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SYNTHESIS OF SPIROETHERS USING RADICAL CYCLISATIONS

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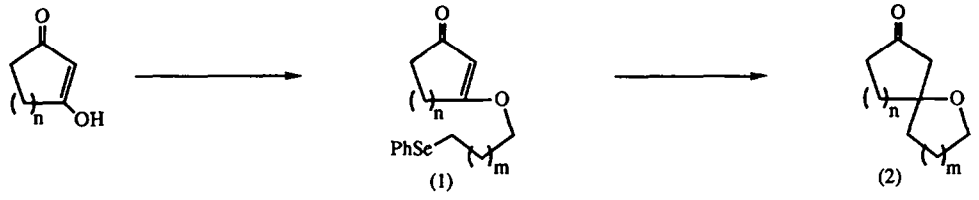
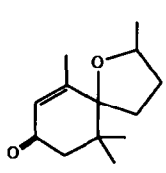
Abstract: A variety of spiroether products, including one bis-spiro compound, are available via a simple radical cyclisation route.

We recently became interested in the synthesis of spirocyclic compounds via the general approach shown in Scheme 1.



Scheme 1

At this time the preparation of spiro-fused products using radical chemistry had received very little attention, and we considered that this method could be useful in the preparation of spiroether-containing natural products such as theaspirone (**3**)[1] or kuroyurinidine (4).[2]



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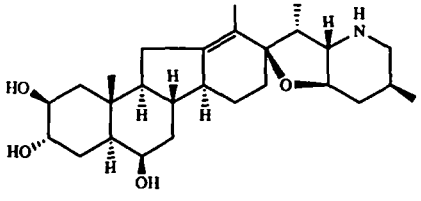

(4)

We previously reported our preliminary results concerning the preparation of spiroethers using this approach,[3] and here we describe further details of this work, including some new stereoselective examples.[4]
We initially examined a route to suitable radical precursors (**1**) which utilised the alkylation of a cyclic 1,3-diketone on oxygen. Thus, treatment of the cyclic diones (**5**) or (**6**) with NaH in DMF followed by heating with bromoselenide (**7a**) gave the desired products (**8**) and (**9**) respectively in satisfactory yield, Scheme 2.

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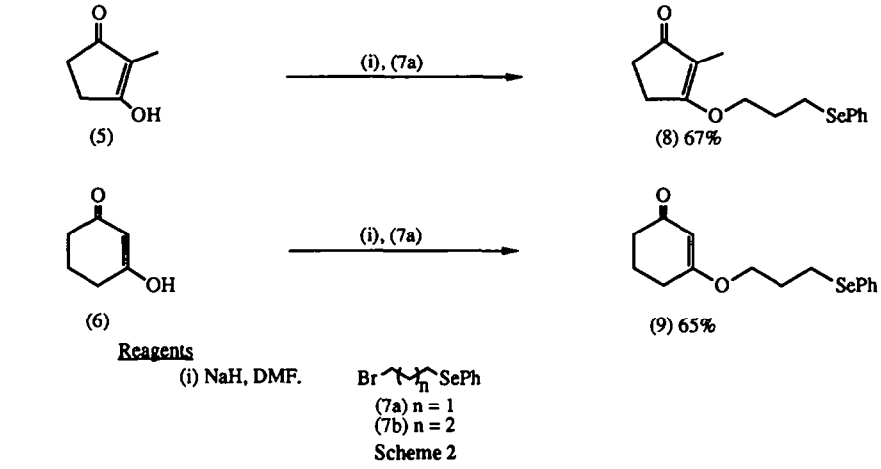
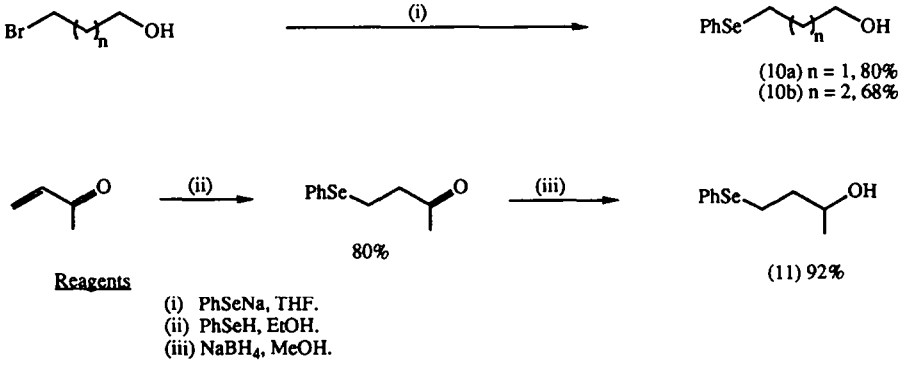


Scheme 2

Whilst this procedure worked with bromide (**7a**), other bromides including the homologous bromoselenide (**7b**) gave much poorer results under the same conditions. We therefore turned to an alternative and simpler procedure, which consisted of direct condensation of the cyclic diones with suitable alcohols. We prepared the necessary compounds straightforwardly using the routes outlined in Scheme 3.

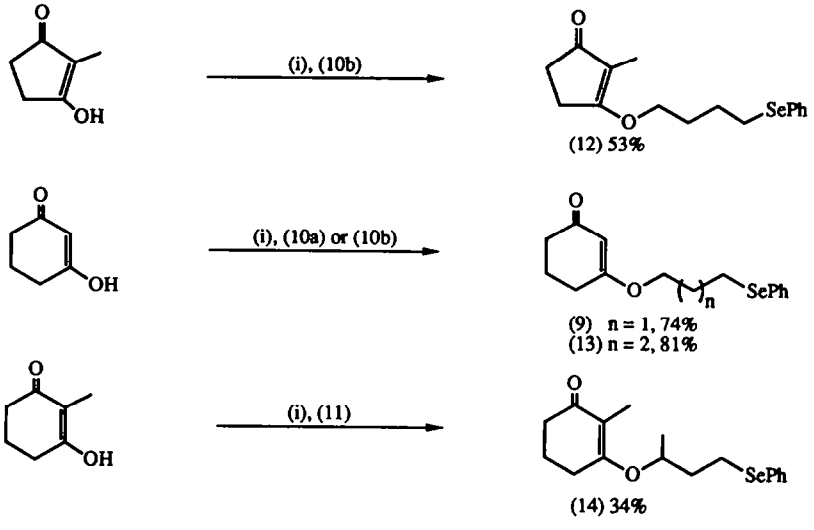


Scheme 3

The primary selenoalcohols (**10a**) and (**10b**) were prepared by reaction of the corresponding bromides with PhSeNa in THF according to the method of Ley *et al.* (PhSeSePh, PhCOPh, Na, ultrasound).[5] The secondary alcohol was also available in high yield by addition of PhSeH (PhSeSePh, EtOH, $NaBH_4$, then HOAc) to methyl vinyl ketone,[6] and subsequent reduction using $NaBH_4$ in MeOH.

Our decision to use these selenides, rather than the more readily available corresponding bromides as radical precursors was due to the advantages we encountered in preliminary cyclisation experiments. In particular, the selenides gave higher isolated yields of product than the corresponding bromides due to simplification of the work-up procedure ($Bu_3SnSePh$ produced as by-product is easily removed by chromatography, no messy aqueous work-up is needed).

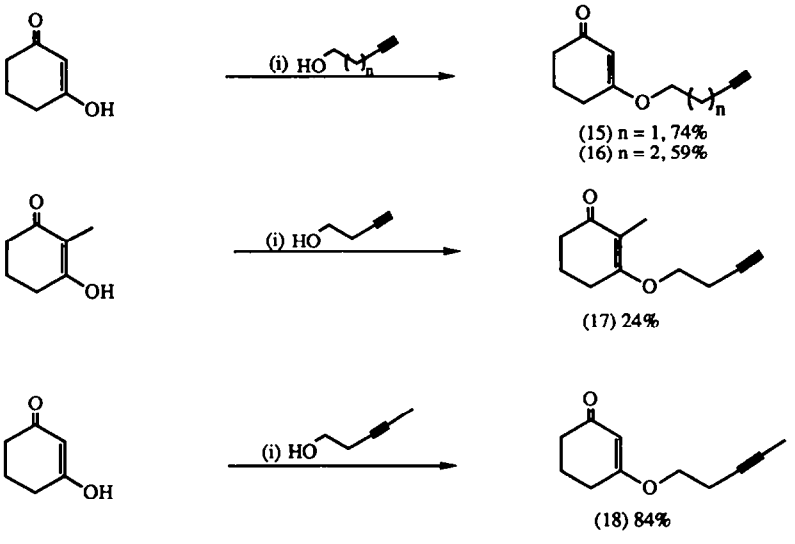
We next condensed the selenoalcohols with several 1,3-diketones. In each case the dione and alcohol were heated together in benzene with catalytic quantities of *p*-toluenesulphonic acid (*p*TSA), under Dean-Stark conditions, Scheme 4.

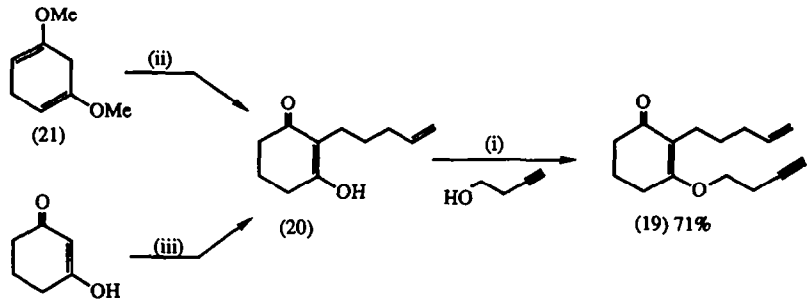


Reagents
(i) Benzene, Δ.

Scheme 4

These condensations proved simple and convenient to carry out, although moderate yields were generally obtained using 2-methylcyclohexane-1,3-dione due to its poor solubility in benzene. Small quantities of cosolvents were tried, in order to improve the solubility, of which dioxane was the best. Substrates (**15**)-(**19**) were also prepared using an acetylenic alcohol in place of the selenoalcohols used previously, Scheme 5.





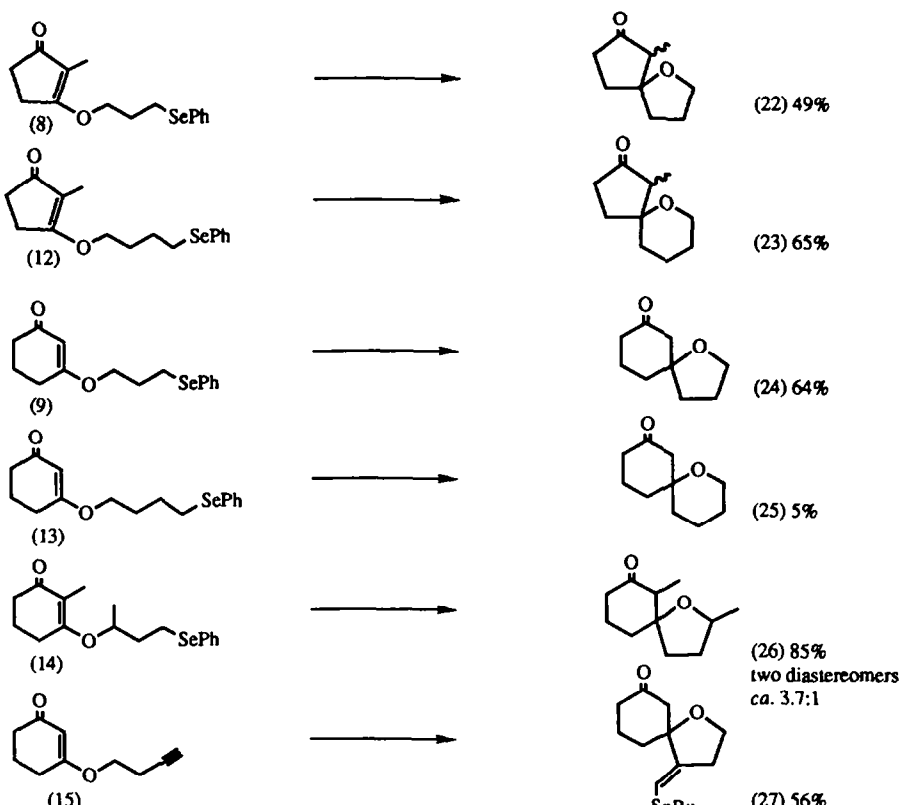
Reagents

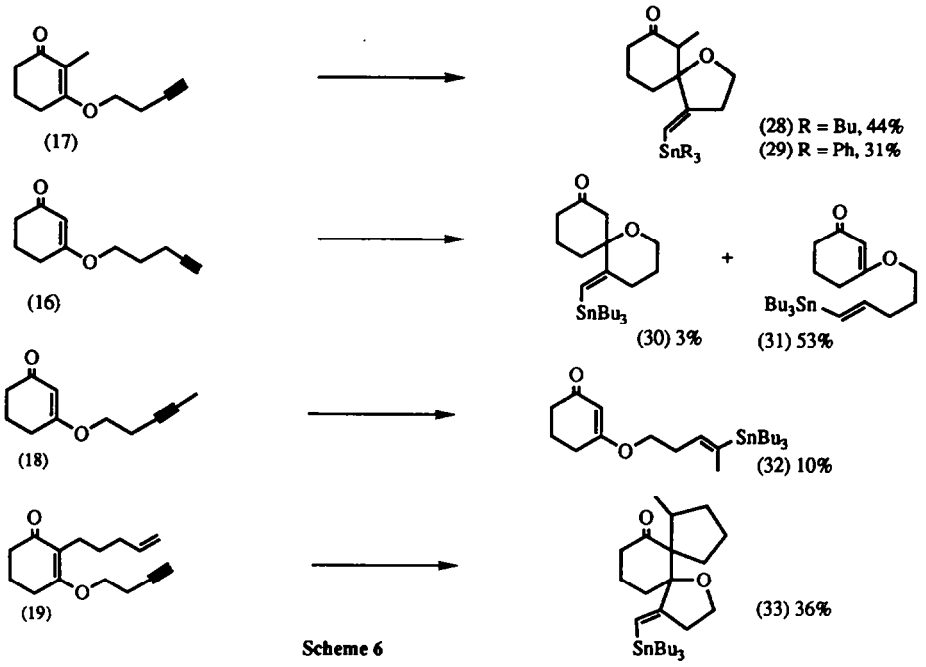
(i) Benzene, Δ, *p*-TSA.
(ii) ^{t}BuLi, THF, $I(CH_2)_3CH{=}CH_2$; HCl_{aq}, acetone.
(iii) $Br(CH_2)_3CH{=}CH_2$, KOH, $dioxane_{aq}$.

Scheme 5

The preparation of the C-2-alkylated dione (**20**) proved remarkably troublesome, with poor yields being obtained via alkylation of bis-vinyl ether (**21**) (30%),[7] or direct *C*-alkylation of cyclohexane-1,3-dione (11%).[8] Fortunately either of these reactions could be conducted on a large scale, thereby giving subsequent access to adequate quantities of (**19**). These acetylenic compounds appeared to be well suited to the hydrostannylation-cyclisation procedures reported by Stork and Mook,[9] and Nozaki *et al.*[10]

The selenides (**8**), (**9**), (**12**) - (**14**), and the acetylenes (**15**)-(**19**) were then subjected to standard cyclisation conditions, which consisted of slow addition (6-7h) of a mixture of Bu_3SnH and AIBN in benzene to a refluxing solution of the starting material in benzene (*ca.* 0.04M). These results are summarised in Scheme 6.





Scheme 6

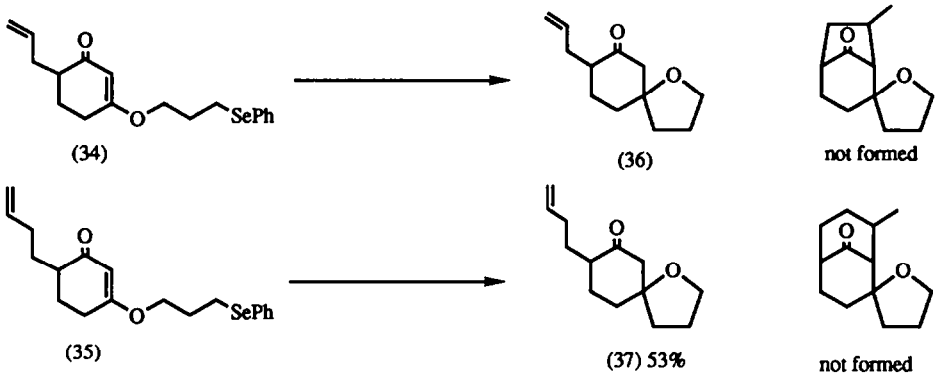
The simple 5-*exo*-trig cyclisations leading to (**22**) and (**24**) proceeded as planned to give the desired products as volatile oils. Experimentation with the cyclisation conditions at this stage indicated that more concentrated reactions resulted in an increase in uncyclised, reduced by-products, whilst more dilute conditions did not improve yields, possibly due to the necessity to remove large volumes of solvent from the volatile products.[11] Compound (**23**) was also formed in good yield via the less common 6-*exo*-trig radical ring-closure.[12] The lack of a hydrogen atom suitably disposed for intramolecular 1,5-H· transfer to the initially formed radical possibly contributes to the success of this ring closure.[13] Despite the ease of formation of (**23**) the other 6-*exo*-trig reactions leading to (**25**) and (**30**) proceeded in very poor yield, with acyclic reduced products predominating. We have no adequate explanation for the low yields in these cases, although an analogous cyclisation to form a carbo-spirocyclic product gives similarly dismal results.[14]

Another unexpected failure was the attempted cyclisation of (**18**), which gave no cyclised products, with only (**32**) being formed in 10% yield. It is possible that cyclisation of the very hindered trisubstituted vinyl radical (formed reversibly) to form a spiro-centre is too energetically demanding.

Both products (**22**) and (**23**) were formed as mixtures of diastereomers (*ca.*1:1 for (**22**) and *ca.* 2:1 for (**23**)), and we consider that this is probably due to a combination of poor steric and/or stereoelectronic control in the reaction of the intermediate five-membered α-ketoradical. We hoped that the use of a six-membered ring precursor would allow some higher degree of stereoselectivity in the cyclisations. Thus in an intermediate cyclohexanone α-ketoradical we might expect significant stereocontrol due to both conformational locking, and stereoelectronic effects (analogous to cyclohexanone enolate alkylations). This expectation was at least partly realised in the cyclisations leading to (**26**), (**28**) and (**29**) which all proceeded with improved levels of stereoselection. Thus (**26**) was formed in high yield as predominantly one isomer, with only two of the four possible diastereomers being detected. The cyclisations leading to (**28**) and (**29**) gave *ca.* 7:1 (nmr) mixtures of diastereomeric products, although the chemical yields were somewhat more modest.

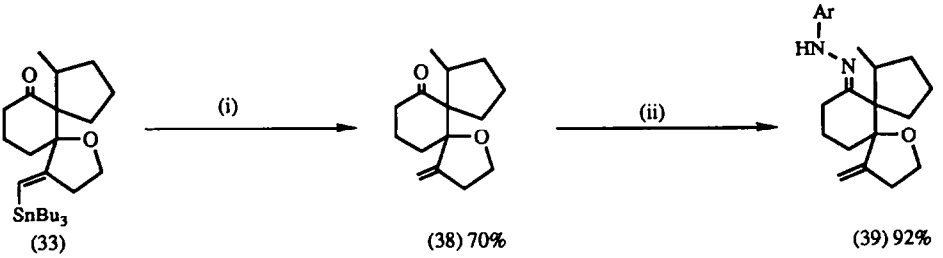
At this point we examined the reactions of (**19**), which could potentially undergo double 5-*exo*-trig cyclisation. Under our standard reaction conditions, the anticipated bis-spiro product (**33**) was formed in 36% yield. Somewhat to our surprise the desired product appeared to be a single diastereomer. No other bis-spirocyclic isomers could be detected, although other minor, singly cyclised products were formed.

Further attempts at bis-cyclisations using the two compounds (**34**) and (**35**), however, gave only the monocyclised products (**36**) and (**37**) respectively, Scheme 7.



Scheme 7

No further attempts to optimise the yields of these cyclisations were made, and instead we focused on the stereochemical aspects of the reactions. Preliminary nmr experiments (nOe) were not helpful in deciding which isomers were formed in the reactions. We considered it most important to solve the structure of the bis-spirocompound (**33**), and therefore prepared a crystalline derivative suitable for an X-ray determination.
Direct conversion of (**33**) into a crystalline ketone derivative (e.g. hydrazone or semicarbazone) was thwarted by the lability of the Bu_3Sn group. Replacement of the Bu_3Sn group with iodine or bromine also proved difficult, however simple destannylation using pyridinium-*p*-toluenesulphonate (PPTS) in CH_2Cl_2 proceeded cleanly to give (**38**). Subsequent reaction with 2,4-dinitrophenylhydrazine then gave the hydrazone derivative (**39**), Scheme 8.



Reagents

(i) PPTS, CH_2Cl_2.
(ii) $ArNHNH_2$, MeOH, catalytic H_2SO_4 (Ar = 2,4-dinitrophenyl).

Scheme 8

Crystals of (**39**) proved suitable for an X-ray determination, the result of which is shown in Fig 1.

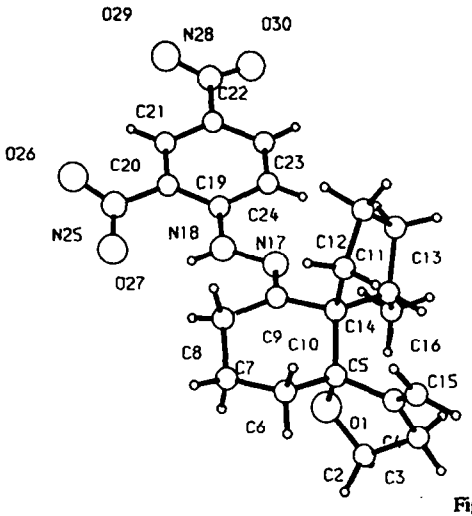
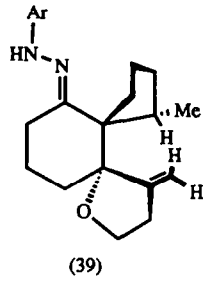
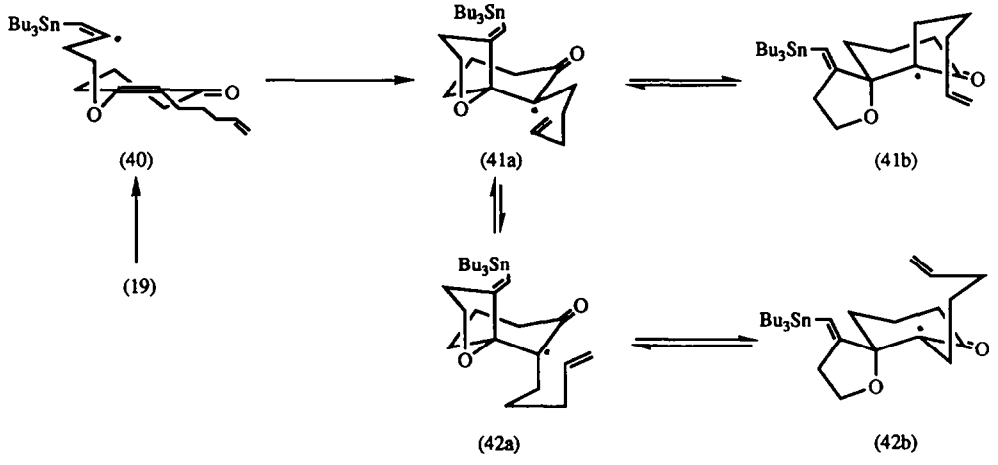


Fig.1



(39)

The structure clearly shows the relative configurations at the important chiral centres formed in the radical cyclisation, although the geometry of the original vinyl stannane carbon-carbon double bond cannot, of course, be deduced. We envisage that this particular isomer arises via the double cyclisation sequence depicted in Scheme 9.



Scheme 9

Thus reversible attack of a tin radical onto acetylene (**19**) gives the intermediate vinyl radical (**40**) (only the *Z*-isomer is thought to cyclise) which then undergoes axial attack on the enone system. The step of key stereochemical consequence is the subsequent cyclisation of the resulting α-keto radical (**41**). Cyclisation of this intermediate in the configuration shown for (**41a**) explains the observed result. Two principal, distinct conformations are possible for this radical (with respect to ring inversion), (**41a**) and (**41b**). Similarly, two conformations of the epimeric radical (**42**) are also possible. The observed result presumably reflects cyclisation via one or both of the conformations (**41a**) and (**41b**) rather than either (**42a**) or (**42b**) to give the final product (**33**). Molecular modelling using simple compounds to represent each conformer did not explain the observed selectivity, although it indicated that relatively little conformational locking of the six-membered ring by the spiro-substitutents occurs. Clearly, other factors such as radical stabilisation (by the ketone group,

or due to alignment of the β-C-O bond) could have primary importance in determining the outcome.
The spirocyclic products obtained here have provided us with a useful insight into the stereocontrol possible in such systems. This approach is now being applied to analogous cyclisations that provide aza-spirocyclic products, which are possibly more important in terms of natural product synthesis.

Acknowledgements
We thank the SERC and Pfizer Central Research, Sandwich, for a CASE Studentship to D.S.M.

Experimental Section
Melting points for solid products were determined using a Reichert Microscope apparatus, and are uncorrected. Products without melting points are colourless oils. Infra-red spectra were recorded on a Perkin-Elmer 298, Philips PU96706 or Pye Unicam SP3-100 grating spectrophotometer. ^{1}H nmr spectra were recorded on a Bruker WP80, Bruker AM250, Bruker AM400, or Bruker AM500 machine with Me_4Si as internal standard. ^{13}C nmr were recorded on a Bruker AM250, Bruker WM250 or General Electric GN500 instrument. Mass spectra were recorded on AEI 902 or VG micromass 70E spectrometers. Microanalyses were performed at the microanalytical laboratory at Pfizer Limited, Sandwich, Kent.
Analytical tlc was performed on Merck precoated silica gel F_{254} plates. Preparative chromatography was carried out on columns of Merck Keiselgel 60 (230-400 mesh).
Solvents were purified by standard techniques. Light petroleum refers to the fraction boiling between 30-40°C.

Crystallographic analysis of $C_{21}H_{26}N_4O_5$
Crystal data $C_{21}H_{26}N_4O_5$, M = 414.45, triclinic, a = 8.186(2), b= 9.364(1), c = 13.357(2) A, α = 95.29 (1), β = 91.56(2), γ = 97.05 (2), U = 1011.05 A^3, z = 2, Dc = 1.36 g cm^{-3}, F(000) = 440, space group $P\bar{1}$, Cu-kα radiation λ = 1.54178 A, μ(Cu-kα) = 8.25 cm^{-1}.
A crystal of approximate dimensions 0.5 x 0.15 x 0.05 mm was mounted on an Enraf-Nonius CAD4 diffractometer and 25 reflections were used to determine accurate lattice parameters. Intensity data were collected using an ω/2θ scan for $1° < \theta < 60°$. A total of 2993 independent reflections were measured of which 2004 had $I > 3\sigma(I)$ and were considered observed and used in the subsequent refinement. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. Crystallographic calculations were performed using the CRYSTALS system of programs. The structure was solved by direct methods using the MULTAN program. Least squares refinement including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis terminated at R 0.0375 (R_w 0.0445). A final difference map showed no features in excess of 0.13 eA^{-3} .
The resulting molecular structure is illustrated in Figure 1, which also depicts the crystallographic numbering scheme. The cyclohexanimine ring adopts the expected chair conformation with both spiro subsituents arranged such that the substituent-bearing carbon atom is equatorial to the ring. Both 5-membered rings are in the half-chair form with C2 and C3 alternately out of the plane of the heterocycle, and C10 and C11 out of the cyclopentane plane. Both nitro groups are twisted out of the aromatic plane with torsion angles of 13.3 (*ortho*) and 10.2 (*para*). The geometric data are generally unexceptional although the steric crowding of the neighbouring spiro-centres introduces deviations in bond angles from those expected. The extreme differences

are C11-C10-C14 99.7 and C10-C14-C16 120.0, both at sp^3 sites. Final atomic coordinates, thermal parameters, bond lengths, bond angles and observed and calculated structure factors are all listed in a Supplementary Publication. See Notice to Authors, *Tetrahedron*, **40(2)**, ii (1984).

Preparation of 1-Bromo-3-phenylselenopropane (7a)

To a solution of alcohol (**10a**) (10.08 g, 46.9 mmol) in acetonitrile (60 ml) at 0°C was added PPh_3 (12.28 g, 46.9 mmol) and NBS (8.81 g, 46.9 mmol). The solution was stirred at this temperature for 3h, when t.l.c. analysis showed complete consumption of the starting alcohol and formation of a less polar product. The reaction mixture was poured into ether (200 ml), filtered through a short pad of silica, and the solvent removed under reduced pressure.

The crude product was distilled, giving the bromide (**7a**) (7.95 g, 61%), b.p. 102-103°C (0.08 mm Hg) (Found: C, 39.1; H, 4.0. $C_9H_{11}SeBr$ requires C, 38.9; H, 4.0%); ν_{max} (film) 2920, 1580, 1480, 1440, 1240 and 1025 cm^{-1}; δ (80 MHz; $CDCl_3$) 2.98-3.15 (2H, m), 3.0 (2H, t, J 6Hz), 3.48 (2H, t, J 6Hz) and 7.15-7.63 (5H, m); *m/z* 278 (M^+, 100%) and 199 (12, *M-Br*) (Found: M^+ 277.9204. $C_9H_{11}{}^{80}Se^{79}Br$ requires M, 277.9209).

Preparation of 1-Bromo-4-phenylselenobutane (7b)

To a suspension of sodium (0.69 g, 30 mmol) in THF (40 ml) under nitrogen at room temperature was added a solution of DPDS (4.68 g, 15 mmol) in THF (20 ml). The mixture was then sonicated for 6h.

A solution of the freshly prepared sodium phenylselenide (28 mmol) in THF (56 ml) was transferred, via syringe, to a stirred solution of 1,4-dibromobutane (60 g, 279 mmol) in THF (120 ml) at 0°C under nitrogen. The reaction was allowed to warm to room temperature overnight.

The mixture was poured into water (100 ml) and extracted with ether (3 x 60 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure.

The crude product was distiiled giving 1-bromo-4-phenylselenobutane (**7b**) (4.14 g, 51%), b.p. 120-126°C (ca. 0.1 mm Hg); δ (80 MHz; $CDCl_3$) 1.78-2.08 (4H, m), 2.80-3.03 (2H, m), 3.28-3.45 (2H, m, CH_2-Br) and 7.14-7.66 (5H, m).

Preparation of 3-(3-Phenylselenopropanoxy)-2-methylcyclopent-2-en-1-one (8)

To a stirred suspension of NaH (0.18 g, 80% dispersion in oil, 6.04 mmol) in DMF (10 ml) at 0°C under nitrogen was added a solution of 2-methylcyclopentane-1,3-dione (0.67 g, 5.98 mmol) in DMF (2 ml). The reaction was warmed to room temperature and stirred for 20 min. To this was added a solution of bromide (**7a**) (1.83 g, 6.58 mmol) in DMF (5 ml) and the reaction heated to 70°C for 3h, when t.l.c. analysis showed complete consumption of starting material.

The reaction was cooled and poured into a saturated solution of NH_4Cl (20 ml) and extracted with ether (2 x 20 ml). The combined organic extracts were washed with water (2 x 30 ml) and brine (30 ml) then dried ($MgSO_4$), and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (40-80% ether : light petroleum), to give the vinylogous ester (**8**) (1.25 g, 67%) (Found: C, 58.2; H, 6.0. $C_{15}H_{18}O_2Se$ requires C, 58.3; H, 5.9%); ν_{max} (film) 2910, 1685 (*C=O*), 1625 (*C=C*), 1330 and 1110 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.61 (3H, t, J 2Hz), 2.06-2.18 (2H, m), 2.35-2.41 (2H, m), 2.48-2.56 (2H, m), 3.05 (2H, t, J 6Hz), 4.23 (2H, t, J 6Hz), 7.21-7.29 (3H, m) and 7.45-7.53 (2H, m); δ_C (63 MHz; $CDCl_3$) 6.2, 23.5, 25.0, 30.0, 33.3, 67.5, 116.2, 127.4, 129.3, 129.8, 132.4, 184.0 and 205.3 (*C=O*); *m/z* 310 (M^+, 82%) and 199 (100) (Found: M^+ 310.0479. $C_{15}H_{18}O_2{}^{80}Se$ requires M, 310.0467).

Preparation of 3-(3-Phenylselenopropanoxy)cyclohex-2-en-1-one (9), using 1-bromo-3-phenylselenopropane (7a)

To a stirred suspension of NaH (0.38 g, 80% dispersion in oil, 12.67 mmol) in DMF (15 ml) at 0°C under nitrogen was added a solution of cyclohexane-1,3-dione (1.52 g, 13.57 mmol) in DMF (5 ml). The resulting mixture was warmed to room temperature and stirred for 20 min. To this was added a solution of bromide (**7a**) (3.34 g, 12.34 mmol) in DMF (5 ml) and the reaction heated at 70°C for 4h when t.l.c. analysis showed complete consumption of starting material.

The reaction was poured into a saturated solution of NH_4Cl (30 ml) and extracted with ether (2 x 20 ml). The combined organic extracts were washed with water (2 x 30 ml) and brine (30 ml), then dried ($MgSO_4$) and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (20-80% ether : light petroleum) to give vinylogous ester (**9**) (2.48 g, 65%) (Found: C, 58.1; H, 5.9. $C_{15}H_{18}O_2Se$ requires C, 58.3; H, 5.9%); ν_{max} (film) 2940, 1645(*C=O*), 1600(*C=C*), 1365, 1220 and 1180 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.90-2.02 (2H, m), 2.04-2.16 (2H, m), 2.28-2.40 (4H, m), 3.01 (2H, t, J 6Hz), 3.91 (2H, t, J 6Hz), 5.31 (1H, s), 7.22-7.30 (3H, m) and 7.45-7.54 (2H, m); δ_C (63 MHz; $CDCl_3$) 21.2, 23.9, 28.8, 29.1, 36.7, 67.2, 102.9 (*C-2*), 127.0, 129.0, 129.9, 132.6, 177.7 (*C-3*) and 199.5 (*C*=O); *m/z* 310 (M^+, 100%), 199 (32) and 153 (48) (Found: M^+ 310.0476. $C_{15}H_{18}O_2{}^{80}Se$ requires M, 310.0467).

Preparation of 3-Phenylselenopropan-1-ol (10a)

To a suspension of sodium (1.52 g, 66.1 mmol) in THF (70 ml) under nitrogen at room temperature was added a solution of DPDS (10 g, 32 mmol) in THF (20 ml). The reaction was sonicated for 5h, during which time a milky white precipitate formed. A solution of 3-bromopropan-1-ol (8.4 g, 60.4 mmol) in THF (10 ml) was added, and the reaction stirred at room temperature overnight.

The mixture was poured into water (40 ml) and extracted with ether (3 x 40 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure.

The crude product was distilled, giving 3-phenylselenopropan-1-ol (**10a**) (11.28 g, 87%), b.p. 110°C (0.15 mm Hg); ν_{max} (film) 3350 br., 2940, 1580, 1475 and 1440 cm^{-1}; δ (80 MHz; $CDCl_3$) 1.75-2.13 (3H, m, 1H D_2O exch.), 3.0 (2H, t, J 6Hz), 3.75 (2H, t, J 6Hz) and 7.13-7.70 (5H, m); *m/z* 216 (M^+, 72%) and 156 (46).

Preparation of 4-Phenylselenobutan-1-ol (10b)

To a suspension of sodium (1.05 g, 45.7 mmol) in THF (80 ml) under nitrogen at room temperature was added a solution of DPDS (7.0 g, 22.4 mmol) in THF (20 ml). The reaction was sonicated for 6h, during which time a milky white precipitate formed. A solution of 4-bromobutan-1-ol (6.12 g, 40 mmol) in THF (10 ml) was added, and the reaction stirred at room temperature overnight.

The mixture was poured into water (50 ml) and extracted with ether (3 x 40 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure.

The crude product was distilled, giving 4-phenylselenobutan-1-ol (**10b**) (6.22 g, 68%), b.p. 130°C (0.2 mm Hg); ν_{max} (film) 3350 (*OH*), 1580 and 1435 cm^{-1}; δ (80 MHz; $CDCl_3$) 1.50-2.00 (5H, m), 2.78-3.08 (2H, m), 3.50-3.75 (2H, m) and 7.13-7.63 (5H, m); *m/z* 230 (M^+, 42%) and 55 (100, C_4H_7) (Found; M^+ 230.0219. $C_{10}H_{14}O^{80}Se$ requires M, 230.0206).

Preparation of 4-Phenylselenobutan-2-one

To a stirred solution of DPDS (20.7 g, 66.3 mmol) in ethanol (110 ml) under a stream of nitrogen was added,

in portions, $NaBH_4$ (5.04 g, 133 mmol). The colourless solution formed was cooled to 0°C and glacial acetic acid (13.4 ml, 235 mmol) added. A solution of MVK (7.14 g, 102 mmol) in ethanol (15 ml) was added and the resulting mixture stirred at 0°C for 1h.

The reaction was poured into water (250 ml) and extracted with ether (2 x 200 ml). The combined organic extracts were washed with water (200 ml) and brine (200 ml) then dried ($MgSO_4$), and the solvent removed under reduced pressure.

Flash chromatography (3-15% ether : light petroleum) gave 4-phenylselenobutan-2-one (18.61 g, 80%) (lit.,[4] 99%); ν_{max} (film) 2930, 1720 (*C=O*), 1585, 1480 and 1365 cm^{-1}; δ (250 MHz; $CDCl_3$) 2.11 (3H, s, *Me*), 2.81-2.88 (2H, m), 3.02-3.08 (2H, m, CH_2-SePh), 7.22-7.29 (3H, m, *Ph*) and 7.45-7.53 (2H, m, *Ph*); *m/z* 228 (M^+, 100%), 185 (46), 157 (73) and 71 (65).

Preparation of 1-Phenylselenobutan-3-ol (11)

To a stirred solution of 4-phenylselenobutan-2-one (18.20 g, 80 mmol) in methanol (180 ml) at 0°C was added in portions, $NaBH_4$ (4.57 g, 120 mmol). The solution was warmed to room temperature and stirred for 1h.

The reaction was diluted with ether (200 ml) and poured into a saturated solution of NH_4Cl (200 ml). The aqueous phase was extracted with ether (2 x 100 ml), and the combined organic extracts washed with brine (200 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (20-40% ether : light petroleum) to give the alcohol (**11**) (16.23 g, 88%) (Found: C, 52.7; H, 6.3. $C_{10}H_{14}OSe$ requires C, 52.4; H, 6.2%); ν_{max} (film) 3380 (*OH*), 1580, 1480 and 1440 cm^{-1}; δ (250 MHz; $CDCl_3$) 1.19 (3H, d, J 7Hz, *Me*), 1.73-1.87 (3H, m, 1H, D_2O exch.), 2.91-3.09 (2H, m), 3.85-3.99 (1H, m), 7.18-7.30 (3H, m) and 7.45-7.53 (2H, m); *m/z* 230 (M^+, 48%), 157 (18) and 69 (100) (Found: M^+ 230.0209. $C_{10}H_{14}O^{80}Se$ requires M, 230.0206).

Preparation of 3-(3-Phenylselenopropanoxy)cyclohex-2-en-1-one (9) using 3-phenylseleno-1-propanol (10a)

A solution of alcohol (**10a**) (2.0 g, 9.3 mmol), cyclohexane-1,3-dione (1.04 g, 9.3 mmol) and *p*-TSA (10 mg) in benzene (60 ml) was heated under Dean-Stark conditions for 5h. The reaction was cooled, and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (20-80% ether : light petroleum) to give the required vinylogous ester (**9**) (2.14 g, 74%), which was identical to that obtained previously.

Preparation of 3-(4-Phenylselenobutanoxy)-2-methylcyclopent-2-en-1-one (12) using 1-bromo-4-phenylselenobutane (7b)

To a stirred suspension of NaH (91 mg, 80% dispersion in oil, 3.03 mmol) in DMF (5 ml) at 0°C under nitrogen was added a solution of 2-methylcyclopentane-1,3-dione (336 mg, 3 mmol) in DMF (2 ml). The resulting solution was warmed to room temperature and stirred for 20 min. To this was added a solution of bromide (**7b**) (1.05 g, 3.6 mmol) in DMF (2 ml) and the reaction heated at 70°C for 4h.

The reaction was cooled and poured into a saturated solution of NH_4Cl (15 ml) and extracted with ether (2 x 15 ml). The combined organic extracts were washed with water (2 x 30 ml) and brine (20 ml) then dried ($MgSO_4$), and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (20-80% ether : light petroleum) to give the vinylogous ester (**12**) (310 mg, 32%) (Found: C, 59.1; H, 6.35. $C_{16}H_{20}O_2Se$ requires C, 59.4; H, 6.2%); ν_{max} (film) 2940, 1680, 1630, 1580, 1110 and 1060 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.61 (3H, t, J 1Hz, *Me*), 1.78-1.95 (4H, m), 2.39-2.47 (2H, m), 2.56-2.64 (2H, m), 2.93-3.01 (2H, m, CH_2-SePh), 4.13-4.18 (2H, m, CH_2-O), 7.23-7.32 (3H, m, *Ph*) and 7.45-7.54 (2H, m, *Ph*); δ_C (63 MHz; $CDCl_3$) 6.1, 25.1, 26.3, 27.3, 29.5,

33.4, 66.7, 116.2, 127.0, 129.1, 129.9, 132.8, 183.7 and 205.3; *m/z* 324 (M^+, 6%) and 213 (100).

Preparation of 3-(4-Phenylselenobutanoxy)-2-methylcyclopent-2-en-1-one (12) using 4-Phenylselenobutan-1-ol (10b)

A solution of alcohol (**10b**) (2.51 g, 10.96 mmol), 2-methylcyclopentane-1,3-dione (1.23g, 10.98 mmol) and pTSA (10 mg) in benzene (50 ml) was heated under Dean-Stark conditions for 9h. The reaction was cooled and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (30-70% ether : light petroleum) to give the required vinylogous ester (**12**) (1.89 g, 53%), which was identical to that obtained previously.

Preparation of 3-(4-Phenylselenobutanoxy)cyclohex-2-en-1-one (13) from 1-bromo-4-phenylselenobutane (7b)

To a stirred suspension of NaH (79 mg, 80% dispersion in oil, 2.6 mmol) in DMF (5 ml) at 0°C under nitrogen was added cyclohexane-1,3-dione (291 mg, 2.6 mmol) in DMF (2 ml). The resulting mixture was warmed to room temperature and stirred for 20 min. To this was added a solution of bromide (**7b**) (910 mg, 3.1 mmol) in DMF (2 ml) and the reaction heated at 70°C for 3h.

The cooled reaction was poured into a saturated solution of NH_4Cl (20 ml) and extracted with ether (2 x 15 ml). The combined organic extracts were washed with water (2 x 20ml), and brine (20 ml) then dried ($MgSO_4$), and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (20-80% ether : light petroleum) to give vinylogous ester (**13**) (199 mg, 24%) (Found: C, 59.5; H, 6.4. $C_{16}H_{20}OSe$ requires C, 59.4; H, 6.2%); ν_{max} (film) 2940, 1650, 1605, 1480, 1360, 1220 and 1180 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.76-1.88 (4H, m), 1.90-2.03 (2H, m), 2.31-2.40 (4H, m), 2.90-2.96 (2H, m, CH_2-SePh), 3.80-3.85 (2H, m, CH_2-O), 5.32 (1H, s), 7.22-7.31 (3H, m) and 7.44-7.54 (2H, m); δ_C (63 MHz; $CDCl_3$) 21.3, 26.6, 27.3, 28.6, 29.0, 36.8, 67.6, 102.8, 127.0, 129.1, 130.0, 132.8, 177.8 and 199.8; *m/z* 324 (M^+, 14%), 213 (100) and 167 (20).

Preparation of 3-(4-Phenylselenobutanoxy)cyclohex-2-en-1-one (13) from 4-phenylselenobutan-1-ol (10b)

A solution of alcohol (**10b**) (2.12 g, 9.26 mmol), cyclohexane-1,3-dione (1.04 g, 9.29 mmol) and *p*-TSA (11 mg) in benzene (40 ml) was heated under Dean-Stark conditions for 3.5h. The reaction was cooled and the solvent removed under reduced pressure.

The resultant oil was subjected to flash chromatography (10-80% ether : light petroleum) to give the required vinylogous ester (**13**) (2.44 g, 82%), which was identical to that obtained previously.

Preparation of 3-(1-Methyl-3-phenylselenopropanoxy)-2-methylcyclohex-2-en-1-one (14)

A solution of alcohol (**11**) (4.0 g, 17.47 mmol), 2-methylcyclohexane-1,3-dione (1.96 g, 15.56 mmol) and *p*-TSA (16 mg) in a mixture of benzene (50 ml) and dioxane (10 ml) was heated under Dean-Stark conditions for 6h. The reaction was cooled and the solvent removed under reduced pressure.

Flash-chromatography (20-60% ether : light petroleum) gave the required vinylogous ester (**14**) (2.01 g, 38%) (Found: C, 60.8; H, 6.6. $C_{17}H_{22}O_2Se$ requires C, 60.5; H, 6.6%); ν_{max} (film) 2945, 1650, 1620, 1480 and 1380 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.25 (3H, d, J 6Hz), 1.70 (3H, t, J 2Hz), 1.81-2.16 (4H, m), 2.28-2.49 (4H, m), 2.88-3.07 (2H, m, CH_2-SePh), 4.47-4.61 (1H, m), 7.22-7.30 (3H, m, *Ph*) and 7.43-7.51 (2H, m, *Ph*); δ_C (63 MHz; $CDCl_3$) 7.7, 21.0, 21.1, 23.3, 25.7, 36.4, 37.1, 72.6, 116.4, 127.0, 129.2, 129.7, 132.4, 170.7 and 199.0; *m/z* 338 (M^+, 35%), 211 (30), 91 (34) and 55 (100) (Found: M^+ 338.0783. $C_{17}H_{22}O_2{}^{80}Se$ requires M, 338.0779).

Preparation of 3-(But-3-ynyloxy)cyclohex-2-en-1-one (15)

A solution of 3-butyn-1-ol (2.0 g, 28.6 mmol), cyclohexane-1,3-dione (3.2 g, 28.6 mmol) and *p*-TSA (19 mg) in benzene (60 ml) was heated under Dean-Stark conditions for 4h. The reaction was cooled and the benzene removed under reduced pressure.

Flash chromatography (50-100% ether : light petroleum) gave the vinylogous ester (**15**) as a white solid (3.48 g, 74%), m.p. 47-49°C (Found: C, 73.1; H, 7.3. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.4%); ν_{max} (CCl_4) 3320 (C≡C-*H*), 2950, 2115 (*C*≡*C*), 1670 and 1615 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.93-2.11 (3H, m), 3.35 (2H, t, J 6Hz), 2.43 (2H, t, J 7Hz), 2.64 (2H, dt, J 6 and 2 Hz), 3.97 (2H, t, J 6Hz, O-CH_2) and 5.35 (1H, s); δ_C (63 MHz; $CDCl_3$) 19.0, 21.2, 28.8, 36.7, 66.1, 70.3, 79.6, 103.1, 177.3 and 199.6 (*C*=O); *m/z* 164 (M^+, 4%), 95(10) and 69 (77).

Preparation of 3-(Pent-4-ynyloxy)cyclohex-2-en-1-one (16)

A solution of 4-pentyn-1-ol (5 g, 59.5 mmol), cyclohexane-1,3-dione (6.67 g, 59.6 mmol) and *p*-TSA (23 mg) in benzene (60 ml) was heated under Dean-Stark conditions for 7h. The reaction was cooled, and the solvent removed under reduced pressure.

Flash chromatography (20-80% ether : pentane) gave vinylogous ester (**16**) (6.28 g, 59%), m.p. 43-44°C (from Et_2O) (Found: C, 73.9; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); ν_{max} (KBr) 3230 (C≡C-*H*), 2955, 1640 and 1600 cm^{-1}; δ (250 MHz; $CDCl_3$) 1.90-2.04 (5H, m), 2.32-2.44 (6H, m), 3.95 (2H, t, J 6Hz) and 5.38 (1H, s); *m/z* 178 (M^+, 4%), 95 (11) and 66 (100).

Preparation of 3-(But-3-ynyloxy)-2-methylcyclohex-2-en-1-one (17)

A solution of 3-butyn-1-ol (2.9 g, 41.4 mmol), 2-methylcyclohexane-1,3-dione (5 g, 39.7 mmol) and *p*-TSA (26 mg) in a mixture of benzene (100 ml) and dioxane (10 ml) was heated under Dean-Stark conditions for 20h. The reaction was cooled and the solvent removed under reduced pressure.

Flash chromatography (20-50% ether : light petroleum) gave vinylogous ester (**17**) (1.70 g, 24%), m.p. 48-51°C (from Et_2O) (Found: C, 73.8; H, 8.05. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); ν_{max} (CH_2Cl_2) 3320 (C≡C-*H*), 2960, 1650, 1620, 1380 and 1355 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.70 (3H, t, J 2Hz, *Me*), 1.92-2.06 (2H, m), 2.09 (1H, t, J 3Hz), 2.30-2.37 (2H, m), 2.54-2.65 (4H, m) and 4.13 (2H, t, J 6Hz, O-CH_2); δ_C (63 MHz; $CDCl_3$) 7.2, 19.9, 20.7, 25.2, 36.1, 66.4, 70.2, 79.6, 115.5, 170.4 and 198.7 (*C*=O); *m/z* 178 (M^+, 29%), 163 (85, *M*-CH_3), 98 (73) and 53 (100) (Found: M^+ 178.0993. $C_{11}H_{14}O_2$ requires M, 178.0990).

Preparation of 3-(Pent-3-ynyloxy)cyclohex-2-en-1-one (18)

A solution of 3-pentyn-1-ol (5.0 g, 59.5 mmol), cyclohexane-1,3-dione (6.67 g, 59.6 mmol) and *p*-TSA (19 mg) in benzene (60 ml) was heated under Dean-Stark conditions for 7h. The reaction was cooled and the solvent removed under reduced pressure.

Flash chromatography (20-80% ether : pentane) gave vinylogous ester (**18**) (8.92 g, 84%), m.p. 50-51°C (from Et_2O) (Found: C, 73.9; H, 8.0. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); ν_{max} (CCl_4) 2950, 1655, 1610, 1370, 1220 and 1185 cm^{-1}; δ (250 MHz; $CDCl_3$) 1.79 (3H, t, J 2.5Hz), 1.96-2.04 (2H, m), 2.32-2.46 (4H, m), 2.54-2.61 (2H, m), 3.89 (2H, t, J 7Hz) and 5.35 (1H, s); *m/z* 178 (M^+, 14%), 163 (4, *M*-*Me*), 67 (100, C_5H_7) and 39 (79, C_3H_3).

Preparation of 3-(But-3-ynyloxy)-2-(pent-4-enyl)cyclohex-2-en-1-one (19)

A solution of dione (**20**) (500 mg, 2.78 mmol), 3-butyn-1-ol (316 mg, 4.51 mmol) and *p*-TSA (7 mg) in benzene (15 ml) was heated under Dean-Stark conditions for 16h. The reaction was cooled and the benzene removed under reduced pressure.

Flash chromatography (30-100% ether : light petroleum) gave vinylogous ester (**19**) (459 mg, 71%); ν_{max} (film) 3310, 2950, 2130, 1650 and 1630 cm^{-1}; δ_H (80 MHz; $CDCl_3$) 1.15-2.75 (15H, m), 4.13 (2H, t, J 6Hz), 4.88-5.15 (2H, m) and 5.60-6.15 (1H, m); δ_C (63 MHz; $CDCl_3$) 20.1, 21.0, 21.7, 25.4, 27.8, 33.6, 36.5, 65.4, 70.3, 79.7, 113.9, 120.2, 139.3, 170.6 and 198.4; *m/z* (C.I.) 233 (M^+ + H, 33%), 163 (21) and 53 (80) (Found: M^+ 232.1467. $C_{15}H_{20}O_2$ requires M, 232.1458).

Preparation of 2-(Pent-4-enyl)cyclohexane-1,3-dione (20) by the method of Smith[6]

A mixture of cyclohexane-1,3-dione (4.51 g, 40.3 mmol), 5-bromopent-1-ene (9.0 g, 60.4 mmol) and KOH (2.26 g, 40.4 mmol) in a mixture of dioxane (45 ml) and water (15 ml) was heated under reflux for 36h.

The reaction was cooled, poured into water (50 ml) and extracted with ether (2 x 40 ml). The combined organic extracts were washed with brine (40 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure.

Flash chromatography (20-80% ether : light petroleum) gave dione (**20**) (0.78 g, 11%), m.p. 107-109°C (from CH_2Cl_2) (Found: C, 73.1; H, 9.0. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%); ν_{max} (KBr) 2930, 2640, 1640, 1565 and 1365 cm^{-1}; δ (250 MHz; $CDCl_3$) 1.30-2.72 (12H, m), 4.91-5.08 (2H, m), 5.70-5.92 (1H, m) and 7.50 (1H, br.s, O*H*); *m/z* 180 (M^+, 19%) and 69 (18) (Found: M^+ 180.1156. $C_{11}H_{16}O_2$ requires M, 180.1146).

Preparation of 1,5-Dimethoxycyclohexa-1,4-diene (21)

To a vigorously stirred solution of ammonia (700 ml, freshly distilled from sodium metal) at -78°C was added sodium (30 g, 1.3 mmol) over 0.5h.

After a further 0.5h, a solution of 1,3-dimethoxybenzene (32.7 g, 0.24 mol) in anhydrous ether (100 ml) and anhydrous ethanol (62.5 g, 1.36 mol) was added slowly over 2h.

After a further 1.5h, a solution of ethanol (35 ml) and water (35 ml) was carefully added, followed by water (300 ml) until a colourless solution formed. The ammonia was allowed to evaporate, the remaining mixture diluted with brine (700ml) and extracted with a mixture of ether/light petroleum (1:1) (3 x 250 ml) followed by ether (100 ml). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure.

Distillation gave (**21**) (30.2 g, 91%), b.p. 55°C (0.5 mm Hg) (lit.,[5] 56°C, 0.55 mm Hg); ν_{max} (film) 1705, 1670, 1400 and 1210 cm^{-1}; δ (250 MHz; $CDCl_3$) 2.7-2.9 (4H, m), 3.53 (6H, s) and 4.65 (2H, br.t, J 3Hz); *m/z* 140 (M^+, 82%) and 109 (100) (Found: M^+ 140.0836. $C_8H_{12}O_2$ requires M, 140.0834).

Preparation of 2-(Pent-4-enyl)cyclohexane-1,3-dione (20) using the method of Piers[5]

To a solution of ^{t}BuLi (7.4 ml of a 1.7M solution, 12.6 mmol) in THF (20 ml) at -78°C under nitrogen was added diene (**21**) (1.59 g, 11.4 mmol) in THF (5 ml), and the mixture stirred at -78°C for 1h. To the resulting yellow solution was added HMPA (1.63 ml, 13.2 mmol), the reaction turning purple upon addition.

After 10 min, a solution of 5-iodopent-1-ene (2.89 g, 14.7 mmol) in THF (5 ml) was added, and the reaction warmed to room temperature over 7h. The light brown solution was poured into brine (30 ml) and extracted with pentane (2 x 30 ml). The combined pentane extracts were washed with brine (3 x 40 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude 2,4-dimethoxy-3-(pent-4-enyl)hexa-1,4-diene was used without further purification.

To a solution of this alkylated product (2.42 g, 11.6 mmol) in degassed acetone (60 ml) under nitrogen was

added a degassed solution of HCl (20 ml of a 1M solution, 20 mmol), and the mixture stirred at room temperature for 3h. The solvent was removed under reduced pressure, the residue diluted with brine (50 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure.
Recrystallisation from acetone gave (**20**) (0.61 g, 30%), which was identical to that obtained previously.

Preparation of 6-Methyl-1-oxaspiro[4.4]nonan-7-one (22)
To a refluxing solution of vinylogous ester (**8**) (1.28 g, 4.13 mmol) in benzene (140 ml) under nitrogen was added a solution of Bu_3SnH (1.32 g, 4.54 mmol) and AIBN (135 mg, 0.82 mmol) in benzene (70 ml), dropwise over 6.5h.
The reaction was heated under reflux for a further 1h, cooled, and the benzene removed by rotary evaporation.
Two fractions were isolated by flash chromatography (5-40% ether : light petroleum). The first eluted was spiroether (**22**) (312 mg, 49%) as a mixture of diastereomers; ν_{max} (film) 2930, 2860, 1735 and 1450 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.02 (3H, d, J 7Hz), 1.79-2.5 (9H, m) and 3.82-3.93 (2H, m); *m/z* 154 (M^+, 99%), 125 (13) and 97 (100) (Found: M^+ 154.0997. $C_9H_{14}O_2$ requires M, 154.0990).
Followed by reduced, uncyclised product (2-methyl-3-propanoxycyclopent-2-en-1-one) (282 mg, 44%) (80 MHz; $CDCl_3$) 1.23-1.40 (3H, m), 1.75 (3H, br. s), 1.76-2.05 (2H, m), 2.25-2.65 (4H, m) and 3.70 (2H, t, J 7Hz).

Preparation of 7-Methyl-1-oxaspiro[5.4]decan-8-one (23)
To a refluxing solution of vinylogous ester (**12**) (230 mg, 0.71 mmol) in benzene (20 ml) under nitrogen was added a solution of Bu_3SnH (227 mg, 0.78 mmol) and AIBN (23 mg, 0.14 mmol) in benzene (20 ml), dropwise over 6h.
The reaction was heated under reflux for a further 1.5h, cooled, and the benzene removed by rotary evaporation.
Two fractions were isolated by flash chromatography (5-40% ether : light petroleum), the major product being spiroether (**23**) as a mixture of diastereomers (78 mg, 65%); ν_{max} (film) 2940, 1740, 1445 and 1090 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.99-1.03 (3H, m), 1.35-1.79 (6H, m), 1.97-2.73 (5H, m) and 3.62-3.72 (2H, m); δ_C (63 MHz; $CDCl_3$) 10.5 (q, *C-11*), 19.6 (t), 25.6 (t), 29.0 (t), 29.2 (t), 34.8 (t), 52.4 (d, *C-7*), 62.3 (t, *C-2*), 81.3 (s, *C-6*) and 219.8 (s, *C-8*); *m/z* 168 (M^+, 46%) and 111 (100) (Found: M^+ 168.1149. $C_{10}H_{16}O_2$ requires M, 168.1146). The minor product was reduced, uncyclised material (3-butanoxy-2-methylcyclopent-2-en-1-one) (36 mg, 30%); δ (60 MHz; $CDCl_3$) 0.83-1.04 (3H, m), 1.16-1.96 (7H, m), 2.28-2.66 (4H, m) and 3.99 (2H, t, J 7Hz).

Synthesis of 1-Oxaspiro[4.5]decan-7-one (24)
To a refluxing solution of vinylogous ester (**9**) (912 mg, 2.94 mmol) in benzene (100 ml) under nitrogen was added a solution of Bu_3SnH (942 mg, 3.24 mmol) and AIBN (96 mg, 0.6 mmol) in benzene (50 ml), dropwise over 6h.
The reaction was heated under reflux for a further 1h, cooled, and the benzene removed by rotary evaporation.
Two fractions were isolated by flash chromatography (10-40% ether : light petroleum). The first eluted was spiroether (**24**) (291 mg, 64%); ν_{max} (film) 2950, 2860, 1715, 1450 and 1230 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.68-2.09 (8H, m), 2.23-2.41 (2H, m), 2.45 (2H, s, *H-6*) and 3.76-3.91 (2H, m); δ_C (63 MHz, $CDCl_3$) 22.0 (t), 25.5 (t), 36.0 (t), 36.5 (t), 40.5 (t), 53.0 (t), 67.0 (t, *C-2*), 85.0 (s, *C-5*) and 210.0 (s, *C-7*); *m/z* 154 (M^+, 25%); 111(50) and 97 (100) (Found: M^+ 154.1000. $C_9H_{14}O_2$ requires M, 154.0994); followed by reduced, uncyclised product (3-propanoxycyclohex-2-en-1-one) (120 mg, 27%); δ (80 MHz; $CDCl_3$) 0.91-1.10 (3H, m), 1.53-2.15 (4H, m), 2.23-2.50 (4H, m), 3.78 (2H, t, J 7Hz) and 5.33 (1H, s).

Preparation of 1-Oxaspiro[5.5]undecan-8-one (25)

To a refluxing solution of vinylogous ester (**13**) (1.20 g, 3.7 mmol) in benzene (100 ml) under nitrogen was added a solution of Bu_3SnH (1.19 g, 4.1 mmol) and AIBN (122 mg, 0.7 mmol) in benzene (80 ml), dropwise over 6.5h.

The reaction was heated under reflux for a further 1.5h, cooled, and the benzene removed under reduced pressure.

Two fractions were isolated by flash chromatography (5-40% ether : light petroleum), the minor product being spiroether (**25**) (31 mg, 5%); δ_H (250 MHz; $CDCl_3$) 1.44-2.44 (11H, m), 2.67 (1H, m) and 3.53-3.70 (2H, m); δ_C (63 MHz; $CDCl_3$) 19.5, 20.5, 26.0, 29.5, 33.0, 35.0, 41.5, 50.5, 61.0 and 210.0; *m/z* 168 (M^+, 52%), 125 (59) and 111 (100) (Found: M^+ 168.1146. $C_{10}H_{16}O_2$ requires M, 168.1146). The major product was reduced, uncyclised material (3-butanoxycyclohex-2-en-1-one) (456 mg, 73%); δ (60 MHz; $CDCl_3$) 0.66-2.50 (13H, m), 3.83 (2H, t, J 7Hz) and 5.27 (1H, s).

Preparation of 2,6-Dimethyl-1-oxaspiro[4.5]decan-7-one (26)

To a refluxing solution of (**14**) (1.51 g, 4.48 mmol) in benzene (110 ml) was added a solution of Bu_3SnH (1.44 g, 4.95 mmol) and AIBN (147 mg, 0.90 mmol) in benzene (110 ml), dropwise over 5.5h.

The reaction was heated under reflux for a further 1h, cooled, and the solvent removed under reduced pressure. Flash chromatography (5-30% ether : light petroleum) gave spiroether (**26**) as two diastereomers. Major isomer (547 mg, 67%); ν_{max} (film) 2970, 1710 (*C=O*), 1455 and 1100 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.03 (3H, d, J 7Hz), 1.26 (3H, d, J 6Hz); 1.38-1.74 (4H, m), 1.81-2.05 (4H, m), 2.22-2.40 (2H, m), 2.63 (1H, q, J 7Hz) and 4.03-4.11 (1H, m); δ_C (63 MHz; $CDCl_3$) 8.8 (*C-11*) 20.4 (*C-12*), 20.7, 31.7, 35.5, 37.6, 40.5, 55.2 (*C-6*), 74.5 (*C-2*), 87.5 (*C-5*) and 211.4 (*C-7*); *m/z* 182 (M^+, 16%), 139 (26) and 111 (100) (Found: M^+ 182.1328. $C_{11}H_{18}O_2$ requires M, 182.1302). Minor isomer (148 mg, 18%); ν_{max} (film) 2895, 1710 (*C=O*), 1120 and 950 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.05 (3H, d, J 7Hz), 1.19 (3H, d, J 6Hz), 1.58-1.83 (4H, m), 1.86-2.07 (4H, m), 2.17-2.30 (1H, m), 2.34-2.48 (2H, m) and 3.99 (1H, m); *m/z* 182 (M^+, 73%), 139 (44), 111 (100) and 55 (65) (Found: M^+ 182.1284. $C_{11}H_{18}O_2$ requires M, 182.1302).

Preparation of (*E*)-4-(Tributylstannylmethylene)-1-oxaspiro[4.5]decan-7-one (27)

To a refluxing solution of (**15**) (525 mg, 3.2 mmol) in benzene (100 ml) under nitrogen was added a solution of Bu_3SnH (1.02 g, 3.51 mmol) and AIBN (105 mg, 0.64 mmol) in benzene (60 ml), dropwise over 6h.

The reaction was heated under reflux for a further 1h, cooled, and the benzene removed under reduced pressure.

The resultant oil was subjected to flash chromatography (10-80% ether : light petroleum) to give spiroether (**27**) (810 mg, 56%) (Found: C, 58.3; H, 8.9. $C_{22}H_{40}O_2Sn$ requires C, 58.0; H, 8.9%); ν_{max} (film) 2940, 1720, 1620, 1450 and 1050 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.84-1.03 (15H, m), 1.23-1.61 (12H, m), 1.73-1.86 (2H, m), 1.90-2.09 (2H, m), 2.23-2.47 (4H, m), 2.48-2.61 (2H, m), 3.81-3.90 (2H, m) and 5.67 (1H, t, J 1Hz); δ_C (63 MHz; $CDCl_3$) 9.8, 13.7, 21.8, 27.2, 34.7, 34.8, 40.7, 51.4, 64.5, 87.0. 117.1, 162.7 and 210.1; *m/z* 456 (M^+, 0.1%), 397 (38), 368 (34) and 165 (100).

Preparation of (*E*)-6-Methyl-4-(tributylstannylmethylene)-1-oxaspiro[4.5]decan-7-one (28)

To a refluxing solution of (**17**) (500 mg, 2.81 mmol) in benzene (50 ml) under nitrogen was added a solution of Bu_3SnH (899 mg, 3.09 mmol) and AIBN (92 mg, 0.56 mmol) in benzene (100 ml), dropwise over 5.5h.

The reaction was heated under reflux for a further 2h, cooled, and the solvent removed under reduced pressure. Flash chromatography (5-40% ether : light petroleum) gave spiroether (**28**) (575 mg, 44%) (Found: C, 59.1; H, 9.3. $C_{23}H_{42}O_2Sn$ requires C, 58.9; H, 9.0%); major diastereomer: ν_{max} (film) 2960, 2910, 1715, (*C=O*),

1620 and 1460 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.83-0.94 (15H, m), 1.04 (3H, d, J 7Hz, *6-Me*), 1.20-2.06 (15H, m), 2.23-2.70 (6H, m), 3.88-3.96 (2H, m) and 5.30 (1H, t, J~1Hz); δ_C (63 MHz; $CDCl_3$) 9.8, 10.1, 13.6, 19.6, 27.1, 29.0, 34.2, 35.9, 39.1, 53.0, 64.8, 88.3, 119.8, 157.7 and 221.9; minor diastereomer: δ (250 MHz; $CDCl_3$) 0.86-0.99 (18H, m), 1.24-2.06 (15H, m), 2.26-2.64 (6H, m), 3.74 (1H, q, J 7Hz), 3.82-4.02 (1H, m) and 5.70 (1H t, J~1Hz); *m/z* (combined) 413 (M^+ - 57, 15%), 383 (12) and 179 (100).

Preparation of (*E*)-6-Methyl-4-(triphenylstannylmethylene)-1-oxaspiro[4.5]decan-7-one (29)

To a refluxing solution of (**17**) (267 mg, 1.5 mmol) in benzene (40 ml) under nitrogen was added a solution of Ph_3SnH (579 mg, 1.65 mmol) and AIBN (49 mg, 0.3 mmol) in benzene (40 ml), dropwise over 6h.

The reaction was heated under reflux for a further 1h, cooled, and the benzene removed under reduced pressure.

Flash chromatography (5-30% ether : light petroleum) gave spiroether (**29**) (246 mg, 31%) (Found: C, 66.0; H, 5.9. $C_{29}H_{30}O_2Sn$ requires C, 65.8; H, 5.7%); major diastereomer: ν_{max} (film) 2730, 1715, 1620 (*C=C*) and 1430 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.16 (3H, d, J 7Hz, *6-Me*), 1.77-2.73 (9H, m), 3.82 (2H, t, J 7Hz), 5.66 (1H, t, J~1Hz), 7.33-7.60 (15H, m); δ_C (63 MHz; $CDCl_3$) 10.6, 19.9, 33.8, 36.5, 39.0, 52.8, 64.6, 88.9, 115.8, 128.7, 129.1, 136.8, 137.1, 162.5 and 211.7; minor diastereomer: δ (250 MHz; $CDCl_3$) 1.03 (3H, d, J 7Hz, *6-Me*), 1.78-2.73 (9H, m), 3.61-3.74 (2H, m), 6.04 (1H, t, J~1Hz) and 7.40-7.66 (15H, m); *m/z* 530 (M^+, 1%), 453 (12) and 351 (75) (Found: M^+ 530.1261. $C_{29}H_{30}O_2{}^{120}Sn$ requires M, 530.1259).

Preparation of (*E*)-5-(Tributylstannylmethylene)-1-oxaspiro[5.5]undecan-8-one (30)

To a refluxing solution of vinylogous ester (**16**) (1.0 g, 5.6 mmol) in benzene (140 ml) under nitrogen was added a solution of Bu_3SnH (1.8 g, 6.2 mmol) and AIBN (185 mg, 1.1 mmol) in benzene (140 ml), dropwise over 5.5 h.

The reaction was heated under reflux for a further 1h, cooled, and the solvent removed under reduced pressure.

Two fractions were isolated by flash chromatography (5-40% ether : light petroleum), the minor product being the spiroether (**30**) (85 mg, 3%) (Found: C, 59.2; H, 9.1. $C_{23}H_{42}O_2Sn$ requires C, 58.9; H, 9.0%); ν_{max}(film) 2940, 2865, 1720(*C=O*), 1600(*C=C*) and 1090 cm^{-1}; δ (250 MHz, $CDCl_3$) 0.85-0.96 (15H, m), 1.22-1.54 (14H, m), 1.63-2.03 (4H, m), 2.14-2.50 (4H, m), 2.55-2.73 (2H, m), 3.64-3.76 (2H, m) and 5.59 (1H, s); *m/z* 413 (M^+ - C_4H_9, 100%), 251 (30) and 179 (64); (Found: M^+ - C_4H_9 413.1481. $C_{19}H_{33}O_2{}^{120}Sn$ requires 413.1493).

The major product was uncyclised vinyl stannane (**31**) (1.38 g, 52%) (Found: C, 59.3; H, 8.9. $C_{23}H_{42}O_2Sn$ requires C, 58.9; H, 9.0%); ν_{max}(film) 2960, 2930, 1660, 1605, 1570, 1220, 1185 cm^{-1}; δ (250 MHz ; $CDCl_3$) 0.83-0.95 (15H, m), 1.22-1.57 (13H, m), 1.78-2.04 (4H, m), 2.14-2.44 (5H, m), 3.84 (2H, t, J 7Hz), 5.35 (1H, s) and 5.87-6.08 (2H, m); *m/z* 413 (M^+ - C_4H_9, 100%) and 151 (30) (Found: M^+ - C_4H_9 413.1517. $C_{19}H_{33}O_2{}^{120}Sn$ requires 413.1493).

Attempted cyclisation of (18)

To a refluxing solution of (**18**) (500 mg, 2.81 mmol) in benzene (79 ml) under nitrogen was added a solution of Bu_3SnH (901 mg, 3.1 mmol) and AIBN (94 mg, 0.57 mmol) in benzene (70 ml), dropwise over 5.5 h.

The reaction was heated under reflux for a further 1h, cooled, and the benzene removed under reduced pressure.

Flash chromatography of the residue (20-100% ether : light petroleum) gave uncyclised hydrostannylated product (**32**) (126 mg, 10%); ν_{max} (film) 2920, 1665, 1605, 1220, and 1180 cm^{-1}; δ (250 MHz ; $CDCl_3$) 0.83-0.99 (18H, m), 1.21-1.38 (5H, m), 1.39-1.62 (4H, m), 1.64-2.06 (6H, m), 2.30-2.46 (4H, m), 2.56 (1H, m), 3.69-3.87 (2H, m), 5.33 (1H, s) and 6.13-6.23 (1H, m); *m/z* 413 (M^+ - C_4H_9, 100%), and 177

(22) (Found: $M^+ - C_4H_9$ 413. 1495. $C_{19}H_{33}O_2{}^{120}Sn$ requires 413.1493) and recovered starting material (424 mg).

Preparation of *(4E)-(5RS, 6RS, 11RS)*-11-Methyl-4-(tributylstannylmethylene)-1-oxadispiro[4.0.4.4]tetradecan-7-one (33)

To a refluxing solution of vinylogous ester (**19**) (339 mg, 1.46 mmol) in benzene (25 ml) under nitrogen was added a solution of Bu_3SnH (510 mg, 1.75 mmol) and AIBN (48 mg, 0.3 mmol) in benzene (45 ml), dropwise over 6 h.

The reaction was heated under reflux for a further 2h, cooled, and the benzene removed under reduced pressure.

Flash chromatography of the residue (2-10% ether : light petroleum) gave the bis-spiro product (**33**) (275 mg, 36%) (Found: C, 62.35; H, 9.3. $C_{27}H_{48}O_2Sn$ requires C, 62.0; H, 9.2%); ν_{max} (film) 2940, 1710, 1620, 1470 and 1055 cm^{-1}; δ_H (500 MHz ; $CDCl_3$) 0.81-0.97 (15H, m), 1.05 (3H, d, J 6Hz, *11-Me*), 1.23-1.93 (21H, m), 2.04-2.63 (6H, m), 3.80 (1H, q, J 7Hz), 3.89-3.98 (1H, m) and 5.93 (1H, t, J~1Hz); δ_C (63 MHz ; $CDCl_3$) 9.9 (t), 13.6 (q), 17.8 (q), 18.5 (t), 23.1 (t), 27.1 (t), 29.1 (t), 31.6 (t), 33.1 (t), 35.3 (t), 37.1 (t), 39.2 (t), 39.9 (d, *C-11*), 64.4 (t, *C-2*), 66.3 (s, *C-6*), 90.5 (s, *C-5*), 119.7 (d, *C-16*), 160.4 (s, *C-4*) and 212.8 (s, *C-7*); *m/z* (NH_3 C.I.) 525 ($M^+ + H$, 100%), 233 (95) and 109 (100) [Found: (NH_3 C.I.) $M^+ + H$ 525.2757. $C_{27}H_{49}O_2{}^{120}Sn$ requires M, 525.2741].

Preparation of 6-(But-3-enyl)-3-(3-phenylselenopropanoxy)cyclohex-2-en-1-one (35)

To a solution of LDA (7.6 mmol) in THF (10 ml) at -78°C under nitrogen was added a solution of vinylogous ester (**13**) (2.14 g, 6.19 mmol) in THF (5 ml) and the mixture maintained at -78°C for 1h. To this was added HMPA (1 ml) and the mixture stirred for a further 20 min. A solution of 4-iodobut-1-ene (2.15 g, 13.8 mmol) in THF (3 ml) was added, the solution maintained at -78°C for a further 1.5h, and then allowed to warm to room temperature overnight.

The reaction mixture was poured into a solution of NH_4Cl (20 ml) and extracted with ether (2 x 15 ml). The combined organic extracts were washed four times successively with water (20 ml) and brine (20 ml) then dried ($MgSO_4$), and the solvent removed under reduced pressure

Flash chromatography (10-60% ether : light petroleum) gave the alkylated vinylogous ester (**35**) (1.12g, 45%) (Found: C, 62.9; H, 6.7. $C_{19}H_{24}O_2Se$ requires C, 62.8; H, 6.7%); ν_{max} (film) 2945, 1655, 1610, 1580, 1370 and 1190 cm^{-1}; δ (250 MHz; $CDCl_3$) 1.37-1.52 (1H, m), 1.63-1.79 (1H, m), 1.92-2.27 (7H, m), 2.34-2.43 (2H, m), 3.00 (2H, t, J 7Hz), 3.92 (2H, t, J 6Hz), 4.93-5.09 (2H, m), 5.28 (1H, s), 5.80 (1H, m), 7.23-7.31 (3H, m) and 7.44-7.53 (2H, m); *m/z* 364 (M^+, 100%), 157(29) and 111(23) (Found: M^+ 364.0975. $C_{19}H_{24}O_2{}^{80}Se$ requires M, 364.0935).

Attempted bis-cyclisation of (35)

To a refluxing solution of (**35**) (656 mg, 1.81 mmol) in benzene (40 ml) was added a solution of Bu_3SnH (577 mg, 1.98 mmol) and AIBN (59 mg, 0.36 mmol) in benzene (40 ml), dropwise over 6.5 h.

The reaction was heated under reflux for a further 2h, cooled, and the benzene removed under reduced pressure.

Three fractions were isolated by flash-chromatography (5-60% ether : light petroleum): (**37**) (200 mg, 53%); ν_{max} ($CHCl_3$) 2920, 2870, 1705(*C=O*), 1640(*C=C*), 1450 and 930 cm^{-1}; δ (250 MHz; $CDCl_3$) 1.21-1.38 (2H, m), 1.60-2.30 (11H, m), 2.44 (2H, s), 3.72-3.89 (2H, m), 4.90-5.04 (2H, m) and 5.78 (1H, m); *m/z* 208 (M^+, 5%), 97 (88), and 84 (100) (Found : M^+ 208.1445. $C_{13}H_{20}O_2$ requires M, 208.1458); followed by reduced, uncyclised product 6-(but-3-enyl)-3-propanoxycyclohex-2-en-1-one (49 mg, 13%); ν_{max} (film) 2940,

1705, 1660, 1610, 1455, 1375 and 1190 cm^{-1}; δ (250 MHz ; $CDCl_3$) 0.99 (3H, t, J 7Hz), 1.21-2.51 (10H, m), 3.75-3.86 (2H, m), 4.93-5.10 (2H, m), 5.21 (1H, s) and 5.70-5.90 (2H, m); *m/z* 208 (M^+, 40%), 154 (90), 112 (78), 97 (100) and 84 (45) (Found : M^+ 208.1452. $C_{13}H_{20}O_2$ requires M, 208.1458); and recovered starting material (**35**) (126 mg).

Preparation of (*5SR, 6RS, 11RS*)-11-Methyl-4-methylene-1-oxadispiro[4.0.4.4]tetradecan-7-one (38)

To a solution of (**33**) (390 mg, 0,75 mmol) in CH_2Cl_2 (4 ml) was added PPTS (377 mg, 1.5 mmol) and the reaction stirred at room temperature for 24 h until t.l.c. analysis showed complete consumption of starting material and formation of a more polar product. The solvent was removed under reduced pressure and the crude product chromatographed (5-10% ether : light petroleum) to give the destannylated product (**38**) (122 mg, 70%) (Found : C, 76.9; H, 9.5. $C_{15}H_{22}O_2$ requires C, 76,9; H, 9.5%); ν_{max} (film) 3950, 1700 (*C=O*), 1655, 1435 and 1065 cm^{-1}; δ_H (250 MHz ; $CDCl_3$) 1.12 (3H, d, J 6Hz, *11-Me*), 1.40-2.63 (13H, m), 2.66-2.76 (2H, m), 3.83 (1H, q, J 7Hz), 3.95-4.03 (1H, m), 4.72 (1H, t, J 2Hz) and 5.15 (1H, t, J 2Hz); δ_C (125 MHz; $CDCl_3$) 17.9, 18.8, 23.1, 32.0, 33.0, 35.4, 35.6, 39.3, 40.2, 64.8, 66.6 (*C-6*), 89.8 (*C-5*), 107.5 (*C-16*), 152.0 (*C-4*) and 213.2 (*C-7*), *m/z* 234 (M^+, 8%) and 109 (100).

Preparation of the 2,4-Dinitrophenylhydrazone (39)

To an alcoholic solution of 2,4-dinitrophenylhydrazine (3 ml) at 60°C was added the bis-spiro compound (**38**) (57 mg, 0.24 mmol) in ethanol (0.5 ml). The solution was allowed to cool to room temperature, and the crystalline precipitate filtered off to give hydrazone derivative (**39**) (93 mg, 92%). A small portion was recrystallised for X-ray analysis, m.p. 116-118°C (from ethyl acetate-hexane); ν_{max} ($CHCl_3$) 3320 (*NH*), 2950, 1620, 1590 and 1340 cm^{-1}; δ (400 MHz; $CDCl_3$) 1.12 (3H, d, J 6Hz), 1.46-2.61 (13H, m), 2.63-2.75 (2H, m), 3.80 (1H, m), 3.94-3.99 (1H, m), 4.69 (1H, t, J 2Hz), 5.10 (1H, t, J 2Hz), 7.93 (1H, m), 8.30 (1H, m), 9.13 (1H, d, J 2Hz) and 11.28 (1H, s); *m/z* 414 (M^+, 3%), 232 (47) and 182 (2) (Found : M^+ 414.1879. $C_{21}H_{26}N_4O_5$ requires M, 414.1897.

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