Tetrahedron Vol. 47, No. 33, pp. 6795-6812, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

Carbocyclic Ring Expansion Reactions *via* Radical Chain Processes. Part II.

Jack E. Baldwin*, Robert M. Adlington, and Jeremy Robertson.

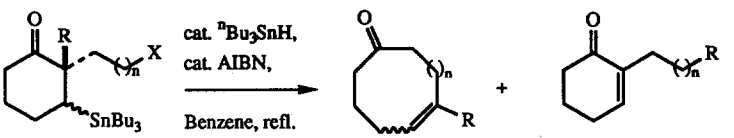
The Dyson Perrins Laboratory, University of Oxford,
South Parks Road, Oxford, OX1 3QY.

(*Received in UK* 17 *May* 1991)

Key Words: ring expansion; homolytic; tributylstannane derivatives; cycloalkanone; rearrangement.

Abstract: *The further exploitation of the homolytic ring expansion reaction of cyclohexanone derivatives[1] is described. The application of this methodology to the preparation of exomethylene cycloalkanones, α-alkylated cyclodecanones, indanones, and decalinols is described.*

We have recently reported a novel method for the homolytic ring expansion of a number of cyclohexanone derivatives by one, three, and four carbon atoms to provide, respectively, seven, nine, and ten membered cycloalkenones with defined olefin geometry[1] (Scheme 1).

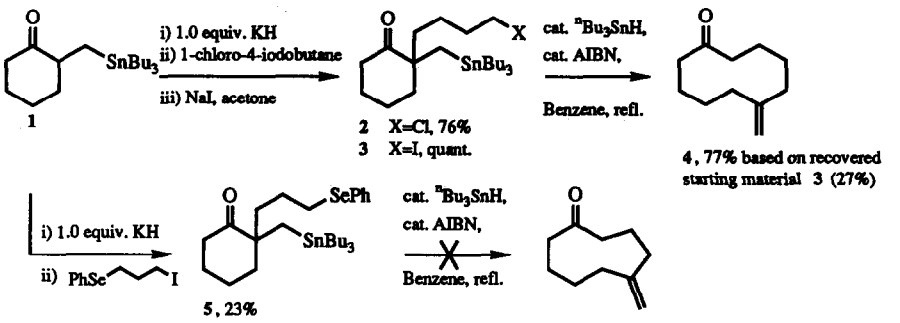


Scheme 1

In this report we wish to discuss results of some further studies in this area in which we have varied i) the relative disposition of the tributylstannyl substituent and the radical-carrying side-chain, ii) the structure of the cyclohexyl ring precursor, and iii) the nature of the side-chain radical.

i) Variation of the relative disposition of the tributylstannyl group and the radical-carrying side-chain.

In our previous work[1], all ring expansion precursors have possessed a 2-alkyl radical-carrying side-chain and a 3-tributylstannyl substituent which resulted in the formation of cycloalkenones with the double bond *endo-* to the ring. To access cyclic molecules with *exo-* situated double bonds an alternative arrangement of the substituents in the precursor was required. Alkylation of 2-(tributylstannylmethyl)-cyclohexanone **1**[2] with 1-chloro-4-iodobutane, using 1.0 equiv. potassium hydride as the base in THF at room temperature (allowing 1h for deprotonation and enolate equilibration), followed by Finkelstein reaction[3] afforded the 2,2-disubstituted precursor **3** in reasonable yield. This compound underwent slow ring expansion to the desired *exo*-methylene compound **4**[4] in 77% yield (based on recovered starting material **3**) (Scheme 2).



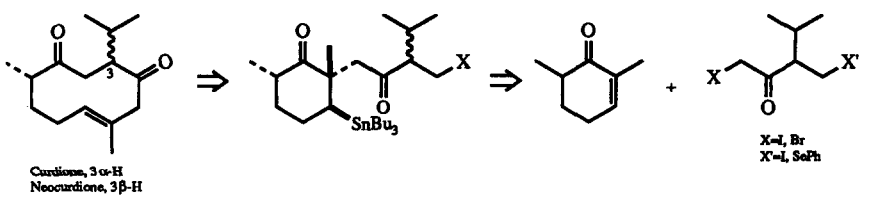
Scheme 2

Scheme 2 also shows that, although alkylation of ketone **1** with 1-iodo-3-phenylselenopropane[1] was possible, the yield of alkylated material **5** was extremely poor. In any case, compound **5** subsequently failed to undergo homolytic ring expansion, products arising from elimination of the phenylselenyl residue and decomposition being obtained instead.

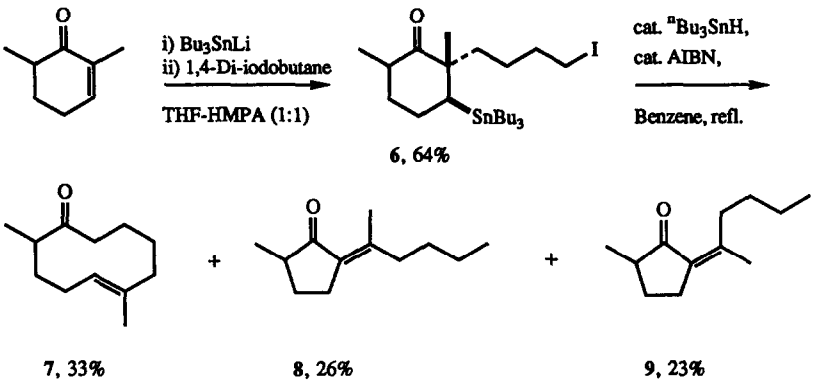
ii) Variation of cyclohexyl ring structure.

a) Preparation and homolytic reaction of a 2,2,6-trialkyl-substituted cyclohexanone derivative.

With the application of this homolytic ring expansion methodology to natural product synthesis in mind (e.g. curdione and neocurdione[5], Scheme 3), we required, as a model, information on the reactivity of substrates possessing more sterically hindered carbonyl groups in potential ring expansion reactions. Towards this end the 1,4-addition[6] of tributylstannyl lithium to 2,6-dimethylcyclohex-2-enone[7] followed by enolate alkylation with 1,4-di-iodobutane[1] was carried out to provide the ring expansion precursor **6** in 64% yield. This substrate was obtained as a single diastereomer with the presumed relative configuration shown (Scheme 4) based on our previous results[1]. On heating a 5mmolar solution of substrate **6**, in benzene in the presence of catalytic quantities of AIBN and tributyltin hydride for 72h, the starting material was consumed to provide three compounds **7**, **8**, and **9** in isolated yields of 33, 26, and 23% respectively (Scheme 4).

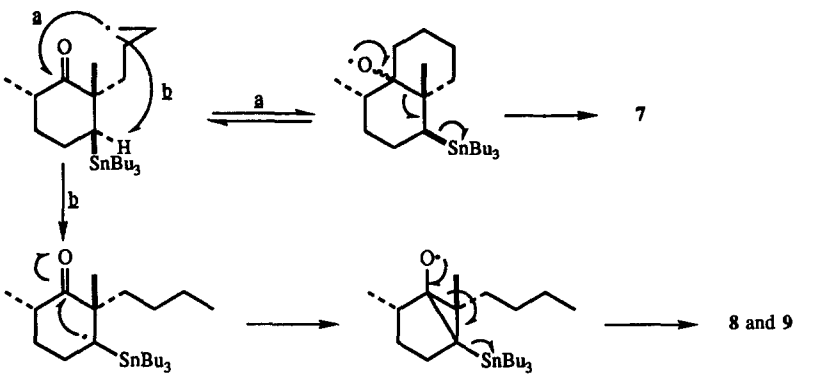


Scheme 3



Scheme 4

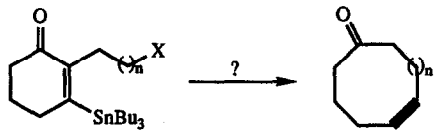
Although this reaction was successful, resulting in some formation of the desired product **7** (pathway a), the competing production of ring contracted enones **8** and **9** was not predicted. These compounds would appear to arise from hydrogen atom abstraction α- to the tributylstannyl group followed by transannular cyclisation and fragmentation of the so-formed bicyclic radical (pathway b). The presence of the 6-methyl substituent is apparently sufficient to render the carbonyl group less sterically available to the 1° radical which is then capable of alternative reaction (Scheme 5).



Scheme 5

b) Indanones from attempted routes to cycloalkynones.

To investigate further the applicability of this methodology towards medium ring synthesis we proposed to access cycloalkynones (currently produced by such procedures as the Eschenmoser fragmentation[8]) which required the synthesis and subsequent ring expansion of cyclohex-2-enone substrates of the type **10** (Scheme 6).

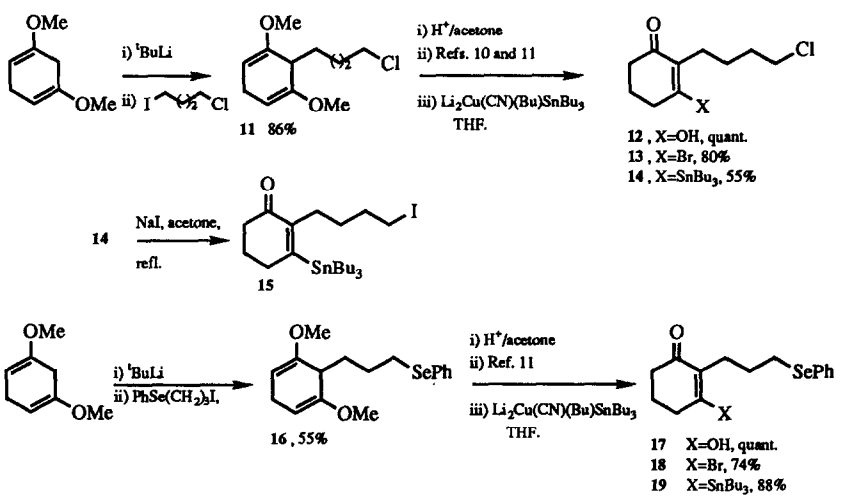


10

X=I, SePh
n=2, 3

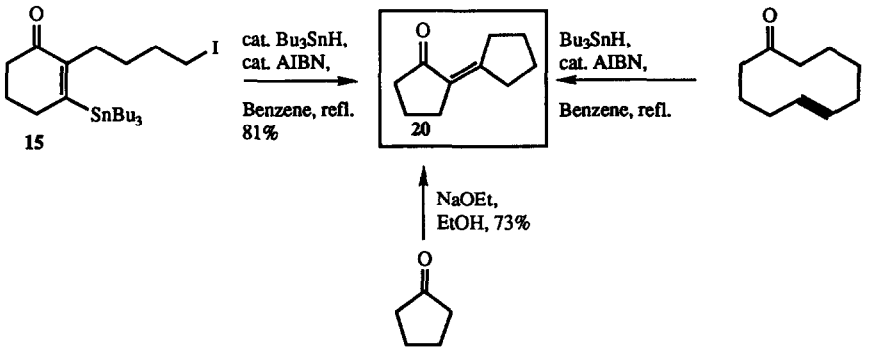
Scheme 6

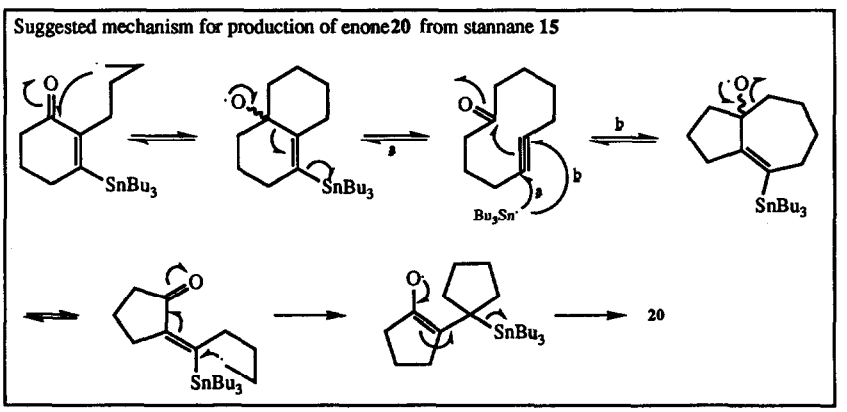
The most direct route to such precursors was envisaged to be *via* 2-alkylation of cyclohexane-1,3-dione, with a suitably functionalised electrophile, followed by conversion of the enol moiety to a vinyl stannane function. The initial preparation of the 2-alkylated cyclohexane-1,3-diones was achieved using the procedure of Piers[9] which employs 2,4-dimethoxycyclohexa-1,4-diene as the dione equivalent thus circumventing the well documented problems of *O*-alkylation associated with direct alkylation of cyclic 1,3-diones. Minor modifications (dispensation of HMPA in the solvent mixture and a lower alkylation temperature of -100°C) of Piers' protocol for alkylation of this diene allowed the preparation of alkylated diene **11**, in high yield, which was hydrolysed to the dione **12** using aqueous hydrochloric acid in degassed acetone. This was converted to the corresponding bromo-enone **13** using either triphenylphosphine dibromide[10] or the Vilsmeier reagent derived from oxalyl bromide and DMF[11], the latter providing generally higher yields. Finally, 1,4-addition of the tributylstannyl group followed by elimination of the bromide was effected using the cuprate reagent $Li_2Cu(CN)(Bu)SnBu_3$[12] to give vinyl stannane **14**. Compound **14** was converted to the corresponding iodide **15** *via* Finkelstein reaction[3]. The synthetic series was repeated using 1-iodo-3-phenylselenopropane[1] as the electrophile in the initial diene alkylation step to access a three carbon side-chain analogue to stannane **15**. The subsequent steps to stannane **19** paralleled those used in the preparation of stannane **14** (Scheme 7).



Scheme 7

Exposure of substrate **15** to thermal homolysis conditions resulted in the formation of an unexpected product **20**, the structure of which was established by comparison of its spectroscopic (^1H and ^{13}C n.m.r., i.r., and mass spectrum) properties with those of genuine material produced by aldol reaction of cyclopentanone[13]. Interestingly, this enone could also be produced by the isomerisation of cyclodec-5-ynone (obtained using the procedure of Eschenmoser[8]) under homolytic conditions (0.1-1.0 equiv. tributyltin hydride, cat. AIBN, benzene refl.) suggesting the possible intermediacy of the alkynone in the radical reaction of stannane **15** (Scheme 8). The addition-elimination step, which results in the formation of the five-membered ring, is analogous to the reaction developed by Baldwin and Kelly for the direct acrylation of alkyl halides[14].

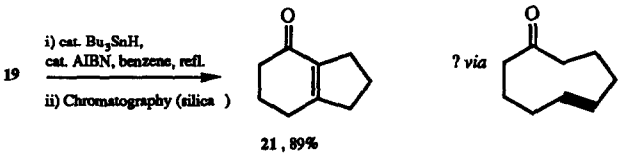




Scheme 8

Substrate **19** did not, however, afford an analogous product, instead chromatography (SiO_2) of the crude residue resulted in the isolation of the indanone derivative **21** in high yield. Comparison of the ^1H n.m.r. spectra of the isolated product and of the total crude residue, directly after removal of the solvent, revealed distinct discrepancies in both the form and chemical shift of the resonances above 2.0 p.p.m. In the light of the known[15] isomerisation of cyclonon-5-ynone to indanone derivative **21** on silica or alumina it is suggested that this cycloalkynone *is* initially produced but isomerises to the isolated product during purification by chromatography. Unfortunately, the literature data for the alkynone was not of sufficient quality to allow this

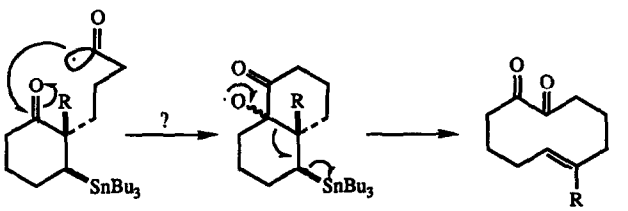
suggestion to be fully substantiated and attempts to distil the product directly from the crude product met with extensive decomposition; that distillate which was obtained consisted largely of compound **21** (Scheme 9).



Scheme 9

iii) Variation of the side-chain radical.

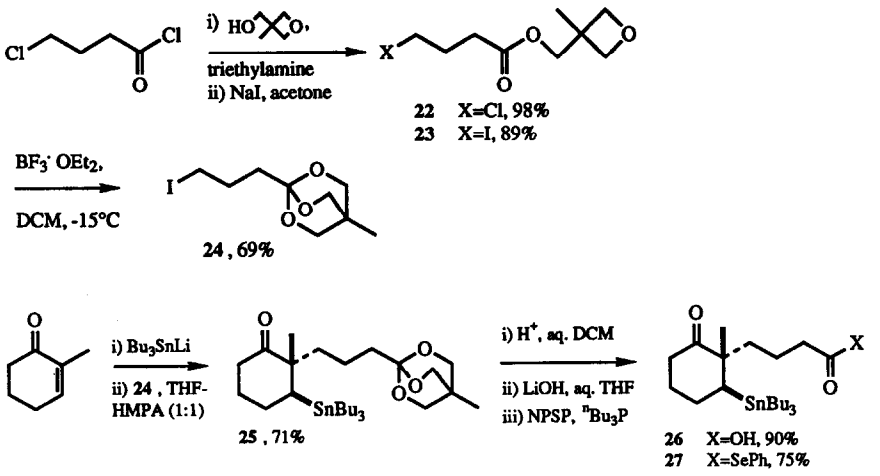
In an approach to the less common medium ring 1,2-diones it was envisaged that the initial production and cyclisation of an acyl radical onto the carbonyl group, followed by further fragmentation, would offer a plausible route to compounds of this type (Scheme 10).



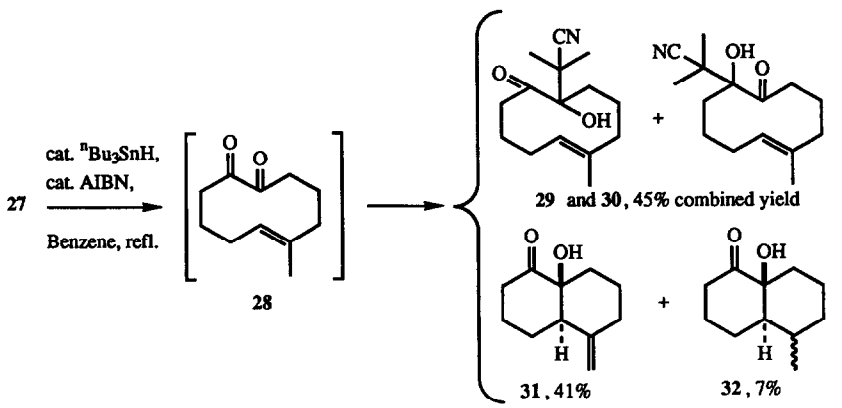
Scheme 10

The chosen acyl radical precursor, an acyl selenide[16], was synthesised from 4-chlorobutyryl chloride using Corey's orthoester methodology for the protection of the carboxyl function[17] during the alkylation step. 1,4-addition of tributylstannyl lithium to 2-methylcyclohex-2-enone[18] followed by enolate alkylation with iodide **24** proceeded efficiently to yield the protected precursor **25**. This was deprotected in two steps to carboxylic acid **26** and converted to the corresponding acyl selenide **27**, in high yield, using *N*-phenylselenophthalimide (NPSP) and tributyl phosphine[19] (Scheme 11).

Substrate **27** was found to be reactive to the general radical reaction conditions, heating for 16h in benzene resulted in complete consumption of the starting material with the production of four compounds **29-32** all of which can be rationalised as being derived from a first formed 1,2-dione **28**. Compounds **29** and **30**, an inseparable mixture, arose from addition of isobutyronitrile radical to either of the carbonyl goups of the desired medium ring 1,2-dione **28**. Compound **31** can be rationalised by intramolecular ene reaction – this reaction being analogous to the work of Wender[20] and Lange[21] in which *trans*- decalinols were obtained directly from fragmentation of precursors to cyclodecenone derivatives. The formation of compound **32** probably occurs by transannular hydrostannation (from the catalytic (ca. 10%) tributyltin hydride used to initiate the reaction) followed by hydrolysis of the Sn-O bond during chromatography on silica (Scheme 12).



Scheme 11



Scheme 12

Summary.

We have shown that the application of the methodology developed in our earlier report[1] can be extended to more demanding substrates. Of critical importance in the success of potential homolytic ring expansion reactions of this type is the steric availability of the cyclohexanone carbonyl group as exemplified by the co-formation of the ring contracted cyclopentanones **8** and **9** in addition to the desired cyclodecanone **7** from the 2,2,6-trialkyl-substituted cyclohexanone **6**. The stability of the desired products to the conditions required for ring expansion has bearing on the synthetic utility of the ring expansion process since although in all cases we have demonstrated the ring expansion process to be successful further reaction may ensue resulting in unpredicted compounds. Synthetically useful compounds may, however, be obtained in specific cases as

exemplified by the formation of the exomethylene cycloalkanone **4** and the decalinol derivative **31**, neither of which are as readily available from existing synthetic procedures.

Experimental.

Infrared (i.r.) spectra were obtained using a Perkin-Elmer 681 spectrometer. Nuclear magnetic resonance (n.m.r.) spectra were obtained using Varian Gemini 200 or Brüker AM 500 machines and were run in $CDCl_3$. Chemical shifts are quoted in parts per million (δ p.p.m.) using residual chloroform as an internal reference. Coupling constants (*J*) are quoted to the nearest 0.5Hz. Mass spectra were recorded on a V.G. Micromass 30F (E.I./C.I.), a V.G. Micromass ZAB 1F (E.I./C.I./F.D.) or a V.G. Trio-1 system (GCMS). Microanalyses were performed in the Dyson Perrins Laboratory.

All solvents were distilled before use; tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl, hexamethylphosphoric triamide (HMPA) from calcium hydride. 'Petrol' refers to that fraction of light petroleum ether boiling between 30-40°C. Other reagents were used as obtained from the manufacturers.

2-(4'-Chlorobutyl)-2-(tributylstannylmethyl)-cyclohexanone **2**. 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 (**1**[2], 500mg, 1.25mmol) was added as a solution in THF (2ml) and the mixture stirred at room temperature for 1h 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 (**2**, 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, ($CH_3C_2H_4CH_2$-)$_3$Sn-), 1.12-1.61 and 1.67-1.95 (26H, complex m, ($CH_3C_2H_4CH_2$-)$_3$Sn-, CH_2SnBu_3, $C_3H_6CH_2Cl$, and $C_3H_6CH_2CO$-), 2.33-2.45 (2H, m, CH_2CO-), 3.55 (2H, t, *J* 6.5Hz, CH_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 **3**. Sodium iodide (0.55g, 3.67 mmol) was dissolved in the minimum quantity of acetone (ca. 5ml) and the chloride (**2**, 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 (**3**, 355mg, quant.) which was a colourless oil requiring no further purification at this stage. (Found: C, 47.19; H, 8.04. $C_{23}H_{45}IOSn$ requires C, 47.37; H, 7.78%); $\nu_{max.}$ (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).

Ring expansion of stannane **3**. A mixture of stannane **3** (237mg, 0.51mmol), AIBN (0.2equiv.) and tributylstannane (0.1equiv.) was heated at reflux in degassed benzene. 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 (**3**, 81mg, 27%) and the isolation of the required ring expanded compound *6-methylenecyclodecanone*[4] (**4**, 47mg, 56%), a waxy solid, m.p. 29-31°C (lit.,[4] 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, $C\underline{H}_2C(=CH_2)C\underline{H}_2$-), 2.49 (4H, ca. t, *J* 8.0Hz, $C\underline{H}_2COC\underline{H}_2$-), 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).

2-(3'-Phenylselenopropyl)-2-(tributylstannylmethyl)-cyclohexanone **5**. Use of the alkylation procedure used for the preparation of **2** but with 1-iodo-3-phenylselenopropane (1.1 equiv.) as the alkylating agent on a 0.25mmol scale led to the formation of a mixture of products. The requisite compound **5** was obtained in low yield (34mg, 23%). (Found: C, 56.39; H, 8.32. $C_{28}H_{48}OSeSn$ requires C, 56.21; H, 8.09%); $\nu_{max.}$ (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, $(C\underline{H}_3C_2H_4C\underline{H}_2)_3Sn$-), 1.09-1.96 (24H, m, $C_2\underline{H}_4CH_2SePh$, $C\underline{H}_2Sn(CH_2C_2\underline{H}_4CH_3)_3$, and $C_3\underline{H}_6CH_2CO$-), 2.36 (2H, t, *J* 6.5Hz, $C\underline{H}_2CO$-), 2.89 (2H, t, *J* 6.5Hz, $C\underline{H}_2SePh$), 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).

trans-2,6-Dimethyl-2-(4'-iodobutyl)-3-tributylstannylcyclohexanone **6**. Tributylstannyl lithium (1.1 equiv.) in THF (8ml) was prepared by the general procedure described in reference 1 and cooled to -78°C. 2,6-Dimethylcyclohex-2-enone[7] (500mg, 4.03mmol) was added and stirring continued for 1h before allowing the mixture to -23°C. HMPA (8.5ml) and 1,4-di-iodobutane (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 **6** as a colourless oil (1.54g, 64%). (Found: C, 48.57; H, 8.09. $C_{24}H_{47}IOSn$ requires C, 48.27; H, 7.93%); $\nu_{max.}$ (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, $(C\underline{H}_3C_2H_4C\underline{H}_2$-$)_3Sn$- and 6-$C\underline{H}_3$-), 1.17 (3H, s, 2-$C\underline{H}_3$-), 1.20-1.59 (16H, m, $(CH_3C_2\underline{H}_4CH_2$-$)_3Sn$- 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·, ^{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 **6**. A mixture of the stannane (**6**, 100mg, 0.17mmol), AIBN (1mg, cat.) and tributyltin hydride (2µl, cat.) were heated at reflux in degassed benzene (35ml) for a total of 72h with

periodic additions of AIBN (1mg) and tributyltin hydride (2μl). 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* (**8**, 8mg, 26%) and *Z-2-hex-2'-ylidene-5-methylcyclopentanone* (**9**, 7mg, 23%), both fragrant, colourless oils. For **8** $\nu_{max.}$ (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<u>H</u>3-), 1.12 (3H, d, *J* 7.0Hz, 5-C<u>H</u>3-), 1.22-1.58 (6H, m, C<u>H</u>2CH(CH3)- and C2<u>H</u>4CH3), 2.03-2.73 (3H, m, C<u>H</u>(CH3)CO- and C<u>H</u>2C(CH3)=), 2.12 (2H, t, *J* 7.5Hz, C<u>H</u>2C(CO-)=), 2.21 (3H, s, C<u>H</u>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., NH3) 198 (MNH_4^+, 6%), 181 (MH^+, 100), 179 (10), 138 (11). For **9** $\nu_{max.}$ (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<u>H</u>3-), 1.11 (3H, d, *J* 7.0Hz, 5-C<u>H</u>3-), 1.26-1.53 (6H, m, C2<u>H</u>4CH3 and C<u>H</u>2CH(CH3)-), 1.84 (3H, s, C<u>H</u>3CR=), 2.06-2.64 (4H, m, C<u>H</u>2C(CO-)=C(CH3)C<u>H</u>2-), 2.72 (1H, <u>ca</u>. t, *J* 7.0Hz, C<u>H</u>(CH3)CO-); *m/z* (GCMS, C.I., NH3) 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* (**7**, 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<u>H</u>3-), 1.46-1.77 (4H, m, C(8)<u>H</u>2C(9)<u>H</u>2-), 1.70 (3H, s, C<u>H</u>3CR=), 1.85-2.44 (9H, m, C2<u>H</u>4C<u>H</u>(CH3)CO-, C<u>H</u>2CO-, and C<u>H</u>2C(CH3)=), 4.88-5.04 (1H, m, C<u>H</u>=); *m/z* (GCMS, C.I., NH3) 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 (**6**, 0.34 and 0.84mmol); in both cases approximately the same ratio of products was visible in the crude ^{1}H n.m.r. spectrum.

General procedure for the alkylation of 2,4-dimethoxycyclohexa-1,4-diene. To a solution of 2,4-dimethoxycyclohexa-1,4-diene (1.0 equiv.) in THF (<u>ca</u>. 10ml/mmol) at -78°C was added dropwise ^{t}butyl lithium (1.5 equiv. of a 1.7<u>M</u> 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 (<u>ca</u>. 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 **11**. 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<u>H</u>2C2H4Cl), 1.65-1.82 (4H, m, C<u>H</u>2CH2C<u>H</u>2CH2Cl), 2.77-2.86 (2H, m, C<u>H</u>2CH=), 2.90-3.02 (1H, m, C(3)<u>H</u>-), 3.52 (2H, t, *J* 7.5Hz, C<u>H</u>2Cl), 3.56 (6H, s, 2xC<u>H</u>3-), 4.74 (2H, t, *J* 4.0Hz, 2xC<u>H</u>=); *m/z* (GCMS, C.I., NH3) 231 (MH^+, ^{37}Cl, 32%), 229 (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 in degassed acetone (10ml/mmol diene) at room temperature was added hydrochloric acid (1.1 equiv. of a 1M solution) and the mixture stirred for a further 4h. The acetone was removed *in vacuo*, the residue added to brine (ca. 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 **12**. Obtained from the diene **11** 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, $CH_2C_2H_4Cl$), 1.67-1.86 (2H, m, CH_2CH_2Cl), 1.88-2.07 (2H, m, CH_2CH_2CO-), 2.33-2.48 (2H, m, *J* 6.5Hz, $CH_2C_3H_6Cl$), 2.48 (4H, t, *J* 6.5Hz, 2xCH_2CO-), 3.54 (2H, t, *J* 7.5Hz, CH_2Cl[) increased complexity in the spectrum and a signal at δ 3.43, due to C(2)H-, indicated the presence of the diketo-tautomer]; *m/z* (GCMS, C.I., NH_3) 167 (M^+-Cl·, 100%), 153 (35), 151 (17), 138 (6).

General procedure for the bromination of the cyclohexane-1,3-dione derivatives. Method 1[10]: To an ice cold solution of triphenyl phosphine (1.1 equiv.) in benzene (5ml/mmol) was added a 1M solution of bromine (1.1 equiv.) in benzene. To the resulting yellow suspension was added successively triethylamine (1.1 equiv.) and the dione derivative. The mixture was stirred at room temperature for 3h then the solution filtered through a plug of silica, the residue being washed thoroughly with ether. The combined filtrates were concentrated *in vacuo* and the crude products purified as detailed below.
Method 2[11]: To a mixture of the dione derivative, DMF (1.3 equiv.) and dichloromethane (5ml/mmol) at 0°C was added oxalyl bromide (1.2 equiv.) over 5min. The reaction mixture was allowed to warm to room temperature and the whole stirred for a further 0.5h. Ether (4x the volume of dichloromethane used) and water (2x the volume of dichloromethane) were added and the mixture stirred for 5min. The organic layer was separated, dried ($MgSO_4$), and concentrated to produce the crude bromo-enones which were purified as detailed below.

3-Bromo-2-(4'-chlorobutyl)-cyclohex-2-enone **13**. Prepared in 42% yield (Method 1 in the general procedure) from the dione (**12**, 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 (ca. 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,

$CH_2C_3H_6Cl$), 1.79 (2H, ca. quin., CH_2CH_2Cl), 2.02 (2H, ca. quin.) and 2.38-2.55 (4H, m, $CH_2C_3H_6Cl$ and C_2H_4CO-), 2.91 (2H, t, $CH_2C(Br)$=), 3.56 (2H, t, CH_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).

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 (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 were purified as described below.

2-(4'-Chlorobutyl)-3-tributylstannylcyclohex-2-enone **14**. Obtained from bromo-enone **13** in 55% yield (0.19mmol scale) as a colourless oil after flash chromatography (20:1 petrol:ether). The ^1H 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, $(CH_3C_3H_6$-$)_3Sn$-), 1.01 (6H, t, *J* 8.0Hz, $(C_3H_7CH_2$-$)_3Sn$-), 1.21-1.60 (14H, m, $(CH_3C_2H_4CH_2$-$)_3Sn$- 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-(4'-Iodobutyl)-3-tributylstannylcyclohex-2-enone **15**. A mixture of the chloride (**14**, 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 **15** 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, $(CH_3C_3H_6$-$)_3Sn$-), 1.02 (6H, t, *J* 8.0Hz, $(C_3H_7CH_2$-$)_3Sn$-), 1.22-1.73 (14H, m, $(CH_3C_2H_4CH_2$-$)_3Sn$- and $CH_2C_2H_4I$), 1.77-2.02 (4H, m, CH_2CH_2I and CH_2CO-), 2.14-2.29 (2H, m, $CH_2C(CO$-$)$=), 2.39 (2H, t, *J* 7.0Hz) and 2.49 (2H, t, *J* 7.0Hz,

CH_2CO- and $CH_2C(SnBu_3)$=), 3.20 (2H, t, *J* 6.5Hz, CH_2I); *m/z* (D.C.I., NH_3) 569 (MH^+, ^{120}Sn, 100%), 567 (78), 565 (44), 512 (M^+-^{n}Bu·, 25), 151 (40).

2,4-Dimethoxy-(3'-phenylselenopropyl)-cyclohexa-2,4-diene **16**. Using the general alkylation procedure described above with 1-iodo-3-phenylselenopropane (1.1 equiv.) the title compound **16** 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, CH_2CH_2SePh), 1.74-1.89 (2H, m, CH_2CHR-), 2.70-2.98 (5H, m, CH_2CH=, CHR-, and CH_2SePh), 3.51 (6H, s, 2xCH_3-), 4.68 (2H, t, *J* 4.0Hz, 2xCH=), 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 **17**. The title compound, prepared using the general hydrolysis procedure, 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, ca. quin., *J* 6.5Hz, CH_2CH_2SePh), 1.97 (2H, ca. quin., *J* 6.5Hz, CH_2CH_2CO-), 2.43 (4H, t, *J* 6.5Hz, CH_2CO- and $CH_2C(CO$-)=), 2.55-2.69 (2H, m, $CH_2C(OH)$=), 2.93 (2H, t, *J* 6.5Hz, CH_2SePh), 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 ($CH(CO$-$)_2$-); *m/z* (GCMS, E.I.) 310 (M^+, 11%), 153 (M^+-PhSe·, 100), 136 (27), 110 (4).

3-Bromo-2-(3'-phenylselenopropyl)-cyclohex-2-enone **18**. Prepared by Method 2 of the general bromination procedure given above. The title compound was obtained in 74% yield (over two steps from the diene **16**, 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., CH_2CH_2SePh), 2.02 (2H, quin., CH_2CH_2CO-), 2.46 (2H, t, $CH_2C(CO$-)=), 2.57 (2H, t, CH_2CO-) the preceding resonances displayed coupling constants of 7.0Hz, 2.82-3.01 (4H, m, CH_2SePh and $CH_2C(Br)$=), 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 **19**. Using the general procedure given above, from the bromo-enone (**18**, 425mg, 1.14mmol), the vinyl stannane **19** was prepared as a colourless oil after flash chromatography (25:1 to 5:1 petrol:ether) (586mg, 88%). (Found: C, 55.59; H, 7.87. $C_{27}H_{44}OSeSn$ requires C, 55.69; H, 7.62%); $\nu_{max.}$ (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, ($CH_3C_3H_6$-)$_3$Sn-), 0.98 (6H, t, *J* 8.0Hz, ($C_3H_7CH_2$-)$_3$Sn-), 1.18-1.58 (12H, m, ($CH_3C_2H_4CH_2$-)$_3$Sn-), 1.67-2.02 (4H, m, CH_2CH_2CO- and CH_2CH_2SePh), 2.21-2.51 (6H, m, CH_2CO-, $CH_2C(SnBu_3)$=, and $CH_2C(CO$-)=), 2.91 (2H, t, *J* 8.0Hz, CH_2SePh), 7.18-7.32 (3H, m, Ph- *m*- and *p*- protons), 7.43-7.53 (2H, m, Ph- *o*- protons); *m/z* (E.I.) 527 (M^+-^{n}Bu·, $^{80}Se^{120}Sn$, 92%), 525 (100), 523 (77), 427 (19), 293 (22), 137 (50), 91 (17), 79 (29).

2-Cyclopentylidene-cyclopentanone **20**. A mixture of the vinyl stannane (**15**, 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 **20** 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, $C_2H_4CH_2C$(=)- in cyclopentylidene ring), 1.93 (2H, ca. quin., *J* 7.0Hz, CH_2CH_2CO-), 2.31 (4H, t, *J* 7.0Hz, CH_2C= *anti*- to carbonyl and $CH_2C(CO$-)=), 2.48-2.63 (2H, m, CH_2C= *syn*- to carbonyl), 2.71-2.88 (2H, m, CH_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[13] and to that obtained by the isomerisation of cyclodec-5-ynone under free radical conditions.

Attempted ring expansion of the stannane **19**. A mixture of the stannane (**19**, 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* (**21**[15] 41mg, 89%), a colourless oil, as the only isolable product which was contaminated with a small amount of tin-containing impurity. $\nu_{max.}$ (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)H_2-), 2.00 (2H, quin., *J* 6.5Hz, CH_2CH_2CO-), 2.25-2.39 (4H, m, C(1)H_2C= and $CH_2C(CO$-)=), 2.46-2.62 (4H, m, CH_2CO- and C(7)H_2C=); 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 **23**. To a solution of 3-(hydroxymethyl)-3-methyloxetane (10g, 98mmol) and triethylamine (15ml, 0.11mol) in ether (150ml) at 0°C was added dropwise a solution of 4-chlorobutyrylchloride (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 (**22**, 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, CH_3-), 2.13 (2H, quin., CH_2CH_2Cl), 2.58 (2H, t, CH_2CO-), 3.63

(2H, t, CH_2Cl), 4.21 (2H, s, $CH_2O.CO$-), 4.40 (2H, d) and 4.54 (2H, d, CH_2OCH_2-) all coupling constants 6.5Hz.

A mixture of the chloride (**22**, 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 (**23**, 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, CH_3-), 2.18 (2H, quin., *J* 7.0Hz, CH_2CH_2I), 2.54 (2H, t, *J* 7.0Hz, CH_2CO-), 3.27 (2H, t, *J* 7.0Hz, CH_2I), 4.20 (2H, s, $CH_2O.CO$-), 4.41 (2H, d, *J* 6.5Hz) and 4.54 (2H, d, *J* 6.5Hz, CH_2OCH_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 **24**. To a solution of boron trifluoride etherate (2.3ml, 18.7mmol) in dichloromethane (150ml) at -15°C was added a solution of the ester (**23**, 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 (**24**, 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, CH_3-), 1.76 (2H, t, *J* 8.0Hz, $CH_2C(OR)_3$), 1.89-2.08 (2H, m, CH_2CH_2I), 3.22 (2H, t, *J* 6.5Hz, CH_2I), 3.88 (6H, s, 3xCH_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-tributylstannylcyclohexanone **25**. Tributylstannyl lithium prepared from bis-tributyltin (5.56ml, 11 mmol) and ^{n}butyl lithium (7.14ml of a 1.54M solution in hexanes, 11mmol) in THF (15ml) was cooled to -78°C and 2-methylcyclohex-2-enone[18] (1.1g, 10mmol) added. After 0.5h the mixture was warmed to -23°C and HMPA (15ml) added followed by the iodide (**24**, 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 **25** 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, ($CH_3C_2H_4CH_2$-)$_3$Sn-), 0.80 (3H, s, 4"-CH_3-), 1.08 (3H, s, 2-CH_3-), 1.17-2.13 (23H, m, ($CH_3C_2H_4CH_2$-)$_3$Sn-, $C_3H_6C(OR)_3$, and $C_2H_4CH(SnBu_3)$-), 2.38 (2H, t, *J* 6.5Hz, CH_2CO-), 3.89 (6H, s, 3xCH_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 **26**. A mixture of the orthoester (**25**, 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 purified further 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 (**26**, 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, ($CH_3C_2H_4CH_2$-)$_3$Sn-), 1.10 (3H, s, CH_3-), 1.18-1.65 (15H, m, ($CH_3C_2H_4CH_2$-)$_3$SnCHR- and $CH_2C_2H_4CO_2H$), 1.74-2.05 (6H, m, $C_2H_4CH_2CO$- and $CH_2CH_2CO_2H$), 2.23-2.52 (4H, m, CH_2CO- and CH_2CO_2H); *m/z* (E.I.) 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).

trans-2-Methyl-2-((3'-phenylselenocarbonyl)-propyl)-3-tributylstannylcyclohexanone **27**. To a solution of the acid (**26**, 2.0g, 4.1mmol) and tributyl phosphine (2.04ml, 8.2mmol) in THF (20ml) was added in one portion NPSP[19] (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 (**27**, 1.93g, 75%) as a colourless oil. (Found: C, 55.99; H, 7.92. $C_{29}H_{48}O_2SeSn$ requires C, 55.61; H, 7.72%); $\nu_{max.}$ (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, ($CH_3C_2H_4CH_2$-)$_3$Sn-), 1.11 (3H, s, CH_3-), 1.21-1.69 (17H, m) and 1.77-2.03 (4H, m, ($CH_3C_2H_4CH_2$-)$_3$SnCHR-, $C_2H_4CH_2COSePh$, and $C_2H_4CH_2CO$-), 2.26-2.54 (2H, m, CH_2CO-), 2.71 (2H, t, *J* 6.5Hz, $CH_2COSePh$), 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 **27**. A mixture of the radical precursor (**27**, 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. (**29** and **30**, 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, $(CH_3)_2C(CN)$-), 1.66 (3H, s, CH_3CR=), 3.26 (1H, ddd, *J* 16.5, 15, 4.0Hz, CHHCO-), 4.37 (1H, s, OH), 5.12 (1H, dd, *J* 12, 3.5Hz, CH=); Isomer #2 (40% by examination of integral ratios) 1.12 (3H, s) and 1.45 (3H, s, $(CH_3)_2C(CN)$-), 1.68 (3H, s, CH_3CR=), 3.40 (1H, ddd, *J* 16, 15, 3.5Hz, CHHCO-), 4.42 (1H, s, OH), 5.17 (1H, ca. t, *J* 6.0Hz, CH=); 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 *trans-8a-hydroxy-5-methylene-decahydro-1-naphthalenone* (**31**, 210mg, 41%), a white solid which was recrystallised for data (m.p. 72-3°C, hexane). (Found: C, 73.00; H, 8.97. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%); $\nu_{max.}$ ($CHCl_3$) 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, OH), 3.00 (1H, td, *J* 13, 6.5Hz, CHHCO-), 4.80 (1H, s) and 5.01 (1H, s, CH_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 *trans-8a(β)-hydroxy-5(α)-methyl-decahydro-1-naphthalenone* (**32**, 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, CH_3-), 1.24-2.30 (14H, m, ring protons), 3.00 (1H, td, *J* 14,6.5Hz, CHHCO-); 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).

Acknowledgment.
We thank the SERC and ICI Pharmaceuticals, Alderley Park for financial support.

References.

1. a) J.E. Baldwin, R.M. Adlington, and J. Robertson, *J. Chem. Soc., Chem. Commun.*, **1988**, 1404;
   b) J.E. Baldwin, R.M. Adlington, and J. Robertson, *Tetrahedron*, **1989**, *45*, 909.
2. K. Nakatani and S. Isoe, *Tetrahedron Lett.*, **1984**, *25*, 5335.
3. H. Finkelstein, *Berichte*, **1910**, *43*, 1528.
4. K.B. Becker and J.L. Chappuis, *Helv. Chim. Acta.*, **1979**, *62*, 34.
5. K. Harimaya, T. Ohkura, J-F. Gao, Y. Iitaka, E. Osawa, and S. Inayama, *Chem. Pharm. Bull.*, **1987**, *35*, 3866, and references cited therein.
6. W.C. Still, *J. Am. Chem. Soc.*, **1977**, *99*, 4836.
7. A. Fauve, M.F. Renard, and H. Veschambre, *J. Org. Chem.*, **1987**, *52*, 4893.
8. a) A. Eschenmoser, D. Felix, and G. Ohloff, *Helv. Chim. Acta.*, **1967**, *50*, 708;
   b) J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K.H. Shulte-Elte, E. Sund, G. Ohloff, J. Kalvoda, H. Kaufmann, P. Wieland, and G. Anner, *Helv. Chim. Acta.*, **1967**, *50*, 2101.
9. E. Piers and J.R. Grierson, *J. Org. Chem.*, **1977**, *42*, 3755.
10. E. Piers, J.R. Grierson, C.K. Lau, and I. Nagakura, *Can. J. Chem.*, **1982**, *60*, 210.
11. R.E. Mewshaw, *Tetrahedron Lett.*, **1989**, *30*, 3753.
12. B.H. Lipshutz, E.L. Elbworth, S.H. Dimock, and D.C. Reuter, *Tetrahedron Lett.*, **1989**, *30*, 2065.
13. J. Plesek, *Collect. Czech. Chem. Commun.*, **1956**, *21*, 368.
14 J.E. Baldwin and D.R. Kelly, *J. Chem. Soc., Chem Commun.*, **1985**, 682.
15. G.L. Lange and T.-W. Hall, *J. Org. Chem.*, **1974**, *39*, 3819.
16. D.L. Boger and R.J. Mathvink, *J. Org. Chem.*, **1989**, *54*, 1777 and references cited therein.

17. E.J. Corey and N. Raju, *Tetrahedron Lett.*, **1983**, *24*, 5571.
18. E.W. Warnhoff, D.G. Martin, and W.S. Johnson, *Org. Synth.*, Coll. Vol. IV, **1963**, 162.
19. a) K.C. Nicolaou, D.A. Claremon, W.E. Barnette, and S.P. Seitz, *J. Am. Chem. Soc.*, **1979**, *101*, 3704;
    b) P.A. Grieco, J.Y. Jaw, D.A. Claremon, and K.C. Nicolaou, *J. Org. Chem.*, **1981**, *46*, 1215.
20. a) P.A. Wender and J.C. Hubbs, *J. Org. Chem.*, **1980**, *45*, 365;
    b) P.A. Wender and L.J. Letendre, *J. Org. Chem.*, **1980**, *45*, 367.
21. a) G.L Lange, M.-A. Huggins, and E. Neidert, *Tetrahedron Lett.*, **1976**, 4409;
    b) G.L. Lange and F.C. McCarthy, *Tetrahedron Lett.*, **1978**, 4749.