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TOTAL SYNTHESIS OF THE INSECT ANTIFEEDANT AJUGARIN I AND DEGRADATION STUDIES OF RELATED CLERODANE DITERPENES

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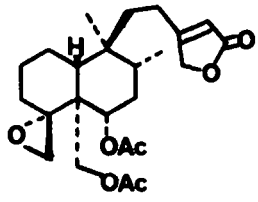
Abstract The first total synthesis of the diterpene clerodane insect antifeedant ajugarin I (1) has been achieved. The key step of the synthesis discloses the use of the 1,3-dithiolane unit to stereochemically direct the conjugate addition of a but-3-enyl cuprate to set in place the C-10 sp_3 carbon centre. The trans-fused ring geometry was obtained by conjugate additon of a vinyl cuprate to an enone and regio and stereoselectively trapping the resulting enolate with formaldehyde. Introduction of the necessary butenolide side chain was achieved by conjugate addition of a sulphone stabilised anion to ethyl-4-(t-butyldimethylsilyloxy)but-2-ynoate followed by work-up with fluoride. Final hydroxyl directed epoxidation was not specific giving both the natural product ajugarin I and its 4-epi isomer. Chemical modification of the insect antifeedant clerodin hemiacetal afforded a series of side chain modified structures for biological evaluation.

Over 400 clerodane diterpene natural products are now known[1] some of which have useful biological properties. The Ajuga remota (Labiatae) plant, which is not attacked by predatory insects stimulated interest as a potential source of novel deterrent chemicals. Isolation studies led to the characterisation of five clerodane polyoxygenated diterpenes[2] of which ajugarin I (1) was the major component. Biological evaluation of (1) showed it to be a strong antifeedant against a variety of insect species.

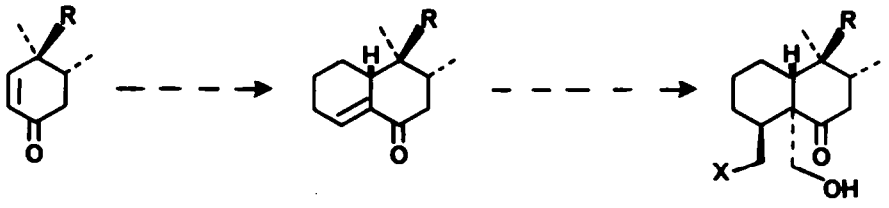


(1)

Several synthetic approaches to clerodane related compounds have now been reported[3] together with a limited number of total syntheses of the natural products.[4]

Our interest in understanding the functional group requirement for biological activity led us to develop general synthetic strategies to this class of compounds.[5] Here we show how these methods can now be applied to a more challenging total synthesis of the antifeedant ajugarin I (1).

The key elements of the synthesis require a stereoselective annelation of an appropriately substituted cyclohexenone derivative to afford a decalin enone followed by conjugate addition and regio- and stereoselective hydroxymethylation (Scheme 1). Further chemical manipulation of the functional groups would then lead to the required product.

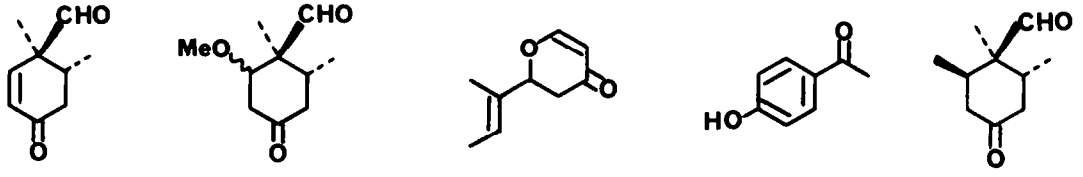


Scheme 1.

Despite this apparently simple plan considerable tactical effort was required to achieve these goals.

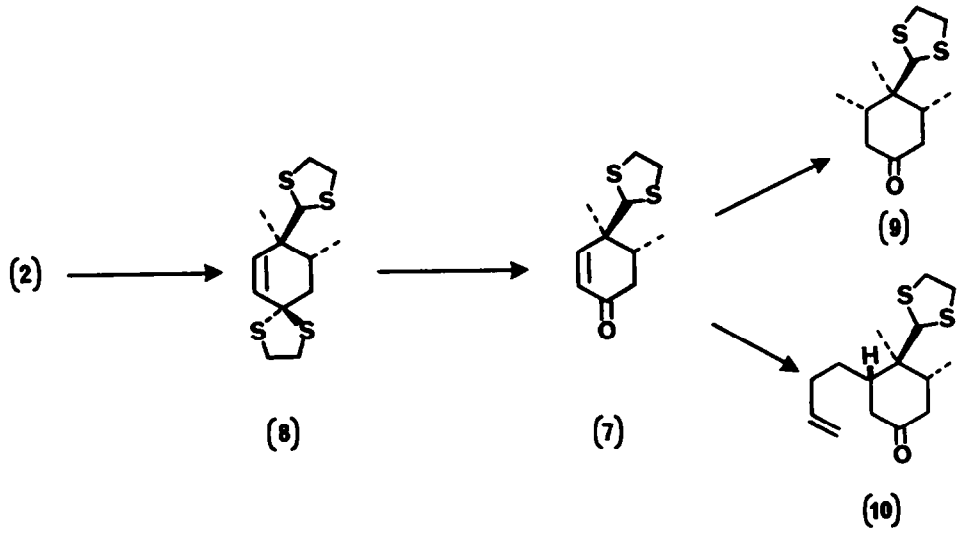
Preparation of the starting enone (2) was achieved by Diels-Alder reaction between 1-methoxy-3-trimethylsilyloxybutadiene (Danishefsky's diene)[6] and (E)-2-methylbut-2-enal at 140°. This reaction, upon aqueous hydrochloric acid work-up, gave (2) together with the methyl ethers (3) which were separately converted to (2) by further acid treatment with p-toluenesulphonic acid under reflux in benzene. The combined yield of (2) by this process was 48% owing to additional by-products also being formed. These side products (4) and (5) were characterised as resulting from Diels-Alder reaction between the diene and the carbonyl group of the initial aldehyde and of a similar reaction of the diene with 4-methoxy-3-buten-2-one (i.e. the hydrolysis product of the diene).

The next phase of the synthesis required the stereoselective conjugate addition of a cuprate

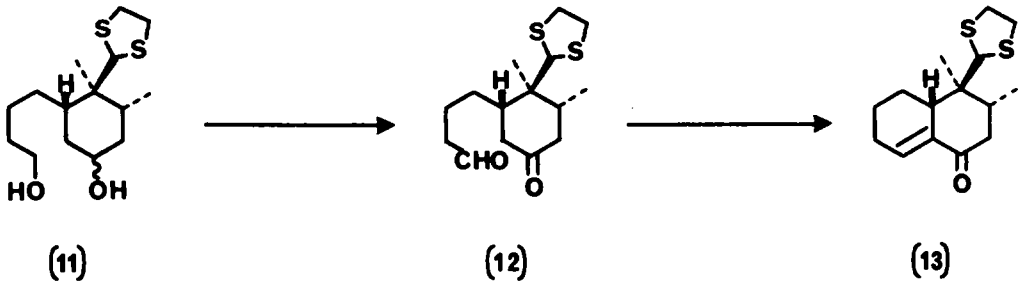


(2) (3) (4) (5) (6)

species to the enone (2), or a derivative, such that the cuprate added from the same side as the methyl substituents. However, with dimethylcopper lithium, for example, addition occurred exclusively from the top face to give (6). C-4 Groups other than formyl showed similar reactivity. To overcome this problem we reasoned that a 1,3-dithiolane group in place of the aldehyde might well bind strongly to the cuprate such that an unusually hindered top face of the molecule would force the second equivalent of cuprate to attack from the required bottom face. The monodithiolane (7) was prepared in two steps from (2) *via* the dithiolane (8) by selective hydrolysis using mercury (II) acetate and cadmium carbonate[7] or more reliably thallium (III) nitrate[8] in good overall yield. Pleasingly when (7) was treated with 2.2 equivalents of dimethylcopper lithium the only product of the reaction was the required compound (9) (60%). With this stereochemical addition problem solved we next studied the conjugate addition of a but-3-enyl side chain. This reaction too proceeded with excellent stereochemical control to give (10) in 92% yield. Addition of oxygen containing side-chains in this cuprate reaction gave poor stereocontrol.



Hydroboration of (10) using borane-dimethyl sulphide followed by basic hydrogen peroxide gave the diol (11) (96%). Attempts to oxidise (11) to the necessary keto-aldehyde (12) using a variety of chromium based reagents were unsuccessful. After much experimentation it was found that the pyridine/SO_3 activated DMSO method[9] cleanly gave (12) in 71% yield. Owing to varying quality of this reagent we preferred to use triphenylbismuth carbonate[10] as a more reliable method, in spite of the slightly lower yield (51%). Aldol condensation of (12) with p-toluene sulphonic acid in boiling benzene afforded the key enone (13) in 80% yield.

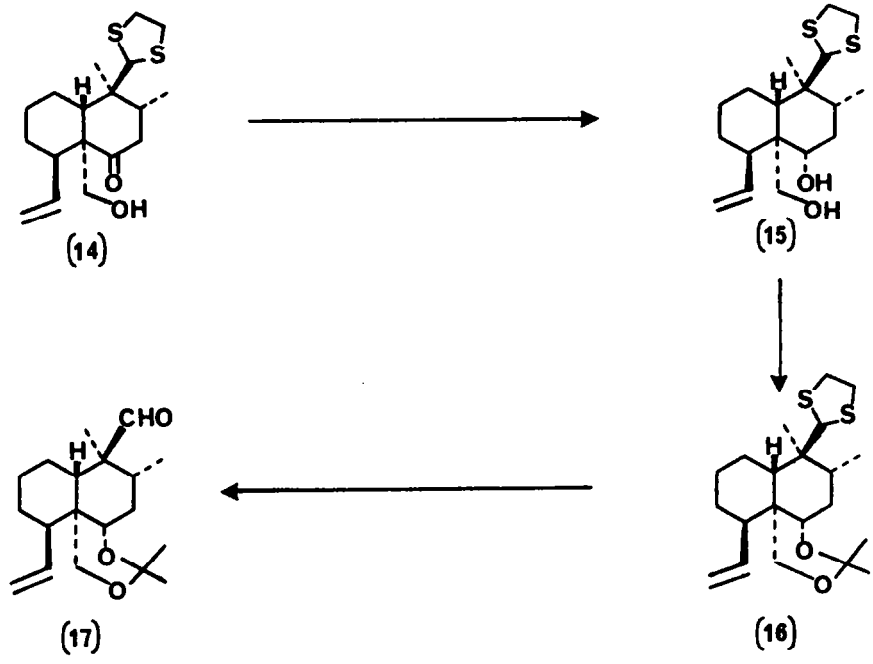


The next stage of the synthesis required the conjugate addition of a group to (13) which could be later unmasked as a methylene substituent at C-4. Simultaneous quenching of any conjugate addition process by formaldehyde should also introduce the primary methylene hydroxyl group at C-5. Several synthetic equivalents to the exo-methylene substituent were investigated without success. Therefore we decided to use the vinyl group as a masked equivalent since this, by ozonolytic cleavage, reductive work-up and elimination should give a methylene group. In addition, by using a vinyl substituent, we would gain synthetic flexibility owing to the robust nature of a carbon-carbon double bond.

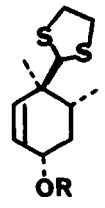
The synthesis of ajugarin I therefore proceeded by conjugate addition of divinylcopper lithium to (13) followed by regio- and stereoselective alkylation of the intermediate enolate with a THF solution of monomeric formaldehyde to produce (14). Some difficulty was experienced in

stereoselectively reducing the carbonyl group in (14) owing to the directing ability of the axial primary hydroxyl substituent. For this reason the free hydroxyl group was silylated using t-butyldimethylsilyl chloride and subsequently treated with $LiAlH_4$ to give the diol (15). The best results (44%) were obtained by conversion of the enone (13) through to (15) without purification of the intermediate silyl derivative. The hydroxyl groups in (15) were conveniently protected as the acetonide (16) (95%) using acetone and anhydrous copper (II) sulphate. Deprotection of the hindered dithiolane (16) to give (17) was achieved using buffered thallium (III) trifluoroacetate[11] in 80% yield. This procedure was noticeably superior to all other methods investigated.

At this point we addressed the problem of the introduction of the side chain. Firstly it was necessary to homologate the hindered aldehyde group in (17) in such a way as to be compatible with the other planned synthetic steps. These included ozonolytic cleavage and elaboration of the vinyl substituent to methylene, and ultimately epoxide functionalities, and the timing for the introduction of the butenolide moiety. In preparation for the studies we chose to investigate some

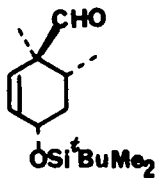


new chemistry which we hoped would find wider application for the introduction of this sensitive moiety. Therefore in model reactions (7) was reduced to (18) using sodium borohydride, protected as the t butyldimethylsilyl derivative (19) and the dithiolane was removed to give the aldehyde (20). This compound reacted smoothly with the anion from phenyltrimethylsilylmethylsulphone by a Peterson olefination sequence to give the vinyl sulphone (21) (92%).[12] We have also applied this method to several other hindered carbonyl groups with equal success. Conjugate reduction of (21) was now possible using lithium triethylborohydride to give the saturated sulphone (22) (97%).



(18) R= H

(19) R= Si^tBuMe_2



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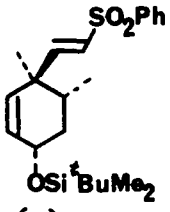

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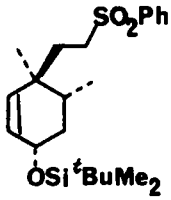

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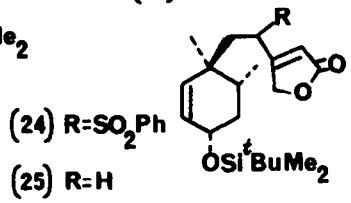
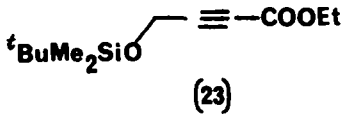


(24) R=SO_2Ph

(25) R=H



(23)

Introduction of the butenolide was achieved by deprotonating the sulphone (22) using n-butyllithium in THF/HMPA, followed by conjugate addition to the acetylenic ester (23). Without isolation of any intermediate, the mixture was then simply treated with tetra-n-butylammonium fluoride to give the butenolide (24) in a moderate 45% yield. Reductive removal of the phenylsulphone in the normal way with sodium amalgam gave (25) (85%).

Having demonstrated the successful preparation of the ethyl butenolide side chain in the model system we were now confident that a similar approach could be applied to the synthesis of ajugarin I Reaction of the aldehyde (17) with the anion from phenyltrimethylsilylmethylsulphone methane gave an addition product from which the (E)-vinyl sulphone (26) was obtained by elimination (96%).† Similar conjugate reduction using lithium triethylborohydride gave the saturated compound (27) (96%). The next stage of the synthesis required ozonolytic cleavage of the appending vinyl substituent.

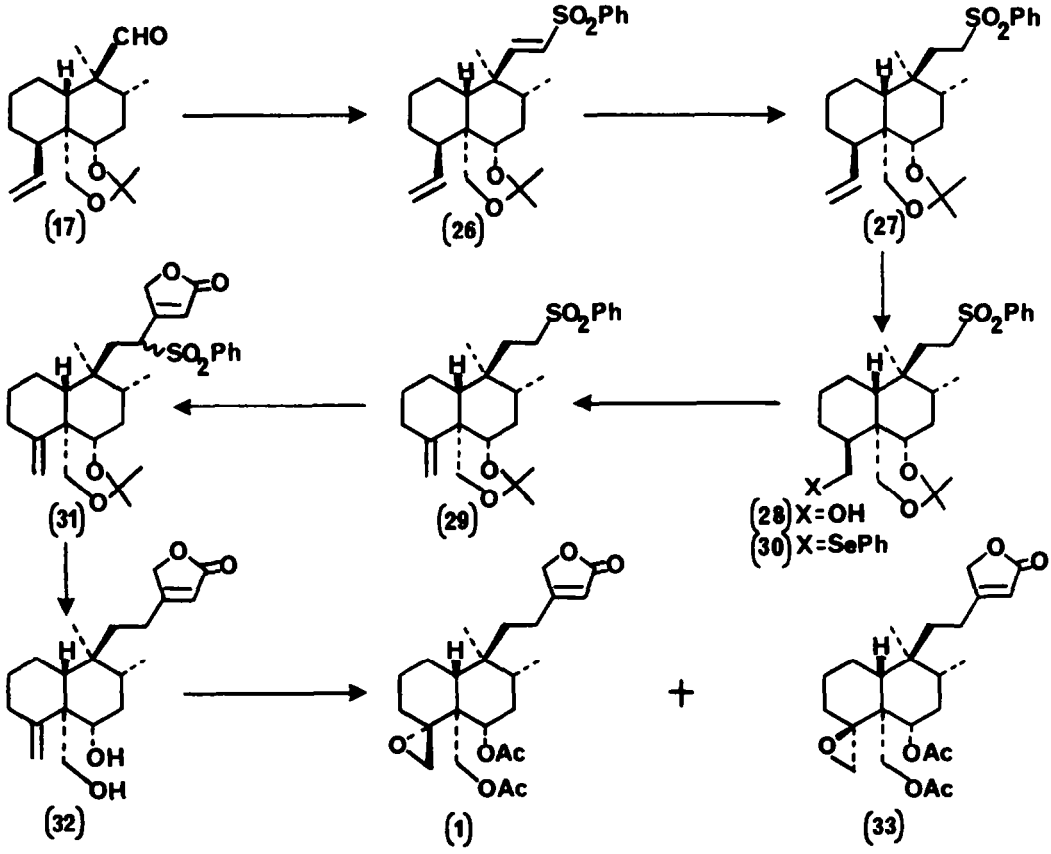
Treatment of (27) with O_3 followed by sodium borohydride work-up gave the hydroxysulphone (28) in essentially quantitative yield. This compound was transformed to the exomethylene derivative (29) via the phenylselenide (30) and syn-elimination of the corresponding selenoxide in 63% overall yield. The selenide (30) was prepared from (28) by reaction with N-phenylselenophthalimide (NPSP) and tri-n-butylphosphine.[13] Deprotonation of (29) with n-butyllithium and coupling with the butenolide synthon (23) gave the compound (31)in 46% yield after fluoride treatment. Reductive removal of the phenylsulphonyl group and deprotection of the acetonide with aqueous trifluoroacetic acid gave the diol (32) (75%).

The planned hydroxyl directed epoxidation of (32) using $VO(acac)_2$ and t-butylhydroperoxide[14] failed to afford useful products owing to the sensitivity of the butenolide ring under these conditions. After several attempts using peracids to effect the epoxidation of (32) we found that buffered m-chloroperbenzoic acid in CH_2Cl_2 at room temperature, followed by acetylation of the diol gave the natural product ajugarin I (1) in 20% yield. The major product in the reaction however was 4-epiajugarin I (33)[3g] which was obtained in 62% yield.

The synthesis of ajugarin I reported above constitutes the first total synthesis of this interesting insect antifeedant compound.

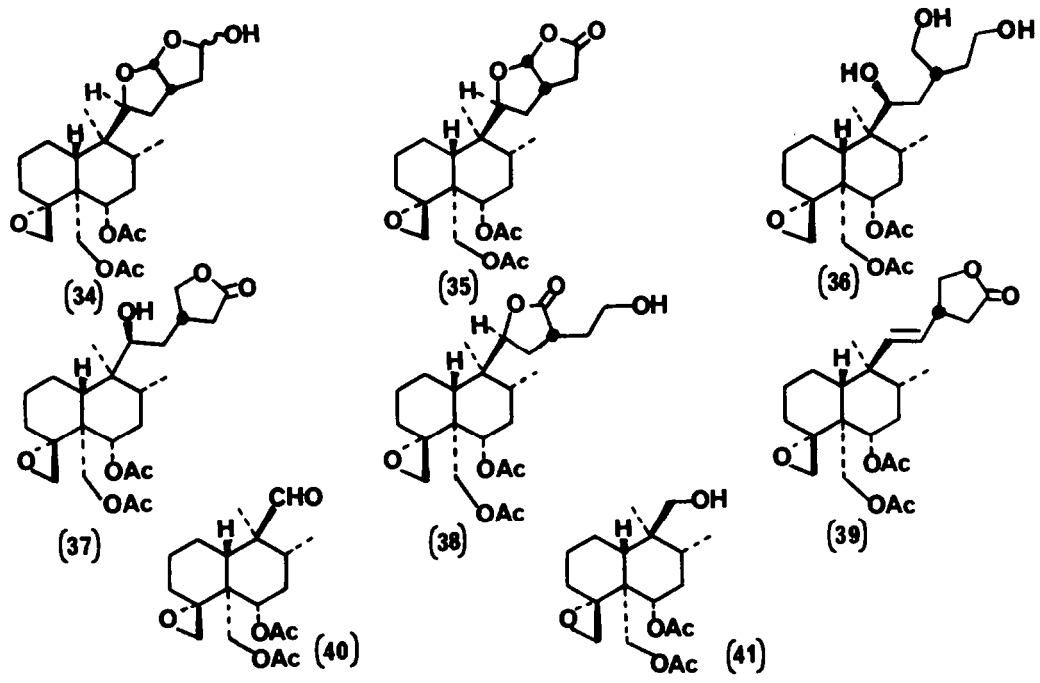
In connection with a wider programme designed to study the functional groups necessary for antifeedant activity we were also interested in other structures related to the ajugarin I molecule. As a quantity of the natural product clerodin hemiacetal (34)[15] was available we have also carried out several chemical modifications of the side chain. In these studies the epoxy diacetate arrangement in the decalin ring system was not varied since we already knew that changing these groups resulted in a dramatic reduction in biological activity.

Oxidation of (34) using barium manganate[16] gave the lactone (35) (80%) while treatment with



excess sodium borohydride produced the very polar triol (36) (83%). This triol with the Fetizon reagent[17] underwent oxidation to the hydroxy lactone (37) (67%). However with different batches of the oxidant some variation was noticed and in one experiment a 3:1 ratio of (37) to the alternative hydroxylactone (38) was obtained. Dehydration of (37) with phosphorus oxychloride in pyridine gave (39) (93%) which is interesting as this compound is an isomer of ajugarin I. Ozonolysis of (39) afforded the novel aldehyde (40) (35%) and on reductive work-up with borohydride gave the alcohol (41) (31%).

These degradation studies thus provided a series of novel structures suitable for biological evaluation.



EXPERIMENTAL

Melting points were determined for solid products using a Kofler hot-stage apparatus and are uncorrected, products without melting points were colourless oils. Infra-red spectra were recorded on a Perkin Elmer 298 a Perkin Elmer 983G grating infra-red spectrophotometer or a Matteson Instruments Sirius 100 FT-IR spectrophotometer using a thin film or solution in $CHCl_3$. ^1H n.m.r. spectra were obtained for solutions in $CDCl_3$ (Me_4Si as internal standard) and were recorded on a Varian EM 360A, Perkin Elmer R32, Varian XL100, Bruker WH 400 or Bruker WM 250 machine. Mass spectra were determined with a VG micromass 7070 B instrument. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel F_{254} plates. Preparative chromatography was carried out on columns of Merck Kieselgel 60.(230-400 mesh). Solvents were purified by standard techniques. Solutions were dried over anhydrous sodium sulphate and evaporated with a rotary evaporator, followed by static evaporation with an oil pump.

Preparation of 4β-Formyl-4α,5α-dimethylcyclohex-2-enone (2)

Into a carefully base-washed and dried 12 oz glass bomb, was placed 4-methoxy-2-trimethylsilyloxy-1,3 butadiene (22g, 0.123mol), tiglaldehyde (13g, 0.154mol) and hydroquinone (5 mg). The bomb was sealed, evacuated and placed in a hot Wood's metal bath (140°C) for 14-18h. During the course of the reaction, the initial pale yellow colour of the mixture changed to a golden brown. After cooling, the crude adducts of three such runs were combined, dissolved in THF (450 ml) and hydrolysed by the addition 2N HCl (1 ml). After 30 min the reaction mixture was carefully neutralised (aqueous sodium bicarbonate) and the product extracted into petroleum ether (3 x 400 ml). The combined organic layers were dried, filtered and the solvent removed *in vacuo* to give the crude enone-aldehyde. Excess tiglaldehyde and 4-methoxy-3-buten-2-one were removed *in vacuo* (0.5 mmHg, 12 h) and the residue distilled under high vacuum through a 5 cm Vigreaux column to give, firstly, 4β-formyl-4α,5α-dimethylcyclohex-2-enone (2) (20.94g, 35%), b.p. 60-62°/2.2 x 10^{-3} mmHg; 90 MHz ($CDCl_3$); δ 9.55 (s, 1H), 6.72 (d, J 10Hz, 1H), 6.06 (d, J 10Hz, 1H), 2.77-2.03 (m, 3H), 1.25 (s, 3H), and 1.08 (d, J 8Hz, 3H); ν_{max} (film) 2720, 1735, and 1695 cm-1; *m/e* 152.0838 (M+), 137, and 123 (Calculated for $C_9H_{12}O_2$: 152.0837). Next, a mixture of what was predominantly the two methyl ethers (3) (in a 1:1 ratio), distilled over (14.34 g) (19.5%), b.p. 70-72oC/5 x 10-3 mmHg. A small amount was separated chromatographically (silica gel, 50:50 ether/pet. ether), to give (i) 4β-formyl-3α-methoxy-4α,5α- dimethylcyclohexanone; δ ($CDCl_3$) 9.32 (s, 1H), 3.62 (dd, J 12, and 5 Hz, 1H), 3.20 (s, 3H), 2.80-2.00 (m, 5H), 1.15(s, 3H), and 0.85 (d, J 6 Hz, 1H); ν_{max} (film) 2830, 2710, 1720, and 1095 cm-1; *m/e* 184.1100 (M+) 168, 156, and 124 (Calculated for $C_{10}H_{16}O_3$: 184.1099); and (ii) the C-3 epimer - namely 4β- formyl-3β-methoxy-4α,5α-dimethylcyclohexanone; δ ($CDCl_3$) 9.51 (s, 1H), 3.65 (dd, J 4, and 4 Hz, 1H), 3.20 (s, 3H), 2.80-2.00 (m, 5H), 1.01 (s, 3H), and 0.89 (d, J 6 Hz, 3H), ν_{max} (film) 2830, 2710, 1720 and 1095.

Conversion of the epimeric methyl ethers (3) into 4β-Formyl-4α,5α-dimethylcyclohex-2-enone.(2)

The mixture of ethers and (7.6 g, 41.3 mmol) obtained above was dissolved in benzene (400 ml),

together with pTSA (1 g) and was heated to reflux for 45 min. After cooling, the reaction mixture was diluted with ether (500 ml) and washed sequentially with aqueous sodium bicarbonate (2 x 50 ml), aqueous ammonium chloride (50 ml) and brine (100 ml). The combined aqueous layers were extracted into ethyl acetate (100 ml) and the combined organic layers were dried and filtered. Removal of the solvent in vacuo gave the crude enone-aldehyde which was distilled, as above, or subjected to column chromatography (silica gel, 50:50, ether/petroleum ether), to give (i) 5,6-dihydro-4H,6(E-2'-but-2'- ene)-pyran-4-one (4) (0.56 g, 9%); δ 100 MHz ($CDCl_3$) 7.26 (d, J 5 Hz, 1H), 5.58 (m, 1H), 5.23 (dd, J 5, and 1.5 Hz, 1H), 4.67 (dd, J 12, and 4 Hz, 1H), 2.75 (dd, J 14, and 12 Hz, 1H), 2.30 (ddd, J 14, 4, and 1.5 Hz, 1H), and 1.72 (m, 6H); ν_{max} (film) 3065, 1680, 1593, 1405, and 1276 cm-1; m/e 152.0846 (M+), 137, 124, and 97 (Calculated for $C_9H_{12}O_2$: 152.0837); and (ii) 4β-formyl-4α,5α-dimethylcyclohex-2-enone (2) (7.6 g, 66%) as before.

Preparation of 4β-Formyl-3β,4α,5α-trimethylcyclohexanone (6) using lithiodimethyl cuprate (6)

An oven dried, 3-necked, 50 ml round-bottomed flask was fitted with a dry three-way tap under (dry) argon. The apparatus was charged with cuprous bromide-dimethyl sulphide complex (220 mg, 1.07 mmol) and all joints were sealed with Parafilm and the apparatus was evacuated and refilled from the balloon four times. The apparatus was then placed in an ice-water bath at 0°C and dry ether (4 ml) was added by syringe. 1M Methyl lithium (2.05 ml, 2.05 mol) was added dropwise, by syringe, to the stirred slurry over 5 min. The reaction mixture immediately went bright yellow and then, after the addition of all the alkyl lithium, colourless. Stirring for 5 min completed the formation of the cuprate giving a totally clear (occasionally tan coloured) solution. After slow cooling to -45°, the enone-aldehyde (2) (0.152 g, 1.0 mmol) in dry ether (5 ml) was added dropwise over 10 min, leading to the immediate formation of a bright yellow precipitate. After stirring for a further 10 min at -45°C, the reaction was quenched by the addition of dry methanol (0.5 ml) and the mixture was allowed to warm to R.T. After pouring into saturated aqueous ammonium chloride (30 ml) and ether (50 ml) vigorous shaking gave a pale yellow organic layer, over a blue aqueous one. (Occasionally, the copper salts did not break-down completely - this was avoided by blowing air through the extraction mixture). Separation, followed by extraction of the aqueous layer into ether (2 x 50 ml), combination of the organic layers, drying, filtration and removal of the solvent in vacuo gave the crude product as a yellow oil. Chromatography (silica gel) 50:50 ether/pet. ether) gave 4β-formyl-3β,4α,5α-trimethylcyclohexanone (6) (0.10 g, 60%), δ 100 MHz ($CDCl_3$) 9.52 (s, 1H), 2.70-1.65 (m, 6H), 1.22 (s, 3H), 1.02 (d, J 3.5 Hz, 3H), and 0.93 (d, J 3.5 Hz, 3H); ν_{max} (film) 2960, 2932, 2880, 2690, and 1720 cm-1; m/e 168.1149, 140, 124, and 109 (Calculated for $C_{10}H_{16}O_2$: 168.1150.

Preparation of 8β-(2'-1',3'-Dithiolan)-8α,9α-dimethyl-1,4-dithiaspiro[4.5]dec-6-ene (8).

A solution of the enone-aldehyde (0.15 g, 1 mmol) (2), redistilled ethane-1,2-dithiol (0.3 ml) and pTSA (10 mg) in benzene (30 ml) was refluxed through a Dean-Stark apparatus until no more water was collected. After cooling, the solution was filtered through a pad of MFC silica gel, and the solvent was removed in vacuo to give an oil which, upon crystallisation (ether/pet. ether), gave 8β-(2'-1,3'-dithiolan)-8α,9α-dimethyl 1,4-dithiaspiro[4.5]dec-6-ene (8) (0.20 g, 66%), m.p. 85.5-86°C; δ ($CDCl_3$) 5.70 (d, J 10 Hz, 1H), 5.65 (d, J 10 Hz, 1H), 4.67 (s, 1H), 3.30 (br, s, 4H,), 3.15 (S, 4H), 2.15-1.95 (m, 3H), 1.00 (s, 3H), and 0.95 (d, J 6 Hz, 3H); ν_{max} (KBr) 3020, 1425, 1275, 825, 778, and 688 cm-1; m/e 304 (M+), 199, 139, and 105 (Found: C, 51.42; H, 6.76; S, 41.82. $C_{13}H_{20}S_4$ requires C, 51.27; H, 6.76; S, 42.11%). The mother liquor was concentrated in vacuo and the residue was chromatographed (slica gel, 4:96 ether/pet. ether) to give a further sample of the bis-dithiolan (8) (72 mg, 23%) as above.

Preparation of 4β(2'-1',3'-Dithiolan)-4α,5α-dimethylcyclohex-2-enone. (7)

(a) From 8β-(2'-1',3'-dithiolan)-8α,9α-dimethyl-1,4-dithiaspric[4,5]dec-6-ene (8).

A stirred solution of bis-dithiolan (8) (5.00 g, 16.4 mmol) in methanol (250 ml) and tetrahydrofran (100 ml) at 0° was treated in portions, with thallium (III) nitrate trihydrate (17.48 g), 39.4 mmol). A white suspension was seen to form immediately. After 5 min the suspension was filtered under reduced pressure through a pad of Merck Kieselgel 60H and then solvent removed under reduced pressure to leave a pale brown oil. This was immediately redissolved in a minimum volume of 70% v/v dichloromethane/40-60 petroleum ether and eluted through silica with further 70% v/v dichloromethane/40-60 petroleum ether to give the desired 4β-(2'-1',3'-dithiolan)-4β,5α-dimethylcyclohex-2-enone (7) (2.50 g, 67%), m.p. 63-64°C (ether/pet. ether); δ 250 MHz ($CDCl_3$) 7.13 (d, J 10 Hz, 1H), 6.02(d, J 10 Hz, 1H), 4.91 (s, 1H), 3.30-3.20 (m, 4H), 2.45-2.20 (m, 3H), 1.18 (s, 3H) and 1.02 (d, J 5 Hz, 3); ν_{max} ($CHCl_3$) 3014 and 1678 cm^{-1}; m/e 228.0641 (M^+) 213, 123, and 105 (Calculated for $C_{11}H_{16}S_2O$: 228.0643). (Found: C, 57.60; 7.18; S, 27.77. $C_{11}H_{16}S_2O$ requires C, 57.85; H, 7.06; S, 28.08%).

(b) By a one-step procedure from 3β-formyl-4α,5α-dimethylcyclohex-2-enone (2)

A solution of the enone-aldehyde (3.04 g, 20 mmol), redistilled ethane-1,2-dithiol (5 ml, 58 mmol) and pTSA (100 mg) in benzene (250 ml) was refluxed through a Dean-Stark apparatus, under nitrogen, for 12 h. After cooling, the solution was diluted with ether (200 ml) and washed with saturated aqueous sodium bicarbonate (2 x 50 ml), followed by brine (50 ml). The organic phase was then vigorously stirred with a mixture of mercury (II) acetate (18 g, 56 mmol), and cadmium carbonate (3 g, 28 mmol), added in portions, and water (50 ml). After 14 h, sodium chloride (25 g)

was added and the organic phase separated. The aqueous phase was re-extracted into ether/benzene (1:1, 3 x 200 ml) and the combined organic layers were dried and filtered through celite. Removal of the solvent *in vacuo*, followed by chromatography (silica gel, 50:50 ether/pet. ether) gave (i) 8β-(2'-1',3'-dithiolan)-8α,9α-dimethyl-1,4-dithia[4,5]dec-6-ene (0.4 g, 6.6%) (8), as above; (ii) the desired 4β-(2'-1',3'-dithiolan)- 4α,5α-dimethylcyclohex-2-enone (2.6 g, 55%), identical to the previous sample (7), and (iii) 3β-formyl-4α-dimethylcyclohex-2-enone (2) (0.3 g, 10%) again identical to the previous sample.

Preparation of 4β-(2'-1',3'-Dithiolan)-3α,4α,5α-trimethyl-cyclohexanone. (9)

To a preformed solution of lithiodimethyl cuprate (4.6 mmol) at -78°C, was added a solution of 4β-(2'-1',3'-dithiolan)-4α,5α-dimethylcyclohex-2-enone (7) (0.456 g, 2 mmol), in dry ether (20 ml), dropwise over 20 min. The stirred reaction mixture was slowly warmed to -30°C over 4 h after which it was poured into saturated aqueous ammonium chloride (20 ml) and worked-up in the usual manner. Chromatography (silica gel, 50:50 ether/pet. ether) of the resultant oil gave 4β-(2'-1',3'-dithiolan)-3α,4α,5α-trimethylcyclohexanone (9) (0.40 g, 82%); δ 250 MHz ($CDCl_3$) 5.50 (s, 1H), 3.30-3.15 (m, 4H), 2.45-2.10 (m, 6H), 1.10 (s, 3H), and 1.05 (d, J 6 Hz, 6H); 13C, 62.9 MHz, 210.76 (s), 64.03 (d), 46.30 (t), 42.39 (s), 38.19 (t), 37.66 (d) 17.23 (q), and 14.43 (q); ν_{max} ($CHCl_3$) 1720 cm-1; m/e 244.0951 (M+), 139, 138, 119, 117, and 105 (Calculated for $C_{12}H_{20}S_2O$: 244.0956) (Found: C, 58.74; H, 8.18; S, 26.24. $C_{12}H_{20}S_2O$ requires: C, 58.97; H, 8.25; S, 26.23%).

Preparation of 3α-But-3'-enyl-4α,5α-dimethyl-4β-(2"-dithiolan)-cyclohexananone. (10)

A solution of but-3-enylmagnesium bromide (21.9 mmol) in ether (15 ml) was added to a slurry of $CuBr.SMe_2$ (2.247 g, 10.9 mmol) in ether (26 ml) at -50°C under argon. The mixture was cooled to -78oC and stirred for 45 min before dropwise addition of a solution of the enone (7) (1.113 g, 4.88 mol) in ether (7 ml). The mixture was stirred at -78°C for 2 h and then warmed to RT during 2 h after which time it was poured into saturated NH_4Cl solution (150 ml). The ether layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extract was dried, filtered and evaporated to give the ketone dithiolan (10) (1.275 g, 92%); 1.03 (3H, d, J 7.0 Hz, Me_5), 1.09 (3H, s, Me_4), 0.80-2.58 (10H, m), 3.19 - 3.27 (4H, m, $H_{4',5'}$), 4.96 - 5.06 (2H, m, $H_{4'}$), 5.08 (1H, s, $H_{2'}$), and 6.70 - 6.88 (1H, m, $H_{3'}$); ν_{max} (film): 1710 and 1635 cm-1; m/z 284 (M+) and 178 (M+-dithiolan); (Found: C, 63.09; H, 8.60. $C_{15}H_{24}OS_2$ requires: C, 63.33; H, 8.50%).

Preparation of 4α,5α-Dimethyl-4β-(2"-1",3"-dithiolan)-3α-(4'-hydroxybutyl)cyclohexanol. (11)

To a solution of the dithiolan ketone (10) (0.76 g, 2.68 mmol) in THF (10 ml) was added borane-dimethyl sulphide (0.27 ml, 2.7 mmol). The solution was stirred for 1 h and water (0.2 ml), 3N NaOH (2.9 ml), and 30% H_2O_2 solution (0.8 ml) added. The mixture was stirred for 1 h, poured into water (20 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extract was washed with water (2 x 5 ml), dried, evaporated and passed through a short pad of silica to give the diol dithiolan (11) (0.78 g, 96%); δ (60 MHz): 0.98 (3H, s, Me_4), 1.04 (3H, d, J 7.0 Hz, Me_5), 0.90 - 2.05 (12H, m), 2.69 (2H, br.s, D_2O exch, OH), 3.15 (4H, s, $H_{4',5'}$), 3.56 (3H, m, $H_{1',4'}$), and 5.00 (1H, s, $H_{2'}$). ν_{max} (film): 3600, 3420, 2910, and 1320 cm-1; m/z 304 (M+); (Found: C, 58.88; H, 9.17. $C_{15}H_{28}O_2S_2$ requires: C, 59.17; H, 9.27%).

Preparation of 3α-Butan-4'-al-4α,5α-dimethyl-4β-(2-"1",3"-dithiolan)-cyclohexanone. (12)

a) To a mixture of diol (11) (0.48 g, 1.58 mmol), DMSO (7.5 ml), CH_2Cl_2 (3.0 ml), and Et_3N (3.8 ml) was added a solution of $py.SO_3$ complex (1.51 g, 9.48 mmol) in DMSO (7.5 ml) in one portion. After 35 min the mixture was poured into water (50 ml) and extracted with EtOAc (3 x 30 ml), each extract being washed with water (3 x 50 ml). The combined EtOAc layer was dried, evaporated and chromatographed (10 - 60% ether - 40:60 petrol) to give the keto-aldehyde (12) (0.336 g, 71%); δ (250 MHz): 1.03 (3H, d, J 7.0 Hz, Me_5), 1.08 (3H, s, Me_4), 0.95 - 1.98 (5H, m), 2.06- 2.63 (7H, m, $H_{2',3',6'}$), 3.22 (4H, m, $H_{4',5'}$), 5.06 (1H, s, $H_{2'}$), and 9.78 (1H, t, J 2.5 Hz, $H_{1'}$); ν_{max} (film): 2920, 2850, 2720, 1710 and 730 cm-1; m/z 300 (M+); (Found: C, 59.91; H, 8.13. $C_{15}H_{24}O_2S_2$ requires: C, 59.96; H, 8.05%).

b) Triphenylbismuth carbonate (3.37 g, 6.7 mmol) was added to a stirred solution of the diol (11) (205 mg, 0.67 mmol) in dichloromethane (25 ml) and the resultant suspension heated at reflux for 24 h, further triphenylbismuthcarbonate (1.67 g, 3.35 mmol) was added after 14 h. After cooling the suspension was filtered through a pad of silica and solvent removed from the filtrate under reduced pressure to leave a pale green oil. This was chromatographed on silica eluting with 50 - 100% v/v ether petrol to give the keto aldehyde (12) (71 mg, 35%) which was identical in all respects to that obtained above.

Preparation of 4α,5α-Dimethyl-5β-(2-1',3'-dithiolan)-6β-bicyclo[4.4.0]-dec-1(10)-en-2-one. (13)

A solution of ketoaldehyde (12) (1.0 g, 3.3 mmol) in benzene (40 ml) containing a little CSA was heated to reflux under Dean-Stark conditions for 1 h. The solution was cooled, washed with saturated $NaHCO_3$ solution (10 ml), dried and evaporated. The residue was chromatographed (10 -

50% ether - 40:60 petrol) to give the enone dithiolan (13) (0.75 g, 80%); δ (250 MHz): 1.00 (3H, s, Me_5), 1.08 (3H, d, J 6.9 Hz, Me_4), 1.38-2.25 (6H, m), 2.15 (1H, dd, J 8.8, 16.6 Hz, H_{3ax}), 2.43 (1H, m, H_4), 2.58 (1H, dd, J 5.9, 16.6 Hz, H_{3eq}), 2.74 (1H, m, H_2), 3.15-3.34 (4H, m, $H_{1',2'}$), 5.02 (1H, s, H_2), and 6.99, (1H, m, H_1); ν_{max} (film): 2915, 1685, 1630, 1610, and 730 cm-1; m/z 284 (M+ + 2) and 178; (Found: C, 63.49; H, 7.91. $C_{15}H_{22}OS_2$ requires: C, 63.78; H, 7.85%).

Preparation of 4α,5α-Dimethyl-4β-(2-1',3'-dithiolan)cyclohex-2-en-1α-ol (18)

To a solution of enone (1.1303 g, 49.5 mmol) in ethanol (20 ml) at 0°C was added $NaBH_4$ (excess) in portions until reaction was complete (TLC). The reaction was then quenched with water (10 ml), and 1N HCl (20 ml) was added. The mixture was extracted with dichloromethane (3 x 20 ml), and the combined organic extracts washed with saturated $NaHCO_3$ solution (20 ml), dried and evaporated. Chromatography (10 - 50% ether - 40:60 petrol) gave the allylic alcohol (18) (0.87g, 77%) ; δ (60 MHz): 0.94 (3H, d, J 7.0 Hz, Me_5), 1.03 (3H, s, Me_4), 0.78-2.08 (3H, m, $H_{5,6}$), 2.50 (1H, br.s, D_2O exch., OH), 3.14 (4H, s, $H_{1',2'}$), 4.22 (1H, dd, J 6.0, 10.0 Hz, H_1), 4.77 (1H, s, H_2), and 5.77 (2H, s, $H_{2,3}$); ν_{max} (film) 3440, 2930, 1660, 1380, and 1020 cm-1; m/z 230 (M+), 202, 164, and 107; (Found: M+, 230.0791. $C_{11}H_{18}OS_2$ requires: M+, 230.0799).

Preparation of 4α,5α-Dimethyl-4β-(2'-1',3'-dithiolan)-1α-t-butyldimethylsilyloxycyclohex-2-ene (19)

To a solution of allylic alcohol (18) (0.87 g, 3.78 mmol) in a mixture of CH_2Cl_2 (10 ml) and pyridine (10 ml) was added DMAP (trace) and TBDMSCl (0.626 g, 4.16 mmol). The mixture was stirred at RT for 6 h and then poured into 1N HCl solution (50 ml). The organic layer was separated and washed with water (30 ml), dried and evaporated. Chromatography (10% ether - 40:60 petrol) gave the silyl ether dithiolan (19) (1.158 g, 89%); δ (60 MHz): 0.10 (6H, s, SiMe), 0.92 (9H, s, $SiBu^t$), 0.95 (3H, d, J 7.0 Hz, Me_5), 1.06 (3H, s, Me_4), 1.0 - 2.2 (3H, m), 3.16 (4H, s), 4.23 (1H, dd, J 6.0, 9.0 Hz), 4.78 (1H, s), and 5.68 (2H, br.s); ν_{max} (film): 2950, 2910, 1460, and 1250 cm-1; m/z 329 (M+-Me), 287, and 239; (Found: C, 59.46, H, 9.26. $C_{17}H_{32}OS_2Si$ requires: C, 59.25; H, 9.36).

Preparation of 4α,5α-Dimethyl-4β-formyl-1α-t-butyldimethylsilyloxycyclohex-2-ene (20)

To a solution of the silyl ether (19) (1.158 g, 3.37 mmol) in THF (15 ml) at RT was added $Tl(OCOCF_3)_3$ (5.49 g, 10.11 mmol) in one portion, causing the solutin to turn bright red in colour. After 2 h saturated $NaHCO_3$ solution (10 ml) was added to the mixture dropwise. The solution was stirred for 10 min before the addition of ether (30 ml) and more $NaHCO_3$ solution (20 ml). The organic layer was separated and the aqueous phase extracted with more ether (3 x 20 ml). The combined organic extract was diluted with 40:60 petrol (150 ml), dried, filtered and evaporated to yield an oily residue. Chromatography (2 - 10% ether - 40:60 petrol) gave the formyl silyl ether (20) (0.677 g, 75%); δ (60 MHz): 0.12 (6H, s, SiMe), 0.92 (9H, s, $SiBu^t$), 0.86 (3H, d, J 7.0 Hz, H_5), 1.02 (3H, s, Me_4), 0.5-1.9 (3H, m), 4.27 (1H, m, H_1), 5.22 (1H, dd, J 2.0, 10.0 Hz, H_2), 5.70 (1H, br.d, J 10.0 Hz, H_3), and 9.23 (1H, s, H_1); ν_{max} (film): 2930, 2860, 1720, and 1250 cm-1; m/z 268 (M+), 253, and 211; (Found: M+-But, 211.1153. $C_{15}H_{23}O_2Si$ requires: M+-But, 211.1154).

Preparation of 4α,5α-Dimethyl-4β-(E)-(2'-phenylsulphonyl)vinyl-1α-t-butyldimethylsilyloxycyclohex-2-ene (21)

To a solution of 1-trimethylsilyl-1-(phenylsulphonyl)methane (0.518 g, 2.28 mmol) in THF (5.0 ml) at -78°C under argon, was added ^nBuLi (1.57 ml of a 1.45 M solution, 2.28 mmol) in hexane. The solution was stirred at -78°C for 30 min before addition of the formyl silyl ether (20) (0.5803 g, 2.17 mmol), in THF (1.5 ml). The solution was stirred at -78°C for 5 min and then allowed to warm to RT and quenched with water (10 ml). The product was extracted into CH_2Cl_2 (3 x 10 ml) and the combined organic extracts dried, evaporated and chromatographed (10 - 60% ether - 40:60 petrol) to give the vinyl sulphone (21) (0.722 g, 92%); δ (60 MHz): δ 0.09 (6H, s, SiMe), 0.84 (3H, d, J 7.0 Hz, Me_5), 0.90 (9H, s, $SiBu^t$), 1.03 (3H, s, Me_4), 0.8-1.9 (3H, m), 4.18 (1H, m, H_1), 5.16 (1H, dd, J 2.0, 10.0 Hz, H_2), 5.60 (1H, br.d, J 10.0 Hz, H_3), 6.13 (1H, d, J 16.0 Hz, $H_{2'}$), 6.84 (1H, d, J 16.0 Hz, $H_{1'}$), and 7.34-7.85 (5H, m, SO_2Ph); ν_{max} (film): 3070, 3030, 1620, and 1140 cm-1; m/z 406 (M+), 391 (M+-Me), and 349; (Found: C, 65.21; H, 8.64. $C_{22}H_{34}O_3SSi$ requires: C, 64.98; H, 8.43%).

Preparation of 4α,5α-Dimethyl-4β-(2'-phenylsulphonyl)ethyl-1α-t-butyldimethylsilyloxycyclohex-2-ene (22)

A solution of $LiHBEt_3$ ("Super Hydride"), (2.0 ml of a 1M solution, 2.0 mmol) in THF was added to the vinyl sulphone (0.722 g, 1.78 mmol) in THF (2.0 ml). The mixture was stirred overnight and then poured into 1N HCl solution (10 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined extracts were washed with water (10 ml), dried, evaporated and subjected to column chromatography (50% ether - 40:60 petrol) to give the sulphone silyl ether (22) (0.704 g, 97%), m.p. 107-109°C, δ (250 MHz): 0.08 (6H, s), 0.78 (3H, d, J 7.0 Hz), 0.83 (3H, s), 0.86 (9H, s), 1.0-1.85 (5H, m, $H_{1',5,6}$), 2.84-3.08 (2H, m, $H_{2'}$), 4.14 (1H, m, H_1), 5.13 (1H, dd, J 2.0, 10.0 Hz), 5.53 (1H, br.d, J 10.0 Hz), and 7.51-7.89 (5H, m); ν_{max} (film) 1470, 1300, 1150, and 840 cm-1; m/z 393 (M+-Me) and 351; (Found: M+-But, 351.1440. $C_{22}H_{36}O_3SSi$ requires: M+-But, 351.1450).

Preparation of Ethyl-4-(t-butyldimethylsilyloxy)but-2-ynoate (23)

To a solution of propargyl alcohol (2.92 ml, 50.2 mmol) in a mixture of pyridine (10 ml) and

CH_2Cl_2 (15 ml), was added DMAP (trace), and TBDMSCl (8.4 g, 56 mol). The solution was stirred for 4 h before pouring into 1N HCl solution (50 ml). The organic layer was separated, washed with water (2 x 30 ml), dried and evaporated to give crude TBDMS protected propargyl alcohol.

A solution of this acetylene in THF (10 ml) was gradually added to a solution of ethyl magnesium bromide (60 ml) in THF (60 ml) causing rapid evolution of ethane gas. When addition was complete the solution was stirred for 30 min before addition *via* catheter to a well-stirred solution of ethyl chloroformate (100 mmol) in THF (80 ml). The mixture was stirred for 10 min and poured into saturated NH_4Cl solution (400 ml) and extracted into ether (2 x 100 ml). The combined ethereal extract was washed with further NH_4Cl solution (2 x 50 ml), dried, evaporated and distilled under reduced pressure to give the acetylenic ester (23) (5.95 g, 49%), b.p. 102°C at 6 mmHg, δ (60 MHz): 0.13 (6H, s, SiMe), 0.92 (9H, s, $SiBu^t$), 1.30 (3H, t, J 7.0 Hz, COCHMe), 4.18 (2H, q, J 7.0 Hz, COCHMe), and 4.40 (2H, s, H_1); ν_{max} (film) 2220, 1710, 1460, 1360, and 1240 cm^{-1}; m/z 227 (M^+-Me) and 185; (Found: C, 59.46; H, 8.98. $C_{12}H_{22}O_3Si$ requires: C, 59.46; 9.15%).

Preparation of 3-[1-phenylsulphonyl-2-(1α,6α-dimethyl-4α-t-butyldimethylsilyloxycyclohex-2-enyl)-ethyl]but-2-en-4-olide (24)

To a stirred solution of sulphone (0.1406 g, 0.345 mmol) in THF (1 ml) and HMPA (0.25 ml) at -78°C under argon was added ^nBuLi (0.25 ml of a 1.51 N solution, 0.38 mmol) in hexane. After 20 min a solution of the acetylenic ester (23) (87.6 mg, 0.362 mmol), in THF (0.2 ml) was added dropwise. The reaction was stirred at -78°C for 15 min, then warmed to RT before pouring into water (10 ml). The mixture was extracted with ether (3 x 10 ml) and the combined ethereal extracts washed with water (3 x 10 ml), and brine (5 ml), then dried and evaporated to an oil. Without purification the residue was dissolved in THF (0.2 ml), and TBAF (0.5 ml of a 1.0 N solution) in THF added. After 1 h the red solution was poured into brine (10 ml) and the product extracted into ether (3 x 10 ml). The ethereal extract was dried, evaporated and chromatographed (20-80% ether - 40:60 petrol) to give the sulphone butenolide (24) (76 mg, 45%), δ (250 MHz, major diastereomer): 0.08 (6H, s, SiMe), 0.76 (3H, d, J 7.0 Hz, Me_8.), 0.88 (12H, s, $SiBu^t$ and Me_3.), 1.00-2.49 (5H, m), 3.79 (1H, br.d, J 10.0 Hz, H_1.), 4.17 (1H, m, H_6.), 4.67(1H, dd, J 1.9, 17.8 Hz, H_4), 4.79 (1H, dd, J 1.9, 17.8 Hz, H_4), 5.03 (1H, br.d, J 10.0 Hz, H_1.), 5.48 (1H, br.d, J 10.0 Hz, H_5.), 5.92 (1H, m, H_2) and 7.59-7.84 (5H, m, SO_2Ph); ν_{max} ($CHCl_3$): 1785 (C=O str.), 1745 (conj. C=O str.), 1630 (C=C str.), ad 1140 cm-1; m/z 475 (M^+-Me) and 433 (M^+-But); (Found: M+-But, 433.1492, calc., 433.1505).

Preparation of 3-[2-(1α,6α-dimethyl-4α-t-butyldimethylsilyloxycyclohex-2-enyl)ethyl]but-2-en-4-olide (25)

To a solution of the sulphone butenolide (24) (23.5 mg, 0.048 mmol) in MeOH (1.5 ml) at -20°C was added Na_2HPO_4 (68 mg, 0.48 mmol) and 4% Na/Hg (0.11 g, 0.19 mmol). The solution was maintained at -20°C for 1.5h during which time further small portions of 4% Na/Hg were added until reaction was complete (TLC). The solution was filtered through a small wad of glass wool, evaporated, and subjected to column chromatography (20 - 80% ether - 40:60 petrol) to give the butenolide (25) (14.2 mg, 85%), m.p. 97-99°C; δ (250 MHz): 0.08 (3H, s, SiMe), 0.09 (3H, s, SiMe) 0.89 (3H, d, J 7.0 Hz, Me_8.), 0.90, (9H, s, $SiBu^t$), 0.91 (3H, s, Me_3.), 1.40-1.77 (5H, m), 2.29 (2H, m, H_1.), 4.25 (1H, m, H_6.), 4.73 (2H, d, J 1.8 Hz), 5.32 (1H, dd, J 2.0, 10.4 Hz, H_4.), 5.60 (1H, br.d, J 10.4 Hz H_5.), and 5.83 (1H, tt, J 1.8, 1.8 Hz, H_2); ν_{max} ($CHCl_3$): 1780, 1745, and 1640 cm-1; m/z 350 (M+) and 293 (M+-But); (Found: M+-But, 293.1582, calc., 293.1573).

Preparation of 4α,5α-Dimethyl-5β-(2'-1',3'-dithiolan)-1α-hydroxymethyl-10β-vinyl-6β-bicyclo[4.4.0]-decan-2-one (14)

A solution of vinylmagnesium bromide (9.2 mmol) in THF (10 ml) was added to a suspension of CuBr.SMe_2 (0.94 g, 4.6 mmol) in ether (10 ml) at -50°C under argon. The resulting green/brown suspension was stirred at -50oC for 1.5 h before addition of the enone (13) (0.59 g, 2.1 mmol) in THF (3.0 ml). The mixture was stirred at -50°C for 1 h and a THF solution of formaldehyde (excess) added. When reaction was complete by TLC the solution was warmed to 0°C, poured into saturated NH_4Cl solution (100 ml) and rapidly extracted with EtOAc (3 x 50 ml). The combined EtOAc layers were washed with water (50 ml), dried, evaporated and chromatographed (10 - 60% ether - 40:60 petrol) to give the hydroxymethyl ketone (0.3693 g, 52%); δ (250 Hz): 0.97 (3H, s, Me_5) 0.99 (3H, d, J 7.0 Hz, Me_4), 1.00-1.92 (7H, m), 2.11 (1H, dd, J 2.5, 13 Hz, H_{3eq}), 2.50 (1H, dd, J 2.5, 10.3 Hz, H_6), 2.68 (1H, m, H_{10}), 2.97 (1H, dd, J 7.0, 13 Hz, H_{3ax}), 3.18-3.32 (4H, m, H_{4a}, $_5$), 3.40 (1H, br.m, D_2O exch., CHOH), 3.87 (2H, br.m, CHOH), 5.04-5.12 (2H, m, H_2.), 5.07 (1H, s, H_2.), and 6.02 (1H, m, H_1.); ν_{max} (film): 3480, 1690, 1630, 910, and 730 cm-1; m/z 235 (M+ -dithiolan); (Found: M+-dithiolan, 235.1697, calc., 235.1698).

Preparation of 4α,5α-dimethyl-5β-(2-1',3'-dithiolan)-1α-hydroxymethyl-10β-vinyl-6β-bicyclo[4.4.0.]-decan-2α-ol (15)

To a solution of keto-alcohol (14) (0.369 g, 1.09 mmol) in DMF (2.0 ml) was added TBDPSCl (0.357 g, 1.30 mmol), and imidazole (0.177 g, 2.60 mmol) and the mixture stirred overnight. The solution was poured into water (30 ml) and extracted with ether (3 x 20 ml), each extract being washed with water (10 ml) and brine (10 ml). The combined ether extract was dried and evaporated to

give the crude silyl ether intermediate. The oily residue was dissolved in THF (15 ml) and $LiAlH_4$ (excess) added. After 30 min the reaction was quenched with water (10 ml) and poured into 1N H_2SO_4 solution (20 ml). The product was extracted into CH_2Cl_2 (3 x 20 ml), the combined extract dried, evaporated and chromatographed (20 - 95% ether - 40:60 petrol) to give the diol dithiolan (15) (0.253 g, 68%); δ (250 MHz): 0.98 (3H, s, Me_5), 1.05 (3H, d, J 7.0 Hz, Me_4), 0.85-2.16 (11H, m), 2.30 (2H, br., D_2O exch., OH), 3.12-3.24 (4H, m, H_{4-5}), 3.72 (1H, dd, J 4.5, 12.5 Hz, H_2), 3.90 (1H, br. d, J 11.7 Hz, CHOH), 4.22 (1H, d, J 11.7 Hz, CHOH), 5.01 (1H, s, $H_{2'}$), 5.16 (1H, dd, J 2.5, 10.0 Hz, $H_{2',cis}$), 5.23 (1H, dd, J 2.5, 16.7 Hz, $H_{2',trans}$), and 6.29 (1H, ddd, J 10.0, 10.0, 16.7 Hz); ν_{max} (film): 3480 and 1635 cm-1; m/z 237 (M+-dithiolan); (Found: M+-dithiolan, 237.1850, calc., 237.1855); (Found: C, 63.24; H, 8.79; $C_{18}H_{30}O_2S_2$ requires: C, 63.11; H, 8.83%).

Preparation of 4α,5α-Dimethyl-5β-(2-1',3'-dithiolan)-[(2α-hydroxy-1α-hydroxymethyl)acetonide]-10β-vinyl-6β-bicyclo[4.4.0]decane (16)

To a solution of the diol (15) (0.253 g, 0.74 mmol) in acetone (5.0 ml) was added anhydrous $CuSO_4$ (2.0 g) and the suspension stirred for 6 h. The mixture was the diluted with ether (20 ml) and filtered through a short pad of celite to give the dithiolan acetonide (16) (0.268 g, 95%): δ (250 MHz): 1.10 (3H, d, J 6.5 Hz), 1.14 (3H, s), 1.36 (3H, s, $Me_{acetonide}$), 1.41 (3H, s, $Me_{acetonide}$), 1.03-2.02 (10H, m), 2.95 (1H, m, H_{10}), 3.12-3.25 (4H, m), 3.73 (1H, dd, J 4.3, 8.7 Hz, H_2), 3.81 (1H, d, J 12.1 Hz, CHOR), 4.07 (1H, d, J 12.1 Hz, CHOR), 5.00 (1H, s), 5.10-5.20 (2H, m), and 6.12 (1H, ddd, J 10.0, 10.0, 16.8 Hz, $H_{1'}$); ν_{max} (film): 2910, 1630, 1445, and 1370 cm-1; m/z 367 (M+-Me) and 277 (M+-dithiolan); (Found: M+-dithiolan 277.2162, calc., 277.2167).

Preparation of 4α,5α-Dimethyl-5β-formyl-[(2α-hydroxy-1α-hydroxy-methyl)acetonide]-10β-vinyl-6β-bicyclo[4.4.0.]decane (17)

To a solution of the dithiolan acetonide (16) (0.147 g, 0.38 mmol) in THF (5.0 ml) was added Na_2HPO_4 (0.27 g, 1.9 mmol) and $Tl(OCOCF_3)_3$ (0.37 g, 0.68 mmol). The solution was stirred for 1 h at RT and saturated $NaHCO_3$ solution (2.0 ml) added dropwise. The mixture was then poured into more saturated $NaHCO_3$ solution (20 ml) and the products extracted into ether (3 x 10 ml). The organic extract was diluted with 40:60 petrol (50 ml), dried, filtered and evaporated to an oily residue. Column chromatography (5 - 30% ether - 40:60 petrol) gave starting dithiolan (20 mg); and the formyl acetonide (17) (70.4 mg,69%, based on recovered starting material), m.p. 92-94°C; δ (250 MHz): 0.73 (3H, d, J 7.3 Hz, Me_4), 0.98 (3H, s, Me_5), 1.41 (3H, s, $Me_{acetonide}$), 1.49 (3H, s, $Me_{acetonide}$), 0.95-1.92 (9H, m), 2.16 (1H, ddd, J 12.7 12.7, 12.7 Hz, H_{3ax}), 3.19 (1H, m, H_{10}), 3.84 (1H, ddd, J 1.2, 5.0, 12.8 Hz, H_2), 3.86 (1H, dd, J 1.2, 12.4 Hz, CHOR), 4.12 (1H, d, J 12.4 Hz, CHOR), 5.18-5.29 (2H, m, $H_{2'}$), 6.13 (1H, ddd, 10.0, 10.0, 16.8 Hz, $H_{1'}$), 9.17 (1H, s, CHO); ν_{max} (film): 1710 and 1630 cm-1; m/z 291 (M+-Me) and 231; (Found: M+-Me, 291.1967, calc., 291.1960); (Found: C, 74.22; H, 9.68. $C_{19}H_{30}O_3$ requires: C, 74.47; H, 9.87%).

Preparation of 4α,5α-Dimethyl-[(2α-hydroxy-1α-hydroxymethyl)-acetonide]-5β-(E)-(2"-phenylsulphonyl)-vinyl-10β-vinyl-6β-bicyclo[4.4.0.]decane (26)

To solution of ^nBuLi (0.204 ml of a 1.66M solution, 0.34 mmol) was added to phenyl trimethylsilylmethylsulphone (77.5 mg, 0.34 mmol) in a mixture of THF (1.0 ml) and HMPA (0.3 ml) at -78°C. The solution was stirred for 10 min and the aldehyde (17) (86.7 mg, 0.28 mmol) added in THF (0.5 ml). The mixture was slowly warmed to 0°C, poured into water (10 ml) and extracted into EtOAc (3 x 10 ml), each EtOAc extract being washed with water (3 x 5 ml) and brine (5 ml). The combined EtOAc layer was then dried and evaporated to give the crude hydroxy-sulphone (0.131 g, 100%); δ (60 MHz): 0.50 (3H, d, J 7.0 Hz), 0.94 (3H, s), 1.37 (3H, s), 1.42 (3H, s), 0.9-2.40 (11H, m), 2.88-4.20 (7H, m, 1H, D_2O exch.), 4.98-6.30 (3H, m), and 7.57-8.00 (5H, m); ν_{max} (film): 3520, 2890, 1630, and 1585 cm-1; m/z 447 (M^+-CH_3), 429 ($M^+-CH_3-H_2O$), 291 and 271; (Found: $M^+-CH_3-H_2O$, 429.2088, calc., 429.2099). The crude product from above (0.131 g, 0.28 mmol) was dissolved in dry CH_2Cl_2 (2.0 ml), and pyridine (0.3 ml), acetic anhydride (0.15 ml) and DMAP (trace) added. The mixture was stirred overnight and poured into saturated $NaHCO_3$ solution (10 ml) and the product extracted into EtOAc (3 x 10 ml). The organic phase was dried and evaporated, and dissolved in dry THF (1 ml) containing TBAF (1 mmol). The dark mixture was stirred for 2 h and poured into water (10 ml). The final product was extracted into EtOAc (3 x 10 ml), the solution dried, evaporated and chromatography (10 - 60% ether - 40:60 petrol) to give the vinyl sulphone acetonide (26) confirmed by x-ray crystallography (0.1206 g, 96%) m.p. 181-183°C; δ (250 MHz): 0.86 (3H, d, J 7.0 Hz, Me_4), 0.92 (3H, s, Me_5), 1.41 (3H, s, $Me_{acetonide}$), 1.47 (3H, s, $Me_{acetonide}$) 0.80-1.80 (9H, m), 2.16 (1H, ddd, J 12.8, 12.8, 12.8 Hz, H_{3ax}), 3.05 (1H, m, H_{10}), 3.80 (1H, m, H_2), 3.80 (1H, d, J 12.9 Hz, CHOR), 4.10 (1H, d, J 12.9 Hz, CHOR), 5.18-5.26 (2H, m, $H_{2'}$), 6.04 (1H, m, $H_{1'}$), 6.18 (1H, d, J 15.6, Hz, $H_{2''}$), 6.66 (1H, d, J 15.6 Hz, $H_{1''}$), and 7.51-7.96 (5H, m, SO_2Ph); ν_{max} ($CHCl_3$): 2860, 1610, and 1140 cm-1; m/z 444 (M+) and 429 (M+-Me); (Found: M+-Me, 429.2109, calc., 429.2099). (Found: C, 70.11; H, 8.24. $C_{26}H_{36}O_4S$ requires: C, 70.24; H, 8.16%).

Preparation of 4α,5α-Dimethyl-[2α-hydroxy-1α-hydromethyl)-acetonide]-5β-(2"-phenylsulphonyl)ethyl-10β-vinyl-6β-bicyclo[4.4.0.]decane (27)

A solution of $LiBH(Et)_3$ in THF (0.5 ml of a 1M solution, 0.5 mmol) was added to a solution of the vinyl sulphone (26) (0.12g, 0.27 mmol) in THF (0.5 ml) under argon. The solution was stirred for 8h before quenching with water (10ml) and extraction of the product into CH_2Cl_2 (3 x 10 ml).

The organic extract was dried, evaporated under reduced pressure, and chromatographed (10 - 60% ether - 40:60 petrol) to give the sulphone acetonide (27) (0.116g, 96%), m.p. 173-174°C; δ(250 MHz): 0.65 (3H, d, J 7.0 Hz, Me_4), 0.78 (3H, s, Me_5), 1.39 (3H, s, $Me_{acetonide}$), 1.44 (3H, s, $Me_{acetonide}$), 0.73 - 1.82 (12H, m), 2.12 (1H, ddd, J 13.0, 13.0, 13.0 Hz, H_{3ax}), 2.82 - 3.06 (2H, m, $H_{2'}$), 3.65 (1H, dd, J 5.0, 12.7 Hz, H_2), 3.88 (1H, d, J 13.2 Hz, CHOR), 4.09 (1H, d, J 13.2 Hz, CHOR), 5.12 - 5.23 (2H, m, $H_{2'}$) 5.97 (1H, ddd, J 10.4, 10.4, 16.8 Hz, $H_{1'}$), 7.56 (3H, m, SO_2Ph), and 7.90 - 7.93 (2H, m, SO_2Ph); ν_{max} ($CHCl_3$): 2880, 1630, 1580, 1300, 1150, and 900 cm-1; m/z 446 (M+), 431 (M+ -Me), and 370; (Found: C, 69.81; H, 8.74. $C_{26}H_{38}O_4S$ requires: C, 69.92; H, 8.58%).

Preparation of 4α,5α-Dimethyl-[(2α-hydroxy-1α-hydroxymethyl)-acetonide]-10β-hydroxymethyl-5β-(2"-phenylsulphonyl)ethyl-6β-bicyclo[4.4.0.]decane (28)

A stream of dry ozone was passed through a solution of the vinyl derivative (27) (24.2 mg, 0.054 mmol) in EtOH (1.5 ml) until no starting material remained (TLC). $NaBH_4$ (excess) was then added in portions until reduction of the intermediate ozonide was complete (TLC). The mixture was then poured into water (5 ml) and the product extracted into CH_2Cl_2 (3 x 5 ml). The organic layer was dried, evaporated and filtered through a short pad of silica to give the sulphone alcohol (28) (24.4 mg, 100%): δ(250 MHz): 0.69 (3H, d, J 6.8 Hz, Me_4), 0.77 (3H, s, Me_5), 1.38 (3H, s, $Me_{acetonide}$), 1.46 (3H, s, $Me_{acetonide}$), 1.04 - 1.78 (11H, m), 2.10 (1H, br., D_2O exch., OH), 2.18 (1H, ddd, J 12.8, 12.8, 12.8 Hz, H_{3ax}), 2.62 (1H, m, H_{10}), 2.81 (1H, ddd, J 5.5, 12.2, 12.2 Hz, $H_{2'}$), 2.96 (1H, ddd, J 4.8, 12.2, 12.2 Hz, $H_{2'}$), 3.56 (1H, dd, J 4.2, 10.7 Hz, CHOH), 3.75 (1H, d, J 12.2 Hz, CHOR), 3.78 (1H, m, H_2), 3.85 (1H, dd, J 6.9, 10.7 Hz, CHOH), 4.14 (1H, d, J 12.2 Hz, CHOR), 7.56 - 7.72 (3H, m, SO_2Ph), and 7.89 - 7.92 (2H, m, SO_2Ph; ν_{max} (film): 3490, 2920, 1300, and 1150 cm-1; m/z 435 (M+ - Me), 357, and 350; (Found: M+ -Me, 435.2196, calc., 435.2205); (Found: C, 66.14; H, 8.47. $C_{25}H_{38}O_5S$ requires: C 66.63; H, 8.50%).

Preparation of 4α,5α-Dimethyl-[(2α-hydroxy-1α-hydroxymethyl)-acetonide]-10β-phenylselenomethyl-5β-(2"-phenylsulphonyl)ethyl-6β-bicyclo[4.4.0.]decane (30)

A mixture of the sulphone alcohol (28) (46.9 mg, 0.104 mmol), NPSP (98.0 mg, 0.323 mmol) and $^nBu_3P$ (80 µl, 0.323 mmol) in THF (0.3 ml) was stirred at RT for 8h. The mixture was diluted with ether (5 ml) and washed with 1N NaOH solution (2 ml) and brine (2 ml). The ether layer was dried, evaporated, and chromatographed (40:60 petrol - 10% ether - 40:60 petrol, then 20 - 80% ether - 40:60 petrol) to give firstly the phenylselenomethyl derivative (30) (17.4 mg, 75%, based on recovered starting material), m.p. 165 - 168°C; δ(250 MHz): 0.67 (3H, d, J 6.7 Hz), 0.77 (3H, s), 1.21 (3H, s), 1.43 (3H, s), 1.02 - 1.98 (11H, m), 2.17 (1H, ddd, J 12.2, 12.2, 12.2 Hz, H_{3ax}), 2.63 (1H, m, H_{10}), 2.79 (1H, d, J 11.1 Hz, CHSePh), 2.80 - 3.02 (2H, m, $H_{2'}$), 3.19 (1H, dd, J 2.6, 11.1 Hz, CHSePh), 3.77 (1H, d, J 12.5 Hz, CHOR), 3.82 (1H, m, H_2), 4.09 (1H, d, J 12.5 Hz), 7.22 - 7.26 (3H, m, SePh), 7.50 - 7.54 (2H, m, SePh), 7.57 - 7.72 (3H, m, SO_2Ph), and 7.89 - 7.93 (2H, m, SO_2Ph); ν_{max} ($CHCl_3$): 3000, 1600, 1580, 1380, and 1140 cm-1; m/z 590 (M+), 575 (M+ -Me), and 532; (Found: M+ 590.1976, calc., 590.1968); further elution gave starting alcohol (28) (29.0 mg).

Preparation of 4α,5α-Dimethyl-[(2α-hydroxy-1α-hydroxymethyl)-acetonide]-10-methylene-5β-(2"-phenyl sulphonyl)ethyl-6β-bicyclo[4.4.0.]decane (29)

Ozone was passed through a solution of the selenide (30) (41 mg, 69.4 µmol) in CH_2Cl_2 (2.0 ml) at -78°C until complete conversion to the corresponding selenoxide had taken place (TLC). The solution was warmed to RT and the solvent removed and replaced by CCl_4 (2.0 ml). Et_2NH (5 drops) was added and the mixture heated to reflux for 20 min. The solution was cooled, evaporated and chromatographed (10 - 60% ether - 40:60 petrol) to give the exomethylene sulphone (29) (25.2 mg, 84%), m.p. 151 - 152°C; δ(250 MHz): 0.70 (3H, d, J 6.5 Hz, Me_4), 0.82 (3H, s, Me_5), 1.28 (3H, s, $Me_{acetonide}$), 1.42 (3H, s, $Me_{acetonide}$), 1.2 - 1.85 (9H, m), 2.17 (1H, ddd, J 11.7, 11.7, 11.7 Hz, H_{3ax}), 2.21 (2H, m, H_9), 2.78 (1H, ddd, J 5.9, 11.8, 11.8 Hz, $H_{2'}$), 2.93 (1H, ddd, J 5.4, 11.8, 11.8 Hz, $H_{2'}$), 3.84 (1H, dd, J 1.0, 12.2 Hz, CHOR), 3.95 (1H, br.dd, J 5.0, 12.1 Hz, H_2), 4.13 (1H, d, J 12.2 Hz, CHOR), 4.88 (1H, br.s, $H_{methylene}$), 5.03 (1H, br.s, $H_{methylene}$), 7.56 - 7.71 (3H, m, SO_2Ph), and 7.88 - 7.91 (2H, m, SO_2Ph); ν_{max} ($CHCl_3$): 2920, 1635 (C=C Str.), 1580, 1440, 1140, and 900 cm-1; m/z 432 (M+), 417 (M+-Me), and 357; (Found: M+, 432.2347, calc., 432.2334); (Found: C, 67.99; H, 8.32. $C_{25}H_{36}O_4S.1/2H_2O$ requires C, 67.99; H, 8.44%).

Preparation of (6α,18-Dihydroxy)acetonide-12-phenylsulphonylcleroda-4,13(14)-dieno-16,15-lactone (31)

To a stirred solution of the exo-methylene sulphone (29) (32.4 mg, 7.5 x 10^{-5} mol) in a mixture of THF (200 µl and HMPA (40 µl) at -78°C under argon, was added ^nBuLi (54 µl of a 1.54N solution, 8.3 x 10^{-5} mmol) in hexane. After 20 min a solution of the acetylenic ester (23) (19.1 mg, 7.9 x 10^{-5} mol) in THF (100 µl) was added dropwise. The solution was allowed to slowly warm to RT and quenched with water (50 µl). The solvent was removed and the involatile residue treated with TBAF (200 µl of a 1N solution, 0.2 mmol) in THF. The mixture was stirred at RT for 1 h, poured into water (5 ml) and extracted with EtOAc (3 x 5 ml). Each organic extract was washed with water (2 x 5 ml) and brine (5 ml), the combined extract was dried, evaporated and chromatographed (20-90% EtOAc - 40:60 petrol), to give firstly recovered sulphone (12.5 mg) and secondly the butenolide sulphone (31) (10.8 mg, 46% based on recovered starting material), m.p. 98-100°C; δ (250 MHz, major diastereoisomer): 0.84 (3H, d, J 7.0 Hz, Me_4), 0.86 (3H, s, Me_5), 1.28 (3H, s, $Me_{acetonide}$), 1.43 (3H, s, $Me_{acetonide}$), 1.57-2.38 (12H, m), 3.82 (1H, br.d, J 10.0 Hz, H_{12}), 3.88 (1H, d, J 12.3 Hz,

CHOR), 3.92 (1H, m, H_6), 4.10 (1H, d, J 12.3 Hz, CHOR), 4.47 (1H, dd, J 1.9, 17.9 Hz, H_{16}), 4.79 (1H, dd, J 1.9, 17.9 Hz, H_{16}), 4.83 (1H, br.s H_{17}), 5.00 (1H, br.s, H_{17}), 5.94 (1H, m, H_{14}), and 7.58-7.82 (5H, m, SO_2Ph); ν_{max} ($CHCl_3$): 1780, 1750, 1630, 1580, 1150, and 1100 cm^{-1}; m/z 499 (M^+-Me), 439 (M^+-Me-HOAc), and 357; (Found: (M^+-Me) 499.2166, calc., 499.2154).

Preparation of 6α,18-Dihydroxycleroda-4,13(14)-dieno-16,15-lactone (32)

To a solution of the sulphone (31) (7.67 mg, 1.49×10^{-1} mol) in MeOH (1.0 ml) at -20°C was added Na_2HPO_4 (21 mg, 14.9×10^{-3} mol) followed by 4% Na/Hg (34 mg, 6.0×10^{-1} mol). The solution was stirred at -20°C for 1 h, further small portions of 4% Na/Hg were added until reaction was complete (TLC). The solution was quenched with water (200 µl) and EtOAc (2 ml) was added. The solids were removed by filtration through a small glass wool plug and the filtrate evaporated to afford an oil. Without further purification the oil was dissolved in CH_3CN (1.0 ml), and water (100 µl), and 10% F_3CCO_2H (1 drop) was added. The mixture was stirred for 30 min at RT before the addition of EtOAc (2.0 ml), and solid $NaHCO_3$ (0.2 g). The mixture was filtered, evaporated to dryness, and subjected to chromatography (EtOAc) to give the butenolide diol (32) (3.74 mg, 75%) as a gum; δ (250 MHz): 0.71 (3H, s, Me_9), 0.86 (3H, dd, J 0.8, 7.4 Hz, Me_4), 1.50-2.12 (12H, m), 2.18-2.32 (2H, m, H_3), 2.39(1H, br., D_2O exch., OH), 2.56 (1H, br., D_2O exch., OH), 3.93 (1H, br.d, J 10.3 Hz, CHOH), 4.08 (1H, m, H_6), 4.12 (1H, d, J 10.3 Hz, CHOH), 4.72 (2H, d, J 1.9 Hz, H_{16}), 5.02 (1H, br.s, H_{17}), 5.15 (1H, br.s, H_{17}), and 5.82 (1H, m, H_{14}); ν_{max} ($CHCl_3$): 3490, 1780, 1750 and 1635 cm^{-1}.

Preparation of Ajugarin I (1) and 4-epi-Ajugarin (33)

A solution of the diol (32) (2.5mg, 7.5×10^{-6} mol) in CH_2Cl_2 (200 µl) was added to a solution of mCPBA (6.5mg, 3.7 x 10-5 mol) mol CH_2Cl_2 (200 µl) containing Na_2HPO_4 (11mg, 7.5 x 10-5 mol) as a buffer. After 10 min the mixture was poured into water (5 ml) and the products extracted into EtOAc (3 x 3 ml). The combined extract was washed with water (3 ml), $NaHCO_3$ solution (3 ml), and brine (3 ml), dried, and the solvent evaporated in vacuo. The residue was dissolved in pyridine (150 µl) and Ac_2O (20µl) and DMAP (trace) added. After 1 h the mixture was diluted with EtOAc (5 ml) and washed with $NaHCO_3$ solution (3 ml) and brine (3 ml). Solvents were removed under reduced pressure and the residue chromatographed (10 - 90% EtOAc - 30:40 petrol) to give firstly 4-epi-ajugarin I (33) (2.01mg 62%), m.p. 170°C; δ (250 MHz): 0.74 (3H, s, Me_9), 0.79 (3H, d, J 7.0 Hz, Me_8), 1.11-2.02 (12H, m), 1.96 (3H, s, OCOMe), 2.05 (3H, s, OCOMe), 2.11-2.35 (2H, m, H_{12}), 2.59 (1H, d, J 4.0 Hz, H_{17}), 2.72 (1H, d, J 4.0 Hz, H_{17}), 4.26, (1H, d, J 11.8 Hz, H_{18}), 4.62 (1H, dd, J 5.2, 10.7 Hz, H_6), 4.74 (2H, d, J 1.6 Hz, H_{16}), 4.83 :(1H, d, J 11.8, Hz, H_{18}), and 5.84 (1H, m, H_{14}); ν_{max} ($CHCl_3$): 2915, 1782, 1742, 1728, and 1639 cm^{-1}; m/z 434 (M^+) and 404 (M^+-H_2CO), (Found: (M^+), 434.2310, calc., 434.2304); followed by ajugarin I (1) (0.65mg 20%), m.p. 190-192°C (MeOH); δ(250 MHz): 0.79 (3H, s, Me_9), 0.84 (3H, d, J 5.8 Hz, Me_8), 1.04-1.65 (12H, m), 2.02-2.34 (2H, m, H_{12}), 1.96 (3H, s, OCOMe), 2.11 (3H, s, OCOMe), 2.23 (1H, d, J 3.8 Hz, H_{17}), 3.00 (1H, dd, J 2.2, 3.8 Hz, H_{17}), 4.37 (1H, d, J 12.1 Hz, H_{18}), 4.71 (1H, m, H_6), 4.75 (2H, d, J 1.8 Hz), 4.85 (1H, d, J 12.1 Hz, H_{18}), and 5.85 (1H, m, H_{14}); ν_{max} ($CHCl_3$): 1782, 1746, 1730, and 1640 cm^{-1}; m/z 434 (M^+) and 404 (M^+-H_2CO); (Found: (M^+) 434.2310, calc., 434.2304).

Preparation of Clerodin Lactone (35)

A solution of clerodin hemiacetal (34) (5 mg, 11 µmol) in dichloromethane (3 ml) was treated with barium manganate (85 mg, 66 µmol) and the resultant suspension stirred for 16 hours. Filtration through celite gave a clerodin lactone (35) (4 mg, 81%) m.p. 170-3°C; δ (250 MHz): 0.86 (3H, d, J 5.8 Hz, Me_{20}), 0.96 (3H, s, Me_{19}), 1.38-2.17 (12H, m), 1.95 (3H, s, OCOMe), 2.11 (3H, s, OCOMe), 2.21 (1H, d, J 2.9 Hz, H_{17}), 2.41 (1H, dd, J 19.1, 3.8 Hz, H_{14}), 2.91 (1H, dd J 19.1, 10.6 Hz, H_{14}), 2.95-3.02 (1H, m, H_7), 3.12-3.26 (1H, m, H_{12}), 4.12 (1H, dd, J 11.5, 4.7 Hz, H_{11}), 4.37 (1H, d J 12.3 Hz, H_{18}), 4.68 (1H, dd J 11.5, 4.7 Hz, H_{13}), 4.89 (1H, d J 12.3 Hz, H_{18}) and 6.05 (1H, d J 5.5 Hz, H_{16}); ν_{max} (film) 2926, 1781 and 1726 cm^{-1}; m/z 434 (M^+-O), 420 (M^+-CH_2O) and 407 (M^+-CH_3CO); (Found: (M^+-CH_2O) 420.2153, calc., 420.2148).

Preparation of 6α,18-Diacetoxy-4α,17-epoxycleroda-11(S),15,16-triol (36)

$NaBH_4$ (59 mg, 1.75 mmol) was added to a solution of clerodin hemiacetal (34)(0.1584 g, 0.35 mmol) in ethanol (10 ml) and CH_2Cl_2 (5 ml) at RT. After 45 min reaction was complete by TLC and the mixture was quenched with water (10 ml) and poured into saturated NH_4Cl solution (20 ml). The product was extracted into EtOAc (4 x 20 ml), and the combined organic extract dried, evaporated and filtered through a short pad of silica-gel to give the triol (36) (0.1326 g, 83%); δ (250 MHz): 0.82 (3H, d, J 5.5 Hz, Me_8), 0.85 (3H, s, Me_9), 1.01-2.38 (15H, m), 1.96 (3H, s, OCOMe), 2.12 (3H, s, OCOMe), 2.22 (1H, d, J 3.6 Hz, H_{17}), 2.88 (3H, v.br. D_2O exch. OH), 3.00 (1H, br.s, H_{17}), 3.60 (1H, m, H_{11}), 3.75 (4H, m, H_{15}, H_{16}), 4.38 (1H, d, J 12.7 Hz, CHOAc), 4.69 (1H, m, H_6), and 4.90 (1H, d, J 12.7 Hz, CHOAc); ν_{max} ($CHCl_3$): 3480 and 1730 cm^{-1}; m/z 438 (M^+-H_2O), 323 (M^+-$C_6H_{13}O_3$); (Found: (M^+-$C_6H_{13}O_3$) 323.1866; calc. 323.1858).

Preparation of 6α,18-Diacetoxy-4α,17-epoxy-11(S)-hydroxycleroda-16,15-lactone. (37)

A mixture of the triol (36) (0.21 g, 0.46 mmol) and Fetizon's reagent (2.76 g, = 10 eq.) was heated to reflux in benzene (10 ml) for 6h. The mixture was cooled, filtered, and subjected to column chromatography (80% ether - 40:60 petrol 30% EtOAc-ether) to give the hydroxy lactone (37)

(0.14 g, 67%), m.p. 125-127°C; δ (250 MHz): 0.82 (3H, d, J 6.0 Hz, Me_8), 0.91 (3H, s, Me_9), 1.04-2.88 (16H, m), 1.96 (3H, s, OCOMe), 2.11 (3H, s, OCOMe), 2.23 (1H, d, J 3.6 Hz, H_{17}), 3.00 (1H, dd, J 2.8, 3.6 Hz, H_{17}), 3.58 (1H, br.d, J 10.7 Hz, H_{11}), 3.92 (1H, dd, J 6.1, 9.0 Hz, H_{16}), 4.37 (1H, d, J 11.0 Hz, CHOAc), 4.45 (1H, dd, J 7.4, 9.0 Hz, H_{16}), 4.68 (1H, dd, J 4.8, 11.0 Hz, H_6), ad 4.88 (1H, d, J 11.0 Hz, CHOAc); ν_{max} ($CHCl_3$): 1775 and 1730 cm-1; m/z 434 (M+-H2O), 422 (M+-CH_2O), and 379; (Found: M+-CH_2O, 422.2297; calc. 422.2304)

Preparation of 6α,18-Diacetoxy-4α,17-epoxy-15-hydroxycleroda-11,16-lactone (38)

A stirred solution of triol (36) (18 mg, 0.039 mmol) in benzene (25 ml) was treated with Fetizon's Reagent (1.00 g, 40 equivalents) and heated at reflux for 62 hours. After cooling the suspension was filtered through celite and the solvent removed in vacuo from the filtrate. Chromatography (silica, ethyl acetate) on the resulting mixture gave hydroxy-lactone (37) (8.7 mg, 51%) as before, and 6α,18-diacetoxy-4α,17-epoxy-15-hyroxy clerodane-11,16-lactone (38) (3.1 mg, 18%), δ (250 MHz) 0.89 (3H, d, J 6.3 Hz, Me_{20}), 0.99 (3H, s, Me_{19}), 1.00-2.38 (14H, m) 1.96 (3H, s, OCOMe), 2.11 (3H, s, OCOMe), 2.23 (1H, d, J 3.9 Hz, H_{17}), 2.77-2.93 (1H, m, H_{13}), 2.98 (1H, dd, J 3.7, 2.4 Hz), 3.82 (2H, bs, H_{15}), 4.36 (1H, d, J 12.6 Hz, H_{18}), 4.60 (1H, dd J 9, 6.8 Hz, H_{11}), 4.69 (1H, dd, J 11.5, 4.7 Hz, H_6), and 4.90 (1H, d, J 12.6 Hz, H_{18}); ν_{max} (film) 3482, 3055, 2916, 2848, 1761, 1726, 1458, 1369 and 1253 cm-1; m/z 422 (M+-CH_2O) and 409 (M+-CH_3CO); (Found: (M+-CH_2O) 422.2297; calc., 422.2304).

Preparation of 6α,18-Diacetoxy-4α,17-epoxycleroda-11(E)-en-16,15-lactone (39)

To a solution of hydroxy lactone (37) (0.14 g, 0.31 mmol) in pyridine (5.0 ml) at -30°C under argon, was added $POCl_3$ (0.2 ml, 2.1 mmol) dropwise. When addition was complete the solution was warmed to 0oC, and maintained at this temperature for 2 days. The mixture was cautiously poured into ice cold $NaHCO_3$ solution (20 ml) and the product extracted into CH_2Cl_2 (4 x 15 ml). The combined CH_2Cl_2 extract was dried, and evaporated and chromatographed (ether) to give the unsaturated lactone (39) (0.1256 g, 93%), m.p. 112-115oC; δ (250 MHz): 0.72 (3H, d, J 7.1 Hz, Me_8), 0.82 (3H, s, Me_9), 1.02-2.18 (10H, m), 1.96 (3H, s, OCOMe), 2.18 (3H, s, OCOMe), 2.23 (1H, d, J 3.8 Hz, H_{17}), 2.33 (1H, dd, J 8.8, 17.3 Hz, H_{14}), 2.68 (1H, dd, J 7.8, 17.3 Hz, H_{14}), 3.01 (1H, dd, J 2.3, 3.8 Hz, H_{17}), 3.22 (1H, m, H_{13}), 3.99 (1H, dd, J 7.8, 9.0 Hz, H_{16}), 4.36 (1H, d, J 12.0 Hz, H_{18}), 4.43 (1H, dd, J 7.5, 9.0 Hz, H_{16}), 4.79 (1H, m, H_6), 4.85 (1H, d, J 12.0 Hz, H_{18}), 5.15 (1H, d, J 15.0 Hz, H_{11}), and 5.29 (1H, dd, J 7.3, 15.0 Hz, H_{12}); ν_{max} ($CHCl_3$): 3020, 1775 (C=O str., 5 ring lactone), 1728 (C=O str., acetate), 1370, 1425, 1235, and 1165 cm-1; m/z 434 (M+) 404 (M+-CH_2O) and 391 (M+-CH_2CO); (Found, C, 66.12; H 7.92: Calc. for $C_{24}H_{34}O_7$ C, 66.34; H 7.89%).

Preparation of 2α-Acetoxy-1α-acetoxymethyl-4α,5α-dimethyl-5β-formyl-6β-bicyclo[4.4.0.]decane-10-0α-spiro-1'-oxiran (40)

Ozone was passed through a solution of the olefinic lactone (39) (53 mg, 0.12 mmol) in CH_2Cl_2 (10 ml) at -40oC for 1h. The solution was warmed to RT and the volume of solvent reduced to 2 ml before addition of excess Me_2S (2 ml). The mixture was stirred at RT for 2 h by which time reaction was complete (TLC). Volatile material was then removed in vacuo and the residue chromatographed (20 - 70% EtOAc - 40:60 petrol) to give the aldehyde (40) (15 mg, 35%); δ (250 MHz): 0.72 (3H, d, J 6.9 Hz, Me_4), 0.98 (3H, s, Me_5), 0.82 - 2.12 (10H, m), 1.98 (3H, s, OCOMe), 2.12 (3H, s, OCOMe), 2.28 (1H, d, J 3.8 Hz, H_1'), 3.07 (1H, dd, J 2.5, 3.8 Hz, H_1'), 4.38 (1H, d, J 12.,3 Hz, CHOAc), 4.81 (1H, d, J 12.3 Hz, CHOAc), 4.85 (1H, dd, J 6.7, 9.6 Hz, H_2), and 9.19 (1H, s, CHO); ν_{max} (film): 1730 and 1710 cm-1

Preparation of 2α-Acetoxy-1α-acetoxymethyl-4α,5α-dimethyl-5β-hydroxymethyl-6β-bicyclo[4.4.0]_decane-10-0α-spiro-1'-oxiran (41)

Ozone was passed through a solution of the olefinic lactone (39) (2 mg, 4.6 μmol) in methanol (10 ml) as -30°C for 1.5 hours. Excess sodium borohydride was added and mixture stirred for 5 hours and then allowed to warm to room temperature. The mixture was poured into brine (20 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried, filtered and solvent removed in vacuo and the residue chromatographed (silica, 70% v/v ethyl acetate, ether) to give the title compound (41) (0.5 mg, 31%); δ (250 MHz) 0.58 (3H, s, Me_5), 0.83 (3H, d, J 6Hz, Me_4), 0.98-2.18 (10H, m), 1.96 (3H, s, OCOMe), 2.12 (3H, s, OCOMe), 2.22 (1H, d, J 3.7 Hz, $H_{1'}$), 3.03 (1H, dd J 3.7, 2Hz, $H_{1'}$), 3.37 (2H, bs. CH_2OH), 4.37 (1H, d, J 11.5 Hz, CH_2OAc), 4.77 (1H, dd J 1.07, 5.8 Hz, H_2), and 4.84 (1H, d, J 11.5 Hz, CH_2OAc); ν_{max} (film) 3446, 2922, 2852, 1729, 1457, 1375 and 1252 cm-1; m/z 337 (MH+), 377 (MH+-H_2O), 324 (M+-CH_2O) and 311 (M+-$COCH_3$); (Found: (M+-CH_2O) 324.1929; calc., 324.1936).

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