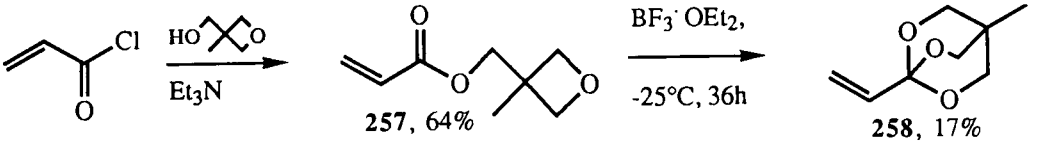
255 in almost quantitative crude yield but this compound proved of little use since its conversion to the corresponding iodide failed to occur, instead the sodium iodide induced ring opening of the orthoester to produce compound **256** in which acetone had become incorporated into the molecule. The structure of this material was deduced on the basis of its ^{1}H n.m.r. (δ 1.42 and 1.46, 2x3H, s, 2x$C\underline{H}_3$-; 3.36, 2H, s, $C\underline{H}_2$I) and mass spectra (343, MH^+, 32%).

Although the iodo-ester **253** could be produced the yield of this compound was extremely low (13%) due to thermal elimination of HI under the high (refluxing xylene) temperature required for the esterification so further work with this compound did not appear attractive. These results are summarised in Scheme 118.



Scheme 118

It was hoped that the acrylate series could be followed, such that the double bond could be funtionalised to allow alkylation, at a later stage but the low yield of products **257** and **258** over the two steps precluded this approach also (Scheme 119).



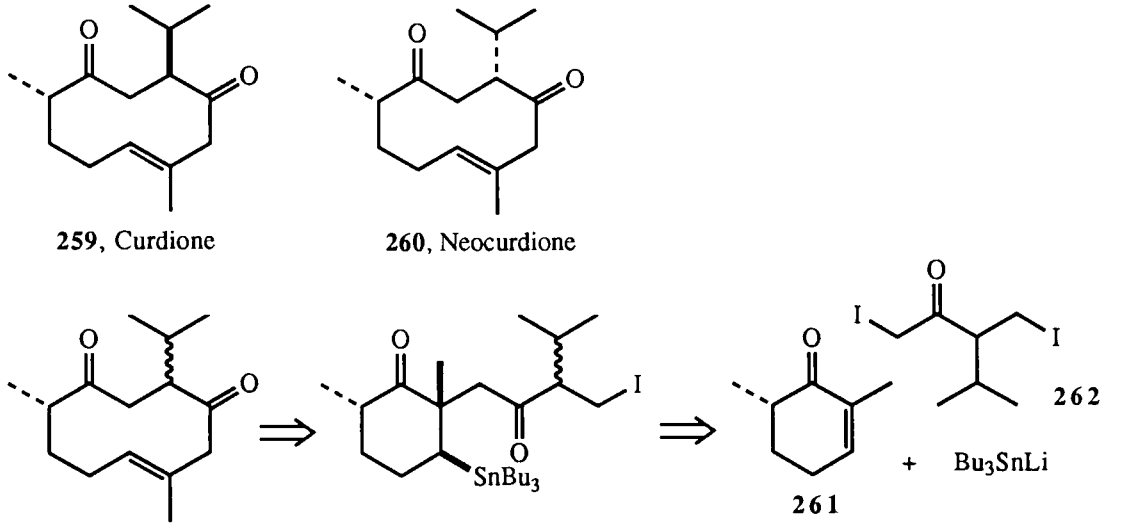
Scheme 119

It was decided at this stage to cease all work concerned with exploring the bounds of this chemistry and to concentrate on the application of the chemistry developed in Section II.1 towards the synthesis of natural products based on a cyclodec-5-enone ring system.

II.5 The attempted synthesis of curdione and neocurdione.

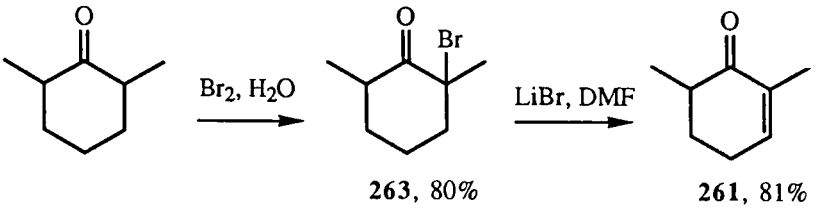
II.5.1 Model work with 1,4-di-iodobutane as the electrophile.

Curdione **259** and neocurdione **260** are biologically active compounds whose structures have been elucidated by a number of groups[189,190]. To date no total synthesis of these compounds has been reported; their particular structure appeared to us to represent a suitable target to which we could apply some of the methodology developed during the course of this project. In the racemic series both of these compounds may be retrosynthetically reduced to the substrates **261** and **262** as shown in Scheme 120.



Scheme 120

The enone **261** has been prepared in an optically pure form[191], however, for our purposes, the procedure of Newman[157b] was used to prepare racemic enone **261** from 2,6-dimethylcyclohexanone (Scheme 121). This compound showed spectroscopic data in agreement with the literature[191].



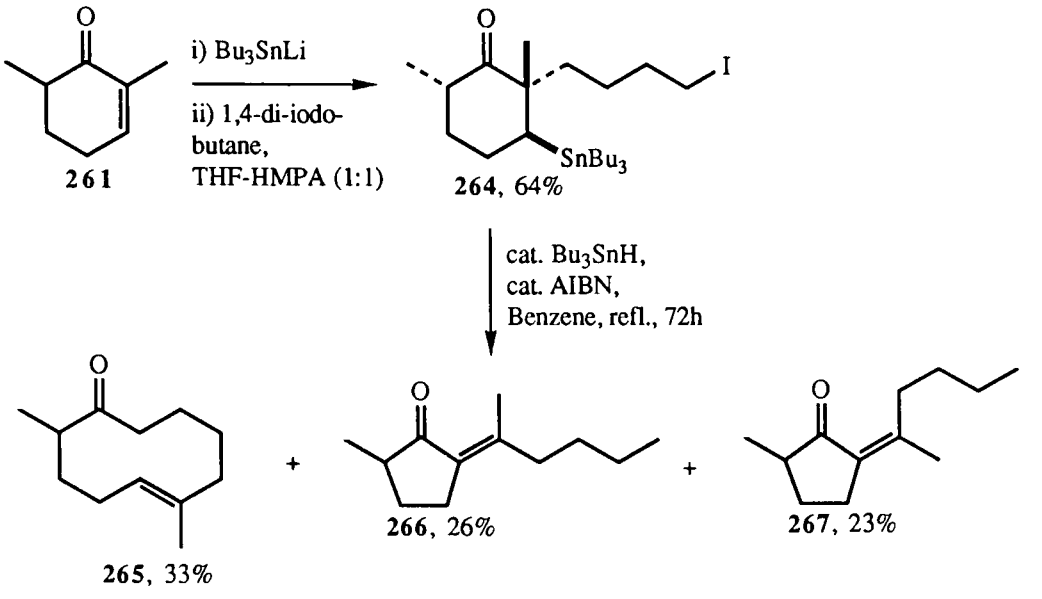
263, 80% **261**, 81%

Scheme 121

Before attempting the synthesis of the electrophile **262**, the reactivity of enone **261** was investigated in its reaction with tributylstannyl lithium and 1,4-di-iodobutane. This reaction proved successful, a single diastereoisomer being obtained in 64% yield presumed, but not proven, to be the stannane **264** with the structure shown. This compound displayed the expected i.r. (1700cm^{-1}, C=O) and ^{1}H n.m.r. data (δ 1.17, 3H, s, 2-C$\underline{H}_3$-; 3.19, 2H, t, C$\underline{H}_2$I). With compound **264** in hand its behaviour towards ring expansion conditions was studied since this reaction would serve as a model for the projected synthesis of the natural products and at this stage no ring expansions had been attempted on substrates possessing 2,2,6-trisubstitution and which would be expected to possess carbonyl groups rather deactivated, on steric grounds, towards radical addition.

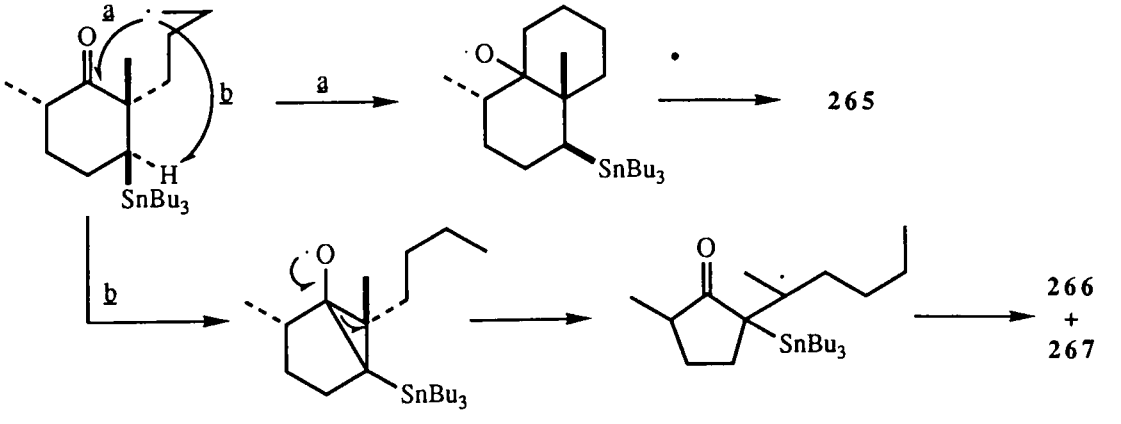
In the event, reaction was complete after 72h at reflux and the desired ring expanded material **265** obtained in 33% yield. This compound displayed data very similar to that of cycloalkenone **102** (Section II.1); of particular diagnostic value was the ^{1}H n.m.r. spectrum which clearly showed the resonance due to the 2-C$\underline{H}_3$- group (δ 0.95, 3H, d), the vinyl methyl group appearing as a singlet at δ 1.70 and the olefinic proton resonating as a multiplet at δ 4.88-5.04. However, in addition to this material, two other components were also isolated after careful chromatography. These were eventually identified as the ring-contracted configurational isomers **266** and **267**. Both possessed i.r. spectra indicative of an α,β-unsaturated five-membered ring ketone (1710 and 1705cm^{-1} respectively), mass spectra indicating a molecular mass of 180, and ^{1}H n.m.r. spectra displaying the characteristic features of (i) a vinyl methyl group (3H, s. **266**: δ 2.21, **267**: δ 1.84), (ii) a terminal methyl group (3H, t. **266**: δ 0.94, **267**: δ 0.91) and (iii) an α-

methyl group (3H, d, **266**: δ 1.12, **267**: δ 1.11). The ^{13}C n.m.r. spectrum of the major product **266** confirmed this assignment. This result is summarised in Scheme 122.



Scheme 122

Presumably the increased steric hindrance at the carbonyl centre forces the 1° radical to seek an alternative reaction pathway which involves less congestion in the transition state. A plausible mechanism for such an alternative process, involving initial intramolecular hydrogen atom abstraction from the carbon α- to the stannyl substituent followed by a ring contraction process, is given in Scheme 123; similar mechanisms have been proposed in work by Nishida[192].



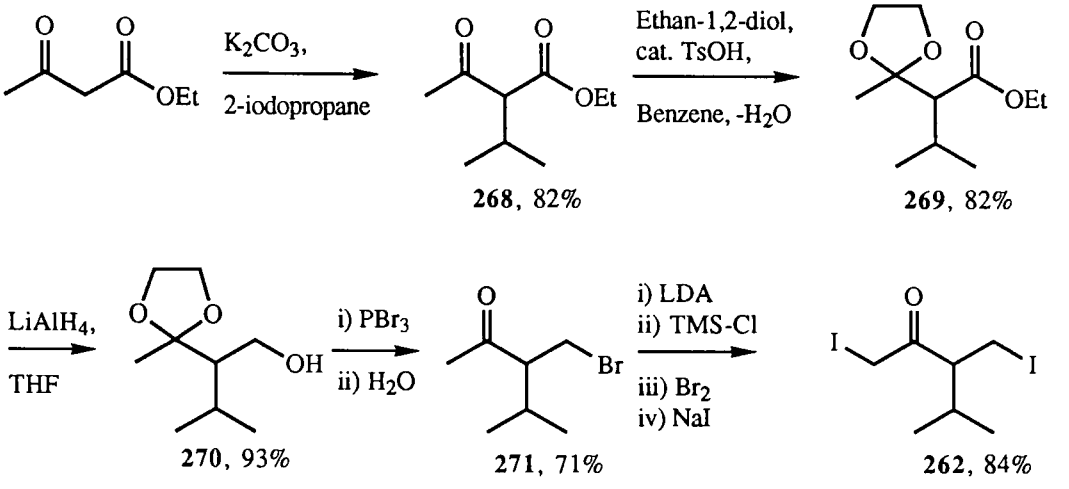
Scheme 123

Although this result was not entirely satisfactory, work in this area was continued since some ring expanded product had been obtained and hope still remained for a synthesis of the natural products.

II.5.2 The preparation and use of α-haloketones as electrophiles in the 1,4-addition-alkylation reaction.

The electrophile **262** required a short synthesis beginning with the alkylation of ethyl acetoacetate with 2-iodopropane under phase transfer conditions[193]. This method circumvents the problems of *O*- and/or di-alkylation which generally compete with systems of this nature. The β-keto ester **268**, obtained in 82% yield, was protected as its ethylene ketal **269** then the ester function fully reduced to the alcohol **270**. This compound was identified by its i.r. (3600-3200cm^{-1}, OH), ^{1}H n.m.r. (δ 3.57-3.83, 2H, m, C$\underline{H_2}$OH; 3.99, 4H, s, -OC$_2\underline{H_4}$O-) and mass spectra (175, MH$^+$, 6%). Alcohol **270** was converted to the corresponding bromide by treatment with phosphorous tribromide, water being added to the liberated acid to deprotect the ketal unit. This one-pot process afforded the bromo-ketone **271** in 71% yield as an unstable oil which rapidly ejected hydrogen bromide at room temperature. The spectroscopic data for this compound [i.r. (1715cm^{-1}, C=O), ^{1}H n.m.r. (δ 2.25, 3H, s, C$\underline{H_3}$CO-; 3.40-3.63, 2H, m, C$\underline{H_2}$Br), mass spectrum (210, MNH$_4^+$, ^{79}Br, 100%)] was in full agreement with the suggested structure. The final stage in the preparation of electrophile **262** was to introduce the α-iodoketone functionality using the procedure of Conia[194] in which the kinetically generated enolate was trapped as its trimethylsilyl derivative, the enol ether then being brominated at low temperature; exchange of the bromide groups for iodide led, in a one-pot process, to the production of the desired functionalised di-iodide **262** in 84% yield on a 0.5mmol scale; this yield dropped significantly when the reaction was repeated on a larger scale, starting material being recovered. Once more, the spectroscopic data of this compound was consistent with the suggested structure, e.g., the ^{1}H n.m.r. spectrum showed an ABq at δ 3.97 and δ 4.04 (2H) indicative of the IC$\underline{H_2}$CO- portion, the protons adjacent to the second iodine atom

resonating at δ 3.12-3.41 (2H, m). The full synthesis of this electrophile is given in Scheme 124.



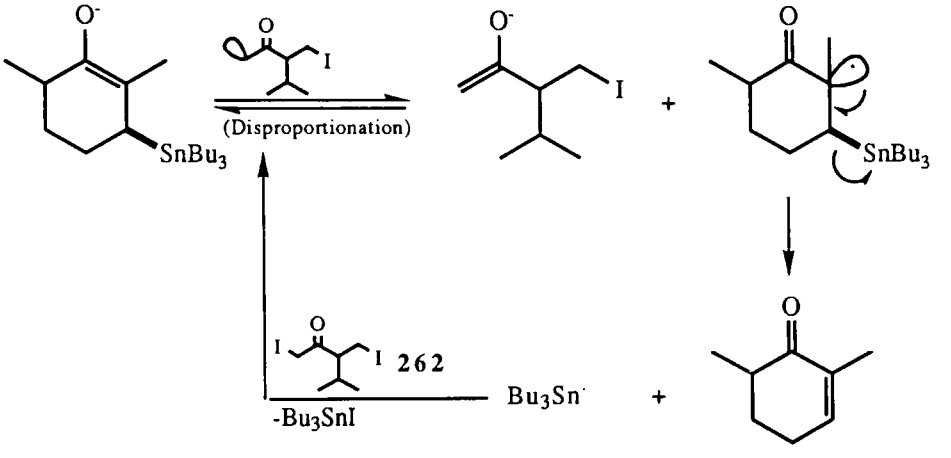
Scheme 124

It was hoped that this alkylating agent would react preferentially at the α- position due to the enhanced reactivity of this centre (towards S_N2 processes) conferred by the carbonyl π-system[195]. Unfortunately, application of the standard procedure for the 1,4-addition-alkylation reaction with enone **261** and this di-iodide resulted in none of the desired compound. Tributyltin iodide was, however, produced in this reaction and it is suggested that the particularly reactive nature of electrophile **262** allows single electron transfer[196] processes whereby tributylstannyl radical is eliminated (c.f. Scheme 57) which is then capable of direct reaction with further molecules of the iodide in a radical-chain process (Scheme 125).

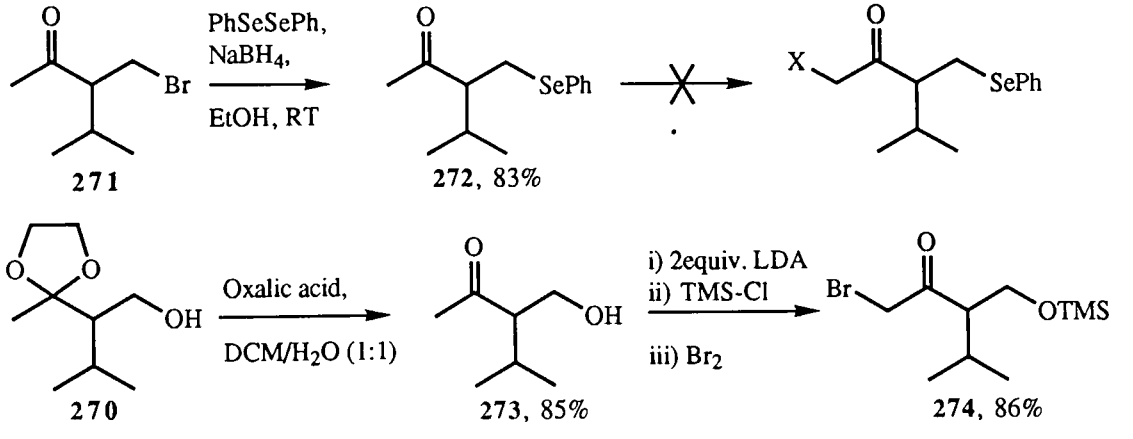
Use of the corresponding α-bromide, stannyl cuprate reagents, and/or variation of the reaction temperature and THF/HMPA ratio resulted in the same failure to isolate the desired stannane.

The less labile substrate **274** was also prepared as detailed in Scheme 126. The selenide **272** could not be brominated at the α-position, a complex mixture of products being obtained under those conditions found to be successful for compound **271**. The protected bromo-alcohol **274** could be prepared in 86% yield from ketone **273** [i.r. (1735,

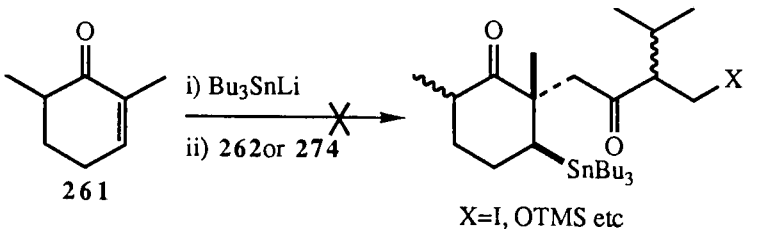
1720cm^{-1}, C=O), ^{1}H n.m.r. (0.11, 9H, s, (C$\underline{H}_3$)$_3$Si-; 3.59-3.85, 2H, m, C$\underline{H}_2$OTMS; 4.05, 2H, s, C$\underline{H}_2$Br), *m/z* (281, MH$^+$, ^{79}Br, 7%)] but this, too, suffered the same fate in the addition-alkylation reaction as the di-iodide **262**. Clearly this chemistry was not applicable to α-halo ketone electrophiles. Attempts to use α-halo ketal analogues were not made since substrates of this type were not easily prepared, due to the instability of the ketones, and it was thought that the steric hindrance in the region of the desired reaction centre would result in the failure of enolate alkylation. This work is summarised in Scheme 126.



Scheme 125



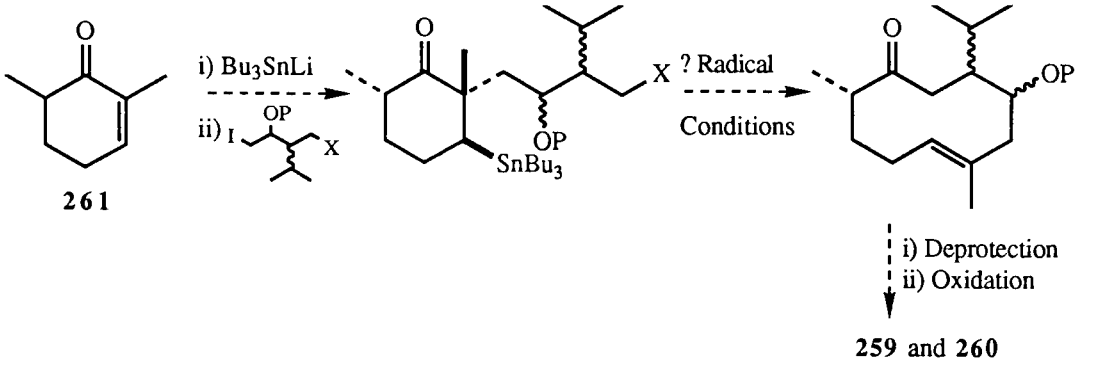
Scheme 126



Scheme 126 (contd.)

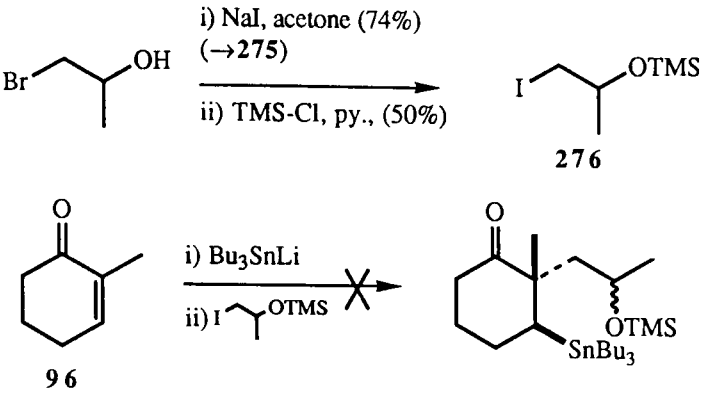
II.5.3 The search for a practical electrophile.

Since the α-halo-ketone and ketal functions could be discarded, the only remaining viable option was to use a protected alcohol function, as the side-chain carbonyl equivalent, in the hope that deprotection and oxidation could be effected after ring expansion (Scheme 127).



Scheme 127

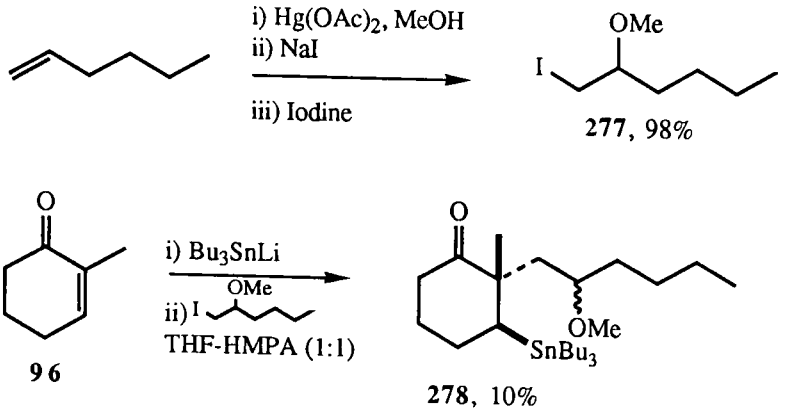
Choice of the smallest possible silyl protecting group and a very simple iodo-alcohol led to the preparation of 1-iodo-2-trimethylsilyloxypropane **276** from bromo-propanol. This substrate failed to undergo successful substitution in an attempted 1,4-addition-alkylation reaction (starting material and a range of minor, unidentified products being observed) and so more complex TMS-protected iodo-alcohols were discounted (Scheme 128).



Scheme 128

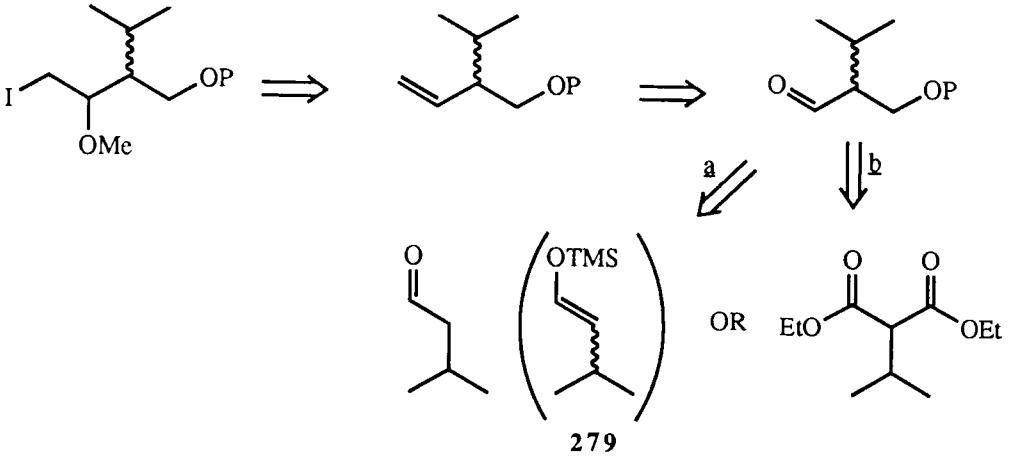
Although alkylation β– to an oxygen bearing carbon is known to be an inefficient process[197], one final attempt was made with the alcohol protected as its methyl ether, chosen as the smallest, and therefore least sterically demanding, alcohol protecting group. A more realistic model **277** was synthesised by methoxy-mercuration[198] of 1-hexene followed by oxidative (iodine) Hg-C bond cleavage. This reaction occurred in very high (98%) yield and provided added justification for proceeding with the synthesis. The product **277** was identified by its ^{1}H n.m.r. (δ 3.03, 1H, ca. quin., C<u>H</u>(OMe)-; 3.27 and 3.30, 2H, 2xd, C<u>H</u>$_2$I; 3.39, 3H, s, C<u>H</u>$_3$O-) and mass spectra (260, MNH_4^+, 17%).

This electrophile was employed in a 1,4-addition-alkylation reaction with enone **96** and tributylstannyl lithium to provide a complex mixture of products. One component was obtained which consisted of two extremely closely running, and therefore inseparable, compounds which were identified as two diastereomers of the alkylated material **278**. Their particular assignment was not made since later work would remove this chiral centre. Unfortunately the yield was very low (10%), reflecting the demands being placed on this reaction, but sufficient material was available to fully characterise the compound, e.g., i.r. spectrum (1705cm^{-1}, C=O), mass spectrum (517, MH^+, ^{120}Sn, 100%), ^{1}H n.m.r. spectrum (δ 1.08, 3H, s, 2-C<u>H</u>$_3$-; 3.04-3.21, 1H, m, C<u>H</u>(OMe); 3.10, 3H, s, C<u>H</u>$_3$O-) peaks arising from the minor diastereoisomer at δ 1.16 (2-C<u>H</u>$_3$-) and δ 3.25 (C<u>H</u>$_3$O-) indicated a product ratio of <u>ca.</u> 3:1 (Scheme 129).



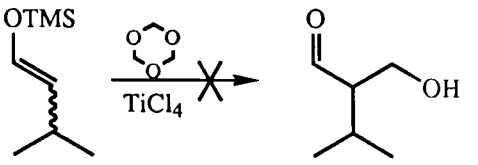
Scheme 129

Although this alkylation reaction was found to be poor, it suggested a straightforward preparation of a side chain which should give some success in a synthesis of this type of natural product (Scheme 130).



Scheme 130

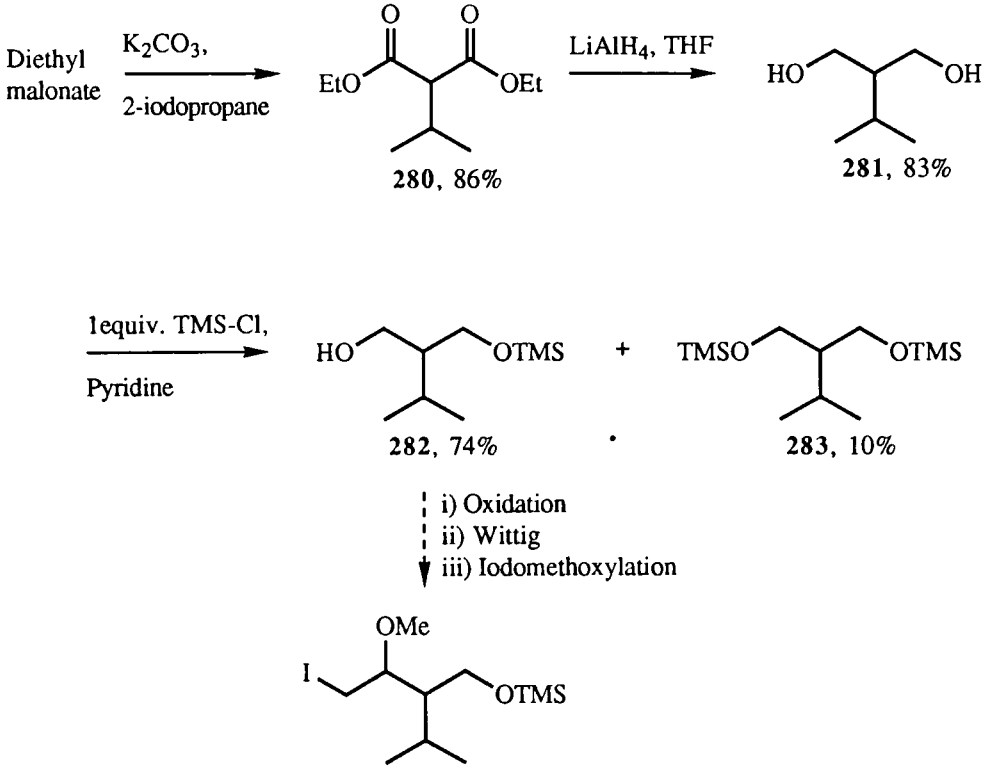
Some preliminary studies have been carried out in this area, the first route (a) being discounted since the aldol reaction between isovaleraldehyde and formaldehyde is exceedingly poor although it has been reported[199]; use of the trimethylsilyl enol ether **279**[200] of isovaleraldehyde did not lead to much improvement in a Lewis acid catalysed aldol reaction with 1,3,5-trioxane[201] (Scheme 131).



279

Scheme 131

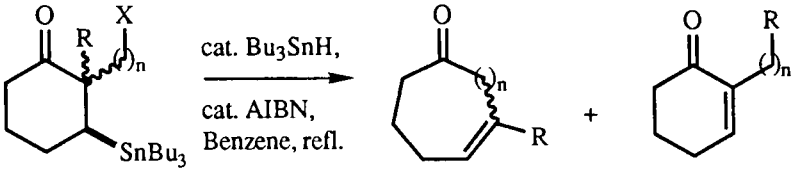
The route from diethyl malonate has given early success, alkylation to compound **280** with 2-iodopropane proceeding in good yield (86%). Subsequent reduction to diol **281** was cleanly effected with lithium aluminium hydride in 83% yield [i.r. (3700-3050cm^{-1}, OH), ^{1}H n.m.r. (δ 3.66-3.93, 4H, m, 2xC$\underline{H_2}$OH). Using a long reaction time and one equivalent of trimethylsilyl chloride in pyridine this diol could be mono-protected to the compound **282**, a small amount of the diprotected compound **283** also being obtained, as shown in Scheme 132. Time constraints have not allowed this route to be completed, however the proposed remainder of the electrophile synthesis is also given.



Scheme 132

II.6 Conclusions.

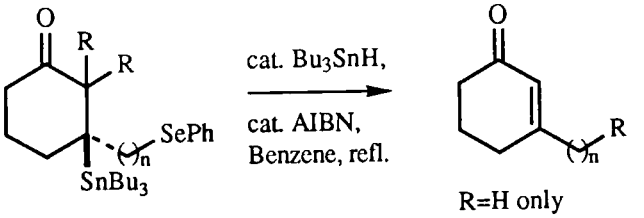
The initial aims of this project, as summarised in Scheme 52, were largely attained, with a number of successful high yielding ring expansions of one, three, and four carbon atoms being achieved. It was also found that the configuration of the olefin in the ring expanded products was dependent upon the relative disposition of the tributylstannyl substituent and radical-carrying side-chain in the cyclohexyl precursor. However, unforeseen intramolecular reductive elimination presented a problem with substrates possessing either a 2-H- or a 2-D- substituent. An isotope effect was found to exist in this latter process with the ratio of ring expanded to reductively eliminated product increasing significantly on substitution of 2-H for 2-D[137] (Scheme 133).



R=H, D, Me, CO_2Me
X=I, SePh
n=1, 3, 4

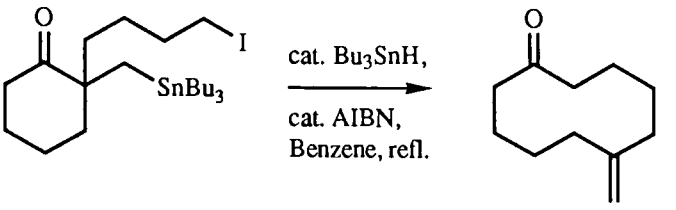
Scheme 133

This process was found to compete to the exclusion of ring expansion in attempted routes to exomethylene cycloalkanones from 3,3-disubstituted precursors. With 2,2-di-substituted precursors ring expansion was possible to the desired compounds however the reaction was found not to be general (Scheme 134).



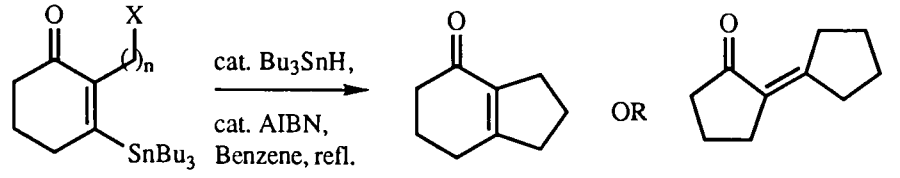
R=H, Me
n=3, 4

Scheme 134



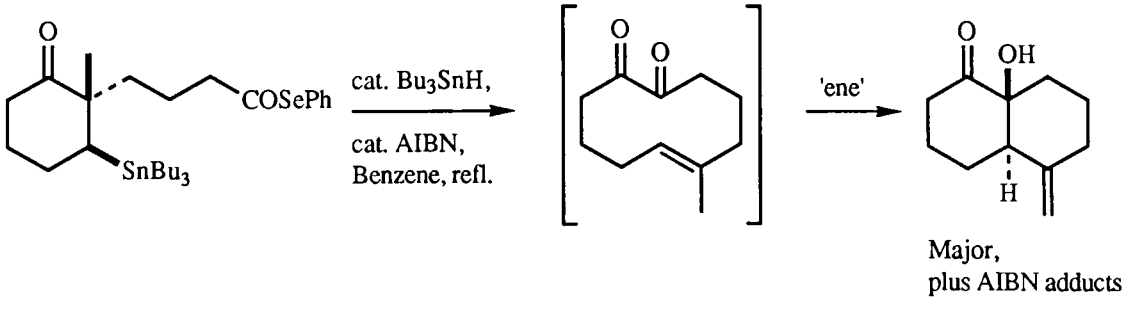
Scheme 134 (contd.)

Problems of a different nature were encountered in further extension of this chemistry. Synthetic routes to precursors, which were hoped to produce cycloalkynones, were devised; on exposure to radical conditions products were obtained which, mechanistically, could be derived from further reaction of the desired products, either under the reaction conditions or during isolation (Scheme 135).



Scheme 135

It has been shown that the scope of the homolytic addition-fragmentation reaction could be extended to include the initial production, and subsequent reaction of, acyl radicals. Once more, the radical reaction was successful to produce the 1,2-dione derivative, however, the reactive nature of this compound enabled it to undergo a selection of subsequent reactions under the reaction conditions, including addition of isobutyronitrile radical to the carbonyl groups and intramolecular ene reaction (Scheme 136).



Scheme 136

This work has therefore established the scope and limitations of the ring expansion reaction. A synthetic approach to a pair of related natural products revealed constraints of a different kind. This synthesis required the preparation of more demanding electrophiles and it has not been possible to prepare a practical electrophile for the initial 1,4-addition alkylation reaction, although model studies indicate that, should such an electrophile become available, the subsequent stages to the natural products are viable.

In conclusion, this project has produced a new method for the preparation of a number of medium ring cycloalkenones. The scope of the 1,4-addition alkylation reaction has been widely examined and it has been shown that only relatively simple enones (cyclopent-2-enone, cyclohex-2-enone) and electrophiles may be used. Precedents have been set for the success, or failure, of proposed homolytic reactions of this type. The success of the ring expansion reactions was found to depend on both the number of carbons in the radical-carrying side-chain and the reactivity of the carbonyl group towards homolytic addition (electronically and sterically). In addition, the stability of the ring expanded product to the conditions used for the ring expansion reaction was also found to have significant bearing on products isolated.

Further work on this area of homolytic ring expansion is currently in progress with substrates possessing 2°, 3°, vinylic, and acetylenic radical-carrying side-chains and/or starting rings other than six membered[202].

CHAPTER III
EXPERIMENTAL

III.1 General Experimental.

Proton n.m.r. spectra were run on one of the following machines: Varian Gemini 200 (200 MHz), Brüker WH 300 (300 MHz), Brüker AM 250 (250 MHz), or a Brüker AM 500 (500 MHz). Chemical shifts (δ) are quoted in parts per million (p.p.m.) downfield of tetramethylsilane, spectra being recorded in deuteriochloroform and referenced to residual protonated solvent. Abbreviations used in the description of resonances are s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet), and br (broad). Coupling constants (*J*) are quoted to the nearest 0.5Hz. Carbon-13 spectra were recorded on a Gemini 200 (50.3 MHz) or Brüker AM 500 (125.8 MHz) in deuteriochloroform.

Infra-red spectra were recorded on a Perkin-Elmer 681 spectrometer and calibrated against polystyrene (1601 and 1030 cm^{-1}), absorption maxima being reported in wavenumbers (cm^{-1}) and classified as strong (s), medium (m), weak (w), or broad (br).

Mass spectra were recorded by Dr. R.T. Aplin and his staff at the Dyson Perrins Laboratory on a V.G. Micromass 30F (E.I./C.I., elecron impact/chemical ionisation), a V.G. Micromass 16F (ACE., alternating chemical ionisation/electron impact), and a V.G. Micromass ZAB 1F (E.I./D.C.I./F.I./F.D., electron impact/desorption chemical ionisation/field ionisation/field desorption). GC mass spectra (GCMS) were recorded by the author on a V.G. TRIO-1 system under chemical ionisation conditions. *m/z* values are reported in Daltons and are followed by their percentage abundance in parentheses.

Elemental microanalyses were performed by Mrs. V. Lamburn of the Dyson Perrins Laboratory.

Melting points were determined on a Büchi 510 apparatus and are uncorrected.

Thin layer chromatography (t.l.c.) was performed on Merck DC-Alufolien $60F_{254}$ 0.2mm precoated plates. Product spots were visualised by the quenching of ultraviolet fluorescence then stained and heated with one of three solutions, as appropriate:

(i) 10% (w/v) ammonium molybdate in 2M sulphuric acid,

(ii) 5% (w/v) *dodeca*-molybdophosphoric acid in ethanol,

(iii) 5% (w/v) potassium permanganate in 0.5% potassium carbonate solution (aqueous).

Preparative layer chromatography (p.l.c.) was performed on silica gel (HF-Blend 41/KG) coated to 1mm on 200x200mm glass plates; these were generally pre-eluted with dichloromethane before use. Flash chromatography was performed by the method of Still *et al.*[203] on silica gel (Merck Kieselgel $60GF_{254}$ 230-400mesh).

Short path or bulb to bulb distillation refers to distillation at reduced pressure using a horizontal Kugelrohr apparatus, the temperature quoted being that of the heating bath.

All solvents were purified and distilled by standard procedures[204] before use. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 30-40°C. Benzene, for radical reactions, was degassed by passing a rapid flow of argon through it for 30-90 minutes, depending on scale.

Organolithium solutions were standardised by titration against 1,3-diphenyl acetone *p*-toluenesulphonyl hydrazone prior to use. The purity of tributyltin hydride was regularly ascertained by ^1H n.m.r. (δ 4.68, 1H, septet, *J* 2.0Hz, Bu_3SnH). Di-iodoalkanes (prepared on a large scale by Finkelstein reaction[164] of the appropriate dibromo-compounds) were distilled and stored in the dark. Di-isopropylamine, HMPA, trimethylsilyl chloride, and triethylamine were heated at reflux over, and distilled from, calcium hydride then stored on molecular sieves (4Å) under argon (except triethylamine which was stored over potassium hydroxide pellets). Triphenyl phosphine and imidazole were recrystallised from hexane immediately before use. Other reagents were used as supplied by the manufacturers.

Reactions were conducted under an inert atmosphere (nitrogen or argon) unless otherwise stated.

III.2 Experimental Procedures.

2-Carbomethoxycyclohex-2-enone **95**. Using the procedure of Reich *et al.*[124] *2-carbomethoxy-2-phenylselenocyclohexanone* was obtained as an off-white solid (m.p. 52-54°C). $\nu_{max.}$ ($CHCl_3$) 3030 (w), 2960 (w), 2880 (w), 1760-1700 (s), 1440 (m), 1260-1200 (s), 1130 (m), 695 (m); δ_H (300 MHz) 1.46-1.59 (1H, m), 1.68-1.85 (2H, m) and 1.94 (1H, td, *J* 13, 4.0Hz, $C_2\underline{H}_4CH_2CO$-), 1.99-2.08 (1H, m) and 2.37-2.52 (2H, m, $CH\underline{H}CO$- and $C\underline{H}_2C(CO_2Me)$-), 2.66 (1H, dtd, *J* 14, 4.0, 2.5Hz, $C\underline{H}HCO$-), 3.72 (3H, s, $CO_2C\underline{H}_3$), 7.27-7.36 (2H, m, Ph- *m*- protons), 7.37-7.45 (1H, m, Ph- *p*- proton), 7.53-7.61 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 312 (M^+, ^{80}Se, 100%), 310 (M^+, ^{78}Se, 58), 234 (18), 156 (78), 127 (38), 95 (47), 77 (69), 67 (64), 59 (33), 55 (51). This selenide was then oxidised according to the literature[124] to yield the title compound **95** as a colourless oil (91%) after purification by flash column chromatography (3:1 petrol:ether). This material was indefinitely stable if stored refrigerated under argon. $\nu_{max.}$ (thin film) 2950 (m), 2880 (w), 1770-1700 (s), 1680 (s), 1435 (m), 1370 (m), 1270 (s), 1220 (m), 1060 (s), 980 (w), 950 (w), 775 (w), 750 (w); δ_H (300 MHz) 2.07 (2H, quin., *J* 7.5Hz, $C\underline{H}_2CH_2CO$-), 2.48-2.58 (4H, m, $C\underline{H}_2CH$= and $C\underline{H}_2CO$-), 3.81 (3H, s, $CO_2C\underline{H}_3$), 7.71 (1H, t, *J* 5.0Hz, $C\underline{H}$=); *m/z* (E.I.) 154 (M^+, 69%), 126 (100), 123 (54), 122 (50), 98 (94), 95 (24), 68 (63), 66 (28), 55 (47), 53 (28).

2-Methylcyclohex-2-enone **96**[125]. The literature procedure was followed to give the title compound **96** as a colourless oil (58%) after bulb to bulb distillation (66°C/14mmHg). $\nu_{max.}$ (thin film) 2940 (s), 2880 (m), 1680 (s), 1455 (m), 1435 (m), 1365 (m), 1180 (m), 1110 (m), 1025 (m), 905 (m), 885 (m), 735 (m), 710 (m), 690 (m); δ_H (250 MHz) 1.75 (3H, t, *J* 3.0Hz, $C\underline{H}_3$-), 1.96 (2H, ca. quin., *J* 6.0Hz, $C\underline{H}_2CH_2CO$-), 2.25-2.35 (2H, m, $C\underline{H}_2CH$=), 2.36-2.45 (2H, m, $C\underline{H}_2CO$-), 6.73 (1H, ca. td, *J* 4.5, 1.5Hz, $C\underline{H}$=); *m/z* (E.I.) 110 (M^+, 42%), 82 (100), 68 (23), 67 (22), 54 (72).

General Procedure for the preparation of the 1-halo-n-phenylseleno-alkanes **110-112**. Sodium borohydride (1.1 equiv.) was added in portions to a stirred solution of diphenyl diselenide (0.5 equiv.) in ethanol (≈4ml/mmol of diphenyl diselenide) at 0°C. The

colourless solution was stirred for 0.5h at this temperature then added dropwise to a cooled (0°C), stirred solution of the appropriate 1,n-dihalide (4-20 equiv.) in ethanol (same volume as above). The mixture was stirred overnight at room temperature then the ethanol removed *in vacuo* and the residue dissolved in a mixture of equal volumes of 10% aqueous sodium carbonate and ether. The aqueous layer was thoroughly extracted with ether then the combined organic portions washed with brine, then dried ($MgSO_4$) and concentrated *in vacuo*. Further purification was carried out as detailed below.

Bromo-phenylselenomethane **110**. The standard procedure was followed using diphenyl diselenide (5.0g, 0.016mol) and dibromomethane (45ml, 0.64mol). The crude product was subjected to bulb to bulb distillation and the *bromo-phenylselenomethane* **110** collected (2.60g, 33%; b.p. 130°C/0.02mm Hg) as a pale yellow oil. $\nu_{max.}$ (thin film) 3060 (m), 2960 (w), 1580 (s), 1480 (s), 1440 (s), 1165 (s), 1090 (m), 1070 (m), 1025 (s), 1000 (m), 775 (m), 735 (s), 690 (s), 620 (s); δ_H (200 MHz) 4.76 (2H, s, $C\underline{H_2}Br$), 7.27-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.50-7.62 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 252 (M^+, $^{80}Se^{81}Br$, 12%), 250 (15), 248 (8), 171 (76), 169 (44), 167 (20), 157 (13), 91 (100), 77 (27), 65 (14), 51 (33). The residue from the distillation consisted of *di(phenylseleno)methane* (**113**, 3.45g, 66%), also a yellow oil. $\nu_{max.}$ (thin film) 3070 (m), 3000 (m), 2930 (m), 1580 (s), 1475 (s), 1440 (s), 1135 (s), 1070 (s), 1020 (s), 1000 (s), 730 (s), 690 (s); δ_H (200 MHz) 4.25 (2H, s, $C\underline{H_2}SePh$), 7.32-7.42 (6H, m, Ph- *m*- and *p*- protons), 7.58-7.70 (4H, m, Ph- *o*- protons); *m/z* (E.I.) 328 (M^+, $^{80}Se_2$, 22%), 326 (22), 324 (14), 171 (74), 169 (45), 167 (21), 157 (12), 91 (100), 77 (25), 65 (15), 51 (25).

1-Iodo-3-phenylselenopropane **111**. The standard procedure with diphenyl diselenide (1.0g, 3.21mmol) and 1,3-di-iodopropane (3.0ml, 26mmol) gave a crude product containing excess di-iodide which was removed by bulb to bulb distillation (≈80°C/0.02 mmHg). The residue was further purified by flash column chromatography (10:1 petrol:ether) to yield the product **111** as a pale yellow oil (2.04g, 96%). This material contained less than 5% of the diselenide **114** by inspection of the integral ratios in the ^1H n.m.r. spectrum. $\nu_{max.}$ (thin film) 3060 (m), 2960 (m), 1575 (s), 1475 (s), 1435 (s),

1280 (m), 1200 (s), 1070 (m), 1020 (s), 1000 (m), 730 (s), 690 (s), 670 (m); δ_H (200 MHz) 2.08-2.28 (2H, m, C$\underline{H}_2$CH$_2$I), 3.01 (2H, t, *J* 8.0 Hz, C$\underline{H}_2$SePh), 3.30 (2H, t, *J* 6.5Hz, C$\underline{H}_2$I), 7.20-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.47-7.58 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 326 (M^+, ^{80}Se, 26%), 324 (14), 296 (33), 199 (43), 197 (24), 169 (100), 157 (28), 155 (17), 127 (23), 91 (26), 77 (20), 65 (5), 51 (13).

1-Iodo-4-phenylselenobutane **112**. The standard procedure with diphenyl diselenide (1.0g, 3.21mmol) and 1,4-di-iodobutane (2.0ml, 19mmol) afforded a crude product which was rendered free of di-iodide by bulb to bulb distillation (≈100°C/0.02mm Hg). The residue was passed through a plug of silica (10:1 petrol:ether eluant) to provide the selenide (**112**, 1.89g, 87%) as a pale yellow oil. This material was contaminated with ≈25% *di(phenylseleno)butane* **115**. $\nu_{max.}$ (thin film) 3070 (m), 3005 (m), 2940 (m), 1580 (m), 1475 (s), 1440 (s), 1260 (m), 1165 (m), 1075 (m), 1000 (m), 690 (s); δ_H (200 MHz) 1.74-2.07 (4H, m, C$_2\underline{H}_4$CH$_2$I), 2.92 (2H, t, *J* 8.0 Hz, C$\underline{H}_2$SePh), 3.18 (2H, t, *J* 7.0 Hz, C$\underline{H}_2$I), 7.18-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.57 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 370 (M^+, $^{80}Se_2$, diselenide, 5%), 368 (diselenide, 5), 340 (M^+, ^{80}Se, 12), 338 (6), 234 (9), 213 (100), 211 (54), 183 (40), 171 (27), 169 (14), 157 (42), 91 (33), 77 (45), 55 (88).

2-Bromocyclohex-2-enone **123**[132]. Following the procedure of Smith[132] the title compound **123** was obtained as a white solid (m.p. 72-75°C, lit.,[132b] 72.5-75°C). $\nu_{max.}$ ($CHCl_3$) 3020 (m), 2960 (m), 2880 (m), 1690 (s), 1600 (m), 1320 (m), 1250-1210 (m), 1125 (m), 995 (m), 905 (m), 820 (m), 705 (m); δ_H (200 MHz) 2.06 (2H, ca. quin., *J* 6.5Hz, C$\underline{H}_2$CH$_2$CO-), 2.43 (2H, ca. quin., *J* 5.5Hz, C$\underline{H}_2$CH=), 2.62 (2H, t, *J* 6.5Hz, C$\underline{H}_2$CO-), 7.42 (1H, t, *J* 4.5Hz, C$\underline{H}$=); *m/z* (E.I.) 176 (M^+, ^{81}Br, 47%), 174 (M^+, ^{79}Br, 48), 148 (56), 146 (60), 135 (15), 133 (17), 120 (27), 118 (29), 95 (15), 67 (100), 55 (62).

6-Bromo-1,4-dioxaspiro[4,5]dec-6-ene **122**[132]. Following the procedure of Smith[132] the ketal **122** was obtained as a colourless oil after purification by flash column

chromatography (5:1 petrol:ether). $\nu_{max.}$ (thin film) 2950 (s), 2890 (s), 2840 (m), 1640 (m), 1440 (m), 1350 (m), 1180 (s), 1110 (s), 1070 (s), 1025 (s), 950 (s), 815 (m), 790 (m), 740 (m); δ_H (200 MHz) 1.69-1.84 (2H, m, $C\underline{H}_2C(OR)_2$-), 1.87-1.98 (2H, m, $C\underline{H}_2CH_2CH$=), 2.02-2.15 (2H, m, $C\underline{H}_2CH$=), 3.90-4.06 (2H, m) and 4.11-4.27 (2H, m, -$OC_2\underline{H}_4O$-), 6.34 (1H, t, *J* 4.0Hz, C<u>H</u>=); *m/z* (E.I.) 220 (M^+, ^{81}Br, 7%), 218 (M^+, ^{79}Br, 8), 192 (96), 190 (100), 148 (30), 146 (31), 139 (35), 99 (78), 55 (41).

General procedure for the preparation and alkylation of the vinyl anion **124**. A solution of the bromoketal **122** in dry THF (≈10ml/mmol of **122**) was cooled to -78°C under argon. ^{n}Butyl lithium (1.25 equiv. of a 1.3<u>M</u> solution in hexanes) was added and the resultant mixture stirred for 1h at -78°C. The electrophile was added and the mixture allowed to come up to room temperature overnight. In cases where alkylation was more difficult the mixture was warmed to -23°C and HMPA (5-12 equiv.) was added after addition of the electrophile. The mixture was quenched with saturated ammonium chloride solution and the aqueous layer extracted thoroughly with ether. The organic layer was then washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude alkylated ketals. Flash column chromatography (10 to 15:1 petrol:ether) afforded the pure compounds as colourless oils.

6-Iodo-1,4-dioxaspiro[4,5]dec-6-ene **125**. The anion derived from the bromoketal **122** (100mg, 0.46mmol) was quenched with 1,3-di-iodopropane (0.21ml, 1.83mmol) and allowed to warm up to room temperature over 14h. Flash column chromatography (8:1 petrol:ether) of the crude material gave *6-iodo-1,4-dioxaspiro[4,5]dec-6-ene* **125** as a colourless oil (117mg, 96%). $\nu_{max.}$ (thin film) 2945 (s), 2885 (s), 2840 (m), 1655 (w), 1440 (m), 1300 (m), 1175 (s), 1110 (s), 1070 (s), 1025 (s), 750 (m); δ_H (200 MHz) 1.72-1.87 (2H, m, $C\underline{H}_2C(OR)_2$-), 1.90-1.99 (2H, m, $C\underline{H}_2CH_2CH$=), 2.03-2.18 (2H, m, $C\underline{H}_2CH$=), 3.91-4.07 (2H, m) and 4.14-4.29 (2H, m, -$OC_2\underline{H}_4O$-), 6.70 (1H, t, *J* 4.0Hz, C<u>H</u>=), δ_C (50.3 MHz) 20.40, 29.27, 34.30, 65.56, 103.44, 106.23, 145.03; *m/z* (ACE, NH_3) 267 (MH^+, 100%), 238 (25), 139 (16), 99 (29).

6-Deutero-1,4-dioxaspiro[4,5]dec-6-ene **126**. The anion derived from the bromo-ketal (**122**, 2.0g, 9.13mmol) was quenched with deuterium oxide (1ml, ≈55mmol) at -78°C then allowed to warm to room temperature over 1h. The work-up described in the general procedure afforded spectroscopically clean ketal **126** (1.12g, 87%). $\nu_{max.}$ (thin film) 3020 (m), 2940 (s), 2880 (s), 2840 (m), 1640 (m), 1455 (m), 1440 (m), 1365 (m), 1260 (m), 1175 (s), 1115 (s), 1075 (s), 1030 (s), 945 (s), 890 (m), 840 (m); δ_H (200 MHz) 1.71-1.86 (4H, m, $C_2\underline{H}_4C(OR)_2$-), 1.96-2.12 (2H, m, $C\underline{H}_2CH$=), 3.92-4.05 (4H, m, $OC_2\underline{H}_4O$-), 5.92-6.03 (1H, m, C<u>H</u>=); *m/z* (E.I.) 141 (M^+, 21%), 113 (100), 69 (44), 55 (14).

6-(3'-Phenylselenopropyl)-1,4-dioxaspiro[4,5]dec-6-ene **127**. The anion derived from the bromoketal (**122**, 300mg, 1.37mmol) was quenched with 1-iodo-3-phenylseleno-propane (**111**, 490mg, 1.51mmol) and allowed to warm up to room temperature over 14h. Work-up and flash column chromatography (15:1 petrol:ether) gave pure ketal **127** (320mg, 69%). (Found: C, 60.26; H, 6.20. $C_{17}H_{22}O_2Se$ requires C, 60.53; H, 6.57%); $\nu_{max.}$ (thin film) 3060 (m), 2950 (s), 2920 (s), 2875 (s), 1670 (s), 1580 (s), 1475 (s), 1435 (s), 1380 (m), 1170 (s), 1110 (s), 1070 (s), 1020 (s), 940 (s), 735 (s), 690 (s); δ_H (250 MHz) 1.69-1.80 (4H, m, $C\underline{H}_2CH_2SePh$ and $C\underline{H}_2C(OR)_2$-), 1.82-2.03 (2H, m, $C\underline{H}_2CH_2CH$=), 2.12-2.23 (4H, m, $C\underline{H}_2CH$= and $C\underline{H}_2CR$=), 2.98 (2H, t, *J* 6.5Hz, $C\underline{H}_2SePh$), 4.02 (4H, s, -$OC_2\underline{H}_4O$-), 5.69-5.75 (1H, m, C<u>H</u>=), 7.23-7.33 (3H, m, Ph-*m*- and *p*- protons), 7.47-7.58 (2H, m, Ph- *o*- protons); *m/z* (ACE, NH_3) 339 (MH^+, ^{80}Se, 41%), 337 (22), 295 (45), 293 (24), 267 (65), 221 (94), 219 (100), 137 (35), 99 (26).

6-(4'-Iodobutyl)-1,4-dioxaspiro[4,5]dec-6-ene **128**. The anion derived from the bromo-ketal (**122**, 500mg, 2.28mmol) was quenched with 1,4-di-iodobutane (0.9ml, 6.82mmol) and allowed up to room temperature over 14h. The usual work-up and flash column chromatography (10:1 petrol:ether) gave the pure ketal (**128**, 724mg, 99%). $\nu_{max.}$ (thin film) 2940 (s), 2880 (s), 2840 (m), 1675 (w), 1455 (m), 1440 (m), 1210 (m), 1175 (s), 1115 (s), 1070 (s), 1025 (s), 945 (s); δ_H (200 MHz) 1.45-1.66 (4H, m, $C_2\underline{H}_4CH_2I$),

1.75-1.92 (4H, m, $C_2\underline{H}_4C(OR)_2$-), 1.96-2.13 (4H, m, $C\underline{H}_2CR$= and $C\underline{H}_2CH$=), 3.19 (2H, t, *J* 8.0Hz, $C\underline{H}_2I$), 3.99 (4H, s, -$OC_2\underline{H}_4O$-), 5.70 (1H, brs, C<u>H</u>=); *m/z* (ACE, NH_3) 323 (MH^+, 100%), 294 (45), 267 (10), 195 (9), 167 (28), 151 (9), 125 (22), 99 (37).

6-(4'-Bromobutyl)-1,4-dioxaspiro[4,5]dec-6-ene **129**. The anion derived from the bromoketal (**122**, 100mg, 0.46mmol) was quenched with 1,4-dibromobutane (0.22ml, 1.84mmol) and allowed to room temperature over 20h. The crude product was purified by flash chromatography (8:1 petrol:ether) to yield *6-(4'-bromobutyl)-1,4-dioxaspiro-[4,5]dec-6-ene* **129** as a colourless oil (60mg, 74% based on recovered bromoketal **122** (35mg)). $\nu_{max.}$ (thin film) 3030 (w), 2940 (s), 2880 (s), 1670 (w), 1440 (m), 1340 (m), 1265 (m), 1170 (s), 1115 (s), 1070 (s), 1030 (s), 940 (s), 730 (s), 695 (m); δ_H (200 MHz) 1.49-1.96 (8H, m, $C_2\underline{H}_4C(OR)_2$- and $C_2\underline{H}_4CH_2Br$), 1.99-2.14 (4H, m, $C\underline{H}_2CH$=CR$C\underline{H}_2$-), 3.43 (2H, t, *J* 6.5Hz, $C\underline{H}_2Br$), 4.00 (4H, s, -$OC_2\underline{H}_4O$-), 5.71 (1H, s, C<u>H</u>=); *m/z* (C.I., NH_3) 277 (MH^+, ^{81}Br, 31%), 275 (MH^+, ^{79}Br, 32), 250 (11), 248 (14), 233 (17), 231 (19), 195 (22), 151 (30), 141 (100), 114 (15), 97 (16), 44 (22).

6-(4'-Phenylselenobutyl)-1,4-dioxaspiro[4,5]dec-6-ene **134**. Sodium borohydride (68mg, 1.70mmol) was added in portions to a solution of diphenyl diselenide (266mg, 0.85mmol) in ethanol (20ml) cooled to 0°C. The colourless solution was stirred for 0.5h at 0°C then a solution of the iodide (**128**, 500mg, 1.55mmol) in ethanol (2ml) was added rapidly. The solution was warmed to room temperature and stirred for 2h. Most of the solvent was removed *in vacuo* then the mixture was partitioned between 1:1 petrol:ether and aqueous sodium carbonate (10%). The organic layer was washed with brine then dried (sodium sulphate) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (15:1 petrol:ether) to give the pure selenide **134** as a colourless oil (520mg, 96%). (Found: C, 61.34; H, 7.02. $C_{18}H_{24}O_2Se$ requires C, 61.53; H, 6.88%); $\nu_{max.}$ (thin film) 3060 (w), 2940 (m), 2880 (m), 1580 (m), 1480 (m), 1435 (m), 1170 (m), 1115 (m), 1020 (m), 945 (m); δ_H (250 MHz) 1.45-1.64 (2H, m) and 1.66-1.78 (6H, m, $C_2\underline{H}_4CH_2SePh$ and $C_2\underline{H}_4C(OR)_2$-), 1.98-2.08 (4H, m, $C\underline{H}_2CR$= and $C\underline{H}_2CH$=), 2.93 (2H, t, *J* 7.5Hz, $C\underline{H}_2SePh$), 3.99 (4H, s, -$OC_2\underline{H}_4O$-), 5.65-5.70 (1H, m, C<u>H</u>=), 7.21-

7.29 (3H, m, Ph- *m*- and *p*- protons), 7.45-7.52 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 353 (MH^+, ^{80}Se, 100%), 351 (66), 307 (18), 305 (9), 99 (12).

General procedure for the hydrolysis of the alkylated ketals. A solution of oxalic acid (3.2 equiv.) in water (10ml/mmol of ketal) was added to a stirred solution of the ketal in dichloromethane (10ml/mmol) at room temperature. The mixture was stirred as rapidly as possible until the hydrolysis was found to be complete by t.l.c. analysis (2-14h). The aqueous layer was extracted with ether and the extracts combined with the organic layer. The combined extracts were washed with saturated sodium hydrogen carbonate solution, then brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the ketones which required no further purification except for the purposes of characterisation in which case small samples were subjected to p.l.c.

2-Deuterocyclohex-2-enone **105**. Hydrolysis of the ketal (**126**, 1.12g, 7.94mmol) gave the pure ketone (**105**, 728mg, 95%) as a colourless, volatile oil. $\nu_{max.}$ (thin film) 3030 (w), 2940 (m), 2870 (m), 1680 (s), 1605 (m), 1430 (m), 1360 (m), 1235 (m), 1170 (m), 1135 (m), 970 (m), 750 (m), 705 (m), 670 (m); δ_H (200 MHz) 1.92-2.09 (2H, m, $C\underline{H}_2CH_2CO$-), 2.26-2.46 (4H, m, $C\underline{H}_2CO$- and $C\underline{H}_2CH$=), 6.96-7.03 (1H, m, C<u>H</u>=); *m/z* (E.I.) 97 (M^+, 25%), 69 (100), 55 (14).

2-(3'-Phenylselenopropyl)-cyclohex-2-enone **130**. Hydrolysis of the ketal (**127**, 180mg, 0.53mmol) afforded the ketone (**130**, 153mg, 98%) as a colourless oil. (Found: C, 61.45; H, 6.27. $C_{15}H_{18}OSe$ requires C, 61.43; H, 6.19%); $\nu_{max.}$ (thin film) 3060 (m), 2930 (s), 2860 (m), 1670 (s), 1580 (m), 1480 (m), 1435 (m), 1375 (m), 1170 (m), 1025 (m), 905 (m), 735 (s), 690 (s); δ_H (250 MHz) 1.65-1.71 (2H, m, $C\underline{H}_2CH_2SePh$), 1.82-1.96 (2H, m, $C\underline{H}_2CH_2CH$=), 2.15-2.20 (4H, m, $C\underline{H}_2CH$= and $C\underline{H}_2CR$=), 2.32 (2H, t, *J* 6.5Hz, $C\underline{H}_2CO$-), 2.82 (2H, t, *J* 6.5Hz, $C\underline{H}_2SePh$), 6.63 (1H, t, *J* 4.0Hz, C<u>H</u>=), 7.12-7.23 (3H, m, Ph- *m*- and *p*- protons), 7.35-7.44 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 294 (M^+, ^{80}Se, 12%), 292 (7), 157 (9), 137 (100), 95 (9), 91 (10), 81 (12), 79 (13), 77 (14), 67 (17).

2-(4'-Iodobutyl)-cyclohex-2-enone **131**. Hydrolysis of the ketal (**128**, 500mg, 1.55mmol) afforded the ketone (**131**, 424mg, 98%) as a colourless oil. $\nu_{max.}$ (thin film) 2930 (s), 2870 (m), 1670 (s), 1430 (m), 1380 (m), 1210 (m), 1175 (m), 910 (m), 730 (m); δ_H (200 MHz) 1.40-1.59 (2H, m, C$\underline{H}_2$C$_2$H$_4$I), 1.69-1.90 (2H, m, C$\underline{H}_2$CH$_2$I), 1.98 (2H, ca. quin., C$\underline{H}_2$CH$_2$CO-), 2.19 (2H, t, *J* 7.0Hz, C$\underline{H}_2$C(CO-)=), 2.30-2.60 (4H, m, C$\underline{H}_2$CO- and C$\underline{H}_2$CH=), 3.20 (2H, t, *J* 7.0Hz, C$\underline{H}_2$I), 6.74 (1H, t, *J* 4.5Hz, C$\underline{H}$=); *m/z* (C.I., NH_3) 296 (MNH_4^+, 47%), 279 (MH^+, 100), 151 (52).

2-(4'-Bromobutyl)-cyclohex-2-enone **132**. Hydrolysis of the ketal (**129**, 40mg, 0.15 mmol) gave spectroscopically clean *2-(4'-bromobutyl)-cyclohex-2-enone* (**132**, 30mg, 87%). $\nu_{max.}$ (thin film) 2940 (m), 2870 (m), 1690-1650 (s), 1455 (m), 1430 (m), 1380 (m), 1250 (m), 1175 (m), 1130 (m), 1100 (m), 910 (m), 735 (m); δ_H (250 MHz) 1.46-1.60 (2H, m, C$\underline{H}_2$C$_2$H$_4$Br), 1.85 (2H, ca. quin., *J* 7.0Hz, C$\underline{H}_2$CH$_2$Br), 1.97 (2H, ca. quin., *J* 6.5Hz, C$\underline{H}_2$CH$_2$CO-), 2.19 (2H, td, *J* 7.0, 1.5Hz, C$\underline{H}_2$CR=CH-), 2.30-2.49 (4H, m, C$\underline{H}_2$CO- and C$\underline{H}_2$CH=), 3.39 (2H, t, *J* 7.0Hz, C$\underline{H}_2$Br), 6.73 (1H, t, *J* 4.5Hz, C$\underline{H}$=); *m/z* (C.I., NH_3) 250 (MNH_4^+, ^{81}Br, 92%), 248 (MNH_4^+, ^{79}Br, 94), 233 (MH^+, ^{81}Br, 97), 231 (MH^+, ^{79}Br, 100), 170 (28), 151 (77), 108 (9), 91 (21).

2-(4'-Phenylselenobutyl)-cyclohex-2-enone **133**. Hydrolysis of the ketal (**134**, 500mg, 1.42mmol) afforded the ketone (**133**, 468mg, 100%) as a colourless oil. (Found: C, 62.48; H, 6.71. $C_{16}H_{20}OSe$ requires C, 62.54; H, 6.56%); $\nu_{max.}$ (thin film) 3060 (m), 2930 (s), 2860 (m), 1670 (s), 1580 (m), 1480 (m), 1435 (m), 1380 (m), 1175 (m), 1020 (m), 910 (m), 735 (s), 690 (m); δ_H (250 MHz) 1.43-1.58 (2H, m) and 1.63-1.77 (2H, m, C$_2\underline{H}_4$CH$_2$SePh), 1.92-2.03 (2H, m, C$\underline{H}_2$CH$_2$CH=), 2.18 (2H, t, *J* 7.5Hz, C$\underline{H}_2$CR=), 2.28-2.36 (2H, m, C$\underline{H}_2$CH=), 2.40 (2H, t, *J* 8.0Hz, C$\underline{H}_2$CO-), 2.91 (2H, t, *J* 8.0Hz, C$\underline{H}_2$SePh), 6.68 (1H, t, *J* 4.0Hz, C$\underline{H}$=), 7.21-7.30 (3H, m, Ph- *m*- and *p*- protons), 7.44-7.53 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 326 (MNH_4^+, ^{80}Se, 40%), 324 (20), 309 (MH^+, ^{80}Se, 100), 307 (50), 305 (20), 151 (61).

General procedure for the preparation of the trans- substrates. To a stirred solution of di-isopropylamine (1.5 equiv.) in anhydrous THF (≈2ml/mmol of enone) at 0°C under argon was added ^{n}butyl lithium (1.05 equiv. of a 1.60M solution in hexanes). The mixture was stirred for 20min at this temperature then tributyltin hydride (1.0 equiv.) was added and the mixture stirred for a further 20min. The yellow solution was cooled to -78°C whereupon the relevant enone was added dropwise as a solution in THF (≈0.5ml/mmol). The mixture was stirred at this temperature until no starting enone remained by t.l.c. analysis (10-30min) then warmed to -23°C. HMPA (12 equiv.) was added and the resulting mixture stirred for 10min. The alkylating agent was added dropwise and the mixture kept at -23°C for a further 4h before being allowed to warm up to room temperature overnight. The mixture was quenched with saturated ammonium chloride solution and the aqueous layer extracted with ether (x5). The combined organic portions were washed with brine then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude products were subjected to flash column chromatography (20:1 petrol:ether then gradient elution to 5:1 petrol:ether). Material obtained in this way contained trace amounts of closely running impurities; absolute purity, for the purposes of characterisation, was obtained by p.l.c.

trans-2-(4'-Iodobutyl)-3-tributylstannylcyclohexanone **97**. The above procedure produced the pure stannane (**97**, 1.61g, 55%) as a colourless oil from cyclohex-2-enone (500mg, 5.21mmol) and 1,4-di-iodobutane (2.75ml, 21mmol). (Found: C, 46.61; H, 8.00. $C_{22}H_{43}IOSn$ requires C, 46.43; H, 7.61%); $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2860 (s), 1710 (s), 1470-1410 (m), 1380 (m), 1170 (m), 1075 (m), 875 (m); δ_H (200 MHz) 0.70-1.05 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.08-2.22 (23H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_3\underline{H}_6CH_2I$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.29-2.49 (3H, m, $C\underline{H}_2COC\underline{H}R$-), 3.17 (2H, t, *J* 7.5Hz, $C\underline{H}_2I$); δ_C (50.3 MHz, DEPT) CH: 34.31, 54.53, CH_2: 16.54, 19.10, 27.56, 28.97 (3), 30.47, 32.61, 33.89, 42.99, CH_3: 13.68; *m/z* (D.C.I., NH_3) 571 (MH^+, ^{120}Sn, 16%), 569 (16), 513 (25), 511 (20), 509 (11), 385 (20), 378 (16), 361 (23), 308 (100), 306 (77), 304 (49), 291 (44), 289 (34), 287 (22), 153 (59), 135 (49), 81 (16), 67 (16), 55 (21).

trans-2-(4'-Iodobutyl)-2-methyl-3-tributylstannylcyclohexanone **98**. From 2-methylcyclohex-2-enone (**96**, 500mg, 4.55mmol) and 1,4-di-iodobutane (2.75ml, 21mmol) was obtained the pure stannane **98** as a colourless oil (1.60g, 60%). (Found: C, 47.09; H, 8.20. $C_{23}H_{45}IOSn$ requires C, 47.37; H, 7.78%); $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (s), 1705 (s), 1480-1410 (m), 1380 (m), 1075 (w), 870 (w); δ_H (200 MHz) 0.82-0.97 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.13 (3H, s, $C\underline{H}_3$-), 1.22-1.68 (16H, m) and 1.72-2.05 (7H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_3\underline{H}_6CH_2I$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.25-2.51 (2H, m, $C\underline{H}_2CO$-), 3.19 (2H, td, *J* 8.0, 3.0Hz, $C\underline{H}_2I$); *m/z* (D.C.I., NH_3) 602 (MNH_4^+, ^{120}Sn, 50%), 600 (39), 598 (22), 457 (34), 455 (28), 453 (14), 308 (66), 306 (50), 304 (24), 184 (52), 167 (27), 149 (100).

trans-2-Carbomethoxy-2-(4'-iodobutyl)-3-tributylstannylcyclohexanone **99**. Using 2-carbomethoxycyclohex-2-enone (**95**, 500mg, 3.25mmol) and 1,4-di-iodobutane (1.29ml, 9.78mmol) and a reaction time of 24h, repeated flash column chromatography (20:1-5:1 petrol:ether then 20:1 petrol:ether), gave the pure stannane (**99**, 35-40%) as a colourless oil. (Found: C, 45.68; H, 7.36. $C_{24}H_{45}IO_3Sn$ requires C, 45.96; H, 7.23%); $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (s), 1730 (m), 1710 (s), 1470-1410 (m), 1375 (m), 1280-1130 (m), 1080 (m); δ_H (200 MHz) 0.74-0.99 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.12-1.59 (16H, m), 1.64-1.88 (6H, m), and 2.04-2.18 (1H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_3\underline{H}_6CH_2I$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.34-2.55 (2H, m, $C\underline{H}_2CO$-), 3.17 (2H, td, *J* 8.0, 4.0Hz, $C\underline{H}_2I$), 3.72 (3H, s, $CO_2C\underline{H}_3$); δ_C (50.3 MHz) 9.77, 10.91, 13.75, 26.53, 26.99, 27.95, 28.92, 29.66, 30.51, 31.36, 34.49, 42.56, 53.07, 64.15, 174.77, 208.69 (^3J (^{119}Sn-^{13}C) 38Hz); *m/z* (F.I.) 628 (M^+, ^{120}Sn, 85%), 626 (74), 624 (44), 571 (set to 100), 569 (79), 567 (55).

trans-2-Deutero-2-(4'-iodobutyl)-3-tributylstannylcyclohexanone **104**. From 2-deuterocyclohex-2-enone (**105**, 500mg, 5.15mmol) and 1,4-di-iodobutane (2.75ml, 21mmol) the stannane **104** was obtained as a colourless oil (1.36g, 48%). (Found: C, 46.21; H(D), 8.06. $C_{22}H_{42}DIOSn$ requires C, 46.34; H(D), 7.60%); $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (s), 1705 (s), 1475-1410 (m), 1375 (m), 1250 (m), 1170 (m), 1075 (m), 870

(m); δ_H (200 MHz) 0.70-1.05 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.09-2.24 (23H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_3\underline{H}_6CH_2I$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.33-2.45 (2H, m, $C\underline{H}_2CO$-), 3.20 (2H, t, *J* 8.0Hz, $C\underline{H}_2I$); *m/z* (F.I.) 571 (M^+, ^{120}Sn, 71%), 569 (51), 567 (45), 514 (set to 100), 512 (51), 510 (35).

trans-2-(5'-Iodopentyl)-3-tributylstannylcyclohexanone **108**. From cyclohex-2-enone (500mg, 5.21mmol) and 1,5-di-iodopentane (2.33ml, 15.7mmol) the stannane **108** was obtained as a colourless oil (1.17g, 39%) after flash chromatography (20:1 then 10:1 petrol:ether). (Found: C, 47.66; H, 8.03. $C_{23}H_{45}OISn$ requires C, 47.37; H, 7.78%); $\nu_{max.}$ (thin film) 2950 (s), 2920 (s), 2850 (s), 1705 (s), 1455 (m), 1375 (m), 1210 (m), 1170 (m), 1070 (m), 1015 (m), 960 (m), 870 (m); δ_H (200 MHz) 0.75-0.97 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.08-2.18 (25H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_4\underline{H}_8CH_2I$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.26-2.53 (3H, m, $C\underline{H}_2COC\underline{H}R$-), 3.18 (2H, t, *J* 8.0Hz, $C\underline{H}_2I$); *m/z* (E.I.) 583 (18), 581 (15), 579 (8), 527 (61), 525 (47), 523 (28), 399 (30), 361 (65), 291 (88), 235 (64), 177 (71), 81 (75), 67 (66), 55 (100).

trans-2-(3'-Phenylselenopropyl)-3-tributylstannylcyclohexanone **116**. The general procedure with cyclohex-2-enone (150mg, 1.56mmol) and 1-iodo-3-phenyl-selenopropane (**111**, 560mg, 1.72mmol) produced pure **116** as a colourless oil (496mg, 56%). (Found: C, 55.84; H, 8.30. $C_{27}H_{46}OSeSn$ requires C, 55.50; H, 7.93%); $\nu_{max.}$ (thin film) 3070 (w), 2960 (s), 2920 (s), 2860 (s), 1705 (s), 1580 (m), 1470-1410 (m), 1375 (m), 1245 (m), 1075 (m), 1025 (m), 735 (m), 690 (s); δ_H (200 MHz) 0.82-0.97 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.20-2.03 (20H, m) and 2.10-2.18 (1H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_2\underline{H}_4CH_2SePh$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.29-2.47 (3H, m, $C\underline{H}_2COC\underline{H}R$-), 2.81-2.99 (2H, m, $C\underline{H}_2SePh$), 7.18-7.32 (3H, m, Ph- *m*- and *p*- protons), 7.41-7.53 (2H, m, Ph- *o*- protons); δ_C (50.3 MHz) 9.46, 14.02, 27.50, 28.03, 28.46, 29.09, 30.31, 31.58, 32.79, 34.22, 42.58, 54.11, 126.42, 128.80, 130.38, 132.23, 213.16 (^3J (^{119}Sn-^{13}C) 45Hz); *m/z* (F.D.) Calc. 586 (91%), 584 (M^+, 100), 582 (74), and 529 (M^+-^{n}Bu·, 91), 527 (100), 525 (75); Found. 584 (14), 580 (11), 529 (M^+-^{n}Bu·, ^{80}Se^{120}Sn, 74), 527 (set to 100), 526 (57), 525 (74).

trans-2-(4'-Phenylselenobutyl)-3-tributylstannylcyclohexanone **117**. From cyclohex-2-enone (75mg, 0.78mmol) and 1-iodo-4-phenylselenobutane (**112**, 290mg, 0.85mmol) the stannane **117** was produced as a colourless oil (255mg, 54%). (Found: C, 56.20; H, 8.17. $C_{28}H_{48}OSeSn$ requires C, 56.21; H, 8.09%); $\nu_{max.}$ (thin film) 3060 (w), 2960 (s), 2920 (s), 2850 (s), 1710 (s), 1580 (w), 1480-1400 (m), 1225 (m), 1075 (m), 1020 (m), 965 (m), 735 (m), 690 (m), 670-640 (w); δ_H (200 MHz) 0.78-1.05 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.18-2.03 (22H, m) and 2.10-2.23 (1H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_3\underline{H}_6CH_2SePh$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.30-2.53 (3H, m, $C\underline{H}_2COC\underline{H}R$-), 2.89 (2H, t, *J* 8.0Hz, $C\underline{H}_2SePh$), 7.20-7.30 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.53 (2H, m, Ph- *o*- protons); *m/z* (F.D.) 600 (M^+, $^{80}Se^{120}Sn$, 100%), 599 (58), 598 (85), 597 (62), 596 (77), 595 (27), 594 (35).

trans-2-Methyl-2-(3'-phenylselenopropyl)-3-tributylstannylcyclohexanone **118**. The general procedure produced stannane **118** (270mg, 50%) as a colourless oil from 2-methylcyclohex-2-enone (**96**, 250mg, 2.27mmol) and 1-iodo-3-phenylselenopropane (**111**, 810mg, 2.48mmol). (Found: C, 56.10; H, 8.30. $C_{28}H_{48}OSeSn$ requires C, 56.21; H, 8.09%); $\nu_{max.}$ (thin film) 3080 (w), 2960 (s), 2930 (s), 2860 (s), 1705 (s), 1580 (m), 1480-1410 (m), 1375 (m), 1245 (w), 1070 (m), 1025 (m), 735 (s), 690 (s); δ_H (200 MHz) 0.76-0.97 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.05 (3H, s, $C\underline{H}_3$-), 1.18-2.04 (21H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_2\underline{H}_4CH_2SePh$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.24-2.43 (2H, m, $C\underline{H}_2CO$-), 2.88 (2H, t, *J* 8.0Hz, $C\underline{H}_2SePh$), 7.14-7.28 (3H, m, Ph- *m*- and *p*- protons), 7.39-7.51 (2H, m, Ph- *o*- protons); δ_C (50.3 MHz) 9.81, 13.63, 17.45, 24.46, 25.10, 25.73, 27.64, 29.55, 30.51, 38.15, 39.11, 39.30, 52.10, 127.01, 129.24, 131.02, 132.74, 215.61 (^3J (^{119}Sn-^{13}C) 32Hz); *m/z* (F.I.) Calc. 600 (M^+, $^{80}Se^{120}Sn$, 91%), 599 (51), 598 (100), 597 (56), 596 (74), 595 (28), 594 (31); Found. 600 (M^+, $^{80}Se^{120}Sn$, 93), 599 (67), 598 (100), 597 (66), 596 (60), 595 (20), 594 (40).

trans-2-Methyl-2-(phenylselenomethyl)-3-tributylstannylcyclohexanone **119**. Obtained from 2-methylcyclohex-2-enone (**96**, 110mg, 1.0mmol) and bromophenylselenomethane

(**110**, 280mg, 1.12mmol) as a colourless oil (288mg, 50%) after flash column chromatography (20:1-15:1 petrol:ether). (Found: C, 54.88; H, 7.57. $C_{26}H_{44}OSeSn$ requires C, 54.77; H, 7.78%); $\nu_{max.}$ (thin film) 3060 (w), 2960 (s), 2930 (s), 2860 (s), 1705 (s), 1580 (m), 1480-1410 (s), 1375 (m), 1070 (m), 1025 (m), 875 (m), 740 (s), 690 (s), 670 (m); δ_H (200 MHz) 0.74-0.99 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.20-1.64 and 1.74-2.16 (17H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn- and $C_2\underline{H}_4C\underline{H}$(SnBu$_3$)-), 1.28 (3H, s, $C\underline{H}_3$-), 2.26-2.58 (2H, m, $C\underline{H}_2$CO-), 2.98 and 3.11 (2H, ABq, *J* 12Hz, $C\underline{H}_2$SePh), 7.17-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.49-7.60 (2H, m, Ph- *o*- protons); *m/z* (E.I.) Calc. for M^{+}-^{n}Bu· 515 ($^{80}Se^{120}Sn$, 91%), 514 (46), 513 (100), 512 (53), 511 (75), 510 (27), 509 (31); Found. 515 (89), 514 (46), 513 (100), 512 (54), 511 (78), 510 (29), 509 (32) [and 389 (46), 345 (75), 291 (95), 235 (65), 177 (76), 77 (57), 67 (47), 55 (89)].

General procedure for the preparation of the cis- substrates. Tributylstannyl lithium (1.0 equiv.) was prepared at 0°C as previously described. The solution was cooled to -78°C and the 2-substituted enone (**130, 133**) was added as a solution in THF (≈0.5ml/mmol). The mixture was warmed to -23°C and HMPA (12.0 equiv.) was added. Stirring was continued at -23°C until 1,4-addition was judged to be complete by t.l.c. analysis (up to 2h). The electrophile (water, deuterium oxide or methyl iodide) was added at -23°C, the mixture warmed to room temperature over 1h (electrophile=water, deuterium oxide) or 14h (electrophile=methyl iodide), then quenched with saturated ammonium chloride solution. The same extractive work-up described above was used to furnish the crude alkylated compounds which were rendered pure by flash column chromatography.

6-Triphenylstannylspiro[4,5]decan-10-one **135**. To a solution of di-isopropylamine (76 µl, 0.54mmol) in dry THF (5ml) was added ^{n}butyl lithium (0.28ml of a 1.3M solution in hexanes, 0.37mmol) at 0°C. The resulting mixture was stirred at this temperature for 0.5h whereupon triphenyltin hydride (126mg, 0.36mmol) was added. After a further 0.5h the solution was cooled to -78°C and the enone (**131**, 100mg, 0.36mmol) was added as a solution in THF (1ml). After 0.5h at -78°C t.l.c. analysis indicated consumption of the starting material and the reaction was quenched with saturated ammonium chloride solution

(5ml). The mixture was allowed to room temperature and the aqueous layer diluted with water (5ml) then washed with ether (3x10ml). The combined organic extracts were washed with brine then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (10:1 then 8:1 petrol:ether) to yield *6-triphenylstannylspiro[4,5]decan-10-one* (**135**, 165mg, 92%) as a white slushy solid. $\nu_{max.}$ ($CHCl_3$) 3070 (m), 2950 (s), 2860 (m), 1700 (s), 1580 (w), 1480 (m), 1430 (s), 1315 (m), 1130 (m), 1075 (s), 1000 (m), 910 (m), 730 (s), 700 (s); δ_H (200 MHz) 1.19-1.72 and 1.79-2.78 (15H, m) unassigned, 7.23-7.50 (9H, m) and 7.56-7.80 (6H, m, arom.) ; δ_C (50.3 MHz, DEPT) CH: 44.26, 128.72, 129.15, 137.45; CH_2: 24.47, 24.68, 28.51, 30.21, 37.02, 37.87, 38.51; *m/z* (E.I.) 502 (M^+, ^{120}Sn, 15%), 501 (8), 500 (12), 499 (6), 498 (7), 351 (100), 197 (48), 151 (22), 120 (22), 91 (18), 78 (34), 67 (46), 55 (19).

cis-2-(4'-Phenylselenobutyl)-3-tributylstannylcyclohexanone **136**. Obtained as a colourless oil (85mg, 51%) from enone **133** (100mg, 0.33mmol) and water (1.0ml, 55.6mmol) after flash column chromatography (15:1-5:1 petrol:ether). (Found: C, 56.30; H, 8.38. $C_{28}H_{48}OSeSn$ requires C, 56.21; H, 8.09%); $\nu_{max.}$ (thin film) 3060 (w), 2950 (s), 2920 (s), 2860 (s), 1702 (s), 1580 (m), 1480-1410 (m), 1375 (m), 1250 (m), 1145 (m), 1075 (m), 1020 (m), 735 (m), 690 (s), 670 (w); δ_H (200 MHz) 0.75-0.97 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.16-1.96 (22H, m) and 2.03-2.32 (2H, m, $C_3\underline{H}_6C\underline{H}RCO$-, $C_2\underline{H}_4C\underline{H}(SnBu_3)$-, and ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-), 2.41-2.50 (2H, m, $C\underline{H}_2CO$-), 2.87 (2H, t, *J* 7.0Hz, $C\underline{H}_2SePh$), 7.22-7.30 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.55 (2H, m, Ph-*o*- protons); *m/z* (C.I., NH_3) 618 (MNH_4^+, $^{80}Se^{120}Sn$, 29%), 617 (22), 616 (28), 615 (34), 614 (31), 601 (71), 600 (51), 599 (theoretical MH^+, 100), 598 (55), 597 (86), 596 (55), 595 (49).

cis-2-Deutero-2-(4'-phenylselenobutyl)-3-tributylstannylcyclohexanone **137**. Following the general procedure the pure deuterated compound **137** was obtained as a colourless oil (75mg, 62% based on recovered starting enone, 38mg) from the enone (**133**, 100mg, 0.33mmol) and deuterium oxide (1.0ml, 55.4mmol). (Found: C, 55.87; H(D), 8.12.

$C_{28}H_{47}DOSeSn$ requires C, 56.11; H(D), 8.07%); $\nu_{max.}$ (thin film) 3070 (w), 2960 (s), 2920 (s), 2860 (s), 1705 (s), 1580 (m), 1480-1410 (m), 1375 (m), 1335 (m), 1075 (m), 1025 (m), 735 (s), 690 (s), 670 (m); δ_H (200 MHz) 0.67-0.97 (15H, m, ($C\underline{H}_3C_2H_4$-$C\underline{H}_2$-)$_3$Sn-), 1.05-1.55 (15H, m) and 1.57-2.04 (8H, m, $C_3\underline{H}_6CH_2SePh$, $C_2\underline{H}_4C\underline{H}$-($SnBu_3$)-, and ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-), 2.06-2.51 (2H, m, $C\underline{H}_2CO$-), 2.88 (2H, t, *J* 7.0Hz, $C\underline{H}_2SePh$), 7.20-7.33 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.53 (2H, m, Ph- *o*- protons); *m/z* (F.D.) Calc. base peak for d_1=599; Found. 602 (70%), 601 (87), 600 (70), 599 (set to 100), 598 (83), 597 (61).

cis-2-Methyl-2-(4'-phenylselenobutyl)-3-tributylstannylcyclohexanone **138**. The general procedure was followed and the stannane **138** obtained as a colourless oil (120mg, 60%) from enone **133** (100mg, 0.33mmol) and methyl iodide (0.11ml, 1.77 mmol). (Found: C, 56.52; H, 8.61. $C_{29}H_{50}OSeSn$ requires C, 56.88; H, 8.23%); $\nu_{max.}$ (thin film) 3070 (w), 2960 (s), 2925 (s), 2855 (s), 1702 (s), 1580 (m), 1480-1420 (m), 1375 (m), 1075 (m), 1025 (m), 910 (m), 735 (s), 690 (m), 670-650 (w); δ_H (500 MHz) 0.76-0.93 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.00 (3H, s, $C\underline{H}_3$-), 1.08 ($C\underline{H}_3$- in *trans*- isomer; integrates as ≈10% of $C\underline{H}_3$- in *cis*- compound), 1.28-1.36 (8H, m), 1.41-1.53 (8H, m), 1.66-1.76 (4H, m), 1.84-2.04 (2H, m), and 2.08-2.15 (1H, m, $C_3\underline{H}_6CH_2SePh$, $C_2\underline{H}_4C\underline{H}(SnBu_3)$-, and ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn), 2.37-2.47 (1H, m) and 2.50 (1H, dt, *J* 9.0, 5.5Hz, $C\underline{H}_2CO$-), 2.89 (2H, ca. q, *J* 7.5Hz, $C\underline{H}_2SePh$), 7.20-7.32 (3H, m, Ph- *m*- and *p*- protons), 7.41-7.56 (2H, m, Ph- *o*- protons); δ_C (50.3 MHz) 9.28, 10.26, 13.70, 22.87, 24.01, 27.16, 29.17, 30.03, 30.49, 31.17, 37.77, 42.87, 52.61, 54.90, 126.88, 128.88, 130.32, 132.61, 216.62 (^3J (^{119}Sn-^{13}C) 29Hz); *m/z* (F.D.) 616 (63%), 615 (43), 614 (M^+, $^{80}Se^{120}Sn$, 93), 613 (46), 612 (100), 611 (45), 610 (55).

Ethyl-1-[2-(4'-phenylselenobutyl)-3-tributylstannylcyclohex-1-enyl]-carbonate **139**. Use of the general procedure for the preparation of the *cis*- substrates with enone (**133**, 100mg, 0.33mmol) and ethyl chloroformate (34μl, 0.36mmol), followed by flash column chromatography (20:1 petrol:ether), afforded the *O*-alkylated material (**139**, 116mg, 52%) as a colourless oil. $\nu_{max.}$ (thin film) 3070 (w), 2960 (s), 2930 (s), 2860 (s), 1750 (s),

1580 (m), 1480-1430 (m), 1370 (m), 1245 (s), 1050 (m), 910 (m), 790 (m), 735 (s), 690 (m); δ_H (200 MHz) 0.76-1.04 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.19-1.73 (22H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_2\underline{H}_4CH_2SePh$, $C\underline{H}_3CH_2O$-, and $C\underline{H}_2C\underline{H}(SnBu_3)$-), 1.77-1.98 (2H, m, $C\underline{H}_2CH_2C(OR)$=), 2.01-2.48 (4H, m, $C\underline{H}_2C(OR)$=$CRC\underline{H}_2$-), 2.91 (2H, t, *J* 6.5Hz, $C\underline{H}_2SePh$), 4.20 (2H, q, *J* 7.0Hz, $C\underline{H}_2O$-), 7.18-7.32 (3H, m, Ph- *m*- and *p*- protons), 7.44-7.55 (2H, m, Ph- *o*- protons); δ_C (50.3 MHz) 9.61, 13.37, 14.14, 23.43, 26.41, 26.63, 27.40, 27.51, 27.96, 28.18, 29.06, 29.28, 29.72, 64.20, 126.74, 129.06, 130.61, 132.60, 138.90, 153.70; *m/z* (F.D.) 672 (M^+, $^{80}Se^{120}Sn$, 99%), 671 (54), 670 (100), 669 (63), 668 (93).

cis-2-(3'-Phenylselenopropyl)-3-tributylstannylcyclohexanone **140**. Use of the above protocol with enone **130** (100mg, 0.34mmol) and water (1.0ml, 55.6mmol) afforded the pure material **140** as a colourless oil (120mg, 60%). (Found: C, 55.83; H, 8.40. $C_{27}H_{46}OSeSn$ requires C, 55.50; H, 7.93%); $\nu_{max.}$ (thin film) 3070 (w), 2960 (s), 2920 (s), 2860 (s), 1710 (s), 1580 (m), 1480-1410 (m), 1375 (m), 1075 (m), 1020 (m), 735 (s), 690 (s), 665 (m); δ_H (200 MHz) 0.76-0.97 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.17-1.71 (16H, m) and 1.76-2.07 (5H, m, $C_2\underline{H}_4CH_2SePh$, $C_2\underline{H}_4C\underline{H}(SnBu_3)$-, and ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-), 2.13-2.32 (1H, m, C<u>H</u>RCO-), 2.33-2.58 (2H, m, $C\underline{H}_2CO$-), 2.89 (2H, t, *J* 8.0Hz, $C\underline{H}_2SePh$), 7.21-7.30 (3H, m, Ph- *m*- and *p*- protons), 7.44-7.53 (2H, m, Ph- *o*- protons); δ_C (50.3 MHz) 9.31, 13.64, 26.76, 27.51, 27.80, 28.38, 29.42, 30.98, 31.56, 33.01, 40.29, 54.62, 126.94, 129.08, 130.40, 132.72, 214.28 (^3J (^{119}Sn-^{13}C) 29Hz); *m/z* (ACE, NH_3) 587 (MH^+, $^{80}Se^{120}Sn$, 40%), 585 (46), 584 (27), 583 (35), 527 (27), 308 (100), 295 (72), 279 (61), 137 (67).

cis-2-Methyl-2-(3'-phenylselenopropyl)-3-tributylstannylcyclohexanone **141**. Obtained as a colourless oil (150mg, 74%) from enone **130** (100mg, 0.34mmol) and methyl iodide (0.11ml, 1,77mmol) after flash column chromatography (20:1 petrol: ether). (Found: C, 56.19; H, 8.29. $C_{28}H_{48}OSeSn$ requires C, 56.21; H, 8.09%); $\nu_{max.}$ (thin film) 3060 (w), 2970 (s), 2920 (s), 2850 (s), 1700 (s), 1580 (m), 1490-1410 (m), 1375 (m), 1230 (m), 1150 (m), 1075 (m), 1020 (m), 735 (s), 690 (s), 670 (m); δ_H (200 MHz) 0.82-1.04 (15H,

m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 0.96 (3H, s, $C\underline{H}_3$-), 1.16-2.55 (23H, m, $C_3\underline{H}_6C\underline{H}(SnBu_3)$-, $C_2\underline{H}_4CH_2SePh$, and ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn), 2.87 (2H, t, *J* 6.5Hz, $C\underline{H}_2SePh$), 7.19-7.30 (3H, m, Ph- *m*- and *p*- protons), 7.41-7.51 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 541 (M^+-^{n}Bu·, $^{78}Se^{120}Sn$, 7%), 291 (30), 269 (100), 235 (22), 213 (56), 177 (34), 153 (26), 121 (12), 91 (12), 77 (19), 57 (53).

General procedure for the ring expansion reaction. The tin containing substrate was dissolved in sodium dried benzene (200ml/mmol) and the solution degassed with argon. Azo-bis-isobutyronitrile (AIBN, 0.2 equiv.) and tributyltin hydride (0.1 equiv.) were added and the mixture heated at reflux under a nitrogen or argon atmosphere. The reaction was monitored by t.l.c. and heating continued until all starting material was consumed, more AIBN and tributyltin hydride being added every 12h in cases of slow reaction. The mixture was cooled to room temperature and the benzene removed *in vacuo* as its azeotrope with carbon tetrachloride. The crude product was subjected to flash column chromatography (≈10:1 petrol:ether). At this stage the product was contaminated with small amounts of tin containing residues; these were removed either by p.l.c. or bulb to bulb distillation depending on the scale of the reaction. The pure products were all volatile oils with characteristic odours.

Ring expansion of stannane **97**. The reaction was complete after 2h at reflux (1.32mmol scale). Flash column chromatography (8:1 petrol:ether and again with 20:1 petrol:ether) gave tin free material consisting of an inseparable mixture of *E-cyclodec-5-enone*[86b] (**100**, 47%) and *2-butylcyclohex-2-enone*[126] (**101**, 36%). For **100** and **101** $\nu_{max.}$ (thin film) 3030 (w), 2930 (s), 2860 (m), 1710 (s), 1675 (s), 1440 (m), 1170 (m), 990 (m); for **100** δ_H (500 MHz) 1.64 (2H, brm, C(8)$\underline{H}_2$-), 1.77 (2H, brm, C(9)$\underline{H}_2$-), 1.93 (2H, brm, C(3)$\underline{H}_2$-), 2.23 (4H, brm, 2 x $C\underline{H}_2CH$=), 2.39 (2H, brm, C(10)$\underline{H}_2CO$-), 2.51 (2H, brm, C(2)$\underline{H}_2CO$-), 5.15 (1H, dt, *J* 15, 7.5Hz, C(5)$\underline{H}$=CH-), 5.34 (1H, dt, *J* 15, 7.5Hz, CH=C(6)$\underline{H}$-), irradiation at δ1.93 caused partial collapse of the multiplet at δ5.15 whilst that at δ5.34 collapsed to a doublet *J* 15Hz; for **101** δ_H (500 MHz) 0.90 (3H, t, *J* 7.5Hz, $C\underline{H}_3$-), 1.26-1.39 (4H, m, $C_2\underline{H}_4CH_3$), 1.97 (2H, quin., *J* 7.5Hz, $C\underline{H}_2CH_2CO$-), 2.19

(2H, td, *J* 8.5, 1.5Hz, C$\underline{H}_2$C(CO)=), 2.32-2.36 (2H, m, C$\underline{H}_2$CH=), 2.41-2.45 (2H, m, C$\underline{H}_2$CO-), 6.71 (1H, t, *J* 5.0Hz, C$\underline{H}$=); for **100** and **101** *m/z* (ACE, E.I.), 152 (M^+, 79%), 137 (31), 134 (57), 123 (77), 119 (26), 109 (70), 95 (74), 91 (31), 81 (81), 79 (63), 67 (100), 55 (76), 53 (86).

Ring expansion of stannane **98**. This reaction required heating at reflux for 40h (1.71mmol scale). The crude material was subjected to flash column chromatography (20:1 petrol: ether) then bulb to bulb distillation (120-130°C/14mmHg). *E-6-Methylcyclodec-5-enone* **102**[127] was obtained as a fragrant colourless oil (85%). $\nu_{max.}$ (thin film) 3060 (w), 2950 (s), 2930 (s), 2860 (s), 1705 (s), 1625 (m), 1480-1400 (m), 1390-1320 (m), 1170 (m), 1100 (m), 965 (w), 880 (w), 815 (w), 765 (w), 735 (w); δ_H (200 MHz) 1.51-1.67 (2H, m, C(8)$\underline{H}_2$-), 1.71 (3H, s, C$\underline{H}_3$-), 1.74-1.91 (2H, m, C(9)$\underline{H}_2$-), 1.97-2.20 (8H, m, C(3)$\underline{H}_2$C(4)$\underline{H}_2$-, C(7)$\underline{H}_2$- and C(10)$\underline{H}_2$-), 2.33-2.45 (2H, m, C(2)$\underline{H}_2$-), 4.91-5.03 (1H, m, C$\underline{H}$=); δ_C (50.3 MHz) 16.07, 22.42, 25.44, 28.46 (2), 40.12, 42.42, 43.32, 129.37, 134.68, 212.99; *m/z* (ACE, E.I.) 166 (M^+, 25%), 148 (45), 137 (81), 133 (46), 124 (100), 119 (36), 109 (92), 105 (37), 95 (76), 93 (82), 91 (94), 81 (74), 79 (85), 67 (96), 55 (87).

Ring expansion of stannane **99**. This reaction was complete after 50h at reflux (0.40mmol scale). Flash column chromatography (20:1 petrol:ether) then p.l.c. (5:1 petrol:ether) afforded pure *Z-6-carbomethoxycyclodec-5-enone* **103** as a colourless oil (72%). (Found: C, 68.71; H, 8.71. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.63%); $\nu_{max.}$ (thin film) 2990 (m), 2930 (s), 2860 (m), 1680-1750 (s), 1645 (w), 1440 (s), 1380 (m), 1235 (s), 1195 (s), 1165 (m), 1125 (m), 1095 (s), 1020 (m), 815 (m), 785 (m); δ_H (200 MHz) 1.54-1.68 (2H, m, C(9)$\underline{H}_2$-), 1.71-1.88 (2H, m, C(8)$\underline{H}_2$-), 2.04-2.20 (2H, m, C(3)$\underline{H}_2$-), 2.25-2.38 (4H, m, C$\underline{H}_2$C(CO_2Me)= and C$\underline{H}_2$CH=), 2.40-2.54 (4H, m, C(2)$\underline{H}_2$- and C(10)$\underline{H}_2$-), 3.81 (3H, s, C$\underline{H}_3$-), 5.59 (1H, t, *J* 9.0Hz, C$\underline{H}$=); *m/z* (ACE, NH_3) 228 (MNH_4^+, 45%), 211 (MH^+, 100), 193 (70), 179 (12), 135 (20).

Ring expansion of stannane **104**. This was complete after 24h at reflux (1.31mmol scale). Successive flash column chromatography (15:1 then 20:1 petrol:ether) gave clean product consisting of an inseparable mixture of *E-6-deuterocyclodec-5-enone* (**107**, 75%) and *2-(4'-deuterobutyl)-cyclohex-2-enone* (**106**, 10%). For **106** and **107** $\nu_{max.}$ (thin film) 3020 (w), 2930 (s), 2850 (m), 1710 (s), 1675 (m), 1440 (m), 1360 (m), 1170 (m), 1120 (m), 1100 (m), 905 (m), 850 (m), 760 (w); for **107** δ_H (200 MHz) 1.54-2.07 (6H, m, C(3)$\underline{H}_2$- and C(8)$\underline{H}_2$C(9)$\underline{H}_2$-), 2.10-2.32 (4H, m, C$\underline{H}_2$CH=CDC$\underline{H}_2$-), 2.33-2.58 (4H, m, 2 x C$\underline{H}_2$CO-), 5.08-5.21 (1H, m, C$\underline{H}$=CD-); for **106** δ_H (200 MHz) 0.81-0.96 (2H, m, C$\underline{H}_2$D), 1.22-1.43 (4H, m, $C_2\underline{H}_4CH_2D$), 1.91-2.05 (2H, m, C$\underline{H}_2CH_2$CO-), 2.11-2.25 (2H, m, C$\underline{H}_2$C(CO)=), 2.28-2.45 (4H, m, C$\underline{H}_2$CO- and C$\underline{H}_2$CH=), 6.70 (1H, t, *J* 4.5Hz, C$\underline{H}$=); for **106** and **107** δ_D (38.4 MHz) 0.82 (1D, s), 5.32 (ca. 8D, s); δ_C (50.3 MHz, DEPT) for **107** CD: 130.83, CO: 213.06, CH: 134.41, CH_2: 22.12, 27.94, 28.73, 32.96, 34.02, 42.80, 45.45; for **106** only observe CH: 145.03, CH_2: 22.28, 23.17, 25.98, 30.71, 38.52; *m/z* (E.I.) 153 (M^+, 47%), 135 (79), 124 (21), 120 (15), 110 (31), 96 (43), 93 (36), 84 (61), 81 (83), 68 (92), 55 (100).

Attempted ring expansion of stannane **108**. Using the substrate (**108**, 750mg, 1.28mmol), the reaction was complete after 72h. Flash column chromatography of the concentrated mixture (20:1 petrol:ether) led only to the isolation of *2-pentylcyclohex-2-enone* **109**[126a] as a colourless oil with a fragrant odour (183mg, 86%). $\nu_{max.}$ (thin film) 2960 (m), 2930 (m), 2860 (m), 1675 (s), 1460 (m), 1430 (m), 1375 (m), 1250 (m), 1170 (m), 1120 (m), 1090 (m), 900 (m), 730 (m); δ_H (250 MHz) 0.90 (3H, t, *J* 8.5Hz, $C\underline{H}_3$-), 1.18-1.49 (6H, m, $C_3\underline{H}_6CH_3$), 1.98 (2H, ca. quin., *J* 6.5Hz, C$\underline{H}_2CH_2$CO-), 2.17 (2H, t, *J* 7.0Hz, C$\underline{H}_2$CR=), 2.29-2.46 (4H, m, C$\underline{H}_2$CO- and C$\underline{H}_2$CH=), 6.70 (1H, t, *J* 4.0Hz, C$\underline{H}$=), *m/z* (E.I.) 166 (M^+, 82%), 137 (100), 123 (85), 119 (50), 110 (74), 95 (71), 93 (21), 91 (27), 82 (82), 81 (76), 79 (57), 77 (28), 67 (68), 55 (77), 53 (95).

Attempted ring expansion of stannane **116**. Prolonged reaction times in a number of solvents and a variety of initiators led in all cases to decomposition products, no ring expanded products were observed. The only isolable material was *trans-2-allyl-3-tri-*

butylstannylcyclohexanone **120** obtained in variable yield (≈30%). (Found: C, 59.10; H, 9.24. $C_{21}H_{40}OSn$ requires C, 59.04; H, 9.44%); $\nu_{max.}$ (thin film) 3080 (w), 2960 (s), 2920 (s), 2865 (s), 1710 (s), 1640 (m), 1470-1410 (m), 1375 (m), 1340 (m), 1310 (w), 1070 (m), 1020 (m), 1000 (m), 910 (m), 735 (m); δ_H (200 MHz) 0.82-0.95 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.22-1.84 (16H, m) and 1.87-2.22 (3H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C\underline{H}_2CH$=, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.29-2.61 (3H, m, $C\underline{H}_2COC\underline{H}$(allyl)-), 4.91-5.05 (2H, m, $C\underline{H}_2$=), 5.71-5.95 (1H, m, C$\underline{H}$=); *m/z* (E.I.) 427 (18%), 425 (13), 423 (7), 371 (M^+-^{n}Bu·, $^{80}Se^{120}Sn$, 75), 369 (58), 367 (34), 291 (28), 235 (55), 177 (100), 121 (53), 93 (19), 79 (28), 67 (41), 55 (49).

Ring expansion of stannane **117**. This reaction was complete after 24h (0.1mmol scale). The product composition was essentially the same as that obtained from the iodide **97**. The ring expanded product **100** was produced in 42% yield and the reduced material **101** in 33% yield. Data as above.

Ring expansion of stannane **118**. Reaction complete after 14h at reflux (0.5mmol scale). Flash column chromatography (20:1 petrol:ether) gave a mixture of two isomers, which were separable by p.l.c. (10:1 petrol:ether), *E-5-methylcyclonon-5-enone*[45] (**29**, 44%) and *5-methylenecyclononanone*[45] (**30**, 36%). Longer reaction times led to the predominance of the exomethylene isomer. For **29** $\nu_{max.}$ (thin film) 2930 (s), 2860 (m), 1695 (m), 1480-1415 (m), 1390-1370 (m), 1340 (m), 1160 (m), 1115 (m); δ_H (200 MHz) 1.37 (3H, s, C$\underline{H}_3$-), 1.72-1.96 (4H, m, C(3)$\underline{H}_2$- and C(8)$\underline{H}_2$-), 2.00-2.26 (4H, m, $C\underline{H}_2CH$= C(Me)$C\underline{H}_2$-), 2.30-2.42 (4H, m, 2 x $C\underline{H}_2$CO-), 5.51 (1H, t, *J* 8.0Hz, C$\underline{H}$=); *m/z* (C.I., NH_3) 170 (MNH_4^+, 22%), 153 (MH^+, 73), 135 (100), 124 (13), 109 (16), 95 (17), 91 (16), 81 (17), 79 (6), 69 (8), 58 (11). For **30** $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2860 (m), 1705 (m), 1670 (w), 1630 (m), 1480-1410 (m), 1340 (m), 1310 (w), 1245 (w), 1075 (m), 965 (m), 885 (m); δ_H (200 MHz) 1.36-2.06 (10H, m, $C_2(3,4)\underline{H}_4$- and $C_3(6,7,8)\underline{H}_6$-), 2.09-2.19 (2H, m, C(9)$\underline{H}_2$-), 2.25-2.31 (1H, m) and 2.33-2.39 (1H, m, C(2)$\underline{H}_2$-), 4.71 (1H, d, *J* 1.5Hz) and 4.93 (1H, d, *J* 1.5Hz, $C\underline{H}_2$=); *m/z* (E.I.) 152 (M^+,

9%), 136 (6), 124 (8), 120 (5), 110 (13), 106 (10), 96 (16), 92 (100), 80 (22), 70 (46), 68 (14), 66 (13), 56 (37).

Ring expansion of stannane **119**. Reaction complete after 24h at reflux (0.18mmol scale). The crude material was subjected to purification by p.l.c. (3:1 petrol:ether). The product, a colourless oil, was identified as *Z-3-methylcyclohept-3-enone*[131a] (**121**, 87%). $\nu_{max.}$ (thin film) 2960 (m), 2930 (s), 2860 (m), 1710 (m), 1480-1420 (m), 1380 (m), 1290 (w), 1260 (m), 1115 (w), 1020 (w), 800 (w); δ_H (300 MHz) 1.78 (3H, d, *J* 1.5Hz, C$\underline{H}_3$-), 1.94 (2H, quin., *J* 6.0Hz, C$\underline{H}_2$CH$_2$CO-), 2.21-2.30 (2H, m, C$\underline{H}_2$CH=), 2.52-2.58 (2H, m, C(7)$\underline{H}_2$CO-), 3.20 (2H, s, C(2)$\underline{H}_2$CO-), 5.52 (1H, dt, *J* 5.0, 1.5Hz, C$\underline{H}$=); nOe expt: irradiation of the doublet at δ1.78 caused a 12% enhancement of the signal at δ5.52; *m/z* (C.I., NH_3) 142 (MNH_4^+, 53%), 125 (MH^+, 100), 109 (5), 99 (19), 97 (3).

Attempted ring expansion of stannane **136**. The starting material was consumed after 4h at reflux (0.05mmol scale), however, flash column chromatography (20:1 petrol:ether) afforded only *2-butylcyclohex-2-enone*[126] (**101**, 86%). Data as above.

Ring expansion of stannane **137**. This was complete after 2h at reflux (0.12mmol scale). The crude product was purified by p.l.c. (10:1 petrol:ether) to afford *Z-6-deuterocyclodec-5-enone* (**142**, 21%) and *2-(4'-deuterobutyl)-cyclohex-2-enone* (**106**, 58%). For **106** and **142** $\nu_{max.}$ (thin film) 3020 (w), 2930 (s), 2860 (m), 1710 (m), 1675 (s), 1475-1410 (m), 1380 (m), 1175 (m), 1100 (m), 980 (m), 910 (m), 800 (w); for **106** n.m.r. data given above; for **142** the only distinct resonance was at δ5.09-5.25 (1H, m, C$\underline{H}$=), the others (broad and of low intensity) being masked by those of the reduced material **106**; *m/z* (C.I., NH_3) 171 (MNH_4^+, 14%), 154 (MH^+, 100), 137 (34), 125 (9), 111 (10), 105 (10), 95 (8), 91 (7), 82 (11), 58(4).

Ring expansion of stannane **138**. This reaction was complete after 40h at reflux (0.16mmol scale). The crude product was purified by flash column chromatography (20:1 petrol: ether) then p.l.c. (5:1 petrol:ether) to give *Z-6-methylcyclodec-5-enone*[127] (**146**,

89%). This material was contaminated with ≈10% of the *E*- isomer as judged by the integral ratios of the olefinic protons in the n.m.r. spectrum. $\nu_{max.}$ (thin film) 3040 (w), 2930 (s), 2860 (s), 1705 (s), 1625 (m), 1470-1405 (m), 1375 (m), 1250 (m), 1200 (m), 1130 (m), 1010 (m), 970 (m), 800 (m); δ_H (200 MHz) 1.55-1.87 (6H, m, C$\underline{H}_2$CH_2CH= and C_2(8,9)$\underline{H}_4$-), 1.65 (3H, s, C$\underline{H}_3$-), 1.92-2.16 (4H, m, C$\underline{H}_2$CH=C(Me)C$\underline{H}_2$-), 2.29-2.37 (2H, m, C(10)$\underline{H}_2$-), 2.46-2.53 (2H, m, C(2)$\underline{H}_2$-), 4.91-5.03 ("0.1"H, m, C$\underline{H}$= in *E*-isomer), 5.16 (1H, t, *J* 8.5Hz, C$\underline{H}$=); *m/z* (E.I.) 166 (M^+, 7%), 148 (100), 133 (43), 124 (21), 119 (23), 108 (49), 105 (34), 97 (18), 95 (38), 93 (92), 91 (30), 81 (50), 79 (51), 67 (56), 55 (60), 53 (32).

Ring expansion of stannane **140**. After 48h at reflux (0.15mmol scale) t.l.c. showed no remaining starting material. The crude product was subjected to purification by flash column chromatography (20:1 petrol:ether) and the ring expanded material *Z-cyclonon-5-enone*[40] **144** obtained in 87% yield. $\nu_{max.}$ (thin film) 3010 (m), 2970 (s), 2930 (s), 2870 (m), 1705 (s), 1470-1410 (m), 1355 (m), 1250 (m), 1205 (m), 1120 (m), 715 (m), 615 (m); δ_H (250 MHz) 1.84-1.96 (4H, m, 2 x C$\underline{H}_2$CH_2CO-), 2.07-2.18 (4H, m, 2 x C$\underline{H}_2$CH=), 2.44 (4H, t, *J* 6.5Hz, 2 x C$\underline{H}_2$CO-), 5.40-5.55 (2H, m, C$\underline{H}$=C$\underline{H}$-), irradiation of the signal at δ2.13 caused the multiplet at δ5.40-5.55 to collapse to a sharp singlet, no peaks corresponding to the *trans*- compound were observed; *m/z* (E.I.) 138 (M^+, 8%), 120 (68), 109 (13), 95 (28), 82 (46), 79 (35), 67 (72), 55 (100), 54 (93). A small amount of *2-propylcyclohex-2-enone*[136a] (**143**, 4%) was also observed. δ_H (250 MHz) 0.92 (3H, t, *J* 8.0Hz, C$\underline{H}_3$-), 1.23-1.50 (2H, m, C$\underline{H}_2$CH_3), 1.98 (2H, quin., C$\underline{H}_2$CH_2CO-), 2.15 (2H, td, *J* 8.0, 1.0Hz, C$\underline{H}_2$C(CO)=), 2.29-2.45 (4H, C$\underline{H}_2$CO- and C$\underline{H}_2$CH=), 6.70 (1H, t, *J* 5.0Hz, C$\underline{H}$=).

Ring expansion of stannane **141**. The reaction was complete after 24h (0.17mmol scale). The crude product was subjected to p.l.c. (5:1 petrol:ether) and *Z-5-methylcyclonon-5-enone*[45] **145** obtained as a colourless oil (87%). $\nu_{max.}$ (thin film) 3040 (w), 2960 (s), 2930 (s), 2860 (m), 1705 (s), 1470-1400 (m), 1355 (m), 1235 (m), 1105 (m), 885 (m); δ_H (250 MHz) 1.70 (3H, s, C$\underline{H}_3$-), 1.83-1.98 (4H, m, C(3)$\underline{H}_2$- and C(8)$\underline{H}_2$-), 2.05-2.12

(4H, m, $C\underline{H}_2CH=C(Me)-C\underline{H}_2$-), 2.33-2.43 (4H, m, 2 x $C\underline{H}_2CO$-); *m/z* (C.I., NH_3) 170 (MNH_4^+, 9%), 153 (MH^+, 28%), 135 (100), 134 (12).

trans-2-(4'-Iodobutyl)-3-tributylstannylcyclopentanone **148**. From cyclopent-2-enone (100mg, 1.22mmol) and 1,4-di-iodobutane (0.64ml, 4.85mmol) was produced *3-tributylstannylcyclopentanone* (**147**, 180mg, 40%) as a colourless oil after flash chromatography (15:1 petrol:ether). $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (s), 1730 (s), 1470-1400 (m), 1375 (m), 1235 (m), 1185 (m), 1070 (m), 1000 (w), 960 (w), 870 (m); δ_H (200 MHz), 0.72-1.05 (15H, m, $(C\underline{H}_3C_2H_4C\underline{H}_2-)_3Sn$-), 1.16-2.36 (19H, m, $(CH_3C_2\underline{H}_4-CH_2-)_3Sn$- and ring protons); *m/z* (F.I.) 375 (31%), 374 (M^+, ^{120}Sn, 100), 373 (31), 372 (73), 371 (32), 370 (31). Also obtained was the required alkylated material *trans-2-(4'-iodobutyl)-3-tributylstannylcyclopentanone* (**148**, 157mg, 23%). (Found: C, 45.76; H, 7.70. $C_{21}H_{41}OISn$ requires C, 45.43; H, 7.44%); $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (s), 1735 (s), 1460 (m), 1375 (m), 1155 (m), 1075 (m), 960 (m), 870 (m); δ_H (200 MHz) 0.82-0.97 (15H, m, $(C\underline{H}_3C_2H_4C\underline{H}_2-)_3Sn$-), 1.20-1.67 (18H, m, $(CH_3C_2\underline{H}_4CH_2-)_3Sn$-, $C_3\underline{H}_6CH_2I$), 1.72-1.93 (2H, m, $C\underline{H}_2CH_2CO$-), 1.96-2.41 (4H, m, $C\underline{H}_2COC\underline{H}RC\underline{H}(SnBu_3)$-), 3.19 (2H, t, *J* 7.0Hz, $C\underline{H}_2I$); *m/z* (F.I.) 428 (M^+-I·, 100%), 427 (45), 426 (81), 425 (34), 424 (51).

Attempted ring expansion of stannane **148**. Subjecting the stannane (**148**, 150mg, 0.27mmol) to the standard radical conditions (45h) led solely to the formation of *2-butylcyclopent-2-enone* **149**[205], a colourless oil after flash chromatography (20:1 petrol: ether) (31mg, 83%). $\nu_{max.}$ (thin film) 3040 (w), 2960 (m), 2930 (s), 2860 (m), 1705 (m), 1635 (w), 1470-1430 (m), 1380 (w), 1050 (w), 1005 (m), 790 (m), 740 (w); δ_H (200 MHz) 0.89 (3H, t, *J* 7.0Hz, $C\underline{H}_3$-), 1.15-1.68 (4H, m, $C_2\underline{H}_4CH_3$), 2.17 (2H, td, *J* 7.0, 2.5Hz, $C\underline{H}_2CR$=), 2.34-2.45 (2H, m, $C\underline{H}_2CH$=), 2.50-2.63 (2H, m, $C\underline{H}_2CO$-), 7.25-7.35 (1H, m, $C\underline{H}$=); *m/z* (E.I.) 138 (M^+, 56%), 123 (32), 109 (53), 96 (100), 81 (31), 79 (25), 77 (12), 67 (51), 65 (19), 55 (21), 53 (39).

E-Cyclododec-2-enone **150**[124,140]. Using the procedure of Reich *et al.*[124,140] the title compound **150** was obtained as a colourless oil after flash chromatography (3:1 petrol: ether) (81%, quantitative crude yield (spectroscopically clean)). $\nu_{max.}$ (thin film) 2930 (s), 2860 (s), 1690 (s), 1665 (s), 1625 (s), 1465 (m), 1445 (m), 1350 (m), 990 (s), 920 (m), 735 (s); δ_H (250 MHz) 1.13-1,44 (10H, m, $C_5\underline{H}_{10}C_2H_4CO$-), 1.51-1.61 (2H, m, $C\underline{H}_2CH_2CH$=), 1.63-1.75 (2H, m, $C\underline{H}_2CH_2CO$-), 2.23 (2H, ca. quin., *J* 7.0Hz, $C\underline{H}_2CH$=), 2.41-2.50 (2H, m, $C\underline{H}_2CO$-), 6.28 (1H, d, *J* 17Hz, =C<u>H</u>CO-), 6.76 (1H, dt, *J* 17, 7.0Hz, C<u>H</u>=CHCO-); *m/z* (E.I.) 180 (M^+, 9%), 109 (32), 98 (32), 95 (37), 81 (90), 68 (77), 55 (100), 53 (50).

3-Tributylstannylcyclododecanone **151**. The highest yield of this compound was obtained in an attempted 1,4-addition/alkylation reaction. Tributylstannyl lithium (1.50mmol) was generated by the usual procedure except using DME (3ml) as the solvent and with 18C6 (26mg, 98μmol) present. The solution was cooled to -23°C and the enone (**150**, 180mg, 1mmol) added and stirring continued for 1h whereupon HMPA (2.5ml, 14mmol) was added followed immediately by 1,4-di-iodobutane (0.39ml, 3.0mmol). The mixture was allowed to warm up to room temperature overnight then quenched with water (10ml) and the aqueous layer extracted with a 1:1 mixture of petrol and ether (5x15ml). The combined organic portions were washed with brine then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (75:1 petrol:ether) to yield solely the 1,4-addition product (**151**, 195mg, 42%). No alkylated material was observed. $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (m), 1705 (s), 1465 (m), 1375 (m), 1290 (m), 1070 (m), 960 (w), 870 (m); δ_H (200 MHz) 0.76-1.06 (15H, m, $(C\underline{H}_3C_2H_4C\underline{H}_2\text{-})_3Sn$-), 1.16-1.75 (29H, m, $(CH_3C_2\underline{H}_4CH_2\text{-})_3Sn$- and $C_8\underline{H}_{16}C\underline{H}(SnBu_3)$-), 1.79-1.99 (1H, m), 2.21 (1H, ddd, *J* 15, 7.0, 4.0Hz) and 2.39-2.81 (2H, m, $C\underline{H}_2COC\underline{H}_2$-); *m/z* (F.I.) 472 ($M^+$, ^{120}Sn, 15%), 471 (10), 470 (15), 469 (10), 468 (8), 415 (M^+-^{n}Bu·, ^{120}Sn, 100), 414 (45), 413 (97), 412 (35), 411 (48).

Cyclohex-2-enone, N,N-*dimethyl hydrazone* **152**[143]. Using the procedure of Corey and Enders[143] the title compound was obtained in quantitative crude yield as a fluorescent

yellow oil however this yield dropped to ca. 60% on distillation (48°C/0.5mmHg) due to extensive polymerisation on heating. $\nu_{max.}$ (thin film) 3040 (m), 2950 (s), 2860 (s), 2880 (m), 1630 (m), 1600 (m), 1480-1420 (m), 1020 (m), 990 (s), 970 (s), 870 (m), 735 (s), 665 (m); δ_H (200 MHz; an approximately 1:1 mixture of *E*- and *Z*- isomers, integration values normalised) 1.69-1.95 (2H, m, CH_2CH_2C=NR-), 2.13-2.29 (2H, m, CH_2CH=), 2.34-2.45 and 2.61 (2H, m, CH_2C=NR-), 2.47 (3H, s) and 2.51 (3H, s, $N(CH_3)_2$), 6.13 (0.5H, dt, *J* 10, 2.0Hz, CHC=NR-), 6.29 (0.5H, dt, *J* 10, 4.0Hz, CHC=NR-), 6.34 (0.5H, dt, *J* 10, 4Hz, CH_2CH=) 6.72 (0.5H, dt, *J* 10, 2Hz, CH_2CH=); *m/z* (C.I., NH_3) 139 (MH^+, 100%), 138 (10).

3-Bromocyclohex-2-enone **160** *(This section also constitutes the general procedure for the bromination of the diones,* vide infra*).* This compound was prepared by one of two methods: Method 1: using the procedure of Piers *et al.*[146], in which the brominating agent is tri-phenylphosphine dibromide, yields of 56% and 62% (45mmol scale) were obtained. Method 2: using the Vilsmeier reagent derived from *N,N*-dimethylformamide and oxalyl bromide[147] a yield of 92% was obtained (1mmol scale). The crude product was in each case purified by flash chromatography (3:1 petrol:ether) to yield the pure bromo-enone **160** as a colourless oil. $\nu_{max.}$ (thin film) 2960 (m), 2880 (w), 1680 (s), 1610 (s), 1580 (m), 1430 (s), 1340 (s), 1325 (s), 1285 (s), 1230 (s), 1185 (s), 1140 (s), 975 (s), 885 (s), 740 (s); δ_H (200 MHz) 2.09 (2H, ca. quin., *J* 7.0Hz, CH_2CH_2CO-), 2.42 (2H, t, *J* 7.0Hz, CH_2CO-), 2.82 (2H, t, *J* 7.0Hz, $CH_2C(Br)$=), 6.49 (1H, s, CH=); *m/z* (E.I.) 175 (42%), 173 (43), 147 (48), 145 (53), 119 (32), 117 (33), 65 (100), 55 (32).

3-Butylcyclohex-2-enone **159**[149]. To a solution of lithium 2-thienylcyanocuprate (4.4ml of a 0.25M solution in THF, 1.1mmol) in THF (5ml) at -78°C was added ^{n}butyl lithium (0.88ml of a 1.25M solution in hexanes, 1.1mmol) and the resultant mixture stirred for 5min. A solution of the bromo-enone (**160**, 175mg, 1mmol) in THF (1ml) was added dropwise; after 10min the solution was allowed to 0°C and stirred at this temperature for 1h. The mixture was quenched with ammonia solution (10ml of saturated ammonium chloride (aq.) containing 15% by volume concentrated ammonia) and the resulting deep

blue aqueous portion extracted with ether (5x10ml). The extracts were washed with brine then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield a dark brown oil which was rendered pure by flash chromatography (3:1 petrol:ether) to give the title compound (**159**, 142mg, 93%) as a colourless oil with a distinctive nutty odour. Data for this compound is given above in the procedure for the attempted ring expansion of the stannane **169**.

3-Butyl-3-tributylstannylcyclohexanone **161**. Tributylstannyl lithium (1.1 equiv.) was prepared in THF (2ml) using the general procedure and quenched with the enone (**159**, 100mg, 0.66mmol) at -78°C. After 2.5h at -78°C the mixture was allowed to room temperature over 1h and worked-up in the usual manner. The crude residue was purified by flash chromatography (20:1 petrol:ether) to yield the pure stannane **161** as a colourless oil (251mg, 86%). $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2870 (s), 1715 (s), 1460 (s), 1380 (m), 1230 (m), 1075 (m), 910 (m), 890-860 (m), 735 (s), 700-640 (m); δ_H (200 MHz) 0.76-1.02 (18H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2)_3Sn$- and $C\underline{H}_3$-), 1.13-1.16 (18H, m, ($CH_3C_2\underline{H}_4$-$CH_2)_3Sn$- and $C_3\underline{H}_6CH_3$), 1.70-1.88 (2H, m, $C\underline{H}_2C_2H_4CO$-), 1.91-2.14 (2H, m, $C\underline{H}_2CH_2CO$-), 2.22-2.39 (4H, m, $C\underline{H}_2COC\underline{H}_2$-); *m/z* (E.I.) 387 ($M^+$-^{n}Bu·, ^{120}Sn, 62%), 386 (28), 385 (48), 384 (21), 383 (28), 331 (14), 291 (39), 235 (76), 179 (77), 121 (30), 97 (26), 81 (20), 69 (37), 55 (100).

3-Phenylsulphonylcyclohexanone **162**[151b]. The literature procedure[151a] was followed to yield the sulphone as a white solid after purification by flash column chromatography (1:1 then 1:3 petrol:ethyl acetate) m.p. 81-83°C; $\nu_{max.}$ ($CHCl_3$) 3030 (m), 2970 (w), 1720 (s), 1450 (m), 1315 (s), 1250-1200 (m), 1155 (s), 1090 (m), 915 (w), 890 (w), 790 (m), 640 (w); δ_H (200 MHz) 1.49-1.78 (1H, m) and 1.82-2.09 (1H, m, $C\underline{H}_2CH(SO_2Ph)$-), 2.15-2.50 (4H, m, $C_2\underline{H}_4CO$-), 2.57 (2H, d, *J* 8.0Hz, $COC\underline{H}_2CH(SO_2Ph)$-), 3.19-3.39 (1H, m, $C\underline{H}(SO_2Ph)$-), 7.51-7.76 (3H, m, Ph- *m*- and *p*- protons), 7.87 (2H, d, *J* 8.0Hz, Ph- *o*- protons); *m/z* (D.C.I., NH_3) 258 (17%), 257 (38), 256 (MNH_4^+, ^{32}S, 100), 160 (9), 114 (34), 97 (50), 68 (13), 58 (9), 55 (9).

7-Phenylsulphonyl-1,4-dioxaspiro[4,5]decane **163**[151b]. A mixture of the ketone (**162**, 6.80g, 28.6mmol), *p*-toluene sulphonic acid (25mg, 130μmol) and ethan-1,2-diol (2.4ml, 43mmol) were heated at reflux in benzene (60ml) and dichloromethane (10ml) with removal of water using a Dean-Stark trap. After 12h the dichloromethane was run off and heating continued for a further 24h at which time ca. 30ml of solvent was distilled off. The cooled residue was washed with sodium hydroxide (2x10ml of a 5% (aq.) solution) and brine (10ml) then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the title compound **163** as a white solid which was spectroscopically clean and pure by t.l.c. analysis (7.19g, 89%). m.p. 113-115°C; $\nu_{max.}$ ($CHCl_3$) 3030 (m), 2960 (m), 2895 (m), 1590 (w), 1450 (m), 1310 (s), 1240-1210 (s), 1085 (m), 1030 (m), 940 (m), 920 (m), 885 (m), 850 (m), 690 (s); δ_H (200 MHz) 1.22-1.53 (4H, m, $C_2\underline{H}_4C(OR)_2$-), 1.58-1.89 (2H, m, $C\underline{H}_2CH(SO_2Ph)$-), 1.93-2.20 (2H, m, $(RO)_2CC\underline{H}_2CH(SO_2Ph)$-), 3.22 (1H, tt, *J* 13, 4.0Hz, $C\underline{H}(SO_2Ph)$-), 3.83-4.05 (4H, m, $-OC_2\underline{H}_4O$-), 7.51-7.74 (3H, m, Ph- *m*- and *p*- protons), 7.87 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 300 (MNH_4^+, 26%), 283 (MH^+, 28), 141 (100), 99 (9).

7-(4'-Iodobutyl)-7-phenylsulphonyl-1,4-dioxaspiro[4,5]decane **164**. To a solution of the ketal sulphone (**163**, 1.0g, 3.55mmol) and triphenyl methane (5mg) in THF (10ml) was added ^{n}butyl lithium (3.55ml of a 1.25M solution in hexanes, 4.44mmol) until the red colour of the indicator just persisted. After a further 5min at room temperature 1,4-di-iodobutane (1.4ml, 10.6mmol) was added dropwise then the mixture heated at reflux for 2h by which time the red colour became discharged and a white precipitate formed. The cooled mixture was quenched with water (25ml) and the aqueous layer extracted with ether (3x10ml). The combined organic portions were washed with brine then dried ($MgSO_4$), filtered, and concentrated to yield a viscous oil which was purified by flash chromatography (3:1 to 1:1 petrol:ether then 1:1 petrol:ethyl acetate). The product **164** was obtained as a gum (1.09g, 66%). $\nu_{max.}$ ($CHCl_3$) 3020 (m), 2960 (s), 2890 (m), 1450 (s), 1290 (s), 1175 (m), 1140 (s), 1100 (s), 1035 (m), 950 (m), 910 (s), 690 (s); δ_H (200 MHz) 1.25-1.50 (2H, m) and 1.57-2.22 (10H, m, $C_3\underline{H}_6C(SO_2Ph)RC_3\underline{H}_6$-), 2.00 (2H, s, $(OR)_2CC\underline{H}_2C(SO_2Ph)R'$-), 3.21 (2H, t, *J* 6.5Hz, $C\underline{H}_2I$), 3.83-4.08 (4H, m, $-OC_2$-$\underline{H}_4O$-

), 7.51-7.74 (3H, m, Ph- *m*- and *p*- protons), 7.82-7.98 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 482 (MNH_4^+, 13%), 465 (MH^+, 13), 342 (23), 323 (100), 231 (6), 195 (32), 99 (38).

7-(4'-Phenylselenobutyl)-7-phenylsulphonyl-1,4-dioxaspiro[4,5]decane **165**. Sodium phenylselenide (1.90mmol) was generated in ethanol (7ml) using the general procedure described above for the preparation of electrophiles **110-112**. The anion was quenched with the iodide (**164**, 800mg, 1.72mmol) and after 3h the mixture worked-up in the usual manner to yield the crude selenide **165** as a gum which was clean enough to use in subsequent steps (850mg, ca. quantitative). $\nu_{max.}$ ($CHCl_3$) 3040 (w), 3020 (m), 2960 (s), 2890 (m), 1580 (m), 1490-1430 (m), 1290 (s), 1140 (s), 1100 (s), 1025 (m), 950 (m), 910 (s), 695 (s); δ_H (200 MHz) 1.24-1.49 (2H, m) and 1.57-1.93 (10H, m, $C_3\underline{H}_6C(SO_2Ph)RC_3\underline{H}_6$-), 1.99 (2H, s, $(OR)_2CC\underline{H}_2C(SO_2Ph)R'$-), 2.91 (2H, t, *J* 6.5Hz, $C\underline{H}_2SePh$), 3.90 (4H, s, $-OC_2\underline{H}_4O$-), 7.18-7.34 (3H, m, PhSe- *m*- and *p*- protons), 7.42-7.71 (5H, m, $PhSO_2$- *m*- and *p*- protons and PhSe- *o*- protons), 7.78-7.94 (2H, m, $PhSO_2$- *o*- protons); *m/z* (C.I., NH_3) 512 (MNH_4^+, ^{80}Se, 18%), 494 (M^+, ^{80}Se, 14), 372 (13), 353 (100), 351 (60), 337 (36), 231 (15), 195 (47), 99 (62).

7-(3'-Phenylselenopropyl)-7-phenylsulphonyl-1,4-dioxaspiro[4,5]decane **166**. The sulphone (**163**, 282mg, 1mmol) was alkylated using the above procedure (for iodide **164**) with 1-iodo-3-phenylselenopropane (**111**, 342mg, 1.05mmol). The reaction was complete after 6h at reflux and was worked-up as above. Flash chromatography (1:1 petrol:ether) gave the pure selenide (**166**, 300mg, 63%) as a pale yellow gum. $\nu_{max.}$ ($CHCl_3$) 3070 (w), 3020 (m), 2960 (m), 2890 (w), 1580 (w), 1480 (m), 1450 (m), 1285 (m), 1135 (s), 1100 (m), 1030 (m), 910 (m), 690 (s); δ_H (200 MHz) 1.21-1.83 (6H, m) and 1.88-2.16 (4H, m, $C_3\underline{H}_6C(SO_2Ph)RC_2\underline{H}_4$-), 1.99 (2H, s, $(RO)_2CC\underline{H}_2C(SO_2Ph)R'$-), 3.71-4.02 (4H, m, $-OC_2\underline{H}_4O$-), 7.17-7.38 (3H, m, PhSe- *m*- and *p*- protons), 7.45-7.71 (5H, m, $PhSO_2$- *m*- and *p*- protons and PhSe- *o*- protons), 7.74-7.92 (2H, m, $PhSO_2$- *o*- protons); *m/z* (C.I., NH_3) 498 (MNH_4^+, ^{80}Se, 23%), 481 (MH^+, 12), 480 (M^+, 5), 339 (64), 323 (100), 181 (45), 99 (57).

3-(4'-Phenylselenobutyl)-cyclohex-2-enone **167**. The ketal (**165**, 500mg, 1.01mmol) dissolved in 1,4-dioxan (8ml) was mixed with oxalic acid (410mg, 3.26mmol) dissolved in water (5ml). The mixture was stirred rapidly and heated at reflux for 12h then the cooled reaction made alkaline with excess solid potassium carbonate. After stirring for 0.5h the mixture was extracted with ether (3x25ml) and the extracts dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (4:1 then 2:1 petrol:ether) to yield the enone **167** as a colourless oil (200mg, 67%). $\nu_{max.}$ (thin film) 3030 (m), 2940 (s), 1670 (s), 1615 (s), 1580 (s), 1480 (s), 1470-1410 (s), 1330 (m), 1260 (m), 1195 (m), 1150 (m), 1075 (m), 1025 (m), 970 (m), 895 (m), 740 (s), 695 (s); δ_H (200 MHz) 1.58-1.82 (4H, m, $C_2\underline{H}_4CH_2SePh$), 1.96 (2H, ca. quin., *J* 6.5Hz, $C\underline{H}_2CH_2CO$-), 2.14-2.29 (4H, m, $C\underline{H}_2C(C\underline{H}_2R)$=), 2.34 (2H, t, *J* 6.5Hz, $C\underline{H}_2CO$-), 2.91 (2H, t, *J* 6.5Hz, $C\underline{H}_2SePh$), 5.87 (1H, s, C<u>H</u>=), 7.18-7.32 (3H, m, Ph- *m*- and *p*-protons), 7.40-7.53 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 326 (MNH_4^+, 10%), 309 (MH^+, ^{80}Se, 88), 307 (MH^+, ^{78}Se, 44), 293 (100), 291 (53), 170 (49), 151 (65), 134 (12).

3-(3'-Phenylselenopropyl)-cyclohex-2-enone **168**. The hydrolysis conditions used for the preparation of the enone **167** (above) were applied to the ketal (**166**, 240mg, 0.5mmol). Flash chromatography (1:1 petrol:ether) of the crude product afforded the title compound **168** as a colourless oil (145mg, 99%). $\nu_{max.}$ (thin film) 3060 (w), 2940 (s), 2870 (m), 1670 (s), 1625 (m), 1580 (m), 1460-1410 (m), 1255 (m), 1195 (m), 1025 (m), 890 (m), 740 (s), 690 (s); δ_H (200 MHz) 1.82-2.07 (4H, m, $C\underline{H}_2CH_2SePh$ and $C\underline{H}_2CH_2CO$-), 2.26 (2H, t, *J* 6.0Hz) and 2.35 (4H, ca. t, *J* 6.0Hz, $C\underline{H}_2CO$- and $C\underline{H}_2C(C\underline{H}_2R)$=), 2.91 (2H, t, *J* 7.0Hz, $C\underline{H}_2SePh$), 5.87 (1H, s, C<u>H</u>=), 7.21-7.38 (3H, m, Ph- *m*- and *p*-protons), 7.45-7.59 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 312 (MNH_4^+, ^{80}Se, 3%), 295 (MH^+, ^{80}Se, 100), 293 (MH^+, ^{78}Se, 58), 137 (16), 110 (13).

3-(4'-Phenylselenobutyl)-3-tributylstannylcyclohexanone **169**. Tributylstannyl lithium (1.0 equiv.) was prepared in THF (3ml), using the general procedure, and cooled to -78°C

whereupon the enone (**167**, 100mg, 0.33mmol) was added dropwise as a solution in THF (1ml). The mixture was stirred for 1h then quenched with saturated ammonium chloride solution (5ml) before being allowed to room temperature. The usual extractive work-up and flash chromatography (20:1 petrol:ether) afforded the pure stannane **169** as a colourless oil (159mg, 82%). $\nu_{max.}$ (thin film) 3000-2790 (s), 1715 (s), 1460 (s), 1380 (m), 1230 (m), 1070 (m), 910 (m), 735 (s), 660 (m); δ_H (200 MHz) 0.76-1.01 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.20-1.88 (20H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_3\underline{H}_6CH_2SePh$, and $C\underline{H}_2C_2H_4CO$-), 1.92-2.11 (2H, m, $C\underline{H}_2CH_2CO$-), 2.18-2.40 (3H, m) and 2.47-2.71 (1H, m, $C\underline{H}_2COC\underline{H}_2$-), 2.93 (2H, t, *J* 7.0Hz, $C\underline{H}_2SePh$), 7.18-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.56 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 618 (MNH_4^+, 2%), 601 (MH^+, 23), 600 (13), 599 (27), 598 (15), 597 (23), 541 (12), 309 (100), 291 (24), 217 (17), 153 (28); Calculated: 601 (91), 600 (51), 599 (100), 598 (56), 597 (74), 596 (28), 595 (31).

3-(3'-Phenylselenopropyl)-3-tributylstannylcyclohexanone **170**. Tributylstannyl lithium (1.05 equiv.) was prepared in THF (3ml), according to the general procedure, and cooled to -78°C whereupon the enone (**168**, 100mg, 0.34mmol) was added dropwise as a solution in THF (0.5ml). The mixture was stirred at this temperature for 0.5h then allowed to come to room temperature <u>before</u> being quenched with saturated ammonium chloride solution (2ml). Extractive work-up and flash chromatography (20:1 to 2:1 petrol:ether) led to the isolation of the title compound **170** as a colourless oil (21mg, 36% - low yield possibly arising from alternative quench procedure c.f. stannane **169**). (Found: C, 55.56; H, 7.86. $C_{27}H_{46}OSeSn$ requires C, 55.50; H, 7.93%); $\nu_{max.}$ (thin film) 3000-2780 (s), 1715 (s), 1455 (m), 1380 (m), 1225 (m), 1070 (m), 905 (m), 740 (s), 650 (s); δ_H (200 MHz) 0.69-0.99 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.17-1.51 (12H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-), 1.54-1.85 (6H, m, $C_2\underline{H}_4CH_2SePh$ and $C\underline{H}_2C_2H_4CO$-), 1.88-2.09 (2H, m, $C\underline{H}_2CH_2CO$-), 2.25 and 2.58 (2H, ABq, *J* 13Hz, $C(SnBu_3)RC\underline{H}_2CO$-), 2.19-2.37 (2H, m, $CH_2C\underline{H}_2CO$-), 2.76-2.98 (2H, m, $C\underline{H}_2SePh$), 7.18-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.54 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 529 (M^+-^{n}Bu·, $^{120}Sn^{80}Se$,

55%), 527 (62), 525 (48), 387 (11), 371 (13), 291 (38), 235 (19), 177 (39), 137 (65), 85 (74), 71 (75), 57 (100).

Attempted ring expansion of stannane **169**. The reaction of the stannane (**169**, 100mg, 0.17mmol) towards the general radical conditions described above was 90% complete after 20h at reflux. The concentrated residue was subjected to flash chromatography (10:1 petrol:ether) to give starting material (**169**, 10mg, 10%) and *3-butylcyclohex-2-enone*[149] (**159**, 20mg, 77%) as a colourless oil with a distinctive "nutty" odour. $\nu_{max.}$ (thin film) 3020 (w), 2960 (s), 2940 (s), 2890 (s), 1670 (s), 1615 (s), 1480-1410 (m), 1350 (m), 1330 (m), 1255 (m), 1195 (m), 1140 (w), 970 (m), 890 (m), 735 (m); δ_H (250 MHz) 0.93 (3H, t, *J* 7.0Hz, C$\underline{H}_3$-), 1.31 (2H, ca. quin., *J* 7.0Hz, C$\underline{H}_2$CH$_3$), 1.48 (2H, ca. quin., *J* 7.0Hz, C$\underline{H}_2$C$_2$H$_5$), 1.99 (2H, ca. quin., *J* 7.0Hz, C$\underline{H}_2$CH$_2$CO-), 2.13-2.41 (6H, m, C$\underline{H}_2$CO- and C$\underline{H}_2$C(C$\underline{H}_2$)=), 5.88 (1H, s, C$\underline{H}$=); *m/z* (GCMS, C.I., NH_3) 170 (MNH_4^+, 5%), 153 (MH^+, 100).

Attempted ring expansion of stannane **170**. The radical reaction of the stannane (**170**, 21mg, 36 μmol) was complete after 72h at reflux. The concentrated residue was purified by p.l.c. (2:1 petrol:ether) to yield a mixture of *2,3-dicyano-2,3-dimethylbutane* and *3-propylcyclohex-2-enone*[153] (**171**, combined mass 9.8mg). $\nu_{max.}$ (thin film) 3020 (m), 3000 (m), 2975 (w), 1660 (s), 1625 (w), 1465 (s), 1390 (m), 1145 (m); δ_H (200 MHz) 0.94 (3H, t, *J* 7.5Hz, C$\underline{H}_3$-), 1.47-1.67 (2H, m, C$\underline{H}_2$CH$_3$), 1.99 (2H, ca. quin., *J* 6.5Hz, C$\underline{H}_2$CH$_2$CO-), 2.21 (2H, t, *J* 6.5Hz) and 2.29 (2H, t, *J* 6.5Hz, C$\underline{H}_2$C(C$\underline{H}_2$)=), 2.38 (2H, t, *J* 6.5Hz, C$\underline{H}_2$CO-), 5.88 (1H, s, C$\underline{H}$=); *m/z* (GCMS, C.I., NH_3) 156 (MNH_4^+, 6%), 139 (MH^+, 100), 110 (4), 82 (12).

2-Methyl-3-phenylsulphonylcyclohexanone **172**. 2-Methylcyclohex-2-enone (**96**, 2.0g, 18.2mmol) and sodium phenylsulphinate (4.47g, 27.3mmol) were stirred at room temperature in glacial acetic acid (25ml) until equilibrium had been reached (ca. 100h). The mixture was poured into water (100ml) and extracted with ether (7x20ml). The combined extracts were washed with saturated sodium hydrogen carbonate solution (2x20ml) and

brine then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2:1 petrol:ethyl acetate) to yield starting enone (**96**, ca. 1g, 50%) and the desired sulphone (**172**, 1.98g, 43%) as white needles (m.p. 101-3°C); $\nu_{max.}$ ($CHCl_3$) 3030 (m), 2960 (m), 2880 (w), 1718 (s), 1450 (s), 1310 (s), 1150 (s), 1090 (s), 1025 (m), 970 (m), 840 (m), 690 (s), 625 (s); δ_H (200 MHz) 1.41 (3H, d, *J* 7.5Hz, $C\underline{H}_3$-), 1.49-1.70 (1H, m), 1.91-2.37 (4H, m) and 2.47-2.68 (1H, m, $C_3\underline{H}_6CO$-), 2.95 (1H, ca. qd, *J* 12, 7.5Hz, $C\underline{H}(CH_3)$-), 3.33 (1H, dt, *J* 12, 4.0Hz, $C\underline{H}(SO_2Ph)$-), 7.53-7.75 (3H, m, Ph- *m*- and *p*- protons), 7.84-7.97 (2H, m, Ph- *o*- protons); *m/z* (D.C.I., NH_3) 272 (15%), 271 (35), 270 (MNH_4^+, ^{32}S, 100), 253 (MH^+, ^{32}S, 10), 160 (11), 128 (28), 111 (62), 82 (12). Also observed was the product arising from addition to 5-methylcyclohex-2-enone, an impurity in the starting enone **96**; this was identified as *2-methyl-5-phenylsulphonylcyclohexanone* (136mg, 3%); white needles, m.p. 134-6°C (petrol/ethyl acetate); $\nu_{max.}$($CHCl_3$) 3030 (m), 2980 (m), 2940 (m), 2880 (m), 1720 (s), 1450 (s), 1310 (s), 1155 (s), 1090 (s), 1050 (m), 880 (w), 690 (s), 620 (m); δ_H (200 MHz) 1.03 (3H, d, *J* 6.5Hz, $C\underline{H}_3$-), 1.22-1.49 (1H, m), 1.89-2.14 (1H, m) and 2.15-2.50 (3H, m, $C_2\underline{H}_4C\underline{H}(CH_3)CO$-), 2.59 (2H, d, *J* 10Hz, $C\underline{H}_2CO$-), 3.19-3.39 (1H, m, $C\underline{H}(SO_2Ph)$-), 7.53-7.76 (3H, m, Ph- *m*- and *p*- protons), 7.83-7.98 (2H, ca. d, *J* 8.0Hz, Ph- *o*- protons); *m/z* (D.C.I., NH_3) 272 (14%), 271 (34), 270 (MNH_4^+, ^{32}S, 100), 160 (9), 128 (21), 111 (38), 68 (9).

6-Methyl-7-phenylsulphonyl-1,4-dioxaspiro[4,5]decane **173**. The ketone (**172**, 1.90g, 7.54mmol) was subjected to the same protection conditions as those used to prepare ketal **163**. The reaction was complete after 20h at reflux; work-up and flash chromatography (1:1 petrol:ether) gave the pure ketal (**173**, a glass) as an inseparable mixture of diastereomers (1.85g, 83%). $\nu_{max.}$ ($CHCl_3$) 3030 (m), 2990 (w), 2960 (m), 2895 (m), 1450 (s), 1310 (s), 1240-1210 (m), 1150 (s), 1100 (s), 1090 (s), 1040 (m), 955 (m), 690 (s), 625 (m); δ_H (200 MHz, quoted for an approximately 1:1 diastereomeric mixture) 1.23 (3H, d, *J* 6.5Hz, $C\underline{H}_3$-), 1.30 (2H, m) and 1.57-1.96 (4H, m, $C_3\underline{H}_6CH(SO_2Ph)$-), 2.03-2.25 ("0.5H", m) and 2.34-2.51 ("0.5H", m, $C\underline{H}(CH_3)$-), 3.14 ("0.5H", td, *J* 12, 4.0Hz) and 3.35 ("0.5H", dt, *J* 12, 3.0Hz, $C\underline{H}(SO_2Ph)$-), 3.82-4.05 (4H, m, $-OC_2\underline{H}_4O$-), 7.49-

7.71 (3H, m, Ph- *m*- and *p*- protons), 7.80-7.95 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 314 (MNH_4^+, 43%), 297 (MH^+, 63), 155 (100), 128 (34), 111 (65), 94 (13), 78 (21).

6-Methyl-7-(3'-phenylselenopropyl)-7-phenylsulphonyl-1,4-dioxaspiro[4,5]decane **174**. The sulphone (**173**, 585mg, 1.98mmol) was alkylated according to the procedure given for iodide **164** using 1-iodo-3-phenylselenopropane (**111**, 677mg, 2.08mmol). After 6h at reflux the mixture was worked-up and the residue subjected to flash column chromatography (1:1 petrol:ether). The two diastereomers were extremely close running and spectroscopic data given below refers to one of the diastereomers for which one fraction was obtained clean. The title compound **174** was obtained as a gum (670mg, 69%). $\nu_{max.}$ ($CHCl_3$) 3060 (m), 2950 (s), 2880 (m), 1580 (m), 1480-1430 (s), 1390 (s), 1130 (s), 1090 (s), 1020 (m), 925 (m), 735 (s), 690 (s); δ_H (200 MHz) 1.14 (3H, d, *J* 8.0Hz, $C\underline{H}_3$- in the ^1H spectrum of the combined diastereomers the corresponding signal of the other diastereomer appeared at δ 1.47 (d, *J* 8.0Hz)), 1.34-1.93 (8H, m, $C_2\underline{H}_4CH_2SePh$ and $(RO)_2CC_2\underline{H}_4$-), 2.09-2.53 (3H, m, $C\underline{H}_2C(SO_2Ph)RC\underline{H}(CH_3)$-), 2.81-3.15 (2H, m, $C\underline{H}_2SePh$), 3.72-4.10 (4H, m, $-OC_2\underline{H}_4O$-), 7.17-7.35 (3H, m, PhSe- *m*- and *p*- protons), 7.43-7.71 (5H, m, $PhSO_2$- *m*- and *p*- protons and PhSe- *o*- protons), 7.77-7.96 (2H, m, $PhSO_2$- *o*- protons); *m/z* (D.C.I., NH_3) 512 (MNH_4^+, 18%), 495 (11), 353 (100), 337 (12), 323 (88), 197 (33), 155 (11), 113 (18), 99 (72).

7-(4'-Iodobutyl)-6-methyl-7-phenylsulphonyl-1,4-dioxaspiro[4,5]decane **174a**. The ketal sulphone (**173**, 800mg, 2.7mmol) was alkylated under conditions identical to those used in the preparation of iodide **164**. The reaction required 3h at reflux to go to completion; work-up and chromatography (2:1 then 1:1 petrol:ether) afforded the alkylated ketal **174a** as a gum (mixture of diastereomers) (871mg, 68%). $\nu_{max.}$ ($CHCl_3$) 3010 (m), 2960 (s), 2900 (s), 1450 (s), 1295 (s), 1135 (s), 1090 (s), 1035 (m), 955 (m), 930 (m), 910 (s), 695 (s), 655 (m); δ_H (200 MHz) 1.14 (3H, d, *J* 6.5Hz, $C\underline{H}_3$-), 1.38-2.03 (10H, m, $C_3\underline{H}_6CH_2I$ and $C_2\underline{H}_4C(OR)_2$-), 2.07-2.54 (3H, m, $C\underline{H}(CH_3)$- and $C\underline{H}_2C(SO_2Ph)$-), 3.09-3.28 (2H, m, $C\underline{H}_2I$), 3.70-4.07 (4H, m, $-OC_2\underline{H}_4O$-), 7.48-7.70 (3H, m, Ph- *m*- and

p- protons), 7.81-7.92 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 496 (MNH_4^+, 9%), 479 (MH^+, 11), 337 (100), 211 (10), 99 (28).

6-Methyl-7-(4'-phenylselenobutyl)-7-phenylsulphonyl-1,4-dioxaspiro[4,5]decane **175**. Sodium phenylselenide (1.1 equiv.) was generated in ethanol (10ml) using the procedure described for the preparation of the electrophiles **110-112** and quenched with the iodide (**174a**, 700mg, 1.46 mmol). After 14h the reaction was worked-up and the crude material purified by flash chromatography (1:1 petrol:ether) to yield the pure selenide **175** as a gum (mixture of diastereomers) (637mg, 86%). $\nu_{max.}$ ($CHCl_3$) 3020 (w), 2960 (m), 2900 (m), 1585 (w), 1490-1440 (m), 1295 (s), 1140 (s), 1390 (s), 955 (w), 910 (m), 695 (s), 655 (m); δ_H (200 MHz) 1.13 (3H, d, *J* 8.0Hz, $C\underline{H}_3$-), 1.31-1.94 (10H, m, $C_3\underline{H}_6CH_2SePh$ and $C_2\underline{H}_4C(OR)_2$-), 2.03-2.39 (3H, m, $C\underline{H}(CH_3)$- and $C\underline{H}_2C(SO_2Ph)$-), 2.95 (2H, t, *J* 8.0Hz, $C\underline{H}_2SePh$), 3.71-4.06 (4H, m, $-OC_2\underline{H}_4O$-), 7.19-7.33 (3H, m, PhSe- *m*- and *p*- protons), 7.41-7.70 (5H, m, $PhSO_2$- *m*- and *p*- protons and PhSe- *o*- protons), 7.79-7.94 (2H, m, $PhSO_2$- *o*- protons); *m/z* (C.I., NH_3) 526 (MNH_4^+, ^{80}Se, 49%), 524 (MNH_4^+, ^{78}Se, 28), 508 (M^+, ^{80}Se, 12), 506 (M^+, ^{78}Se, 8), 367 (24), 155 (67), 139, (30), 99 (100), 83 (82), 64 (48).

2-Methyl-3-(3'-phenylselenopropyl)-cyclohex-2-enone **176**. Application of the conditions used for the hydrolysis of **164** to the ketal (**174**, 500mg, 1.01mmol) with a reaction time of 20h led, after work-up and flash chromatography (5:1 petrol:ether), to the isolation of the pure enone (**176**, 198mg, 64%). $\nu_{max.}$ (thin film) 3060 (w), 2940 (m), 1665 (s), 1630 (m), 1580 (m), 1480 (m), 1440 (m), 1360 (m), 1020 (m), 735 (s), 690 (s); δ_H (200 MHz) 1.87 (3H, s, $C\underline{H}_3$-), 1.90-1.99 (4H, m, $C\underline{H}_2CH_2CO$- and $C\underline{H}_2CH_2SePh$), 2.24-2.47 (6H, m, $C\underline{H}_2CO$- and $C\underline{H}_2C(C\underline{H}_2)$=), 2.94 (2H, t, *J* 7.5Hz, $C\underline{H}_2SePh$), 7.23-7.36 (3H, m, Ph- *m*- and *p*- protons), 7.46-7.58 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 308 (M^+, 13), 279 (9), 277 (9), 187 (18), 151 (75), 124 (100), 109 (23), 96 (70), 82 (69), 79 (58), 77 (44), 67 (41), 55 (39).

2-Methyl-3-(4'-phenylselenobutyl)-cyclohex-2-enone **177**. The ketal (**175**, 600mg, 1.18 mmol) was subjected to the same hydrolysis conditions as used in the preparation of enone **167**. After 16h at reflux the reaction was worked-up and the residue purified by flash chromatography (3:1 petrol:ether) to give the title compound **177** as a colourless oil (218mg, 57%). $\nu_{max.}$ (thin film) 3070 (w), 2935 (s), 2870 (m), 1665 (s), 1640 (m), 1580 (m), 1480-1410 (m), 1380 (m), 1360 (m), 1330 (m), 1305 (m), 1025 (m), 740 (s), 695 (s); δ_H (200 MHz) 1.49-1.80 (4H, m, $C_2\underline{H}_4CH_2SePh$), 1.75 (3H, s, $C\underline{H}_3$-), 1.89 (2H, ca. quin., *J* 6.5Hz, $C\underline{H}_2CH_2CO$-), 2.15-2.42 (6H, m, $C\underline{H}_2CO$- and $C\underline{H}_2C(C\underline{H}_2)$=), 2.92 (2H, t, *J* 8.0Hz, $C\underline{H}_2SePh$), 7.19-7.32 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.55 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 323 (MH^+, ^{80}Se, 92%), 321 (MH^+, ^{78}Se, 45), 307 (27), 184 (62), 167 (74), 165 (100), 149 (23), 78 (23).

2,2-Dimethyl-3-(3'-phenylselenopropyl)-3-tributylstannylcyclohexanone **178**. To a solution of bis-tributylstannane (197µl, 0.39mmol) in THF (2ml) at 0°C was added ^{n}butyl lithium (253µl of a 1.54M solution in hexanes, 0.39mmol) and the resultant solution stirred for 0.5h. The mixture was cooled to -23°C and the enone (**176**, 100mg, 0.33 mmol) added as a solution in THF (0.5ml). The mixture was stirred for 1h at this temperature then HMPA (1.5ml, 8.6mmol) and methyl iodide (61µl, 0.98mmol) were added and the mixture allowed to room temperature over 20h. The mixture was quenched with water (5ml) and extracted with petrol (5x10ml), the extracts being washed with brine then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an oil which was purified by flash chromatography (20:1 then 10:1 petrol:ether) affording the pure stannane (**178**, 120mg, 60%) as a colourless oil. $\nu_{max.}$ (thin film) 3070 (w), 2960-2920 (s), 2860 (m), 1705 (s), 1580 (m), 1480-1410 (m), 1375 (m), 1070 (m), 1025 (m), 735 (s), 690 (s); δ_H (200 MHz) 0.74 (6H, t, *J* 7.5Hz, $(C_3H_7C\underline{H}_2)_3Sn$-), 0.90 (9H, t, *J* 7.5Hz, $(C\underline{H}_3C_3H_6)_3Sn$-), 1.01 (3H, s, $C\underline{H}_3$-), 1.12 (3H, s, $C\underline{H}_3$-), 1.18-2.12 (20H, m, $(CH_3C_2\underline{H}_4CH_2)_3Sn$-, $C_2\underline{H}_4CH_2SePh$, and $C_2\underline{H}_4CH_2CO$-), 2.21-2.54 (2H, m, $C\underline{H}_2CO$-), 2.80-3.03 (2H, m, $C\underline{H}_2SePh$), 7.18-7.43 (3H, m, Ph- *m*- and *p*- protons), 7.45-7.59 (2H, m, Ph- *o*- protons); *m/z* (D.C.I., NH_3) 613 (MH^+, 7%), 337 (50), 323 (100), 179 (32), 165 (61), 137 (21), 95 (20), 81 (13).

2,2-Dimethyl-3-(4'-phenylselenobutyl)-3-tributylstannylcyclohexanone **179**. Tributylstannyl lithium (1.0 equiv.) was prepared in THF (2ml), as in the general procedure, and cooled to -78°C whereupon the enone (**177**, 200mg, 0.62mmol) was added dropwise as a solution in THF (0.5ml). The mixture was stirred for 1h at this temperature then warmed to -30°C. HMPA (1.1ml, 6.33mmol) was added then, after 15min, methyl iodide (0.19ml, 3.1mmol) added and the resultant mixture allowed to come to room temperature over 20h. The product was then isolated as in the general procedures and rendered pure by flash chromatography (20:1 petrol:ether). The title compound **179** was obtained as a colourless oil (251mg, 64%). (Found: C, 57.62; H, 8.37. $C_{30}H_{52}OSeSn$ requires C, 57.52; H, 8.37%); $\nu_{max.}$ (thin film) 3080 (w), 2960 (s), 2930 (s), 2870 (m), 1705 (s), 1585 (w), 1490-1410 (m), 1385 (w), 1120 (w), 1080 (m), 1025 (m), 915 (w), 735 (s); δ_H (200 MHz) 0.71-0.96 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.03 (3H, s, $C\underline{H}_3$-), 1.14 (3H, s, $C\underline{H}_3$-), 1.18-1.84 (20H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C_3\underline{H}_6CH_2SePh$ and $C\underline{H}_2C_2H_4CO$-), 1.91-2.12 (2H, m, $C\underline{H}_2CH_2CO$-), 2.26-2.47 (2H, m, $C\underline{H}_2CO$-), 2.93 (2H, td, *J* 6.5, 1.5Hz, $C\underline{H}_2SePh$), 7.21-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.55 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 611 (Calc. M^+-CH_3·, 7%), 569 (Calc. M^+-^{n}Bu·, 15), 415 (21), 389 (22), 291 (53), 235 (79), 179 (100), 121 (41), 95 (45), 91 (38), 81 (56), 77 (55), 67 (52), 55 (92).

1-Trimethylsilyloxycyclohexene **183**[206a]. Following a literature procedure[206b] the title compound was obtained in 94% yield from cyclohexanone (2g, 0.02mol) after bulb to bulb distillation (90°C/14mmHg). $\nu_{max.}$ (thin film) 3050 (w), 2930 (s), 2840 (s), 1670 (s), 1445 (m), 1370 (s), 1270 (s), 1250 (s), 1190 (s), 990 (s); δ_H (200 MHz) 0.17 (9H, s, ($C\underline{H}_3$)$_3$Si-), 1.43-1.57 (2H, m, $C\underline{H}_2CH_2CH$=), 1.59-1.74 (2H, m, $C\underline{H}_2CH_2C$(OTMS)=), 1.91-2.07 (4H, m, $C\underline{H}_2C$(OTMS)=CH$C\underline{H}_2$-), 4.87 (1H, ca. s, C$\underline{H}$=).

1-(2'-Oxocyclohexyl)-2-(phenylselenomethyl)-cyclohexanol **184** *and* **185**. To a cooled (-23°C) solution of silyl enol ether (**183**, 170mg, 1mmol) and bromo-phenylselenomethane (**110**, 280mg, 1.12mmol) in dichloromethane (2ml) was added dropwise titanium

tetrachloride (121μl, 1.1mmol) in dichloromethane (1ml). The mixture was stirred for 2h at -23°C then allowed to room temperature over a further 1h and quenched with saturated sodium hydrogen carbonate solution (5ml, CARE!). The aqueous layer was extracted with ether (4x5ml) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (8:1 then 3:1 petrol:ether) then the two diastereomers of the dimeric material separated by p.l.c. (4:1 petrol:ether, 4 runs). Diastereomer #1: (**184**, 71mg, 39% based on starting enol ether). $\nu_{max.}$ (thin film) 3580-3360 (br, m), 3060 (m), 2940 (s), 2860 (s), 1690 (s), 1580 (m), 1480 (s), 1440 (s), 1390 (s), 1130 (s), 980 (m), 930 (m), 735 (s), 690 (s), 670 (m); δ_H (200 MHz) 1.04-1.89 (14H, m, $C_3\underline{H}_6CH_2CO$- and $C_4\underline{H}_8C(OH)R$-), 1.96-2.09 (1H, m, C$\underline{H}$(CH_2SePh)-), 2.14-2.48 (2H, m, $C\underline{H}_2CO$-), 2.75 (2H, dd, *J* 13, 6.5Hz, $C\underline{H}_2SePh$), 3.17 (1H, dd, *J* 12, 3.0Hz, C$\underline{H}$CO-), 3.96 (1H, s, O$\underline{H}$), 7.20-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.47-7.59 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 367 (MH^+, 20%), 366 (M^+, 12), 349 (29), 286 (21), 269 (100), 268 (100), 266 (58), 209 (37), 191 (48), 111 (63), 98 (45), 55 (54). Diastereomer #2: (**185**, 32mg, 18% based on starting enol ether). $\nu_{max.}$ (thin film) 3640-3300 (br, s), 3060 (m), 2940 (s), 2860 (s), 1700 (s), 1580 (s), 1480 (s), 1445 (s), 1310 (s), 1130 (m), 1025 (m), 945 (m), 740 (s), 690 (s), 670 (s); δ_H (200 MHz) 1.15-1.80 (11H, m), 1.82-1.92 (1H, m) and 1.96-2.17 (3H, m, $C_3\underline{H}_6CH_2CO$-, $C_4\underline{H}_8C(OH)R$- and C$\underline{H}$(CH_2SePh)-), 2.25-2.41 (2H, m, $C\underline{H}_2CO$-), 2.64 (1H, dd, *J* 12, 4.0Hz, C$\underline{H}$HSePh), 2.76 (1H, dd, *J* 12, 9.0Hz, CH$\underline{H}$SePh), 3.09 (1H, dd, *J* 12, 4.0Hz, C$\underline{H}$CO-), 3.74 (1H, s, O$\underline{H}$), 7.17-7.31 (3H, m, Ph- *m*- and *p*- protons), 7.42-7.56 (2H, m, Ph- *o*- protons); *m/z* (C.I., NH_3) 367 (MH^+, 45%), 366 (M^+, 33), 349 (55), 347 (29), 286 (16), 269 (62), 268 (57), 209 (70), 191 (100), 111 (41), 98 (27), 55 (37).

2-Bromocyclohexanone **187**. The title compound was prepared according to a modified literature procedure[157]. Bromine (5.8ml, 0.11mol) was added to a rapidly stirred (mechanical stirrer) mixture of cyclohexanone (10g, 0.102mol) and water (50ml) containing glacial acetic acid (2 drops) and ethanol (10ml) as rapidly as decolourisation occurred (≈2h); during this time the temperature of the mixture rose to about 40°C. On completion of the reaction the product was separated from the aqueous phase and combined

with three ether extracts (3x50ml) of the aqueous layer. The combined organic portions were washed with water (50ml) and brine (50ml), then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield crude product which was distilled (110-115°C/14mmHg) to give the pure bromo ketone (**187**, 17.9g, 91%). $\nu_{max.}$ (thin film) 2940 (s), 2870 (s), 1770-1690 (s), 1450 (s), 1430 (s), 1315 (m), 1220 (s), 1120 (s), 1055 (m), 920 (s), 820 (m), 735 (m), 690 (m), 655 (m); δ_H (200 MHz) 1.60-2.09 (4H, m, $C_2\underline{H}_4CH_2CO$-), 2.12-2.42 (3H, m, CH$\underline{H}$CO- and C$\underline{H}_2$CHBr-), 2.86-3.07 (1H, m, C$\underline{H}$HCO-), 4.43 (1H, t, *J* 5.0Hz, C$\underline{H}$(Br)CO-).

2-Phenylsulphonylcyclohexanone **186**[156]. A mixture of the bromo ketone (**187**, 1.0g, 5.65mmol), sodium benzene sulphinate (1.02g, 6.22mmol), tetrabutyl ammonium bromide (182mg, 0.57mmol) and dimethyl sulphoxide (25ml) were stirred at room temperature for 16h resulting in a pink solution. The mixture was poured into water (100ml) then extracted with ethyl acetate (5x20ml), the combined organic extracts being washed with brine then dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (4:1 then 2:1 petrol:ethyl acetate) to give the title compound (**186**, 1.23g, 91%). A small portion was recrystallised from benzene/dichloromethane for data. (m.p. 89-91°C, lit.,[156b] 85-86°C); $\nu_{max.}$ ($CHCl_3$) 3020 (m), 2850 (m), 2875 (m), 1710 (s), 1590 (w), 1450 (s), 1310 (s), 1250-1200 (m), 1150 (s), 1085 (s), 1060 (m), 920 (m), 690 (s), 620 (s); δ_H (200 MHz) 1.57-2.05 (3H, m) and 2.08-2.58 (4H, m, $C_3\underline{H}_6CH\underline{H}CO$-), 2.63-2.86 (1H, m, C$\underline{H}$HCO-), 3.86 (1H, t, *J* 6.0Hz, C$\underline{H}(SO_2Ph)CO$-), 7.45-7.71 (3H, m, Ph-*m*- and *p*- protons), 7.89 (2H, ca. d, *J* 8.0Hz, Ph- *o*- protons); *m/z* (C.I., NH_3) 239 (MH^+, 25%), 238 (M^+, 19), 143 (91), 125 (37), 97 (88), 77 (100), 68 (59), 55 (46).

2-Carbomethoxy-2-(phenylselenomethyl)-cyclohexanone **189**. To a suspension of sodium hydride (31mg of a 60% dispersion in mineral oil, washed with petrol under argon, 0.78mmol) in anhydrous dimethyl sulphoxide (2ml) was added 2-carbomethoxycyclohexanone (100mg, 0.64mmol) and the resultant mixture stirred at room temperature until homogeneous. Bromo-phenylselenomethane (**110**, 193mg, 0.77mmol) was added and stirring continued overnight. Enough water was added to give a homo-

geneous solution which was then extracted with ether (5x). The combined extracts were washed with brine then dried ($MgSO_4$), filtered, and concentrated to give crude material which was purified by flash chromatography (10:1 petrol:ether) after which the product **189** was obtained as a viscous colourless oil (200mg, 96%) which solidified to a glass on prolonged standing. $\nu_{max.}$ (thin film) 3060 (w), 2950 (s), 2870 (m), 1760-1725 (s), 1710 (s), 1580 (m), 1480 (m), 1440 (s), 1265 (s), 1230 (s), 1170 (s), 1135 (s), 820 (m), 740 (s), 690 (s); δ_H (200 MHz) 1.64-1.83 (3H, m) and 1.92-2.13 (1H, m, $C_2\underline{H}_4CH_2CO$-), 2.19-2.37 (1H, m, $CH\underline{H}C(CH_2SePh)$-), 2.43-2.72 (3H, m, $C\underline{H}_2CO$- and $C\underline{H}HC(CH_2SePh)$-), 3.18 and 3.33 (2H, ABq, *J* 13Hz, $C\underline{H}_2SePh$), 3.59 (3H, s, $C\underline{H}_3$-), 7.19-7.38 (3H, m, Ph- *m*- and *p*- protons), 7.47-7.59 (2H, m, Ph- *o*- protons); *m/z* (D.C.I., NH_3) 344 (MNH_4^+, ^{80}Se, 33%), 327 (MH^+, ^{80}Se, 100), 325 (MH^+, ^{78}Se, 61), 295 (14), 249 (13), 169 (39), 155 (15), 109 (23), 81 (19).

2-Methylenecyclohexanone **181**[158]. Use of the literature procedure with cyclohexanone gave the exomethylene compound **181** as an unstable oil which was used as soon as possible after preparation. Data for intermediates: *2-(N,N-dimethylaminomethyl)-cyclohexanone hydrochloride* **190**. m.p. 145-148°C (lit.,[158] 149°C); $\nu_{max.}$ ($CHCl_3$) 2960 (s), 2800-2430 (br, s), 1715 (s), 1470 (s), 1260-1200 (s), 1135 (m), 975 (m), 885 (w), 715 (m), 665 (s); δ_H (200 MHz) 1.32-1.98 (5H, m) and 2.07-2.25 (1H, m, $C_3\underline{H}_6CH_2CO$-), 2.38-2.57 (3H, m, $C\underline{H}_2COC\underline{H}R$-), 2.70 (6H, s, $(C\underline{H}_3)_2NH^+$-), 3.11-3.28 (1H, m) and 3.65 (1H, dd, *J* 13, 5.5Hz, $C\underline{H}_2N^+H(CH_3)_2$), 9.70 (1H, brs, $N\underline{H}^+$-). *2-(N,N-dimethylaminomethyl)-cyclohexanone* **191**. $\nu_{max.}$ (thin film) 2940 (s), 2860 (s), 2820 (s), 2765 (s), 1710 (s), 1450 (s), 1385 (m), 1310 (m), 1220 (m), 1125 (m), 1030 (s), 875 (m), 810 (m), 730 (m), 665 (w); δ_H (200 MHz) 1.27-1.49 (1H, m) and 1.55-2.09 (4H, m, $C\underline{H}HC_2\underline{H}_4CH_2CO$-), 2.18 (6H, s, $(C\underline{H}_3)_2N$-), 2.13-2.57 (5H, m, $C\underline{H}_2COC\underline{H}$-$(CH\underline{H}NMe_2)CH\underline{H}$-), 2.70 (1H, dd, *J* 12, 5.5Hz, $C\underline{H}HNMe_2$). *2-Methylenecyclohexanone* **181**. $\nu_{max.}$ (thin film) 2930 (s), 2860 (s), 1725 (s), 1695 (s), 1615 (m), 1445 (s), 1200 (m), 1180-1105 (s), 1080 (m), 990 (m), 910 (m), 840 (m), 710 (w); δ_H (200 MHz) 1.66-1.93 (4H, m, $C_2\underline{H}_4CH_2CO$-), 2.42 (2H, t, *J* 6.5Hz, $C\underline{H}_2C(CO$-$)=$), 2.55

(2H, td, *J* 6.0, 1.5Hz, $C\underline{H}_2CO$-), 5.13 (1H, ca. q, *J* 2.0Hz) and 5.82 (1H, ca. q, *J* 2.0Hz, $=C\underline{H}_2$).

N-Cyclohexylidenecyclohexylamine **193**[160]. A mixture of cyclohexanone (10g, 0.102 mol), cyclohexylamine (12.8ml, 0.11mol) and *p*-toluene sulphonic acid (ca. 100mg, cat.) was heated at reflux in benzene (100ml) with removal of water (Dean-Stark trap) for 14h. 50ml of the solvent was distilled off then the residue washed with sodium hydroxide (2x10ml of a 5% aqueous solution) and brine (10ml). The solution was dried ($MgSO_4$), filtered, and concentrated to give an oil which was purified by short path distillation (130°C/14mmHg) to give the title compound **193** as a colourless oil (17.2g, 94%). $\nu_{max.}$ (thin film) 2930 (s), 2860 (s), 1660 (s), 1450 (s), 1345 (m), 1310 (m), 1225 (m), 1130 (m), 995 (m), 955 (m), 890 (m), 680 (m); δ_H (200 MHz) 1.04-1.54 (6H, m, $C_3\underline{H}_6CH_2CH(N=)$-), 1.55-1.90 (10H, m, $C\underline{H}_2CH(N=)C\underline{H}_2$- and $C_3\underline{H}_6CH_2C(=N-)$-), 2.21-2.40 (4H, m, $C\underline{H}_2C(=N-)C\underline{H}_2$-), 3.22-3.38 (1H, m, $C\underline{H}(N=)$-).

Iodomethyltributylstannane **194**[161] The literature procedure[161] was followed exactly and the crude product freed of excess tributyltin chloride by short path distillation (bath temperature 130-150°C/0.2mmHg) to give the title compound **194** as a colourless oil (66% on a 21mmol scale). $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2870 (m), 1465 (m), 1380 (m), 1075 (m), 960 (w), 870 (m); δ_H (200 MHz) 0.80-1.05 (15H, m, $(C\underline{H}_3C_2H_4C\underline{H}_2\text{-})_3Sn$-), 1.19-1.74 (12H, m, $(CH_3C_2\underline{H}_4CH_2\text{-})_3Sn$-), 1.94 (2H, s, isotopomer satellites $^2J_{Sn}$ 19.5Hz, $C\underline{H}_2SnBu_3$); *m/z* (E.I.) 375 (M^+-^{n}Bu·, $^{120}Sn^{80}Se$, 100%), 373 (78), 371 (45), 361 (33), 319 (36), 305 (32), 291 (39), 247 (40), 177 (49), 121 (58), 71 (52), 57 (74).

2-(Tributylstannylmethyl)cyclohexanone **192**[100]. LDA was prepared at 0°C from di-isopropylamine (1.17ml, 8.4mmol) and ^{n}butyl lithium (5.47ml of a 1.43M solution in hexanes, 7.8mmol) in THF (20ml). After 5min the imine (**193**, 1.0g, 5.59mmol) was added and the resultant solution stirred for 0.5h at 0°C whereupon the iodide (**194**, 2.65g, 6.13mmol) was added. The reaction was allowed to room temperature over 0.5h and stirring continued for a further 4h. The mixture was partitioned between brine and ether

and the organic layer shaken for 5min with buffered acetic acid [50ml of a solution made up from anhydrous sodium acetate (15g), acetic acid (50ml) and water (50ml)] then washed with saturated sodium hydrogen carbonate solution (6x20ml required to render washings basic, CARE!). The dried ($MgSO_4$) solution was concentrated and the residue purified by flash chromatography (50:1 petrol:ether) to give the pure ketone **192** as a colourless oil (1.6g, 71%). $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (s), 1710 (s), 1470-1420 (m), 1375 (m), 1125 (m), 1070 (m), 875 (m), 830 (m), 735 (m); δ_H (200 MHz) 0.63-1.02 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.17-1.55 (14H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn- and $C\underline{H}_2SnBu_3$), 1.56-1.93 (4H, m) and 1.97-2.17 (2H, m, $C_3\underline{H}_6CH_2CO$-), 2.20-2.70 (3H, m, $C\underline{H}_2COC\underline{H}R$-); *m/z* (C.I., NH_3) 420 (MNH_4^+, 2%), 403 (MH^+, 8), 345 (M^+-^{n}Bu·, ^{120}Sn, 100), 343 (81), 341 (47), 308 (49), 306 (39), 304 (26), 291 (38), 289 (31), 287 (27), 231 (10), 136 (10).

2-(4'-Chlorobutyl)-2-(tributylstannylmethyl)-cyclohexanone **195**. Potassium hydride (250mg of a 20% dispersion in oil, 1.25mmol) was washed with petrol three times in the reaction flask then THF (25ml) added. The ketone (**192**, 500mg, 1.25mmol) was added as a solution in THF (2ml) and the mixture stirred at room temperature for 0.5h to allow equilibration of the enolates. 1-Chloro-4-iodobutane (354mg, 1.62mmol) was added and the mixture stirred for a further 14h after which time water (20ml) was added and the aqueous layer extracted with ether (5x10ml). The combined extracts were washed with brine then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (50:1 petrol:ether) to yield the desired ketone (**195**, 468mg, 76%) as a colourless oil. (Found: C, 56.32; H, 9.14. $C_{23}H_{45}ClOSn$ requires C, 56.18; H, 9.22%); $\nu_{max.}$ (thin film) 2990-2800 (s), 1700 (s), 1460 (s), 1375 (m), 1310 (m), 1290 (m), 1120 (m), 1070 (m), 960 (w), 860 (m), 650 (s); δ_H (200 MHz) 0.75-1.00 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.12-1.61 and 1.67-1.95 (26H, complex m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-, $C\underline{H}_2SnBu_3$, $C_3\underline{H}_6CH_2Cl$, and $C_3\underline{H}_6CH_2CO$-), 2.33-2.45 (2H, m, $C\underline{H}_2CO$-), 3.55 (2H, t, *J* 6.5Hz, $C\underline{H}_2Cl$); *m/z* (D.C.I., NH_3) 491 (5%), 435 (M^+-^{n}Bu·, 100), 433 (88), 431 (47), 308 (15), 291 (6), 167 (23), 149 (16).

2-(4'-Iodobutyl)-2-(tributylstannylmethyl)-cyclohexanone **196**. Sodium iodide (0.55g, 3.67mmol) was dissolved in the minimum quantity of acetone (ca. 5ml) and the chloride (**195**, 300mg, 0.61mmol) added. The mixture was heated at reflux with vigorous stirring for 18h and the acetone removed. Ether (10ml) was added, the mixture filtered, and the residue washed with ether (100ml). The combined filtrates were concentrated to give the iodide (**196**, 355mg, quant.) which was a colourless oil requiring no further purification at this stage. $\nu_{max.}$ (thin film) 2980-2840 (s), 1705 (s), 1470-1410 (m), 1375 (m), 1170 (m), 1125 (m), 1070 (m), 860 (m); δ_H (200 MHz) 0.75-0.99 (15H, m, ($CH_3C_2H_4CH_2$-)$_3$Sn-), 1.12-1.62 and 1.68-1.93 (26H, complex m, ($CH_3C_2H_4CH_2$-)$_3$Sn-, CH_2SnBu_3, $C_3H_6CH_2I$, and $C_3H_6CH_2CO$-), 2.34-2.45 (2H, m, CH_2CO-), 3.20 (2H, t, *J* 6.5Hz, CH_2I); *m/z* (D.C.I., NH_3) 583 (6%), 527 (M^+-^{n}Bu·, 100), 525 (81), 523 (44), 401 (30), 343 (33), 308 (36), 167 (62), 149 (24).

2-(3'-Phenylselenopropyl)-2-(tributylstannylmethyl)-cyclohexanone **198**. Use of the alkylation procedure used for the preparation of **195** but with 1-iodo-3-phenylseleno-propane (**111**, 1.1 equiv.) as the alkylating agent on a 0.25mmol scale led to the formation of a mixture of products. The requisite compound **198** was obtained in low yield (34mg, 23%). $\nu_{max.}$ (thin film) 3035 (w), 2980-2880 (s), 2860 (s), 1700 (s), 1580 (m), 1480-1410 (s), 1375 (m), 1075 (m), 1025 (m), 735 (s), 690 (s); δ_H (200 MHz) 0.63-0.98 (15H, m, ($CH_3C_2H_4CH_2$)$_3$Sn-), 1.09-1.96 (24H, m, $C_2H_4CH_2SePh$, $CH_2Sn(CH_2C_2H_4$-$CH_3)_3$, and $C_3H_6CH_2CO$-), 2.36 (2H, t, *J* 6.5Hz, CH_2CO-), 2.89 (2H, t, *J* 6.5Hz, CH_2SePh), 7.21-7.33 (3H, m, Ph- *m*- and *p*- protons), 7.43-7.56 (2H, m, Ph- *o*- protons); *m/z* (F.D.) 600 (M^+, $^{80}Se^{120}Sn$, 100%), 599 (56), 598 (83), 597 (60), 596 (78), 595 (29), 594 (34).

Ring expansion of stannane **196**. This reaction was terminated after 68h at reflux (0.51mmol scale). Flash column chromatography of the residue (100:1 petrol:ether) led to the recovery of starting material (**196**, 81mg, 27%) and the isolation of the required ring expanded compound *6-methylenecyclodecanone*[165] (**197**, 47mg, 56%), a waxy solid, m.p. 29-31°C (lit.,[165] 31-32°C). $\nu_{max.}$ ($CHCl_3$) 3080 (w), 3010 (m), 2940 (s), 1695 (s),

1640 (w), 1455 (m), 1415 (m), 980 (w), 890 (s); δ_H (200 MHz) 1.63-1.78 (4H, m, C(4)$\underline{H}_2$- and C(8)$\underline{H}_2$-), 1.80-1.95 (4H, m, C(3)$\underline{H}_2$- and C(9)$\underline{H}_2$-), 2.07 (4H, ca. t, *J* 6.0Hz, C$\underline{H}_2$C(=CH$_2$)C$\underline{H}_2$-), 2.49 (4H, ca. t, *J* 8.0Hz, C$\underline{H}_2$COC$\underline{H}_2$-), 4.91 (2H, s, C$\underline{H}_2$=); *m/z* (GCMS, C.I., NH_3) 184 (MNH_4^+, 27%), 167 (MH^+, 19), 149 (100), 108 (5), 94 (4), 81 (4).

3-Tributylstannylcyclohex-2-enone **203**[166b]. Tributylstannyl lithium (1.1 equiv.) was prepared in the usual manner in THF (5ml) then cooled to -23°C and copper thiophenoxide added (prepared by a literature procedure[207], 540mg, 3.13mmol). Stirring was continued for a further 10min then the bromo-enone (**160**, 500mg, 2.86mmol) added as a solution in THF (1ml). After 0.75h at -23°C the reaction was quenched with water (10ml) and allowed to room temperature. The mixture was extracted with ether (5x10ml) and the extracts dried (Na_2SO_4), filtered, and concentrated to yield an orange oil which was purified by flash chromatography (20:1 then 10:1 petrol:ether) to yield the pure vinyl stannane **203** as a colourless oil (566mg, 51%). $\nu_{max.}$ (thin film) 3000-2810 (s), 1675 (s), 1460 (m), 1330 (m), 1250 (m), 1185 (m), 955 (s), 900 (m), 880 (m), 760 (m); δ_H (200 MHz) 0.82-1.12 (15H, m, (C$\underline{H}_3$C$_2$H$_4$C$\underline{H}_2$)$_3$Sn-), 1.21-1.64 (12H, m, (CH$_3$C$_2\underline{H}_4$-CH$_2$)$_3$Sn-), 1.92-2.14 (2H, m, C$\underline{H}_2$CH$_2$CO-), 2.42 (2H, t, *J* 8.0Hz, C$\underline{H}_2$CO-), 2.51 (2H, td, *J* 5.0, 2.5Hz, C$\underline{H}_2$C(SnBu$_3$)=), 6.26 (1H, t, *J* 2.5Hz, C$\underline{H}$=); *m/z* (E.I.) 387 (8%), 329 ($M^{+-n}Bu\cdot$, ^{120}Sn, 92), 327 (73), 325 (42), 291 (14), 273 (100), 217 (98), 177 (38), 146 (27), 121 (35), 95 (41), 67 (98). Accompanying this vinyl stannane were varying amounts (ca. 10%) of the bis-stannane *3,3-di-(tributylstannyl)-cyclohexanone*[166b] **204**. $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2860 (s), 1710 (s), 1460 (m), 1375 (m), 1070 (m), 1020 (m), 960 (m), 735 (m); δ_H (200 MHz) 0.77-1.05 (30H, m, 2x(C$\underline{H}_3$C$_2$H$_4$C$\underline{H}_2$)$_3$Sn-), 1.19-1.67 (24H, m, 2x(CH$_3$C$_2\underline{H}_4$CH$_2$)$_3$Sn-), 1.83-2.01 (2H, m, C$\underline{H}_2$CH$_2$CO-), 2.18 (2H, t, *J* 6.0Hz, CH$_2$C$\underline{H}_2$C(SnBu$_3$)$_2$-), 2.36 (2H, t, *J* 6.5Hz, CH$_2$C$\underline{H}_2$CO-), 2.76 (2H, s, isotopomer satellites of $^3J_{Sn}$ 48 and 68Hz, COC$\underline{H}_2$C(SnBu$_3$)$_2$-); *m/z* (E.I.) 619 ($M^{+-n}Bu\cdot$, ^{120}Sn, 8%), 387 (30), 329 (25), 291 (74), 235 (55), 217 (29), 177 (100), 121 (36), 96 (19), 67 (36), 56 (43).

2-Allylcyclohexane-1,3-dione **205**[170]. Allyl bromide (4.76ml, 55mmol) was added to a mixture of cyclohexane-1,3-dione (5.5g, 49mmol) and copper bronze (0.15g) in potassium hydroxide solution (2.8g of potassium hydroxide in 15ml water, 50mmol) at room temperature and the mixture stirred for 16h. Sodium hydroxide (50ml of a 5% aqueous solution) was added and the mixture washed with ether (2x10ml). The aqueous layer was filtered to remove the copper bronze then acidified to pH 4 with hydrochloric acid (4M) with scratching to prevent oiling out. The product was filtered off and washed with a little water and benzene then recrystallised from hot carbon tetrachloride to give the pure alkylated compound **205** as white needles which became discoloured on isolation (4.93g, 66%), m.p. 117-21°C (dec.) (lit.,[170] 126°C). $\nu_{max.}$ ($CHCl_3$) 3600-2400 (br, m), 3020 (s), 2960 (m), 1740 (m), 1710 (m), 1660-1540 (br, s), 1450-1340 (s), 1190 (s), 1120 (m), 990 (w), 920 (m); δ_H (200 MHz) 1.97 (2H, ca. quin., *J* 6.5Hz, CH_2CH_2CO-), 2.45 (4H, t, *J* 6.5Hz, 2xCH_2CO-), 3.14 (2H, d, *J* 8.0Hz, CH_2CH=), 4.96-5.28 (2H, m, CH_2=), 5.72-5.98 (1H, m, CH=).

2-Allyl-3-bromocyclohex-2-enone **206**[171]. To a slurry of triphenyl phosphine (1.90g, 7.3mmol) in ice-cold benzene (35ml) was added bromine (0.41ml, 7.95mmol) as a solution in benzene (5ml) and the yellow solution stirred for 5min. Triethylamine (1.10ml, 7.92mmol) followed immediately by the dione (**205**, 1.0g, 6.6mmol) were added and the mixture stirred at room temperature for 3h then filtered through silica. The silica was washed thoroughly with ether and the combined organic portions concentrated to yield an oil which was freed of excess phosphine oxide by flash chromatography (3:1 petrol:ether) to give the title compound **206** as a colourless oil (1.11g, 78%). $\nu_{max.}$ (thin film) 3040 (m), 3005 (w), 2960 (m), 1680 (s), 1640 (s), 1620 (s), 1430 (s), 1340 (s), 1280 (s), 1185 (s), 1070 (m), 995 (m), 950-890 (m), 750 (m); δ_H (200 MHz) 2.05 (2H, ca. quin., *J* 6.5Hz, CH_2CH_2CO-), 2.49 (2H, t, *J* 8.0Hz, CH_2CO-), 2.93 (2H, t, *J* 6.5Hz, $CH_2C(Br)$=), 3.23 (2H, d, CH_2CH=), 4.94-5.18 (2H, m, CH_2=), 5.66-5.88 (1H, m, CH=); *m/z* (E.I.) 216 (M^+, ^{81}Br, 15%), 214 (M^+, ^{79}Br, 15), 201 (13), 198 (21), 196 (18), 135 (75), 117 (35), 107 (30), 91 (45), 79 (100), 77 (81), 55 (43), 51 (28).

2-Allyl-3-tributylstannylcyclohex-2-enone **207**. The procedure for generating vinyl stannane **203** from the bromide **160** was followed exactly using bromo-enone (**206**, 500mg, 2.33mmol). The reaction failed to go to completion so was quenched at -23°C with aqueous ammonia (see preparation of **159** above) and the blue solution extracted with ether (5x15ml), the extracts being washed with brine then dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (20:1 petrol:ether) to yield starting material (**206**, 118mg, 24%) and the vinyl stannane **207** as a colourless oil (698mg, 70%). $\nu_{max.}$ (thin film) 3090 (w), 2960 (s), 2930 (s), 2870 (s), 1675 (s), 1640 (m), 1465 (m), 1420 (m), 1380 (m), 1340 (m), 1290 (m), 1185 (m), 1000 (m), 910 (m), 735 (m); δ_H (200 MHz) 0.82-1.10 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2)_3Sn$-), 1.20-1.68 (12H, m, ($CH_3C_2\underline{H}_4CH_2)_3Sn$-), 1.97 (2H, ca. quin., *J* 6.5Hz, $C\underline{H}_2CH_2CO$-), 2.43 (2H, t, *J* 8.0Hz, $C\underline{H}_2CO$-), 2.54 (2H, t, *J* 5.0Hz, $C\underline{H}_2C(SnBu_3)$=), 2.99 (2H, d, *J* 5.0Hz, $C\underline{H}_2CH$=), 4.89-5.05 (2H, m, $C\underline{H}_2$=), 5.74-5.91 (1H, m, C<u>H</u>=); *m/z* (E.I.) 369 (M^+-$^nBu\cdot$, ^{120}Sn, 100%), 368 (45), 367 (84), 366 (39), 365 (53), 313 (33), 255 (17), 235 (18), 177 (26), 135 (26), 117 (19), 91 (30), 79 (21), 78 (20), 55 (17).

2-(Phenylselenomethyl)-2,3,6,7-tetrahydro-4(5H)-benzofuranone **209**. To a solution of the dione (**205**, 25mg, 0.16mmol) in dichloromethane (10ml) at -78°C was added dropwise a solution of phenylselenylchloride (35mg, 0.18mmol) and iodine (2mg, cat.) in dichloromethane (1ml). After 5min the reaction was quenched with potassium carbonate (5ml of a 10% aqueous solution) and allowed to come up to room temperature. The aqueous layer was neutralised with dilute hydrochloric acid then extracted with dichloromethane (4x10ml) and the extracts dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified by p.l.c. (3:1 petrol:ether) to yield the cyclised compound **209** as a white solid (36mg, 71%, m.p. 70°C). $\nu_{max.}$($CHCl_3$) 3060 (m), 2945 (s), 1680-1600 (s), 1580 (m), 1480 (s), 1400 (s), 1230 (s), 1180 (s), 1060 (m), 940 (m), 740 (s), 690 (s); δ_H (200 MHz) 2.02 (2H, ca. quin., *J* 6.0Hz, $C\underline{H}_2CH_2CO$-), 2.26-2.47 (4H, m, $C\underline{H}_2CO$- and $C\underline{H}_2C(OR)$=), 2.65 and 3.00 (2H, 2xdd, *J* 15, 7.0Hz, $C\underline{H}_2CH$-(CH_2SePh)OR), 3.16 (2H, 12 line m, $C\underline{H}_2SePh$), 4.95 (1H, 8 line m, C<u>H</u>(O-)-), 7.22-

7.35 (3H, m, Ph- *m*- and *p*- protons), 7.49-7.63 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 308 (M^+, 17%), 151 (100), 123 (15), 95 (14), 84 (18), 77 (23), 55 (23).

2-(Phenylselenomethyl)-7a-tributylstannyl-2,3,3a,6,7,7a-hexahydro-4(5H)-benzofuranone **210** and **211**. Tributylstannyl lithium (1.1 equiv.) prepared in THF (1ml) by the general procedure was quenched at -23°C with the enone (**209**, 25mg, 81μmol). After 1h at this temperature the reaction was quenched with water (5ml) and allowed to come up to room temperature. The usual extractive work-up followed by flash chromatography (20:1 then 5:1 petrol:ether) afforded the two diastereomers of the title compound (**211**, 13mg, 27%) and (**210**, 6mg, 12%). $\nu_{max.}$ (thin film, **210** and **211**) 3075 (w), 2930 (s), 2870 (m), 1710 (s), 1580 (m), 1480-1410 (m), 1075 (m), 1025 (m), 735 (m), 690 (m); δ_H (200 MHz, **211**) 0.72-1.05 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2)_3Sn$-), 1.18-1.80 (14H, m, ($CH_3C_2\underline{H}_4CH_2)_3Sn$- and $C\underline{H}_2C(SnBu_3)$-), 1.94-2.59 (7H, m, $C_2\underline{H}_4COC\underline{H}R$- and $C(3)\underline{H}_2$-), 2.95 and 3.16 (2H, 2xdd, *J* 13, 5.0Hz, $C\underline{H}_2SePh$), 3.94-4.09 (1H, m, $C\underline{H}(OR)$-), 7.19-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.47-7.60 (2H, m, Ph- *o*- protons); δ_H (200 MHz, **210**) characteristic resonance at 4.32-4.47 (1H, m, $C\underline{H}(OR)$-); *m/z* (D.C.I., NH_3) 599 (MH^+, ^{120}Sn, 35%), 597 (24), 391 (19), 309 (100), 291 (23), 252 (10), 194 (11), 153 (85), 151 (76), 96 (13), 55 (17).

1,2-Di-(trimethylsilyloxy)-cyclopentene **212**[208]. Prepared by a literature procedure (Method A(1))[38] as a colourless oil after short path distillation (100°C/14mmHg). $\nu_{max.}$ 2960 (s), 2905 (s), 2860 (s), 1705 (s), 1650 (w), 1445 (m), 1340 (s), 1310 (s), 1250 (s), 1085 (s), 950-800 (s), 755 (m), 690 (m), 627 (m); δ_H (200 MHz) 0.20 (18H, s, $2x(C\underline{H}_3)_3Si$-), 1.78 (2H, quin., *J* 7.5Hz, $C\underline{H}_2CH_2C(OSiMe_3)$=), 2.25 (4H, t, *J* 7.5Hz, $CH_2C(OSiMe_3)$=).

1,4-Dioxaspiro[4,5]decane **213**[176]. Prepared by standard methods from cyclohexanone (5.0g, 51mmol), ethane-1,2-diol (3.55ml, 65mmol) and *p*-toluenesulphonic acid (50mg, cat.) in benzene (75ml) as a colourless oil (7.05g, 97%). $\nu_{max.}$ (thin film) 2940 (s), 2860 (s), 1490-1430 (m), 1370 (m), 1285 (m), 1165 (m), 1105 (s), 1040 (s), 960-900 (m), 845

(m), 830 (m), 770 (w); δ_H (200 MHz) 1.35-1.50 (2H, m, C$\underline{H}_2$C$_2$H$_4$C(OR)$_2$-), 1.53-1.68 (8H, m, 2xC$_2\underline{H}_4$C(OR)$_2$-), 3.96 (4H, s, -OC$_2\underline{H}_4$O-).

Spiro[5,5]undecane-1,5-dione **214**[174]. Prepared by a literature procedure[174] as a pale yellow solid (m.p. 69-71°C, lit.,[174] 71-72°C) after flash chromatography (2:1 dichloromethane:petrol). $\nu_{max.}$ ($CHCl_3$) 3030 (m), 2945 (m), 2860 (w), 1730 (s), 1695 (s), 1470-1420 (m), 1330 (m), 1315 (m), 1170 (m), 1060-1010 (w), 930 (w); δ_H (200 MHz) 1.33-1.47 (2H, m, C(9)$\underline{H}_2$-), 1.50-1.68 (4H, m, C(8)$\underline{H}_2$- and C(10)$\underline{H}_2$-), 1.82-1.96 (6H, m, C(7)$\underline{H}_2$-, C(11)$\underline{H}_2$-, and C$\underline{H}_2$CH$_2$CO-), 2.69 (4H, t, *J* 6.5Hz, 2xC$\underline{H}_2$CO-).

2-Propyl-1,3-dioxolane **215**[177]. Prepared by standard methods from n-butanal (1.09g, 14mmol), ethane-1,2-diol (1.16ml, 21mmol) and *p*-toluenesulphonic acid (13mg, cat.) in benzene (25ml). The pure acetal **215** was obtained as a colourless volatile oil after short path distillation (55°C, 14mmHg) (1.27g, 79%). $\nu_{max.}$ (thin film) 2960 (s), 2880 (s), 1470 (m), 1410 (m), 1170-1090 (m), 1070 (m), 1020 (m), 945 (m), 830 (m), 680 (s); δ_H (200 MHz) 0.95 (3H, t, *J* 6.5Hz, C$\underline{H}_3$-), 1.37-1.54 (2H, m, CH$_3$C$\underline{H}_2$-), 1.58-1.71 (2H, m, C$_2$H$_5$C$\underline{H}_2$-), 3.78-4.03 (4H, m, -OC$_2\underline{H}_4$O-), 4.85 (1H, t, *J* 4.5Hz, C$\underline{H}$(OR)$_2$).

2,4-Dimethoxycyclohexa-1,4-diene **216**[178]. Prepared by the method of Piers *et al.*[178] as a colourless oil (99%, 72mmol scale) after short path distillation (90-95°C/14mmHg). $\nu_{max.}$(thin film) 3060 (m), 3000 (s), 2960-2820 (s), 1700 (s), 1670 (s), 1440 (s), 1395 (s), 1235 (s), 1205 (s), 1145 (s), 1015 (s), 950 (s), 900 (m), 775 (s), 705 (s); δ_H (200 MHz) 2.73-2.93 (4H, m, 2xC$\underline{H}_2$CR=), 3.57 (6H, s, 2xC$\underline{H}_3$-), 4.68 (2H, s, 2xC$\underline{H}$=).

General procedure for the alkylation of the diene **216**. To a solution of the diene (**216**, 1.0 euiv.) in THF (ca. 10ml/mmol **216**) at -78°C was added dropwise ^{t}butyl lithium (1.5 equiv. of a 1.7M solution in pentane) to give a bright yellow solution. The mixture was stirred for 1h at this temperature then cooled to -100°C and the alkylating agent (1.1-1.5 equiv.) added as a solution in THF (ca. 1ml/mmol of alkylating agent). The mixture was then allowed to warm to room temperature over 3h and quenched with brine. The aqueous

layer was extracted with petrol (3x) and the combined extracts dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude products were then purified by flash column chromatography (100:1 petrol:ether) to give colourless oils.

3-(4'-Chlorobutyl)-2,4-dimethoxycyclohexa-1,4-diene **217**. Prepared in 86% yield (5mmol scale) as a colourless oil using 1-chloro-4-iodobutane (1.5 equiv.) as the alkylating agent. $\nu_{max.}$ (thin film) 3060 (m), 3000 (m), 2960-2800 (s), 1695 (s), 1665 (s), 1470-1440 (m), 1395 (s), 1230 (s), 1205 (s), 1145 (s), 775 (m), 650 (w); δ_H (200 MHz) 1.20-1.38 (2H, m, C$\underline{H}_2$C$_2$H$_4$Cl), 1.65-1.82 (4H, m, C$\underline{H}_2$CH$_2$C$\underline{H}_2$CH$_2$Cl), 2.77-2.86 (2H, m, C$\underline{H}_2$CH=), 2.90-3.02 (1H, m, C(3)$\underline{H}$-), 3.52 (2H, t, *J* 7.5Hz, C$\underline{H}_2$Cl), 3.56 (6H, s, 2xC$\underline{H}_3$-), 4.74 (2H, t, *J* 4.0Hz, 2xC$\underline{H}$=); *m/z* (GCMS, C.I., NH_3) 231 (MH^+, ^{37}Cl, 32%), 229 (MH^+, ^{35}Cl, 100), 195 (44), 193 (65), 179 (10), 163 (18), 151 (50), 108 (7).

3-(3'-Chloropropyl)-2,4-dimethoxycyclohexa-1,4-diene **227**. Prepared in 86% yield (5mmol scale) as a colourless oil using 1-bromo-3-chloropropane (1.5 equiv.) as the alkylating agent. $\nu_{max.}$ (thin film) 3060 (w), 3000 (m), 2980-2830 (s), 1690 (s), 1660 (s), 1595 (w), 1450 (s), 1395 (s), 1230 (s), 1205 (s), 1145 (s), 775 (s), 650 (m); δ_H (200 MHz) 1.55-1.72 (2H, m, C$\underline{H}_2$CH$_2$Cl), 1.77-1.89 (2H, m, C$\underline{H}_2$C$_2$H$_4$Cl), 2.75-2.85 (2H, m, C$\underline{H}_2$CH=), 2.90-3.03 (1H, m, C(3)$\underline{H}$-), 3.49 (2H, t, *J* 6.5Hz, C$\underline{H}_2$Cl), 3.55 (6H, s, 2xC$\underline{H}_3$-), 4.73 (2H, t, *J* 3.5Hz, 2xC$\underline{H}$=); *m/z* (GCMS, C.I., NH_3) 219 (MH^+, ^{37}Cl, 30%), 217 (MH^+, ^{35}Cl, 100), 195 (44), 193 (65), 179 (10), 163 (18), 151 (50), 108 (7).

General procedure for the hydrolysis of the alkylated dienes. To a vigorously stirred solution of the diene (**217** or **227**, 1.0=) in degassed acetone (10ml/mmol diene) at room temperature was added hydrochloric acid (1.1= of a 1$\underline{M}$ solution) and the mixture stirred for a further 4h. The acetone was removed *in vacuo*, the residue added to brine (c$\underline{a}$. 5ml/mmol diene) then the aqueous phase extracted with dichloromethane (5x10ml/mmol diene). The organic extracts were dried ($MgSO_4$) and the filtered solution concentrated to yield the diones as white amorphous solids which were in general used crude. Absolute purity, for spectroscopic analysis, was attained by flash chromatography (3:2:1

ether:dichloromethane:petrol) since the products possessed limited stability and problems were encountered in attempted recrystallisations.

2-(4'-Chlorobutyl)-1,3-cyclohexane-1,3-dione **218**. Obtained from the diene **217** in approximately quantitative crude yield as a pale yellow solid (m.p. 95-7°C (dec.)). $\nu_{max.}$ ($CHCl_3$) 3600-2500 (br, s), 1760-1630 (s), 1460-1390 (s), 1285 (s), 1125 (s), 1130 (s), 1070 (m), 1025 (m), 860 (m), 820 (m); δ_H (200 MHz) 1.38-1.59 (2H, m, C<u>H</u>$_2$C$_2$H$_4$Cl), 1.67-1.86 (2H, m, C<u>H</u>$_2$CH$_2$Cl), 1.88-2.07 (2H, m, C<u>H</u>$_2$CH$_2$CO-), 2.33-2.48 (2H, m, *J* 6.5Hz, C<u>H</u>$_2$C$_3$H$_6$Cl), 2.48 (4H, t, *J* 6.5Hz, 2xC<u>H</u>$_2$CO-), 3.54 (2H, t, *J* 7.5Hz, C<u>H</u>$_2$Cl) increased complexity in the spectrum and a signal at δ 3.43, due to C(2)<u>H</u>-, indicated the presence of the diketo- tautomer; *m/z* (GCMS, C.I., NH_3) 167 (M^+-Cl·, 100%), 153 (35), 151 (17), 138 (6).

2-(3'-Chloropropyl)-1,3-cyclohexane-1,3-dione **228**. Obtained from the diene **227** in approximately quantitative crude yield as a white solid (m.p. 135-7°C). $\nu_{max.}$ ($CHCl_3$) 3600-2500 (br, m), 3020 (m), 2960 (m), 1740-1695 (s), 1650-1550 (s), 1380 (s), 1270 (s), 1190 (m), 1140 (m), 1080 (m), 920 (w); δ_H (200 MHz) 1.72-2.24 (4H, m, C$_2$<u>H</u>$_4$CH$_2$Cl), 2.37-2.49 and 2.54-3.01 (6H, complex m, C$_3$<u>H</u>$_6$CO-), 3.45-3.66 (2H, C<u>H</u>$_2$Cl) increased complexity was apparent in this spectrum due to the presence of the diketo- tautomer; *m/z* (GCMS, C.I., NH_3) 153 (M^+-Cl·, 100%), 137 (15), 124 (5).

3-Bromo-2-(4'-chlorobutyl)-cyclohex-2-enone **219**. Prepared in 42% yield (Method 1 in the general procedure for the preparation of **160**) from the dione (**218**, 0.5mmol scale). Lower yields were obtained with this substrate, using Method 1, when the reaction was performed on a larger scale; use of Method 2 resulted in consistently higher yields (<u>ca</u>. 75-85%, scales ranging up to 5mmol). The product was obtained as a colourless oil after flash chromatography (5:1 petrol:ether). $\nu_{max.}$ (thin film) 2950 (s), 2870 (s), 1675 (s), 1615 (s), 1470-1410 (s), 1350-1290 (s), 1130 (s), 1050 (m), 995 (s), 770 (m), 730 (m), 650 (m); δ_H (200 MHz) 1.44-1.62 (2H, m, C<u>H</u>$_2$C$_3$H$_6$Cl), 1.79 (2H, <u>ca</u>. quin., C<u>H</u>$_2$CH$_2$Cl), 2.02 (2H, <u>ca</u>. quin.) and 2.38-2.55 (4H, m, C<u>H</u>$_2$C$_3$H$_6$Cl and C$_2$<u>H</u>$_4$CO-), 2.91 (2H, t,

$C\underline{H}_2C(Br)=$), 3.56 (2H, t, $C\underline{H}_2Cl$) all coupling constants ca. 6.5Hz; *m/z* (GCMS, C.I., NH_3) 284 (MNH_4^+, $^{81}Br^{35}Cl$, 12%), 282 (MNH_4^+, $^{79}Br^{35}Cl$, 9), 267 (MH^+, $^{81}Br^{35}Cl$, 16), 265 (MH^+, $^{79}Br^{35}Cl$, 13), 168 (30), 151 (100), 149 (22).

3-Bromo-2-(3'-chloropropyl)-cyclohex-2-enone **229**. Prepared in 85% yield (Method 1 in the general procedure for the preparation of **160**) from the dione (**228**, 5.3mmol scale) as a colourless oil after flash chromatography (10:1 to 2:1 petrol:ether). $\nu_{max.}$ (thin film) 2960 (m), 2930 (s), 2870 (m), 1715 (w), 1670 (s), 1580 (w), 1470-1410 (m), 1340 (m), 1285 (m), 1075 (w), 910 (m), 735 (s), 650 (m); δ_H (200 MHz) 1.85 (2H, ca. quin., $C\underline{H}_2$-CH_2Cl), 2.04 (2H, ca. quin., $C\underline{H}_2CH_2CO$-), 2.48 (2H, t, $C\underline{H}_2C_2H_4Cl$), 2.59 (2H, t, $C\underline{H}_2CO$-), 2.92 (2H, t, $C\underline{H}_2C(Br)=$), 3.55 (2H, t, $C\underline{H}_2Cl$) all coupling constants ca. 7.0Hz; *m/z* (GCMS, C.I., NH_3) 270 (MNH_4^+, $^{81}Br^{35}Cl$, 65%), 268 (MNH_4^+, $^{79}Br^{35}Cl$, 49), 253 (MH^+, $^{81}Br^{35}Cl$+$^{79}Br^{37}Cl$, 79), 251 (MH^+, $^{79}Br^{35}Cl$, 58), 217 (61), 215 (63), 190 (48), 154 (75), 153 (100), 136 (44), 135 (95), 108 (20), 94 (15), 55 (55).

General procedure for the preparation of the vinyl stannanes from the bromo-enones. A flask containing copper (I) cyanide (1.1 equiv.) was flame dried and allowed to cool under a stream of argon then THF (ca. 1ml/100mg bromo-enone) added. The slurry was cooled to -78°C and ^{n}butyl lithium (2.2 equiv. of a 1.35M solution in hexanes) added. The cold bath was removed for approximately 10min until the solution became homogeneous then the reaction re-cooled to -78°C and tributyltin hydride (2.2 equiv.) added. The solution became yellow; once effervescence had ceased (ca. 10-15min) the bromo-enone (**219** or **229**, 1.0 equiv.) was added in one portion as a solution in THF (ca. 0.5ml/mmol) and stirring continued at -78°C for 5min before allowing the mixture to 0°C over 2h. The mixture was quenched with ammonia solution (saturated ammonium chloride (aq.) containing 15% by volume concentrated ammonia) and stirred until complex formation was completed (about 10min). The mixture was partitioned, the aqueous layer extracted with ether (5x), and the combined organic portions washed with brine, then dried (Na_2SO_4), filtered, and concentrated. The vinyl stannanes **220** or **230** were purified as described below.

2-(4'-Chlorobutyl)-3-tributylstannylcyclohex-2-enone **220**. Obtained from bromo-enone **219** in 55% yield (0.19mmol scale) as a colourless oil after flash chromatography (20:1 petrol:ether). The ^{1}H n.m.r. spectrum indicated the presence of starting material (ca. 10-15%, however, this was not recovered). (Found: C, 55.48; H, 8.67. $C_{22}H_{41}OClSn$ requires C, 55.55; H, 8.69%); $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2870 (m), 1715 (w), 1670 (s), 1580 (w), 1470-1410 (m), 1340 (m), 1285 (m), 1075 (w), 910 (m), 735 (s), 650 (m); δ_H (200 MHz) 0.91 (9H, t, *J* 7.0Hz, ($CH_3C_3H_6$-)$_3$Sn-), 1.01 (6H, t, *J* 8.0Hz, ($C_3H_7CH_2$-)$_3$Sn-), 1.21-1.60 (14H, m, ($CH_3C_2H_4CH_2$-)$_3$Sn- and $CH_2C_2H_4Cl$), 1.80 (2H, ca. quin., CH_2CH_2Cl), 1.96 (2H, ca. quin., CH_2CH_2CO-) and 2.14-2.28 (2H, m, $CH_2C_3H_6Cl$), 2.41 (2H, t) and 2.51 (2H, t, CH_2CO- and $CH_2C(SnBu_3)$=), 3.54 (2H, t, CH_2Cl) all remaining coupling constants ca. 7.0Hz; *m/z* (D.C.I., NH_3) 477 (MH^+, ^{120}Sn, 100%), 476 (45), 475 (73), 473 (35), 419 (23), 269 (11), 151 (39).

2-(3'-Chloropropyl)-3-tributylstannyl-cyclohex-2-enone **230**. Obtained from **229** in 64% yield (0.8mmol scale) as a colourless oil after flash chromatography (20:1 to 5:1 petrol:ether). A small amount of starting material (**229**, 30mg, 15%) was also recovered. $\nu_{max.}$ (thin film) 2940 (s), 2870 (s), 1670 (s), 1580 (w), 1470-1410 (m), 1340 (m), 1270 (m), 1190 (m), 1080 (m), 965 (w), 875 (m), 670 (s); δ_H (200 MHz) 0.92 (9H, t, *J* 6.5Hz, ($CH_3C_3H_6$-)$_3$Sn-), 1.05 (6H, t, *J* 8.0Hz, ($C_3H_7CH_2$-)$_3$Sn-), 1.23-1.63 (12H, m, ($CH_3C_2H_4CH_2$-)$_3$Sn-), 1.77-2.04 (4H, m, $C_2H_4CH_2Cl$), 2.27-2.58 (6H, m, C_3H_6CO-), 3.56 (2H, t, *J* 6.5Hz, CH_2Cl); *m/z* (E.I.) 463 (M^+, 4%), 428 (M^+-Cl·, 9), 405 (M^+-^{n}Bu·, $^{120}Sn^{35}Cl$, 30), 403 (23), 401 (11), 269 (18), 213 (10), 177 (17), 155 (15), 137 (100), 121 (18), 91 (22), 79 (28), 57 (37).

2-(4'-Iodobutyl)-3-tributylstannylcyclohex-2-enone **221**. A mixture of the chloride (**220**, 35mg, 74μmol), sodium iodide (110mg, 0.73mmol) and acetone (1ml) were heated at reflux for 14h. Water (5ml) was added to the cooled solution and the mixture extracted with ether (4x6ml). The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and passed through a plug of silica (eluting with 10:1 petrol:ether) to yield the pure

stannane **221** as a colourless oil (38mg, 90%). (Found: C, 46.64; H, 7.40. $C_{22}H_{41}OISn$ requires C, 46.59; H, 7.29%); $\nu_{max.}$ (thin film) 2960 (s), 2940 (s), 2870 (s), 1710 (w), 1670 (s), 1580 (w), 1460-1405 (m), 1335 (m), 1100 (w), 890 (m), 740 (s), 660 (m); δ_H (200 MHz) 0.91 (9H, t, *J* 7.5Hz, ($C\underline{H}_3C_3H_6$-)$_3$Sn-), 1.02 (6H, t, *J* 8.0Hz, ($C_3H_7C\underline{H}_2$-)$_3$Sn-), 1.22-1.73 (14H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn- and $C\underline{H}_2C_2H_4I$), 1.77-2.02 (4H, m, $C\underline{H}_2CH_2I$ and $C\underline{H}_2CO$-), 2.14-2.29 (2H, m, $C\underline{H}_2C(CO-)=$), 2.39 (2H, t, *J* 7.0Hz) and 2.49 (2H, t, *J* 7.0Hz, $C\underline{H}_2CO$- and $C\underline{H}_2C(SnBu_3)=$), 3.20 (2H, t, *J* 6.5Hz, $C\underline{H}_2I$); *m/z* (D.C.I., NH_3) 569 (MH^+, ^{120}Sn, 100%), 567 (78), 565 (44), 512 (M^+-^{n}Bu·, 25), 151 (40).

Preparation of cyclodec-5-ynone **200** *for purposes of comparison with bicyclic enone* **225**. A literature procedure[180] was used to prepare the title compound **200** in four steps from commercially available 1-decalone; selected data only is given for the intermediates.

8a-Chloro-1-decalone **228**. Prepared in 81% yield from 1-decalone (800mg, 6.6mmol) as a colourless oil after flash chromatography (20:1 petrol:ether). $\nu_{max.}$ (thin film) 2940 (s), 2860 (s), 1720 (s), 1450 (s), 1215 (m), 1230 (s), 1100 (s), 1035 (m), 840 (m), 770 (m), 680 (m); δ_H (200 MHz) 1.14-2.81 (14H, m), 2.96-3.28 (1H, m).

3,4,5,6,7,8-Hexahydro-1(2H)-naphthalenone **223**. Prepared in 70% yield from the chloro-ketone (**228**, 700mg, 3.75mmol) as a colourless oil after flash chromatography (20:1 to 6:1 petrol:ether). $\nu_{max.}$ (thin film) 2930 (s), 2860 (s), 1660 (s), 1630 (s), 1385 (s), 1285 (s), 1190 (s), 1155 (m), 910 (m), 845 (m), 730 (s); δ_H (200 MHz) 1.51-1.68 (4H, m, C(6)$\underline{H}_2$- and C(7)$\underline{H}_2$-), 1.93 (2H, quin., *J* 6.0Hz, $C\underline{H}_2CH_2CO$-), 2.09-2.28 (6H, m) and 2.39 (2H, t, *J* 6.0Hz, $C\underline{H}_2CO$-, 3x allylic $C\underline{H}_2$-).

4a,8a-Epoxy-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-napthalenone **224**. Prepared in 37% yield (with 50% recovery of the starting material **224**, 2mmol scale), after flash chromatography (20:1 petrol:ether), as a colourless oil. $\nu_{max.}$ (thin film) 2940 (s), 2875 (m), 1705 (s), 1435 (m), 1175 (m), 945 (s), 850 (s), 825 (m); δ_H (200 MHz) 1.12-1.65 and 1.69-2.17 (12H, complex m, $C_4\underline{H}_8$- and $C_2\underline{H}_4CH_2CO$-), 2.27 (1H, dt, *J* 15.5, 6.5Hz) and 2.58 (1H, dt, *J* 15.5, 4.0Hz, $C\underline{H}_2CO$-).

Cyclodec-5-ynone **200**. The literature procedure[180] was modified to the following: To a solution of the epoxy-ketone (**224**, 120mg, 0.72mmol) in glacial acetic acid (1.2ml) and dichloromethane (1.2ml) at 0°C was added 2,4-dinitrophenylsulphonyl hydrazine (199mg, 0.76mmol). Effervescence occurred immediately. The reaction was allowed to warm to room temperature over 1.5h then quenched by the addition of solid sodium carbonate. Water (5ml) was added and the solution extracted with dichloromethane (2x 10ml), the organic extracts being washed with brine then dried (Na_2SO_4), filtered and concentrated. The residue was distilled (Kugelrohr, bath temperature 70°C/0.3mmHg) to yield the pure alkynone as a colourless oil (105mg, 97%). $\nu_{max.}$ (thin film) 2930 (s), 2870 (m), 1710 (s), 1660 (m), 1540 (m), 1440 (s), 1345 (s), 1190 (s), 1105 (s), 920 (m), 730 (s); δ_H (200 MHz) 1.57-1.73 (2H, m, C(8)$\underline{H}_2$-), 1.87 (2H, quin., *J* 6.0Hz, C(9)$\underline{H}_2$-), 2.03-2.26 (6H, m, C(3)$\underline{H}_2$C(4)$\underline{H}_2$- and C(7)$\underline{H}_2$-), 2.34-2.44 (2H, m, C(10)$\underline{H}_2$-) and 2.80 (2H, ca. t, *J* 6.0Hz, C(2)$\underline{H}_2$CO-); δ_C (50.3 MHz, DEPT) CH_2: 17.92, 19.04, 21.48, 25.40, 26.65, 42.41, 42.51, C(4°): 83.28, 85.65, 211.25.

2-Cyclopentylidene-cyclopentanone **225**. A mixture of the vinyl stannane (**221**, 38mg, 67μmol), AIBN (2mg, cat.) and tributyltin hydride (2μl, cat.) were heated at reflux in benzene for 4h. The solvent was removed *in vacuo* and the residue subjected to p.l.c. (3:1 petrol:ether) to yield the title compound **221** as a fragrant, colourless oil (8.1mg, 81%). $\nu_{max.}$ (thin film) 2960 (s), 2880 (m), 1710 (s), 1640 (s), 1415 (m), 1250 (s), 1170 (m), 1000 (w), 825 (w), 690 (w); δ_H (200 MHz) 1.65-1.80 (4H, m, $C_2\underline{H}_4CH_2C(=)$- in cyclopentylidene ring), 1.93 (2H, ca. quin., *J* 7.0Hz, $C\underline{H}_2CH_2CO$-), 2.31 (4H, t, *J* 7.0Hz, $C\underline{H}_2C$= *anti*- to carbonyl and $C\underline{H}_2C(CO-)$=), 2.48-2.63 (2H, m, $C\underline{H}_2C$= *syn*- to carbonyl), 2.71-2.88 (2H, m, $C\underline{H}_2CO$-); δ_C (50.3 MHz, DEPT) CH_2: 19.91, 25.07, 26.78, 29.36, 32.40, 34.16, 39.68, C(4°): 127.94, 158.73, 207.78; *m/z* (GCMS, C.I., NH_3) 168 (MNH_4^+, 6%), 152 (20), 151 (MH^+, 100), 150 (M^+, 8), 135 (4), 94 (7). This compound was identical in all respects to that obtained by self-aldol condensation of cyclopentanone[181] and to that obtained by the isomerisation of cyclodec-5-ynone[41] **200** under free radical conditions - see Chapter II.

2,4-Dimethoxy-(3'-Phenylselenopropyl)-cyclohexa-2,4-diene **233**. Using the general alkylation procedure described above (compounds **217** and **227**) with 1-iodo-3-phenylselenopropane (**111**, 1.1 equiv.) the title compound **233** was prepared as a colourless oil (55%, 4.21 mmol scale) after flash chromatography (75:1 to 25:1 petrol:ether). $\nu_{max.}$ (thin film) 3060 (w), 3000 (m), 2940 (s), 2830 (s), 1690 (s), 1660 (m), 1595 (m), 1580 (m), 1480-1430 (m), 1395 (m), 1230 (s), 1205 (s), 1150 (s), 775 (m), 735 (m), 690 (w); δ_H (200 MHz) 1.48-1.65 (2H, m, C<u>H</u>$_2$CH$_2$SePh), 1.74-1.89 (2H, m, C<u>H</u>$_2$CHR-), 2.70-2.98 (5H, m, C<u>H</u>$_2$CH=, C<u>H</u>R-, and C<u>H</u>$_2$SePh), 3.51 (6H, s, 2xC<u>H</u>$_3$-), 4.68 (2H, t, *J* 4.0Hz, 2xC<u>H</u>=), 7.16-7.31 (3H, m, Ph- *m*- and *p*- protons), 7.40-7.50 (2H, m, Ph- *o*- protons); *m/z* (GCMS, C.I., NH_3) 339 (MH^+, ^{80}Se, 25%), 337 (MH^+, ^{78}Se, 40), 335 (23), 179 (100), 165 (36), 153 (28), 139 (29), 94 (32), 78 (37).

2-(3'-Phenylselenopropyl)-cyclohexane-1,3-dione **234**. Prepared using the general hydrolysis procedure (for compounds **218** and **228** above). The title compound was obtained in quantitative crude yield (2.07mmol scale) as a white powder (m.p. 139-142°C). $\nu_{max.}$ ($CHCl_3$) 3500-2400 (br, s), 2960 (s), 1660-1540 (s), 1380 (s), 1265 (s), 1185 (s), 1130 (s), 1070 (m), 1025 (m), 860 (m), 820 (m); δ_H (200 MHz) 1.80 (2H, <u>ca</u>. quin., *J* 6.5Hz, C<u>H</u>$_2$CH$_2$SePh), 1.97 (2H, <u>ca</u>. quin., *J* 6.5Hz, C<u>H</u>$_2$CH$_2$CO-), 2.43 (4H, t, *J* 6.5Hz, C<u>H</u>$_2$CO- and C<u>H</u>$_2$C(CO-)=), 2.55-2.69 (2H, m, C<u>H</u>$_2$C(OH)=), 2.93 (2H, t, *J* 6.5Hz, C<u>H</u>$_2$SePh), 7.20-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.44-7.58 (2H, m, Ph- *o*- protons) diketo- tautomer seen by a signal at δ 3.43 (C<u>H</u>(CO-)$_2$-); *m/z* (GCMS, E.I.) 310 (M^+, 11%), 153 (M^+-PhSe·, 100), 136 (27), 110 (**4**) .

3-Bromo-2-(3'-phenylselenopropyl)-cyclohex-2-enone **235**. Prepared by Method 2 of the general procedure given for the preparation of enone **160** above. The title compound was obtained in 74% yield (over two steps from the diene **233**, 1.77mmol scale) as a colourless oil after flash chromatography (10:1 to 2:1 petrol:ether). $\nu_{max.}$ (thin film) 3070 (w), 2940 (m), 1710 (w), 1680 (s), 1615 (m), 1480 (m), 1340 (m), 1240 (m), 1130 (m), 1025 (m), 740 (s), 690 (m); δ_H (200 MHz) 1.80 (2H, quin., C<u>H</u>$_2$CH$_2$SePh), 2.02 (2H, quin., C<u>H</u>$_2$CH$_2$CO-), 2.46 (2H, t, C<u>H</u>$_2$C(CO-)=), 2.57 (2H, t, C<u>H</u>$_2$CO-) the preceding

resonances displayed coupling constants of 7.0Hz, 2.82-3.01 (4H, m, C$\underline{H}_2$SePh and C$\underline{H}_2$C(Br)=), 7.19-7.33 (3H, m, Ph- *m*- and *p*- protons), 7.44-7.58 (2H, m, Ph- *o*- protons); *m/z* (GCMS, C.I., NH_3) 390 (MNH_4^+, ^{80}Se, 4%), 375 (MH^+, ^{80}Se, 8), 373 (MH^+, ^{80}Se, 10), 291 (10), 217 (90), 215 (51), 153 (100), 137 (45), 78 (41).

2-(3'-Phenylselenopropyl)-3-tributylstannylcyclohex-2-enone **232**. Using the general procedure given above, from the bromo-enone (**235**, 425mg, 1.14mmol), the vinyl stannane **232** was prepared as a colourless oil after flash chromatography (25:1 to 5:1 petrol:ether) (586mg, 88%). $\nu_{max.}$ (thin film) 3070 (w), 2950 (s), 2870 (m), 1715 (w), 1670 (s), 1580 (w), 1490-1410 (m), 1340 (m), 1075 (m), 1025 (m), 735 (s), 690 (m); δ_H (200 MHz) 0.89 (9H, t, *J* 7.0Hz, (C$\underline{H}_3$C$_3$H$_6$-)$_3$Sn-), 0.98 (6H, t, *J* 8.0Hz, (C$_3$H$_7$C$\underline{H}_2$-)$_3$Sn-), 1.18-1.58 (12H, m, (CH$_3$C$_2\underline{H}_4$CH$_2$-)$_3$Sn-), 1.67-2.02 (4H, m, C$\underline{H}_2$CH$_2$CO- and C$\underline{H}_2$CH$_2$SePh), 2.21-2.51 (6H, m, C$\underline{H}_2$CO-, C$\underline{H}_2$C(SnBu$_3$), and C$\underline{H}_2$C(CO-)=), 2.91 (2H, t, *J* 8.0Hz, C$\underline{H}_2$SePh), 7.18-7.32 (3H, m, Ph- *m*- and *p*- protons), 7.43-7.53 (2H, m, Ph- *o*- protons); *m/z* 527 (M^+-^{n}Bu·, ^{80}Se^{120}Sn, 92%), 525 (100), 523 (77), 427 (19), 293 (22), 137 (50), 91 (17), 79 (29).

Attempted ring expansion of the stannane **232**. A mixture of the stannane (**232**, 200mg, 0.34mmol), AIBN (11mg, cat.) and tributyltin hydride (9µl, cat.) were heated at reflux for 90h with periodic additions of AIBN and tributyltin hydride. The concentrated residue was purified by flash chromatography (10:1 to 5:1 petrol:ether) to yield *6,7-dihydro-4(5H)-indanone* (**23**[40], 46mg, 98%), a colourless oil, as the only isolable product. The ^{1}H n.m.r. spectrum of the crude residue (i.e., before exposure to silica) indicated that the isolated product was formed *via* an intermediate, suggested to be the required cycloalkynone **237**, however attempts to repeat this reaction and distil out the product directly from the crude mixture resulted in extensive decomposition so this hypothesis remains unsubstantiated. $\nu_{max.}$ (thin film) 2940 (s), 2870 (s), 1665 (s), 1635 (s), 1450 (m), 1430 (s), 1390 (s), 1200 (m), 1120 (m), 920 (s), 730 (s), 645 (m); δ_H (200 MHz) 1.62-1.90 (2H, m, C(2)$\underline{H}_2$-), 2.00 (2H, quin., *J* 6.5Hz, C$\underline{H}_2$CH$_2$CO-), 2.25-2.39 (4H, m, C(1)$\underline{H}_2$= and C$\underline{H}_2$C(CO-)=), 2.46-2.62 (4H, m, C$\underline{H}_2$CO- and C(7)$\underline{H}_2$C=); δ_C (50.3

MHz, DEPT) CH_2: 21.33, 23.29, 26.46, 28.91, 37.53, 41.86, C(4°): 137.80, 165.90, 198.23; *m/z* (GCMS, C.I., NH_3) 154 (MNH_4^+, 4%), 137 (MH^+, 100), 108 (11).

3-(Hydroxymethyl)-3-methyloxetane, 4-iodobutanoate ester **243**. To a solution of 3-(hydroxymethyl)-3-methyloxetane (**240**, 10g, 98mmol) and triethylamine (15ml, 0.11mol) in ether (150ml) at 0°C was added dropwise a solution of 4-chloro-butyrylchloride (11.2ml, 0.1mol) in ether (25ml). The mixture was allowed to warm to room temperature then stirred for a further 1h. Water (150ml) was added, the layers separated and the aqueous portion extracted with ether (3x100ml). The combined organic portions were washed with brine then dried ($MgSO_4$), filtered, and concentrated to yield the 4-chlorobutanoate ester (**242**, 19.8g, 98%) which was used directly in the next reaction. $\nu_{max.}$ (thin film) 2960 (s), 2880 (s), 1740 (s), 1380 (m), 1300-1120 (m), 980 (s), 835 (m), 735 (s); δ_H (200 MHz) 1.36 (3H, s, C<u>H</u>$_3$-), 2.13 (2H, quin., C<u>H</u>$_2$CH$_2$Cl), 2.58 (2H, t, C<u>H</u>$_2$CO-), 3.63 (2H, t, C<u>H</u>$_2$Cl), 4.21 (2H, s, C<u>H</u>$_2$O.CO-), 4.40 (2H, d) and 4.54 (2H, d, CH$_2$OC<u>H</u>$_2$-) all coupling constants 6.5Hz.

A mixture of the chloride (**242**, 19.8g, 96mmol) and sodium iodide (36g, 0.24mol) were heated at reflux in acetone (100ml) for 12h then the solvent was removed and the residue taken up in ether (250ml). The inorganic solids were filtered off and the solution concentrated *in vacuo* to yield the title compound (**243**, 25.5g, 89%) as a colourless oil after flash chromatography (10:1 petrol:ether). $\nu_{max.}$ (thin film) 2950 (s), 2875 (s), 1740 (s), 1660 (w), 1380 (m) 1320-1120 (m), 980 (s), 915 (m), 835 (m), 730(s); δ_H (200 MHz) 1.35 (3H, s, C<u>H</u>$_3$-), 2.18 (2H, quin., *J* 7.0Hz, C<u>H</u>$_2$CH$_2$I), 2.54 (2H, t, *J* 7.0Hz, C<u>H</u>$_2$CO-), 3.27 (2H, t, *J* 7.0Hz, C<u>H</u>$_2$I), 4.20 (2H, s, C<u>H</u>$_2$O.CO-), 4.41 (2H, d, *J* 6.5Hz) and 4.54 (2H, d, *J* 6.5Hz, C<u>H</u>$_2$OC<u>H</u>$_2$-); *m/z* (GCMS, C.I., NH_3) 316 (MNH_4^+, 5%), 299 (MH^+, 100), 207 (18), 173 (55), 171 (41), 104 (18), 70 (25), 58 (20).

1-(3'-Iodopropyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane **244**. To a solution of boron trifluoride etherate (2.3ml, 18.7mmol) in dichloromethane (150ml) at -15°C was added a solution of the ester (**243**, 22.2g, 74.5mmol) in dichloromethane (10ml) and the resulting solution stirred at this temperature for 48h. The mixture was quenched at -15°C with

triethylamine (11.4ml, 82mmol) and transferred *via* cannula into ether (1000ml) to precipitate out the boron trifluoride-triethylamine complex which was filtered off through Celite®. The concentrated solution was subjected to flash chromatography (7:1 to 5:1 petrol:ether containing 2% triethylamine) to yield the pure orthoester (**244**, 15.3g, 69%) as a colourless oil. $\nu_{max.}$ (thin film) 2970 (s), 2930 (s), 2880 (s), 1400 (s), 1265 (s), 1230 (s), 1175 (s), 1120 (m), 1060 (s), 990 (s), 940 (m), 890 (s); δ_H (200 MHz) 0.79 (3H, s, $C\underline{H}_3$-), 1.76 (2H, t, *J* 8.0Hz, $C\underline{H}_2C(OR)_3$), 1.89-2.08 (2H, m, $C\underline{H}_2CH_2I$), 3.22 (2H, t, *J* 6.5Hz, $C\underline{H}_2I$), 3.88 (6H, s, 3x$C\underline{H}_2O$-); *m/z* (GCMS, C.I., NH_3) 316 (MNH_4^+, 6%), 299 (MH^+, 88), 171 (25), 104 (100), 85 (13), 70 (63), 58 (25).

trans-2-Methyl-2-(3'-(4"-methyl-2",6",7"-trioxabicyclo[2,2,2]oct-1"-yl))-3-tributyl-stannylcyclohexanone **245**. Tributylstannyl lithium prepared from bis-tributyltin (5.56ml, 11mmol) and ^{n}butyl lithium (7.14ml of a 1.54M solution in hexanes, 11mmol) in THF (15ml) was cooled to -78°C and the enone (**96**, 1.1g, 10mmol) added. After 0.5h the mixture was warmed to -23°C and HMPA (15ml) added followed by the iodide (**244**, 3.28g, 11mmol). The reaction was allowed to warm up to room temperature over 14h and the crude product isolated as above then purified by flash chromatography (6:1 petrol: ether containing 1% triethylamine). The title compound **245** was obtained as a colourless oil (4.07g, 71%). $\nu_{max.}$ (thin film) 2960 (s), 2920 (s), 2860 (s), 1700 (s), 1460 (m), 1395 (m), 1290 (m), 1060 (s), 990 (s), 910 (m), 730 (s); δ_H (200 MHz) 0.67-0.97 (15H, m, $(C\underline{H}_3C_2H_4C\underline{H}_2\text{-})_3Sn$-), 0.80 (3H, s, 4"-$C\underline{H}_3$-), 1.08 (3H, s, 2-$C\underline{H}_3$-), 1.17-2.13 (23H, m, $(CH_3C_2\underline{H}_4CH_2\text{-})_3Sn$-, $C_3\underline{H}_6C(OR)_3$, and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.38 (2H, t, *J* 6.5Hz, $C\underline{H}_2CO$-), 3.89 (6H, s, 3x$C\underline{H}_2O$-); *m/z* (E.I.) 572 (M^+, ^{120}Sn, 2%), 515 (M^+-^{n}Bu·, 37), 513 (28), 511 (16), 291 (21), 235 (26), 179 (62), 177 (60), 121 (28), 105 (100), 72 (32), 55 (76).

4-(1-Methyl-2'-oxo-6'-tributylstannylcyclohexyl)-butanoic acid **246**. A mixture of the orthoester (**245**, 3.90g, 6.82mmol), dichloromethane (25ml) and hydrochloric acid (20.5 ml of a 1M solution, 20.5mmol) were stirred at room temperature for 3h. Water (50ml) and ether (50ml) were added, the layers separated and the organic portion combined with

four ether extracts (4x25ml) of the aqueous layer. The solution was dried ($MgSO_4$), filtered, and concentrated to yield the partially hydrolysed diol, a viscous oil, which was never isolated but used directly in the next step. The ester was then dissolved in THF (18ml) and lithium hydroxide solution added (573mg, 13.6mmol in water (2ml)), the mixture being brought to reflux with vigorous stirring. Heating was continued for 18h then the mixture cooled, and water (20ml) added followed by dilute hydrochloric acid to pH4-5. The solution was extracted with dichloromethane (4x15ml) and the extracts dried ($MgSO_4$), filtered and concentrated to yield the acid (**246**, 3.0g, 90% over the two steps), a syrupy oil, which was pure by t.l.c. and spectroscopic analysis. $\nu_{max.}$ (thin film) 3700-3000 (m), 2960 (s), 2930 (s), 2860 (m), 1730-1690 (s), 1460 (m), 1420 (m), 1380 (w), 1060 (w), 880 (w); δ_H (200 MHz) 0.69-0.99 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.10 (3H, s, $C\underline{H}_3$-), 1.18-1.65 (15H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3SnC\underline{H}$R- and $C\underline{H}_2C_2H_4CO_2H$), 1.74-2.05 (6H, m, $C_2\underline{H}_4CH_2CO$- and $C\underline{H}_2CH_2CO_2H$), 2.23-2.52 (4H, m, $C\underline{H}_2CO$- and $C\underline{H}_2CO_2H$); *m/z* 488 (M^+, ^{120}Sn, 4%), 431 (M^+-^{n}Bu·, 100), 429 (72), 427 (45), 413 (16), 291 (25), 235 (32), 179 (53), 133 (25), 121 (32), 81 (19), 55 (35).

<u>trans</u>-2-Methyl-2-((3'-phenylselenocarbonyl)-propyl)-3-tributylstannylcyclohexanone **247**. To a solution of the acid (**246**, 2.0g, 4.1mmol) and tributyl phosphine (2.04ml, 8.2mmol) in THF (20ml) was added in one portion NPSP[187] (2.48g, 8.2mmol) at room temperature. After stirring for 14h the solvent was removed and the residue taken directly onto a column (100:1 to 5:1 petrol:ether) to yield the acyl selenide (**247**, 1.93g, 75%) as a colourless oil. $\nu_{max.}$ (thin film) 3060 (w), 2950 (s), 2870 (s), 1730 (s), 1705 (s), 1480-1410 (m), 1380 (m), 1145 (m), 1070 (m), 1025 (m), 740 (s), 690 (s); δ_H (200 MHz) 0.77-0.96 (15H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn-), 1.11 (3H, s, $C\underline{H}_3$-), 1.21-1.69 (17H, m) and 1.77-2.03 (4H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3SnC\underline{H}$R-, $C_2\underline{H}_4CH_2COSePh$, and $C_2\underline{H}_4CH_2CO$-), 2.26-2.54 (2H, m, $C\underline{H}_2CO$-), 2.71 (2H, t, *J* 6.5Hz, $C\underline{H}_2COSePh$), 7.34-7.43 (3H, m, Ph- *m*- and *p*-protons), 7.46-7.58 (2H, m, Ph-*o*- protons); *m/z* (E.I.) 569 (M^+-^{n}Bu·, 13%), 471 (M^+-PhSe·, ^{120}Sn, 35), 469 (26), 467 (15), 389 (41), 291 (100), 275 (25), 235 (35), 179 (35), 137 (20), 79 (45), 67 (35), 55 (46).

Ring expansion of the acyl selenide **247**. A mixture of the radical precursor (**247**, 1.80g, 2.87mmol), AIBN (94mg, cat.) and tributyltin hydride (193μl, cat.) were heated at reflux in degassed benzene (250ml) for 16h (with an extra addition of AIBN, 94mg) by which time no starting material remained (t.l.c.). The solvent was removed and the residue subjected to flash chromatography (10:1 to 2:1 petrol:ether) to yield a mixture of two compounds (arising from the addition of the isobutyronitrile radical to either of the two carbonyls in the initially formed medium ring dione) which ran as one spot on t.l.c. (**249** and **250**, oil, 325mg, 45%). $\nu_{max.}$ (thin film) 3550-3380 (s), 2960 (s), 2930 (s), 2860 (m), 2230 (m), 1695 (s), 1460 (s), 1360 (s), 1145 (s), 1095 (m), 990 (m), 760 (m), 735 (s); δ_H (500 MHz - selected resonances only, as spectrum extremely complex) Isomer #1 (60% by examination of integral ratios) 1.11 (3H, s) and 1.45 (3H, s, $(C\underline{H}_3)_2C(CN)$-), 1.66 (3H, s, $C\underline{H}_3CR$=), 3.26 (1H, ddd, *J* 16.5, 15, 4.0Hz, C<u>H</u>HCO-), 4.37 (1H, s, O<u>H</u>), 5.12 (1H, dd, *J* 12, 3.5Hz, C<u>H</u>=); Isomer #2 (40% by examination of integral ratios) 1.12 (3H, s) and 1.45 (3H, s, $(C\underline{H}_3)_2C(CN)$-), 1.68 (3H, s, $C\underline{H}_3CR$=), 3.40 (1H, ddd, *J* 16, 15, 3.5Hz, C<u>H</u>HCO-), 4.42 (1H, s, O<u>H</u>), 5.17 (1H, ca. t, *J* 6.0Hz, C<u>H</u>=); δ_C (50.3 MHz, DEPT) CH_3: 21.60, 21.89, 22.51, CH_2: 19.40, 19.54, 21.26, 22.64, 23.09, 24.73, 26.79, 27.13, 29.09, 29.49, 33.57, 33.86, CH: 124.74, 127.06, C(4°): 213.64, 213.81 and 37.59, 81.82, 123.96, 134.36, 136.74; *m/z* (GCMS, C.I., NH_3) 267 (MNH_4^+, 14%), 198 (12), 181 (14), 163 (71), 161 (42), 87 (84), 68 (25), 58 (100). Also isolated was a mixture of two further compounds (350mg) which was re-columned (5:1 petrol:ether) to afford *<u>trans</u>-8a-hydroxy-5-methylene-decahydro-1-naphthalenone* (**251**, 210mg, 41%), a white solid which was recrystallised for data (m.p. 72-3°C, hexane). $\nu_{max.}$ ($CHCl_3$) 3600-3200 (m), 2990 (s), 2940 (m), 2870 (m), 1715 (s), 1640 (w), 1460 (s), 1390 (s), 1380 (s), 1145 (s), 960 (m), 905 (m); δ_H (200 MHz) 1.38-2.39 (13H, m, ring protons), 3.00 (1H, td, *J* 13, 6.5Hz, C<u>H</u>HCO-), 4.80 (1H, s) and 5.01 (1H, s, $C\underline{H}_2$=); δ_C (50.3 MHz, DEPT) CH_2: 22.57, 25.62, 31.05, 35.61, 37.13, 110.35, CH: 51.78, C(4°): 77.67, 110.35, 212.35; *m/z* (GCMS, C.I., NH_3) 198 (MNH_4^+, 68%), 181 (MH^+, 22), 163 (100), 145 (14), 137 (21). The minor component *<u>trans</u>-8a(β)-hydroxy-5(α)-methyl-decahydro-1-naphthalenone* (**248**, 38mg, 7%) was also isolated as a glass. $\nu_{max.}$ ($CHCl_3$) 3600-3200 (br, m), 2930 (s), 2860 (m), 1705 (s), 1440 (m), 1380 (m),

1260 (m), 1110 (m), 1015 (m), 950 (s), 905 (m), 740 (w); δ_H (200 MHz) 1.14 (3H, d, *J* 8.0Hz, C<u>H</u>$_3$-), 1.24-2.30 (14H, m, ring protons), 3.00 (1H, td, *J* 14,6.5Hz, C<u>H</u>HCO-); δ_C (50.3 MHz) 15.70, 25.43, 26.34, 32.08, 32.68, 32.98, 47.85, 78.11, 212.68; *m/z* (GCMS, C.I., NH_3) 200 (MNH_4^+, 6%), 182 (M^+, 15), 165 (100), 163 (22), 161 (22).

3-(Hydroxymethyl)-3-methyloxetane, 3-chloropropanoate ester **252**. A mixture of 3-chloropropionic acid (1.09g, 10mmol), 3-(hydroxymethyl)-3-methyloxetane (**240**, 1.02g, 10 mmol) and <u>bis</u>-(tributyltin)-oxide (510µl, 1mmol) were heated at reflux in xylene (150ml), with removal of water (Dean-Stark trap), for 8h. A further portion of the alcohol (1.02g, 10mmol) was added and heating continued for 16h. The cooled solution was washed with saturated sodium hydrogen carbonate solution (2x50ml) then brine (25ml). At this point much polymeric tin-containing material was precipitated which was removed by filtration through Celite®. The filtered solution was concentrated and purified by flash chromatography (5:1 petrol:ether) to yield the pure ester (**252**, 1.05g, 55%) as a colourless oil. $\nu_{max.}$ (thin film) 2970 (m), 2880 (m), 1740 (s), 1460 (w), 1380 (m), 1250-1150 (m), 985 (s), 835 (m), 735 (m); δ_H (200 MHz) 1.37 (3H, s, C<u>H</u>$_3$-), 2.86 (2H, t, *J* 6.5Hz, C<u>H</u>$_2$CO-), 3.80 (2H, t, *J* 6.5Hz, C<u>H</u>$_2$Cl), 4.25 (2H, s, C<u>H</u>$_2$O.CO-), 4.40 (2H, d, *J* 6.0Hz) and 4.53 (2H, d, *J* 6.0Hz, CH$_2$OC<u>H</u>$_2$-); *m/z* (GCMS, C.I., NH_3) 195 (MH^+, ^{37}Cl, 16%), 193 (MH^+, ^{35}Cl, 46), 157 (100), 55 (16).

3-(Hydroxymethyl)-3-methyloxetane, 3-iodopropanoate ester **253**. The ester **253** was obtained, using the procedure described above (for the preparation of the chloro- analogue **252**) with 3-iodo-propanoic acid, on a 10mmol scale. The reaction was terminated after 24h and the isolated residue purified by flash chromatography (5:1 to 3:1 petrol:ether) to yield the title compound **253** as a colourless oil (380mg, 13% - much elimination of HI from the acid) occurred during the reaction. $\nu_{max.}$ (thin film) 2975 (m), 2875 (m), 1740 (s), 1460 (w), 1380 (m), 1220 (m), 1120 (m), 980 (s), 835 (s), 750 (w); δ_H (200 MHz) 1.38 (3H, C<u>H</u>$_3$-), 3.07 (2H, t, *J* 6.5Hz, C<u>H</u>$_2$CO-), 3.36 (2H, t, *J* 6.5Hz, C<u>H</u>$_2$I), 4.24 (2H, s, C<u>H</u>$_2$O.CO-), 4.42 (2H, d, *J* 5.5Hz) and 4.56 (2H, d, *J* 5.5Hz, CH$_2$OC<u>H</u>$_2$-); *m/z*

(GCMS, C.I., NH_3) 302 (MNH_4^+, 1%), 285 (MH^+, 22), 159 (24), 157 (100), 70 (15), 55 (21).

2-(Hydroxymethyl)-2-(iodomethyl)-prop-1-yl-propenoate **254**. A mixture of the chloride (**252**, 1.0g, 5.19mmol) and sodium iodide (3.90g, 26mmol) were heated at reflux in acetone (15ml) for 16h. The acetone was removed, ether (100ml) added, the solution filtered and concentrated to give the title compound (**254**, 1.41g, 96%), a pale yellow oil. $\nu_{max.}$ (thin film) 3600-3200 (s), 2970 (s), 2880 (m), 1725 (s), 1635 (m), 1620 (m), 1470 (s), 1410 (s), 1300 (s), 1200 (s), 1060 (s), 985 (s), 810 (s), 735 (m); δ_H (200 MHz) 1.06 (3H, s, C<u>H</u>$_3$-), 3.25 (2H, s, C<u>H</u>$_2$I), 3.49 (2H, s, C<u>H</u>$_2$OH), 4.18 (2H, s, C<u>H</u>$_2$O.CO-), 5.92 (1H, dd, *J* 10.5, 1.5Hz, C<u>H</u>H= *anti-* to carboxyl), 6.16 (1H, dd, *J* 17, 10.5Hz, C<u>H</u>=), 6.48 (1H, dd, *J* 17, 1.5Hz, C<u>H</u>H= *syn-* to carboxyl); *m/z* (GCMS, C.I., NH_3) 302 (MNH_4^+, 14%), 285 (MH^+, 9), 174 (39), 157 (100), 144 (32), 126 (16), 72 (25), 55 (51).

1-(2'-Chloroethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane **255**. To a solution of the ester (**252**, 550mg, 2.86mmol) in dichloromethane (10ml) at -10°C was added boron trifluoride etherate (88µl, 0.72mmol) and the solution stirred for 48h. The reaction was quenched at -10°C with triethylamine (500µl, 3.6mmol) and transferred *via* cannula into ether (100ml). The boron trifluoride-triethylamine complex was filtered off and the solution concentrated to yield the orthoester (**255**, 550mg, quantitative), a colourless oil which required no further purification. $\nu_{max.}$ (thin film) 2960 (m), 2880 (s), 1400 (m), 1240 (m), 1200 (m), 1055 (s), 1005 (m), 940 (w), 895 (m), 690 (m); δ_H (200 MHz) 0.82 (3H, s, C<u>H</u>$_3$-), 2.18 (2H, <u>ca</u>. t, *J* 8.0Hz, C<u>H</u>$_2$C(OR)$_3$), 3.60 (2H, <u>ca</u>. t, *J* 8.0Hz, C<u>H</u>$_2$Cl), 3.90 (6H, s, 3xC<u>H</u>$_2$O-); *m/z* (GCMS, C.I., NH_3) 195 (MH^+, ^{37}Cl, 32%), 193 (MH^+, ^{35}Cl, 94), 157 (100), 72 (25), 70 (38), 55 (47).

5-(Hydroxymethyl)-2,2,5-trimethyl-1,3-dioxane, 3-iodopropanoate ester **256**. A mixture of the orthoester (**255**, 500mg, 2.6mmol) and sodium iodide (1.95g, 13mmol) was heated at reflux in acetone (7ml) for 24h. The crude material was isolated in the previously

described manner then purified by flash chromatography (5:1 petrol:ether containing 1% triethylamine) to give the title compound (**256**, 394mg, 44%) as the only isolable material. $\nu_{max.}$ (thin film) 2970 (s), 2875 (s), 1740 (s), 1460 (m), 1380 (m), 1100 (m), 960 (w), 840 (m), 735 (m), 660 (m); δ_H (200 MHz) 0.88 (3H, s, 5-C$\underline{H}_3$-), 1.42 (3H, s) and 1.46 (3H, s, 2x 2-C$\underline{H}_3$-), 3.04 (2H, t, *J* 8.0Hz, C$\underline{H}_2$CO-), 3.36 (2H, t, *J* 8.0Hz, C$\underline{H}_2$I), 3.68 (4H, ca. s, 2xC$\underline{H}_2$O-), 4.25 (2H, s, C$\underline{H}_2$O.CO-); *m/z* (GCMS, C.I., NH_3) 360 (MNH_4^+, 4%), 343 (MH^+, 32), 327 (17), 285 (86), 215 (17), 159 (46), 157 (100), 58 (19).

3-(Hydroxymethyl)-3-methyloxetane, propenoate ester **257**. Prepared by the procedure described above (for **242**) using acryloyl chloride (4.06ml, 50mmol) and 3-(hydroxymethyl)-3-methyloxetane (**240**, 5.10g, 50mmol) in ether (200ml) containing triethylamine (8.35ml, 60mmol). The same work-up procedure was used to afford the spectroscopically clean ester **257** as a colourless oil (4.98g, 64% - this yield was average for this reaction which was run a number of times). $\nu_{max.}$ (thin film) 2970 (m), 2880 (m), 1730 (s), 1630 (m), 1410 (s), 1260 (s), 1190 (s), 1060 (m), 985 (m), 810 (m), 735 (m); δ_H (200 MHz) 1.37 (3H, s, C$\underline{H}_3$-), 4.27 (2H, s, C$\underline{H}_2$O.CO-), 4.41 (2H, d, *J* 6.5Hz) and 4.56 (2H, d, *J* 6.5Hz, C$\underline{H}_2$OC$\underline{H}_2$-), 5.89 (1H, dd, *J* 10.5, 1.5Hz, C$\underline{H}$H= *anti-* to carboxyl), 6.18 (1H, dd, *J* 18.5, 10.5Hz, C$\underline{H}$=), 6.47 (1H, dd, *J* 18.5, 1.5Hz, CH$\underline{H}$= *syn-* to carboxyl); *m/z* (GCMS, C.I., NH_3) 174 (MNH_4^+, 3%), 157 (MH^+, 100), 55 (9).

4-Methyl-1-vinyl-2,6,7-trioxabicyclo[2,2,2]octane **258**. The ester (**257**, 3.0g, 19mmol) was subjected to the isomerisation conditions described above (for **244**) with the exceptions that more boron trifluoride etherate was used (2.37ml, 19.2mmol) and the reaction was run at -25°C for 36h. The mixture was quenched and the product isolated as before. Purification was achieved by flash chromatography (7:1 petrol:ether containing 1% triethylamine) to yield the orthoester **256** as a white solid (498mg, 17% - this yield could not be improved) (m.p. 60-61°C). $\nu_{max.}$ ($CHCl_3$) 3020 (m), 2980-2940 (s), 2880 (s), 1420 (s), 1305 (s), 1275 (m), 1100 (s), 1040 (s), 980 (s), 955 (s), 880 (m); δ_H (200 MHz) 0.84 (3H, s, C$\underline{H}_3$-), 3.98 (6H, s, 3xC$\underline{H}_2$O-), 5.32 (1H, dd, *J* 10.5, 1.5Hz, C$\underline{H}$H= *anti-* to orthoester group), 5.65 (1H, dd, *J* 18.5, 1.5Hz, CH$\underline{H}$= *syn-* to orthoester group),

5.83 (1H, dd, *J* 18.5, 10.5Hz, C<u>H</u>=); *m/z* (GCMS, C.I., NH_3) 157 (MH^+, 100%), 126 (5), 55 (13).

2,6-Dimethylcyclohex-2-enone **261**[191]. To a rapidly stirred mixture of 2,6-dimethylcyclohexanone (5.0g, 40.3mmol), water (25ml), ethanol (5ml), and acetic acid (1 drop) was added, with warming (40-50°C), bromine (2.25ml, 43.6mmol) as rapidly as decolourisation occurred. The aqueous layer was extracted with ether (4x20ml) and the extracts washed with brine (10ml), dried ($MgSO_4$), filtered, and concentrated. This material was dissolved in *N,N*-dimethylformamide (12ml) and lithium bromide (3.48g, 40mmol) added. The mixture was stirred at 100°C for 2h then cooled to room temperature whereupon ether (30ml) and sulphuric acid (30ml of a 2.5% aqueous solution) were added. The mixture was stirred rapidly for 16h. The aqueous layer was saturated with sodium chloride and extracted with ether (4x20ml). The combined extracts were washed with saturated sodium hydrogen carbonate solution (2x20ml) and brine (15ml) then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting oil was purified by short path distillation (bath temperature 70°C/14mmHg) to yield the enone **261** as a colourless oil (3.20g, 64%). $\nu_{max.}$ (thin film) 3020-2800 (s), 1690-1620 (s), 1450 (s), 1375 (s), 1200 (s), 1120 (s), 1080 (s), 995 (s), 885 (s), 825 (m), 710 (m); δ_H (200 MHz) 1.19 (3H, d, *J* 6.5Hz, 6-C<u>H</u>$_3$-), 1.63-1.92 (1H, m, C<u>H</u>HCH(CH$_3$)-), 1.81 (3H, d, *J* 2.0Hz, C<u>H</u>$_3$C(CO-)=), 1.98-2.19 (1H, m, CH<u>H</u>CH(CH$_3$)-), 2.27-2.53 (3H, m, C<u>H</u>(CH$_3$)CO- and C<u>H</u>$_2$CH=), 6.70 (1H, <u>ca</u>. s, C<u>H</u>=).

<u>trans</u>-2,6-Dimethyl-2-(4'-iodobutyl)-3-tributylstannylcyclohexanone **264**. Tributylstannyl lithium (1.1 equiv.) in THF (8ml) was prepared by the general procedure described above and cooled to -78°C. The enone (**261**, 500mg, 4.03mmol) was added and stirring continued for 1h before allowing the mixture to -23°C. HMPA (8.5ml) and the 1,4-diiodobutane (1.59ml, 12.1mmol) were added and the mixture allowed to room temperature over 20h. The reaction was quenched with saturated ammonium chloride solution (5ml) and water (5ml), the aqueous portion extracted with ether (5x15ml) and the combined extracts washed with brine (20ml), dried ($MgSO_4$), filtered and the solvent removed. The

crude product was purified by flash chromatography (50:1 to 25:1 petrol:ether) to yield the title compound **264** as a colourless oil (1.54g, 64%). $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2860 (s), 1700 (s), 1460 (s), 1375 (s), 1240 (m), 1185 (m), 1070 (m), 965 (m), 870 (m), 660 (m); δ_H (200 MHz) 0.72-1.10 (18H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn- and 6-$C\underline{H}_3$-), 1.17 (3H, s, 2-$C\underline{H}_3$-), 1.20-1.59 (16H, m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn- and $C_2\underline{H}_4C_2H_4I$), 1.64-2.40 (7H, m, $C\underline{H}_2CH_2I$ and $C_2\underline{H}_4C\underline{H}(SnBu_3)$-), 2.50-2.75 (1H, m, $C\underline{H}(CH_3)CO$-), 3.19 (2H, t, *J* 8.0Hz, $C\underline{H}_2I$); *m/z* (E.I.) 541 ($M^{+-n}Bu\cdot$, ^{120}Sn, 46%), 539 (39), 537 (23), 413 (19), 361 (49), 291 (100), 179 (39), 163 (52), 121 (30), 109 (39), 95 (44), 81 (63), 55 (71).

Ring expansion of the stannane **264**. A mixture of the stannane (**264**, 100mg, 0.17mmol), AIBN (1mg, cat.) and tributyltin hydride (2µl, cat.) were heated at reflux in degassed benzene for a total of 72h with periodic additions of AIBN and tributyltin hydride. The cooled solution was concentrated *in vacuo* to yield an oil which was subjected to flash chromatography (50:1 petrol:ether) to produce two components. The first component was further chromatographed (500:1 to 100:1 petrol:ether) and was found to consist of two compounds: *E-2-hex-2'-ylidene-5-methylcyclopentanone* (**266**, 8mg, 26%) and *Z-2-hex-2'-ylidene-5-methylcyclopentanone* (**267**, 7mg, 23%), both fragrant, colourless oils. For **266** $\nu_{max.}$ (thin film) 2960 (s), 2940 (s), 2875 (s), 1710 (s), 1630 (s), 1460 (m), 1375 (m), 1265 (m), 1180 (m), 960 (m), 865 (w); δ_H (200 MHz) 0.94 (3H, t, *J* 7.0Hz, 6'-$C\underline{H}_3$-), 1.12 (3H, d, *J* 7.0Hz, 5-$C\underline{H}_3$-), 1.22-1.58 (6H, m, $C\underline{H}_2CH(CH_3)$- and $C_2\underline{H}_4CH_3$), 2.03-2.73 (3H, m, $C\underline{H}(CH_3)CO$- and $C\underline{H}_2C(CH_3)$=), 2.12 (2H, t, *J* 7.5Hz, $C\underline{H}_2C(CO$-)=), 2.21 (3H, s, $C\underline{H}_3CR$=); δ_C (50.3 MHz) 13.75, 14.58, 18.33, 22.78, 26.67, 28.47, 29.17, 37.78, 45.28, 130.83, 151.81, 210.00; *m/z* (GCMS, C.I., NH_3) 198 (MNH_4^+, 6%), 181 (MH^+, 100), 179 (10), 138 (11). For **267** $\nu_{max.}$ (thin film) 2960 (s), 2935 (s), 2880 (m), 1705 (s), 1630 (s), 1455 (m), 1375 (m), 1180 (m), 910 (s), 735 (s); δ_H (200 MHz) 0.91 (3H, t, *J* 7.0Hz, 6'-$C\underline{H}_3$-), 1.11 (3H, d, *J* 7.0Hz, 5-$C\underline{H}_3$-), 1.26-1.53 (6H, m, $C_2\underline{H}_4CH_3$ and $C\underline{H}_2CH(CH_3)$-), 1.84 (3H, s, $C\underline{H}_3CR$=), 2.06-2.64 (4H, m, $C\underline{H}_2C(CO$-)=$C(CH_3)C\underline{H}_2$-), 2.72 (1H, ca. t, *J* 7.0Hz, $C\underline{H}(CH_3)CO$-); *m/z* (GCMS, C.I., NH_3) 198 (MNH_4^+, 6%), 181 (MH^+, 100), 179 (8). The second component was further purified by p.l.c. (1:1 petrol:ether) and identified as the desired ring expanded material *E*-

2,6-dimethylcyclodec-5-enone (**265**, 10mg, 33%), a colourless oil with a characteristic odour. $\nu_{max.}$ (thin film) 2930 (s), 2860 (m), 1710 (s), 1630 (w), 1450 (s), 1375 (m), 1105 (m), 1085 (m), 945 (w), 840 (w); δ_H (200 MHz) 0.95 (3H, d, *J* 7.0Hz, 2-C$\underline{H}_3$-), 1.46-1.77 (4H, m, C(8)$\underline{H}_2$C(9)$\underline{H}_2$-), 1.70 (3H, s, C$\underline{H}_3$CR=), 1.85-2.44 (9H, m, $C_2\underline{H}_4C\underline{H}(CH_3)CO$-, C$\underline{H}_2$CO-, and C$\underline{H}_2C(CH_3)$=), 4.88-5.04 (1H, m, C$\underline{H}$=); *m/z* (GCMS, C.I., NH_3) 198 (MNH_4^+, 4%), 181 (MH^+, 3%), 163 (100), 162 (33), 147 (25), 133 (10), 119 (9), 105 (12), 91 (11). This reaction was repeated twice on larger scales; in both cases the same ratio of products was visible in the crude ^{1}H n.m.r. spectrum.

3-Ethoxycarbonyl-4-methylpentan-2-one **268**[193] Prepared by the method of Kirschleger[193] as a colourless oil after flash chromatography (10:1 to 8:1 petrol:ether) (82%, 77mmol scale). $\nu_{max.}$ (thin film) 2970 (s), 2880 (m), 1770-1690 (s), 1470 (m), 1370 (s), 1300 (m), 1180 (s), 1120 (s), 1045 (m), 1025 (m); δ_H (200 MHz) 0.93 (3H, d, *J* 8.0Hz) and 0.97 (3H, d, *J* 8.0Hz, $(C\underline{H}_3)_2$CH-), 1.27 (3H, t, *J* 7.5Hz, C$\underline{H}_3CH_2O$-), 2.21 (3H, s, C$\underline{H}_3$CO-), 2.30-2.54 (1H, m, $(CH_3)_2C\underline{H}$-), 3.18 (1H, d, *J* 9.0Hz, C$\underline{H}(CO_2Et)$-), 4.18 (2H, q, *J* 7.5Hz, C$\underline{H}_2$O-); *m/z* (GCMS, C.I., NH_3) 190 (MNH_4^+, 59%), 173 (MH^+, 100), 127 (6), 100 (5), 58 (8).

2-(1'-Ethoxycarbonyl-2'-methylprop-1'-yl)-2-methyl-1,3-dioxolane **269**. A mixture of the β–ketoester (**268**, 5.0g, 29.1mmol), ethan-1,2-diol (2.02ml, 36.3mmol) and *p*-toluene-sulphonic acid (28mg, 0.15mmol) were heated at reflux, with vigorous stirring, in benzene (75ml) with removal of water (Dean-Stark trap) for 24h. The cooled solution was washed with saturated sodium hydrogen carbonate solution (2x10ml) then brine (10ml) and dried ($MgSO_4$). The solution was concentrated *in vacuo* to yield the ketal **269** as a pale yellow oil which required no further purification (6.26g, quantitative). $\nu_{max.}$ (thin film) 3040-2860 (s), 1735 (s), 1470 (s), 1380 (s), 1040 (s), 950 (m), 880 (m), 790 (m), 760 (m), 680 (m); δ_H (200 MHz) 0.93 (3H, d, *J* 6.5Hz) and 1.05 (3H, d, *J* 6.5Hz, $(C\underline{H}_3)_2$CH-), 1.29 (3H, t, *J* 6.5Hz, C$\underline{H}_3CH_2O$-), 1.51 (3H, s, 2-C$\underline{H}_3$-), 1.98-2.17 (1H, m, $(CH_3)_2C\underline{H}$-), 2.38 (1H, d, *J* 10.5Hz, C$\underline{H}(CO_2Et)$-), 3.87-4.06 (4H, m, -$OC_2\underline{H}_4O$-),

4.19 (2H, q, *J* 6.5Hz, $CH_3C\underline{H}_2O$-); *m/z* (GCMS, C.I., NH_3) 234 (MNH_4^+, 4%), 217 (MH^+, 100), 190 (8), 173 (10), 87 (66).

2-(1'-Hydroxy-3'-methylbut-2'-yl)-2-methyl-1,3-dioxolane **270**. To a suspension of lithium aluminium hydride (1.76g, 46.3mmol) in THF (150ml) at 0°C was added dropwise a solution of the ester (**269**, 5.0g, 23.2mmol) in THF (50ml). The reaction was allowed to warm slowly to room temperature and stirred for 20h then re-cooled to 0°C. Saturated sodium sulphate solution was added dropwise until the aluminium salts became white and settled to the bottom of the flask. The colourless organic layer was decanted then the residue diluted with water. The aqueous portion was extracted with ether (5x50ml) and these extracts combined with the decanted THF solution. The combined organic portions were washed with brine then dried ($MgSO_4$), filtered, and concentrated to yield the title compound **270** as a colourless oil (3.75g, 93%) which required no further purification. $\nu_{max.}$ (thin film) 3600-3200 (s), 2990-2840 (s), 1470 (m), 1380 (m), 1260 (m), 1165 (s), 1040 (s), 950 (m), 870 (m); δ_H (200 MHz) 0.90 (3H, d, *J* 6.5Hz) and 1.06 (3H, d, *J* 6.5Hz, $(C\underline{H}_3)_2CH$-), 1.37 (3H, s, 2-$C\underline{H}_3$-), 1.74 (1H, dt, *J* 8.0, 3.5Hz, $C\underline{H}(CH_2OH)$-), 1.84-2.04 (1H, m, $(CH_3)_2C\underline{H}$-), 3.19 (1H, dd, *J* 8.0, 2.5Hz, [?] O<u>H</u>), 3.57-3.83 (2H, m, $C\underline{H}_2OH$), 3.99 (4H, <u>ca</u>. s, $-OC_2\underline{H}_4O$-); *m/z* (GCMS, C.I., NH_3) 175 (MH^+, 6%), 145 (100), 118 (7), 87 (20).

3-(Bromomethyl)-4-methylpentan-2-one **271**. To a solution of the ketal (**270**, 2.0g, 11.5mmol) in dichloromethane (10ml) was added at 0°C phosphorous tribromide (0.4ml, 4.21mmol). The mixture was stirred for a further 45min at 0°C, allowed to room temperature, then quenched with water (5ml). The mixture was stirred a further 3h to ensure complete deprotection of the ketal, water (5ml) added and the aqueous layer extracted with ether (3x5ml). The combined organic portions were dried ($MgSO_4$), filtered, and concentrated to yield an oil which was subjected to flash chromatography (10:1 petrol: ether). The title compound **271** was obtained as a colourless oil (1.57g, 71%) which possessed limited stability at room temperature. $\nu_{max.}$ (thin film) 2960 (s), 2880 (m), 1715 (s), 1470 (m), 1425 (m), 1370 (m), 1270 (m), 1175 (m), 1045 (m), 950 (w); δ_H (200

MHz) 0.96 (6H, ca., t, *J* 6.5Hz, $(CH_3)_2CH$-), 1.86-2.05 (1H, m, $(CH_3)_2CH$-), 2.25 (3H, s, CH_3CO-), 2.84 (1H, ddd, *J* 11, 7.0, 4.0 Hz, $CH(CH_2Br)$-), 3.40-3.63 (2H, m, CH_2Br); *m/z* (GCMS, C.I., NH_3) 212 (MNH_4^+, ^{81}Br, 96%), 210 (MNH_4^+, ^{79}Br, 100), 166 (10), 130 (15), 113 (27), 70 (10), 58 (14).

1-Iodo-3-(iodomethyl)-4-methylpentan-2-one **262**. LDA prepared from di-isopropylamine (91µl, 0.65mmol) and ^{n}butyl lithium (336µl of a 1.54M solution in hexanes, 0.52 mmol) in THF (2ml) was cooled to -78°C and the ketone (**271**, 100mg, 0.52mmol) added. The solution was stirred for 1.5h at -78°C then trimethylsilyl chloride (99µl, 0.78mmol) added and the mixture allowed to room temperature. The solution was re-cooled to -78°C and a solution of bromine (30µl, 0.58mmol) in dichloromethane (0.5ml) was added dropwise. The mixture was allowed to attain room temperature over ca. 3h then all volatile components were removed *in vacuo*. Acetone (1ml) was added followed by sodium iodide (390mg, 2.6mmol) and the mixture stirred at 25°C for 16h. Water (5ml) was added and the aqueous layer extracted with ether (4x10ml). The combined organic portions were washed with sodium thiosulphate solution (10%, 6ml) then brine (6ml) and dried ($MgSO_4$). The filtered, concentrated residue was rapidly purified by flash chromatography (10:1 petrol:ether) to yield the title compound **262** as an unstable, light-sensitive colourless oil (160mg, 84% attempts to repeat this reaction on a larger scale met with significant reductions in the yield). $\nu_{max.}$ (thin film) 2960 (s), 2880 (s), 1730-1700 (s), 1465 (s), 1420-1360 (s), 1255 (m), 1190 (s), 1040 (m), 1020 (m), 940 (w); δ_H (200 MHz) 0.94 (3H, d, *J* 7.0Hz) and 1.02 (3H, d, *J* 7.0Hz, $(CH_3)_2CH$-), 1.90-2.15 (1H, m, $(CH_3)_2CH$-), 3.12-3.41 (3H, m, $CH(^iPr)CH_2I$), 3.97 and 4.04 (2H, ABq, *J* 12Hz, ICH_2CO-); *m/z* (GCMS, C.I., NH_3) 257 (MNH_4^+-I·, 15%), 132 (32), 130 (MNH_4^+-2I·, 100), 113 (MH^+-2I·, 88), 97 (15), 69 (19), 58 (25) - a small amount (ca. 5%) of the 1-bromide was also visible 338 (MNH_4^+, ^{81}Br, 7%), 336 (MNH_4^+, ^{79}Br, 8%), 212 (74), 210 (73), 130 (100), 113 (80), 97 (14), 69 (25), 58 (29).

4-Methyl-3-(phenylselenomethyl)-pentan-2-one **272**. Sodium phenylselenide (1.1 equiv.) was prepared by the procedure described above and was quenched with the bromide (**271**,

5.0g, 25.9mmol). After 5h at room temperature the solvent was removed and saturated sodium hydrogen carbonate solution added (100ml). The mixture was extracted with 1:1 petrol:ether (5x50ml) and the extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (15:1 petrol:ether) to yield the pure selenide **272** as a colourless oil (5.83g, 83%). $\nu_{max.}$ (thin film) 3060 (m), 2960 (s), 2870 (s), 1710 (s), 1575 (s), 1475 (s), 1435 (s), 1365 (s), 1170 (m), 1020 (s), 730 (s), 690 (s); δ_H (200 MHz) 0.93 (6H, ca., t, *J* 7.5Hz, $(C\underline{H}_3)_2CH$-), 1.85-2.06 (1H, m, $(CH_3)_2C\underline{H}$-), 2.17 (3H, s, $C\underline{H}_3CO$-), 2.68 (1H, ddd, *J* 10.5, 6.5, 4.5Hz, $C\underline{H}CH_2SePh$), 2.96-3.15 (2H, m, $C\underline{H}_2SePh$), 7.19-7.34 (3H, m, Ph- *m*- and *p*- protons), 7.43-7.55 (2H, m, Ph- *o*- protons); *m/z* (GCMS, C.I., NH_3) 288 (MNH_4^+, ^{80}Se, 100%), 286 (MNH_4^+, ^{78}Se, 51), 271 (MH^+, ^{80}Se, 44), 269 (MH^+, ^{79}Se, 25), 193 (16), 130 (75), 113 (47), 97 (44), 58 (19).

3-(Hydroxymethyl)-4-methylpentan-2-one **273**. A mixture of the ketal (**270**, 750mg, 4.31mmol), oxalic acid (1.74g, 13.8mmol), water (5ml) and dichloromethane (5ml) was stirred rapidly for 6h. The layers were partitioned and the aqueous layer extracted with ether (5x5ml), the extracts combined with the organic layer and the resultant solution washed with saturated sodium hydrogen carbonate solution (6ml) then brine (6ml). The solution was dried (Na_2SO_4), filtered, and concentrated to yield an oil which was subjected to flash chromatography (2:1 to 1:1 petrol:ether). The title compound **273** was obtained as a colourless oil (478mg, 85%). $\nu_{max.}$ (thin film) 3600-3200 (br, m), 2960 (s), 2880 (m), 1705 (s), 1470 (m), 1360 (m), 1170 (m), 1020 (m), 920 (w), 735 (s); δ_H (200 MHz) 0.91 (3H, d, *J* 6.5Hz) and 0.97 (3H, d, *J* 6.5Hz, $(C\underline{H}_3)_2CH$-), 1.95-2.16 (1H, m, $(CH_3)_2C\underline{H}$-), 2.22 (3H, s, $C\underline{H}_3CO$-), 2.56 (1H, ca. td, *J* 8.0, 4.0Hz, $C\underline{H}CH_2OH$), 3.72 (1H, dd, *J* 12, 4.0Hz) and 3.89 (1H, dd, *J* 12, 8.0Hz, $C\underline{H}_2OH$); 148 (MNH_4^+, 8%), 131 (14), 130 (42), 118 (100), 113 (22), 99 (62), 97 (48), 85 (18), 69 (13), 58 (37).

1-Bromo-4-methyl-3-(trimethylsilyloxymethyl)-pentan-2-one **274**. LDA (2.1 equiv.) was prepared, using the general procedure, in THF (30ml) and cooled to -78°C. The ketone (**273**, 450mg, 3.46mmol) was added and the mixture stirred for 1h after which time

trimethylsilyl chloride (1.32ml, 10.4mmol) was added and the solution allowed to room temperature. The reaction was re-cooled to -78°C and bromine (357µl, 6.92mmol) in dichloromethane (10ml) added dropwise. After allowing to warm to room temperature the solution was quenched with water (50ml) and the resultant mixture extracted with ether (4x20ml). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated; the resulting oil was purified by flash chromatography (100:1 to 20:1 petrol:ether) to yield the title compound **274** as a colourless oil (840mg, 86%). $\nu_{max.}$ (thin film) 2960 (s), 2880 (m), 1735 (m), 1720 (m), 1470 (m), 1390 (m), 1255 (s), 1095 (s), 870 (s), 845 (s), 750 (m); δ_H (200 MHz) 0.11 (9H, s, $(C\underline{H}_3)_3Si$-), 0.92 (6H, ca. t, *J* 6.5Hz, $(C\underline{H}_3)_2CH$-), 1.85-2.06 (1H, m, $(CH_3)_2C\underline{H}$-), 2.83 (1H, td, *J* 9.0, 5.5Hz, $C\underline{H}CH_2OTMS$), 3.59-3.85 (2H, m, $C\underline{H}_2OTMS$), 4.05 (2H, s, $C\underline{H}_2Br$); *m/z* (GCMS, C.I., NH_3) 300 (MNH_4^+, ^{81}Br, 4%), 298 (MNH_4^+, ^{79}Br, 4), 283 (MH^+, ^{81}Br, 7), 281 (MH^+, ^{79}Br, 7), 203 (100), 187 (9), 130 (13), 90 (31).

1-Iodopropan-2-ol **275**. A mixture of 1-bromopropan-2-ol (1g, 7.2mmol) and sodium iodide (2.16g, 14.4mmol) was stirred at room temperature in acetone (6ml) for 24h. The usual isolation procedure followed by flash chromatography (5:1 petrol:ether) afforded the title compound **275** as a colourless oil (993mg, 74% - reflects purity of starting material in this case). $\nu_{max.}$ (thin film) 3600-3100 (s), 2980 (m), 1455 (m), 1415 (m), 1375 (s), 1190 (s), 1125 (s), 1015 (s), 935 (m), 860 (w), 810 (w); δ_H (200 MHz) 1.32 (3H, d, *J* 6.5Hz, $C\underline{H}_3$-), 3.24 (1H, dd, *J* 11, 6.5Hz) and 3.36 (1H, dd, *J* 11, 4.0Hz, $C\underline{H}_2I$), 3.67-3.85 (1H, m, $C\underline{H}(OH)$-).

1-Iodo-2-trimethylsilyloxypropane **276**. To a solution of the alcohol (**275**, 800mg, 4.3mmol) in pyridine (8ml) was added at room temperature trimethylsilyl chloride (0.6ml, 4.7mmol) and stirring continued for 18h. The pyridine was removed *in vacuo* then the residue taken into petrol (25ml), filtered and concentrated. The product **276** was obtained as a colourless oil (556mg, 50% - competing epoxide formation?). $\nu_{max.}$ (thin film) 2960 (m), 1440 (m), 1375 (m), 1250 (s), 1140 (s), 1080 (s), 985 (m), 890 (m), 840 (s), 750 (m); δ_H (200 MHz) 0.14 (9H, s, $(C\underline{H}_3)_3Si$-), 1.27 (3H, d, *J* 6.5Hz, $C\underline{H}_3$-), 3.14 (2H,d, *J*

6.5Hz, $C\underline{H}_2I$), 3.76-3.93 (1H, m, $C\underline{H}$(OTMS)-); *m/z* (GCMS, C.I., NH_3) 259 (MH^+, 3%), 186 (7), 131 (6), 91 (17), 90 (100), 74 (4), 58 (4).

1-Iodo-2-methoxyhexane **277**. To a solution of 1-hexene (8.4g, 0.1mol) in methanol (84ml) was added mercuric acetate (30.6g, 96mmol) and the mixture heated at reflux for 10min. Aqueous potassium iodide (18.3g, 0.11mol in 36ml) was added and heating continued for 10min. The mixture was treated with iodine (28g, 0.11mol), the solution heated for 15min then, after cooling to room temperature, the solids were dissolved by the addition of aqueous potassium iodide (20g, 0.12mol in 100ml) and excess iodine removed by adding solid sodium thiosulphate in small portions. The mixture was extracted with ether (6x100ml), the combined extracts washed with brine (50ml) then dried ($MgSO_4$), filtered and concentrated to yield an oil (70g). 10g of the crude product was subjected to flash chromatography (4:1 petrol:ether) to yield the title compound **277** as a pale yellow oil (3.40g, - indicated total yield of 98%). $\nu_{max.}$ (thin film) 2950 (s), 2870 (s), 2820 (s), 1460 (m), 1180 (m), 1095 (s), 960 (w), 730 (w); δ_H (200 MHz) 0.92 (3H, t, *J* 6.5Hz, $C\underline{H}_3$-), 1.25-1.42 (4H, m, $C_2\underline{H}_4CH_3$), 1.52-1.65 (2H, m, $C\underline{H}_2CH$(OMe)-), 3.03 (1H, ca. quin., *J* 5.5Hz, $C\underline{H}$(OMe)-), 3.27 (1H, d, *J* 2.0Hz) and 3.30 (1H, d, *J* 2.5Hz, $C\underline{H}_2I$), 3.39 (3H, s, $C\underline{H}_3O$-); *m/z* (GCMS, C.I., NH_3) 260 (MNH_4^+, 17%), 228 (24), 185 (13), 118 (25), 115 (100), 102 (38), 101 (69), 100 (65), 86 (29), 58 (68).

trans-2-(2'-Methoxyhexyl)-2-methyl-3-tributylstannylcyclohexanone **278**. Tributylstannyl lithium (1.1 equiv.) in THF (5ml) was cooled to -78°C and the enone (**96**, 500mg, 4.55 mmol) added. Stirring was continued for 1h, the mixture warmed to -23°C, HMPA (6ml) and the iodide (1.32g, 5.45mmol) added, then the reaction allowed to warm to room temperature over 18h. The crude product was isolated as in the general procedure and purified by flash chromatography (100:1 to 10:1 petrol:ether) to give a range of minor unidentified compounds along with the title compound (**278**, 236mg, 10%) as a colourless oil. $\nu_{max.}$ (thin film) 2960 (s), 2930 (s), 2870 (m), 1705 (s), 1465 (m), 1380 (m), 1090 (m), 1020 (w), 870 (w); δ_H (200 MHz) 0.76-1.02 (18H, m, ($C\underline{H}_3C_2H_4C\underline{H}_2$-)$_3$Sn- and 6'-$C\underline{H}_3$-), 1.08 (3H, s, 2-$C\underline{H}_3$-), 1.20-2.09 and 2.12-2.80 (27H, complex m, ($CH_3C_2\underline{H}_4CH_2$-)$_3$Sn-,

$C_3\underline{H}_6C\underline{H}$(Sn-$Bu_3$)-, and $C_3\underline{H}_6CH(OMe)C\underline{H}_2$-), 3.04-3.21 (1H, m, C<u>H</u>(OMe)-), 3.10 (3H, s, $C\underline{H}_3O$-) peaks at δ 1.16 (3H, s) and 3.25 (3H, s), integrating to <u>ca</u>. 30% of the major peaks, indicated the presence of the minor diastereomer; *m/z* (C.I., NH_3) 517 (MH^+, ^{120}Sn, 100%), 515 (83), 513 (51), 459 (66), 427 (39), 308 (49), 291 (47), 224 (35), 193 (53), 138 (22), 101 (59).

3-Methyl-1-trimethylsilyloxybutane **279**[200]. Prepared by the method of Cazeau[200] as a mixture of configurational isomers. $\nu_{max.}$ (thin film) 3025 (m), 2960 (s), 2875 (m), 1655 (s), 1470 (m), 1405 (m), 1255 (s), 1165 (m), 1075 (s), 885 (s), 845 (s), 750 (m), 645 (m); δ_H (200 MHz) *E*-isomer: 0.19 (9H, s, $(C\underline{H}_3)_3Si$-), 0.96 (6H, <u>ca</u>. t, *J* 8.0Hz, $(C\underline{H}_3)_2CH$-), 2.12-2.36 (1H, m, $(C\underline{H}_3)_2CH$-), 4.99 (1H, dd, *J* 12, 8.0Hz, C(^{i}Pr-)<u>H</u>=), 6.20 (1H, d, *J* 12Hz, C(OTMS)<u>H</u>=). *Z*-isomer: 0.19 (9H, s, $(C\underline{H}_3)_3Si$-), 0.96 (6H, <u>ca</u>. t, *J* 8.0Hz, $(C\underline{H}_3)_2CH$-), 2.68-2.90 (1H, m, $(C\underline{H}_3)_2CH$-), 4.38 (1H, dd, *J* 9.0, 5.5Hz, C(^{i}Pr-)<u>H</u>=), 6.05 (1H, d, *J* 12Hz, C(OTMS)<u>H</u>=); *m/z* (GCMS, C.I., NH_3) 159 (MH^+, 29%), 143 (16), 90 (100).

Ethyl 2-ethoxycarbonyl-3-methyl-butanoate **280**. A mixture of diethyl malonate (16g, 0.1mol), potassium carbonate (21g, 0.15mol), and 2-iodopropane (11ml, 0.11mol) were heated at 90°C for 18h. The volatile components were removed *in vacuo* then ether (250ml) added, the solids filtered off and the solvent removed. The crude product was distilled (100-104°C) to yield the title compound **280** as a colourless oil (17.4g, 86%). $\nu_{max.}$ (thin film) 2980 (s), 1755 (s), 1735 (s), 1470 (m), 1370 (s), 1305 (s), 1240-1110 (m), 1095 (m), 1035 (s); δ_H (200 MHz) 1.02 (6H, d, *J* 6.5Hz, $(C\underline{H}_3)_2CH$-), 1.28 (6H, t, *J* 7.0Hz, 2x $C\underline{H}_3CH_2O$-), 2.28-2.53 (1H, m, $(CH_3)_2C\underline{H}$-), 3.12 (1H, d, *J* 8.0Hz, C<u>H</u>$(CO_2Et)_2$-), 4.22 (4H, q, *J* 7.0Hz, $C\underline{H}_2O$-); *m/z* (GCMS, C.I., NH_3) 220 (MNH_4^+, 20%), 203 (MH^+, 100), 160 (6).

2-(Hydroxymethyl)-3-methylbutan-1-ol **281**. To a suspension of lithium aluminium hydride (3.04g, 80mmol) in THF (150ml) at 0°C was added a solution of the ester (**280**, 4.04g, 20mmol) in THF (50ml). The mixture was stirred for 24h during which time the

temperature was allowed to reach ambient then re-cooled to 0°C. Saturated sodium sulphate solution was added dropwise until the aluminium salts became white and separated out. The colourless organic layer was decanted and combined with ether extracts (6x50ml) of the residue. The combined organic portions were washed with brine (100ml), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (10:1 ether:petrol) to yield the title compound **281** as a colourless oil (1.97g, 83%). $\nu_{max.}$ (thin film) 3700-3050 (s), 2960 (s), 1470 (s), 1390 (s), 1370 (s), 1100-990 (s), 980 (m), 920 (w), 735 (w); δ_H (200 MHz) 0.91 (6H, d, *J* 6.5Hz, $(C\underline{H}_3)_2CH$-), 1.46-1.62 (1H, m, $(CH_3)_2C\underline{H}$-), 1.65-1.83 (1H, m, $C\underline{H}(CH_2OH)_2$), 3.66-3.93 (4H, m, $2xC\underline{H}_2OH$); *m/z* (E.I.) 118 (M^+, 15%), 100 (100), 97 (21), 70 (33).

3-Methyl-2-(trimethylsilyloxymethyl)-butan-1-ol **282**. A mixture of the diol (**281**, 1.0g, 8.6mmol) and trimethylsilyl chloride (1.1ml, 8.64mmol) were stirred in pyridine (10ml) for 48h. Most of the pyridine was removed *in vacuo* and the residue distilled (short path) to give a forerun of the di-protected compound (**283**, ca. 100mg) $\nu_{max.}$ (thin film) 2960 (s), 2880 (s), 1470 (m), 1395 (m), 1250 (s), 1150-1050 (s), 1020 (s), 890-810 (s), 745 (m), 685 (m); δ_H (200 MHz) 0.00 (18H, s, $2x(C\underline{H}_3)_3Si$-), 0.82 (6H, d, *J* 7.5Hz, $(C\underline{H}_3)_2CH$-), 1.25-1.42 (1H, m, $(CH_3)_2C\underline{H}$-), 1.61-1.83 (1H, m, $C\underline{H}(CH_2OTMS)_2$), 3.40-3.58 (4H, m, $2xC\underline{H}_2OTMS$); *m/z* (GCMS, C.I., NH_3) 263 (MH^+, 100%), 164 (10), 129 (13), 90 (55), 74 (10), 58 (9) and the required mono-protected diol (**282**, bath temperature 75°C/14mmHg, 1.21g, 74%), a colourless oil. $\nu_{max.}$ 3600-3050 (s), 2960 (s), 2880 (s), 1470 (m), 1390 (m), 1370 (m), 1255 (s), 1100-1000 (s), 845 (s), 755 (m); δ_H (200 MHz) 0.11 (9H, s, $(C\underline{H}_3)_3Si$-), 0.86-0.99 (6H, m, $(C\underline{H}_3)_2CH$-), 1.36-1.92 (2H, m, $(CH_3)_2C\underline{H}C\underline{H}R_2$), 3.47-3.67 (2H, m, $C\underline{H}_2OTMS$), 3.70-3.95 (2H, m, $C\underline{H}_2OH$); *m/z* (GCMS, C.I., NH_3) 191 (MH^+, 100%), 173 (11), 98 (49), 92 (60), 91 (61), 90 (75), 75 (43), 74 (54), 58 (37).

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