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A HIGHLY CONVERGENT TOTAL SYNTHESIS OF THE SPIROACETAL MACROLIDE (+)-MILBEMYCIN β_1

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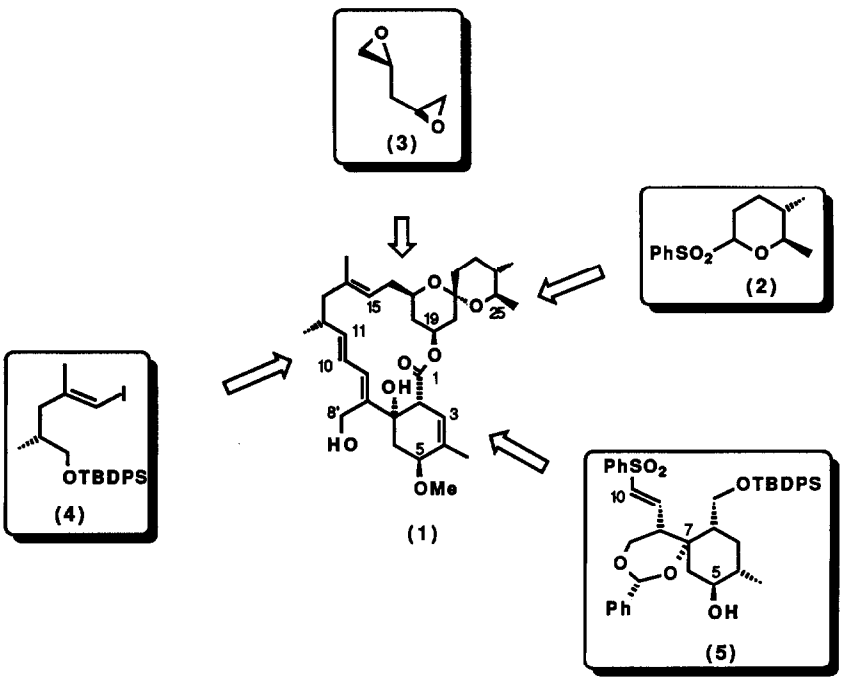
Summary: A highly convergent synthesis of the macrolide natural product milbemycin β_1 is reported. The key features of this synthesis include the introduction of the C11-C15 side chain by selective ring opening of a symmetrical 1,4-pentane bis-epoxide (3) followed by reaction with the anion derived from the 2,3-*trans*-dimethyl-6-phenylsulphonyl pyran (2) to afford the "northern" C11-C25 fragment (33) of milbemycin β_1. Coupling of the derived C11-C25 aldehyde unit (37) with a C1-C10 southern zone fragment (5) was achieved *via* a novel deconjugative vinyl sulphone anion sequence to give a product containing all the carbon substituents of the natural product. Final manipulations involved macrolactonisation and subsequent introduction of the important 3,4-double bond by selenoxide *syn*-elimination. Methylation of the C-5 hydroxyl group was accomplished as the penultimate step with methyl iodide and silver (I) oxide under ultrasonication.

As targets for organic synthesis the milbemycins[1] and avermectins[2] have attracted special attention owing to their exceedingly potent antiparasitic and insecticidal activity.[3] The presence of the architecturally interesting spiroacetal in these compounds has led to the development of many new methods for the preparation of this unit.[4] Several fragment syntheses, coupling strategies and analogue syntheses have also been reported.[5,6]

Our continued interest in these molecules[7] has led us into much new chemistry,[8] some of which is exploited below in the total synthesis of milbemycin β_1.[9] Our route to (1) employs a highly convergent approach, bringing together key structural elements as illustrated in Scheme 1.

The choice of the various coupling fragments was governed by several important factors. The synthesis of tetrahydropyranyl phenylsulphone (2) utilizes methodology developed by our group for the formation of carbon-carbon bonds at the 2-position of cyclic ethers,[10] allowing subsequent elaboration to spiroacetals *via* intermediate enol ethers.[11] The symmetrical bis-epoxide (3) is an ideal coupling fragment in that it is doubly activated towards ring opening, facilitating the introduction of the relevant side chains. Furthermore, its stereogenic centres are common to *all* milbemycins and avermectins. Use of the C11-C15 iodide (4), *via* its cuprate, ensures the correct *E*-geometry for the C-14,15 double bond, a cause of problems in other milbemycin syntheses. Finally, the C1-

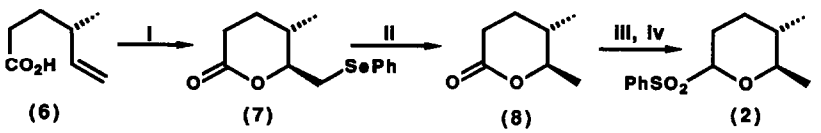
C10 "southern" unit (5) was designed to effect a deconjugative anion coupling *via* a Julia type reaction to establish the required *E*,*E*-1,3-diene portion of milbemycin β_1. The choice of (5) as a 3,4-dihydro derivative was deliberate; others have noted problems,[12] such as conjugation or epimerisation at C-2, if the 3,4-double bond is present at an early stage of the synthesis. This strategy for milbemycin β_1 synthesis is very versatile and in principle could be applied to many members of the milbemycin or avermectin classes.



Scheme 1

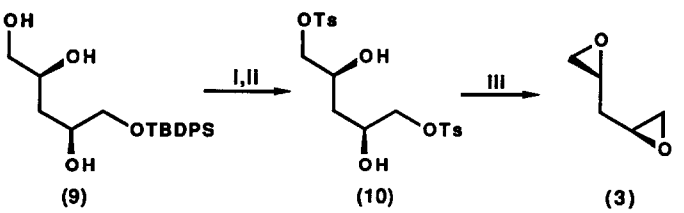
Preparation of the phenylsulphone (2) was straightforward, and started from the carboxylic acid (6).[13] Selenolactonization[14] of (6) under thermodynamic conditions using N-(phenylseleno)phthalimide and tin (IV) chloride[15] in boiling dichloromethane produced the *trans*-diequatorial product (7) in excellent yield (78% + trace *cis* isomer). Reductive removal of the phenylselenenyl substituent with tri-n-butyltin hydride afforded the known lactone (8). [1e, 1f] This in turn was converted to (2) under our standard conditions of diisobutylaluminium hydride reduction followed by treatment with phenylsulphinic acid[11] (Scheme 2). In this way, (2) was obtained as a 6:1

mixture of α:β anomers, respectively.



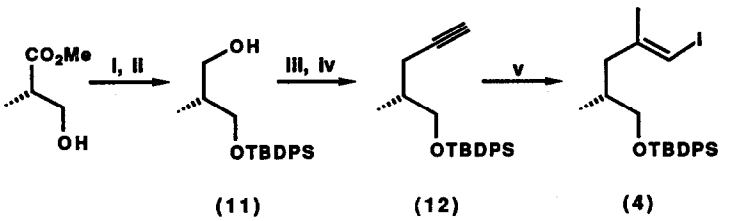
Scheme 2
(i) NPSP, $SnCl_4$, DCM, reflux, 78%; (ii) $^nBu_3SnH$, AIBN, DME, 80°C, 87%; (iii) DIBAL, toluene, -78°C, 94%; (iv) $PhSO_2H$, CSA, DCM, 3h, 91%.

As a starting point for the synthesis of the *bis*-epoxide (3), triol (9) was prepared from ribonic acid-γ-lactone by a literature route.[16] Reaction of (9) with tetra-n-butylammonium fluoride afforded the crude tetraol which was converted to the *bis*-tosylate (10) using tosyl chloride in pyridine. Formation of (3) was accomplished in 60% yield simply by treatment of (10) with a basic ion exchange resin (IR-400) (Scheme 3).



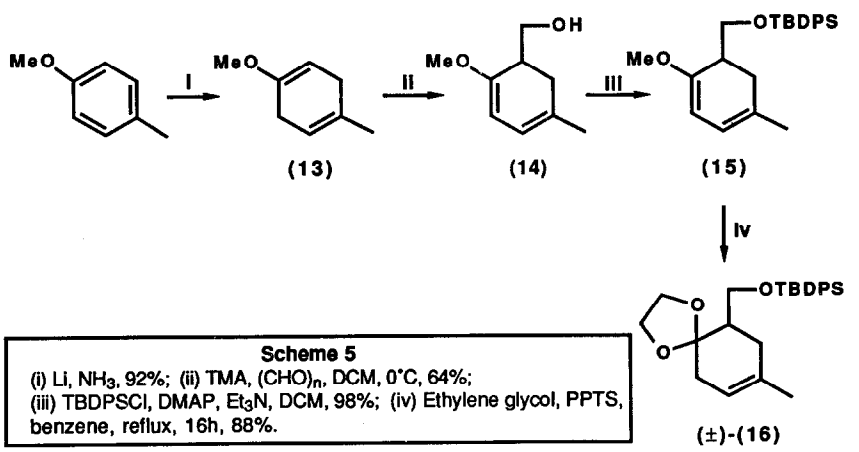
Scheme 3
(i) TBAF, THF; (ii) TsCl, py, 65%; (iii) IR-400, DCM, 60%.

The vinyl iodide (4) was obtained from (S)-(+)-methyl 3-hydroxy-2-methylpropionate. Silylation with t-butyldiphenylsilylchloride followed by diisobutylaluminium hydride reduction of the ester gave the protected diol (11). This was converted to the acetylene (12) by tosylation and nucleophilic displacement with lithium acetylide-ethylene diamine complex in dimethylsulphoxide. Finally compound (12), upon carboalumination[17] with trimethylaluminium and dicyclopentadienyl zirconium dichloride and quenching with iodine, gave (4). This sequence provided (4) in 49% overall yield from the commercially available (S)-(+)-methyl 3-hydroxy-2-methylpropionate (Scheme 4).



Scheme 4
(i) TBDPSCl, imidazole, DMF, 98%; (ii) DIBAL, toluene, 79%; (iii) TsCl, py, DMAP, 86%; (iv) LiC≡CH. $H_2N(CH_2)_2NH_2$, DMSO, 83%; (v) Cp_2ZrCl_2, Me_3Al, then I_2, 89%.

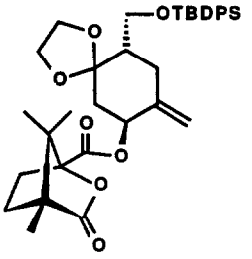
Synthesis of the southern hemisphere fragment (5) was more involved and required a multi-step operation. 4-Methylanisole was reduced under Birch conditions to afford the known dihydro species (13) which, after Prins reaction with formaldehyde in the presence of trimethylaluminium,[18] gave the alcohol (14). Following protection as the t-butyldiphenylsilyl ether (15), conversion of the reactive enol ether to the more stable 1,3-dioxolane (16) was accomplished. This sequence of reactions could be performed readily on a large scale (≈ 100 g) in 51% overall yield from the anisole (Scheme 5).



Scheme 5
(i) Li, NH_3, 92%; (ii) TMA, $(CHO)_n$, DCM, 0°C, 64%; (iii) TBDPSCl, DMAP, Et_3N, DCM, 98%; (iv) Ethylene glycol, PPTS, benzene, reflux, 16h, 88%.

Attempts to asymmetrically hydroborate[19] (16) to the optically pure product were unsatisfactory due to difficulties experienced in reaction scale-up. We therefore opted for a resolution method to obtain the desired chiral material (Scheme 6). Selective *cis*-glycolation of (16) with N-methyl morpholine-N-oxide and catalytic osmium tetroxide afforded the diol (17) in 71% yield, along with a small amount (4%) of the readily separated undesired diastereoisomeric diol. Reaction of the racemic diol (17) with (1S)-(-)-camphanic acid chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) afforded the corresponding diastereoisomeric camphanic ester derivatives (18) and (19) which were separable by HPLC or MPLC.

In order to determine the absolute configuration of the appropriate structures we resorted to X-ray crystallography of a derivative of the diastereoisomer (19). Treatment of (19) with thionyl chloride in pyridine afforded the crystalline *exo*-alkene (20), the X-ray structure of which is shown in Figure 1.



(20)

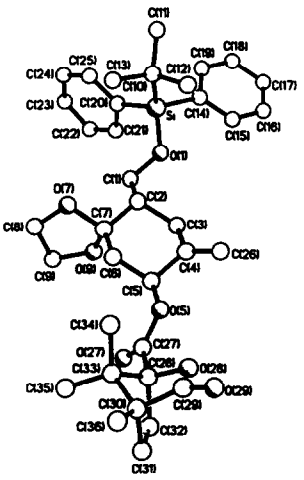
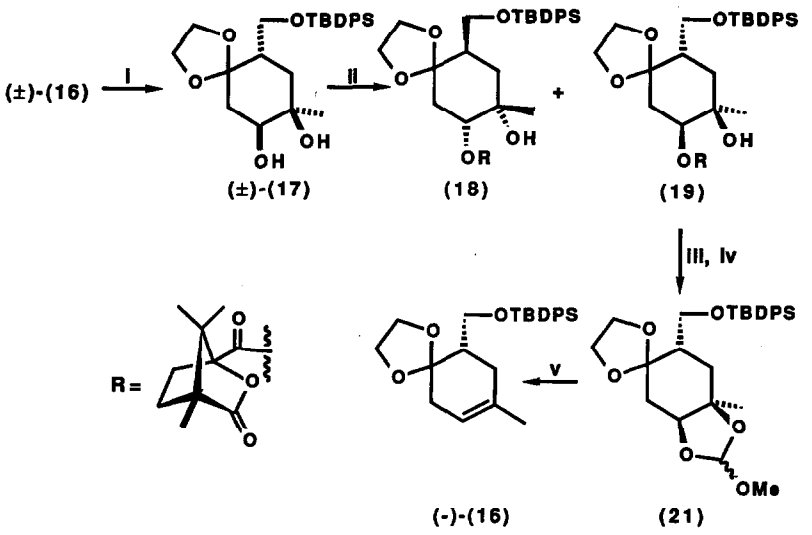


Figure 1

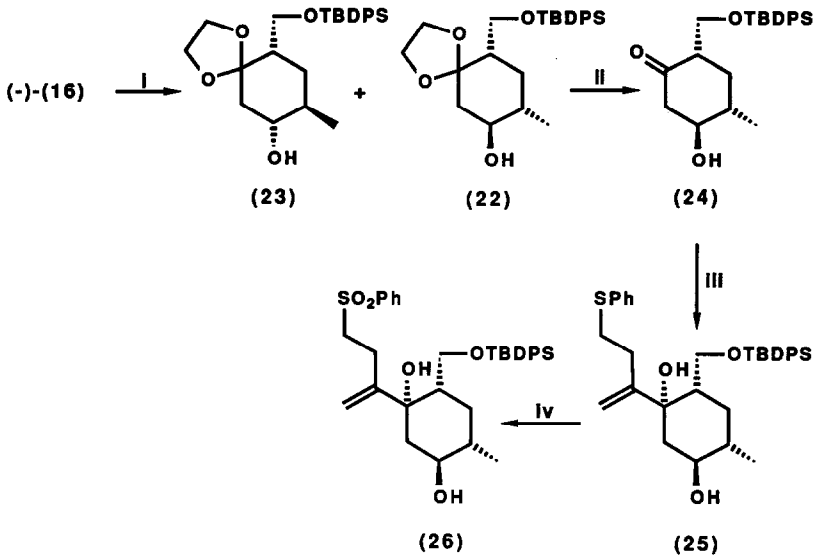
The absolute configuration revealed by this X-ray study was corroborated by the known absolute configuration of the camphanic ester portion. The asymmetric centres in (20), and hence in the ester (19), were thus established.

Following methanolysis of the diastereoisomer (19) to optically pure diol (-)-(17), transformation *via* the orthoformates[20] (21) gave the homochiral alkene (-)-(16) in 83% yield from (19).



Scheme 6
(i) OsO_4, NMO, $^tBuOH/H_2O$, 71%; (ii)1S-(-)-camphanic acid chloride, Et_3N, DMAP, DCM; (iii) K_2CO_3, MeOH, 88%; (iv) $(MeO)_3CH$, PPTS, DCM, 100%; (v) Ac_2O, reflux, 94%.

The synthesis was continued by conventional hydroboration of (-)-(16) to give (22) (88%) together with 4% of the diastereoisomeric alcohol (23). Removal of the dioxolane protecting group of (22) was not easy owing to competing β-elimination under usual conditions. However, use of $PdCl_2(CH_3CN)_2$[21] in acetone reproducibly gave the cyclohexanone (24) in 98% yield. Addition of 2-lithio-4-phenylthiobut-1-ene[22] to this ketone (24) in THF-ether at -78°C gave (25) in excellent yield (87%). The sterically demanding nature of the C-1 tert-butyldiphenylsilyloxy group, as anticipated, very favourably controlled the diastereoselectivity (>95:5) of this process. Proof of the stereochemistry at the newly-formed C-7 stereocentre in (25) comes from X-ray crystal structure determination of a later compound (*vide infra*). Oxidation of (25) was normally performed by using mCPBA to give the crude sulphoxides, which were then reacted with Oxone® to provide the sulphone (26) in 88% yield from the sulphide (Scheme 7).

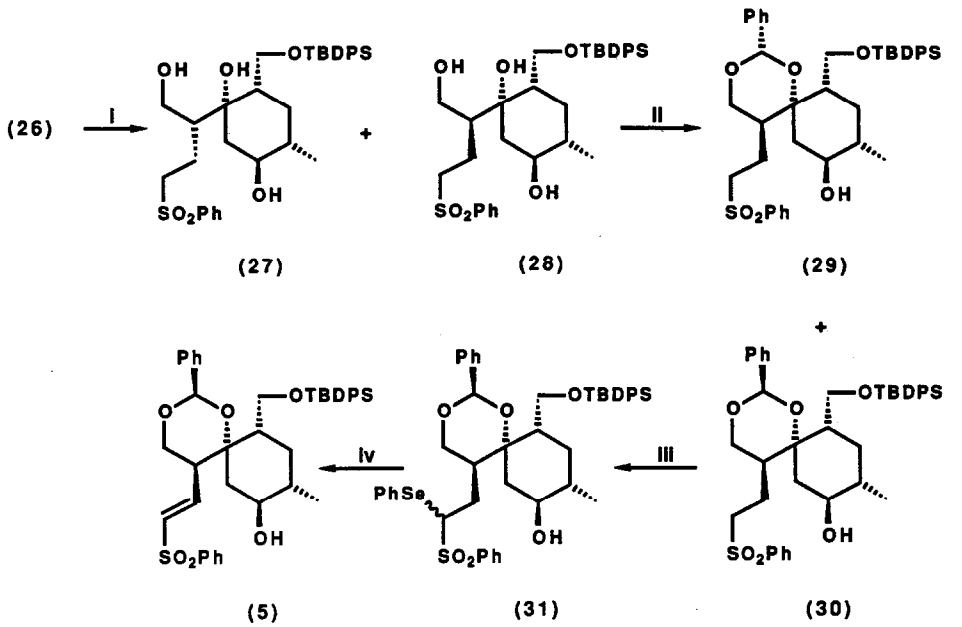


Scheme 7

(i) BH_3.DMS, THF, then aq.NaOH, H_2O_2; (ii) $PdCl_2(CH_3CN)_2$, acetone, 98%; (iii) 2-lithio-4-phenylthio-but-1-ene, THF/ether, -78°C, 87%; (iv) mCPBA, DCM, then Oxone®, MeOH/THF/H_2O, 88%.

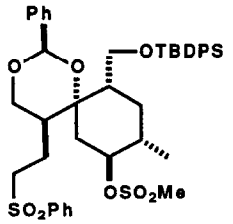
While the sulphone (26) can be manipulated in a variety of ways to various coupling fragments,[7] for the present synthesis it was transformed to the southern zone unit (5) by the following reactions. Stereoselective hydroboration of (26) gave a 1:4 ratio of products (27) and (28). Reaction of the major isomer (28) with pyridinium tosylate and benzaldehyde under Dean-Stark conditions gave a 1:1 mixture of the separable acetals (29) and (30). To simplify spectroscopic interpretations of the ensuing compounds, only one of the acetals, (30), was carried through the synthesis; the acetal (29) could be recycled to the 1:1 mixture of (29) and (30) by re-exposure to the acetalisation reaction conditions. Treatment of (30) with 2 equivalents of *tert*-butyllithium followed by quenching of the resulting α-sulphonyl-carbanion with phenylselenenyl chloride gave the diastereoisomeric selenides (31) which, upon oxidation with m-CPBA, smoothly underwent *syn*-elimination *via* the selenoxides to the *E*-vinyl sulphone coupling fragment (5) (Scheme 8).

Proof of the relative stereochemistry of (27), (28), (29) and (30) follows from the conversion of racemic (30) to the crystalline mesylate (32) which proved suitable for X-ray structure determination (Figure 2).



Scheme 8

(i) BH_3.DMS, THF, then aq.NaOH, H_2O_2, 85%; (ii) PhCHO, PPTS, benzene, reflux, 97%
(iii) 2.2 eq.^{t}BuLi, THF, -78°C, then PhSeCl, 79%; (iv) mCPBA, DCM/aq.$NaHCO_3$, 99%.



(32)

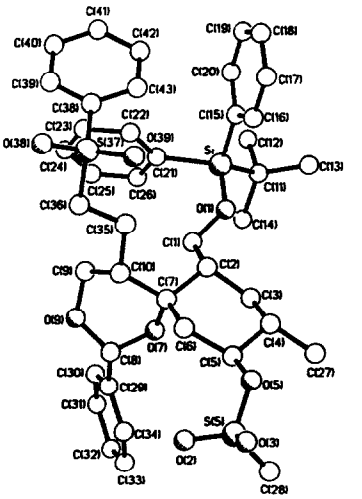
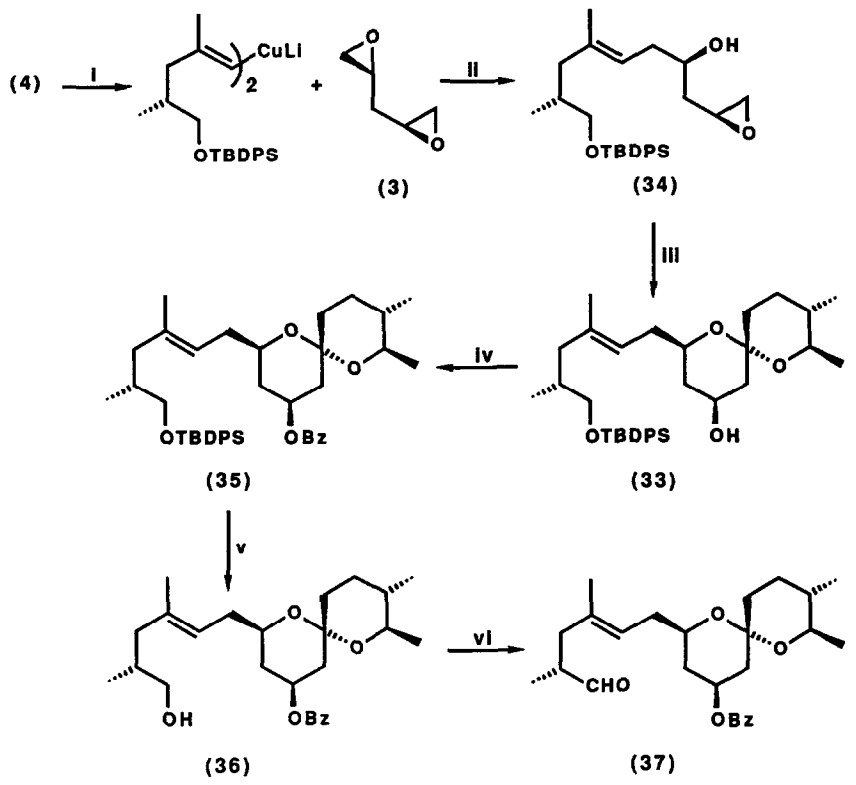


Figure 2

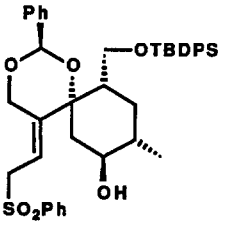
With all the structural pieces proposed in Scheme 1 to hand, we were at last in a position to study their coupling towards milbemycin β_1. We first addressed the construction of the "northern" C11-C25 portion, compound (33). The cuprate generated from the iodide (4) was reacted with the epoxide (3) at -65°C for 4 hours to give the epoxyalcohol (34) in 53% yield. This was complexed with titanium (IV) isopropoxide at -20°C and reacted at -78°C with the anion from the sulphone (2). Upon work-up with 5% sulphuric acid, an 80% yield of the spiroacetal (33) was realised. Compound (33) was subsequently progressed to a fragment suitable for coupling with the sulphone (5) by benzoylation to (35) (85%), deprotection with tetra-n-butylammonium fluoride to (36) (95%) and oxidation to the aldehyde (37) (85%) using tetra-n-propylammonium perruthenate (TPAP)[23] (Scheme 9).



Scheme 9

(i) 2.2 eq. ^{t}BuLi, -120°C to -78°C, 1h, then 0.5 eq. CuI, -40°C; (ii) -65°C, 4h, 53%; (iii) $Ti(O^iPr)_4$, sulphone anion (from (2) +1 eq. ^{n}BuLi , THF,-78°C), THF, -78°C, then 5% aq. H_2SO_4, 80%; (iv) PhCOCl, py, DMAP, 85%; (v) TBAF, THF, 95%; (vi) TPAP, NMO, 4Å ground sieves, DCM, 85%.

Coupling of the northern unit (37) to the southern fragment (5) was examined next. It was anticipated that vinylogous elimination of benzaldehyde from the allylic anion generated from (5) would be more difficult than in an analogous acyclic structure. The benzylidene ring was expected to geometrically constrain the allyl anion HOMO and the C-O σ^* orbitals in such a way that overlap could not readily be achieved. In addition, MNDO calculations[24] on such systems indicate that the largest HOMO coefficient occurs on the C atom α- to the phenylsulphonyl group, while the smallest HOMO coefficient occurs at C-8, a factor favouring alkylation of the allyl anion at C-10. The dianion formed by treatment of (5) with two equivalents of *tert*-butyllithium at -78°C in THF indeed reacted with (37) through its C-10 carbon to afford the hydroxy sulphones (38) in 84% yield. The apparently exclusive formation of the required *E*- geometry at Δ^8 in this coupling reaction may be attributed to the minimisation of non-bonded interactions between the bulky phenylsulphonyl and TBDPS groups. A small amount of the allylic sulphone (39), resulting from proton quench at C-10 of unreacted anion, could be separated from the addition products.

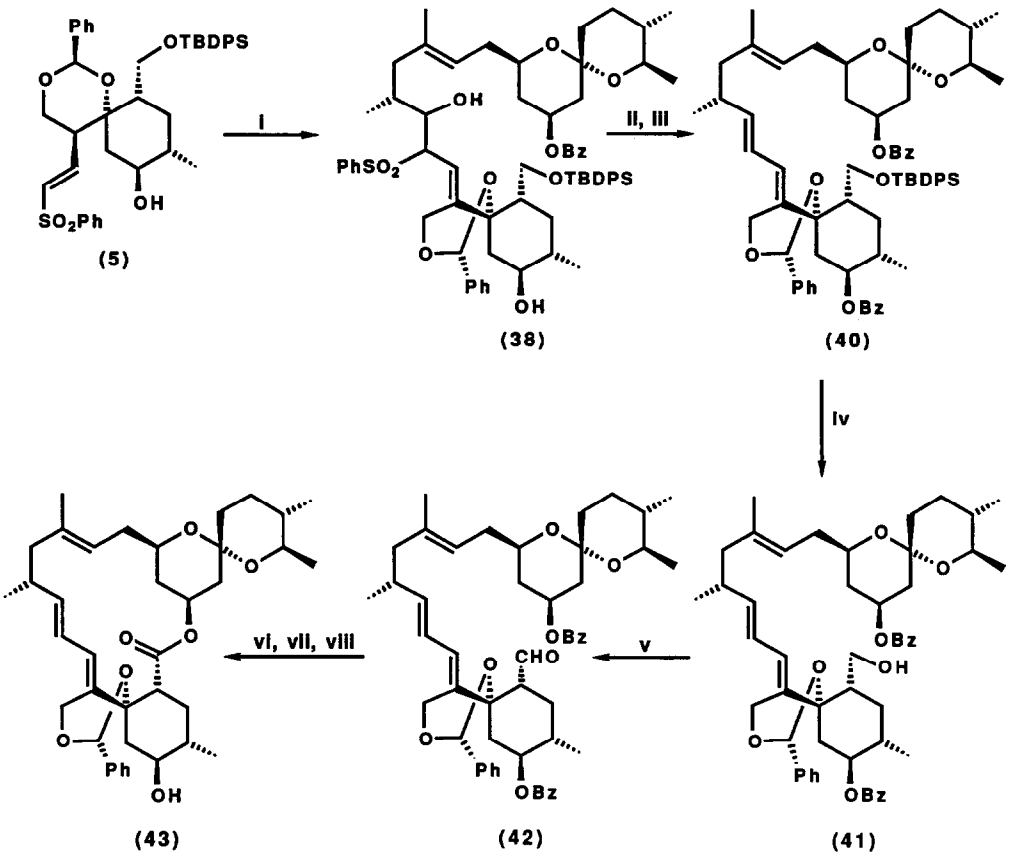


(39)

Reductive elimination using 6% Na/Hg in THF/MeOH at -40°C followed by benzoylation (PhCOCl, DMAP, pyridine) gave the *E,E*-diene (40). Deprotection with tetra-n-butylammonium fluoride gave the C-1 alcohol (41) which was oxidised in two stages; TPAP afforded the aldehyde (42) which was further oxidised with sodium chlorite[25] to the carboxylic acid. After treatment with methanolic sodium methoxide to remove the benzoyl groups, macrolactonisation was achieved using 2-chloro-1-methylpyridinium iodide[26] to produce (43) (Scheme 10).

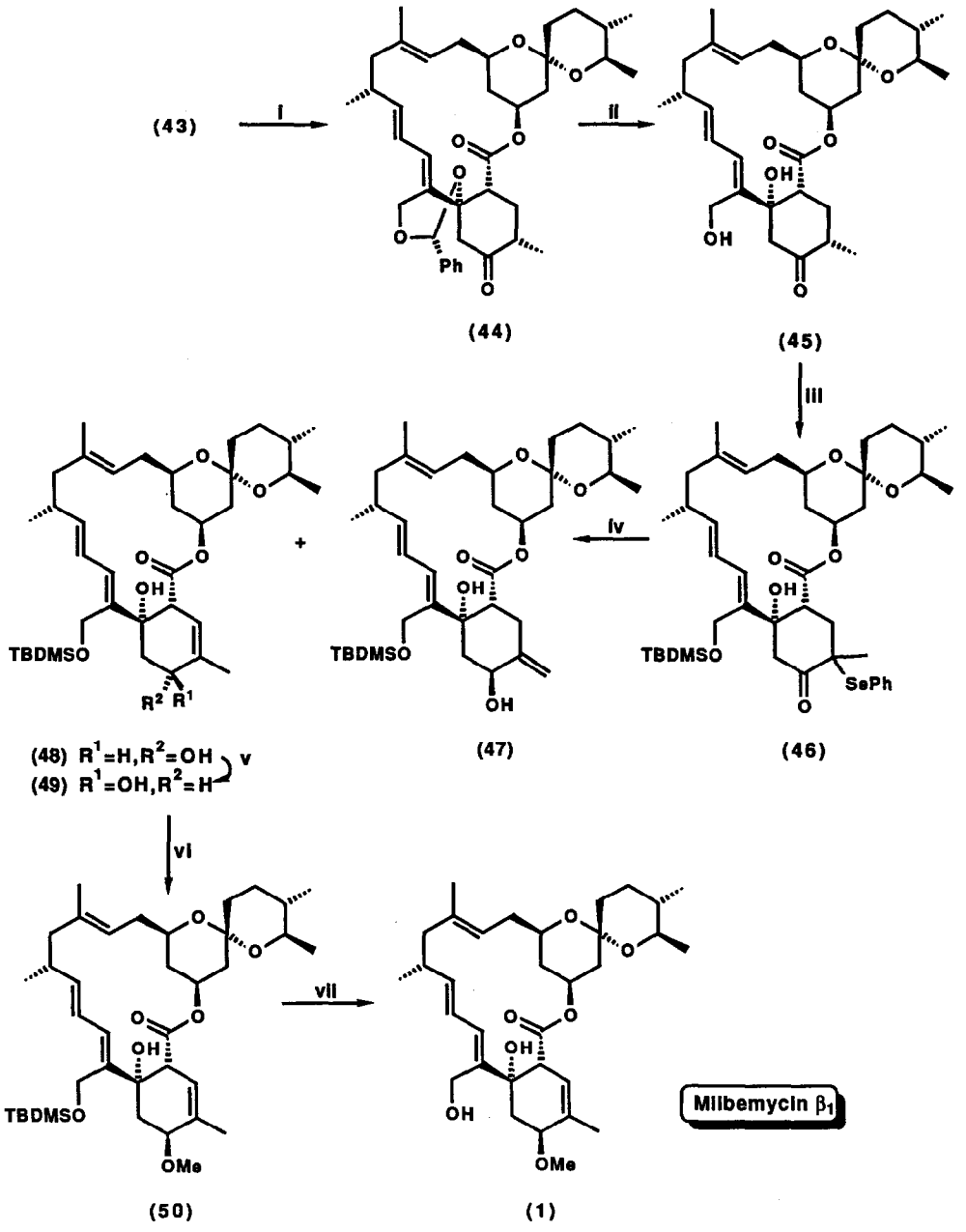
For the final stages of the synthesis, several alternative sequences were investigated; only the successful route is reported here. The macrolide (43) was oxidised, once again using the TPAP reagent, to give the C-5 ketone (44) (83%). This was deprotected with moist trifluoroacetic acid to (45) before reaction with t-butyldimethylsilyl triflate and triethylamine to protect the primary hydroxyl group and simultaneously generate the thermodynamic silyl enol ether at C4-C5. Treatment with phenylselenenyl chloride gave the ketoselenide (46) (Scheme 11). Oxidation of (46) with the Davis oxaziridine reagent[27] gave the intermediate selenoxides which underwent spontaneous *syn*-elimination at room temperature to give the *exo*- and *endo*-products in a 1:2 ratio by ^{1}H nmr. Owing to the possibility of aromatisation of these compounds they were most conveniently handled by work-up of this mixture

with cerium (III) chloride / sodium borohydride[28] to give the alcohols (47), (48) and (49) in a 1:1:1 ratio (81%). The compound (48) could be recycled to (49) by oxidation (TPAP) and reduction as described above. Finally, methylation of (49) with methyl iodide and silver (I) oxide under ultrasonication[29] gave (50), which was deprotected with HF / pyridine in acetonitrile to provide the natural product (+)-milbemycin β_1[30] (1) in 55% yield for the last two steps (Scheme 11). The synthetic sample was identical by ^1H nmr, ^{13}C nmr, IR, mass spectrometry, $[\alpha]_D$ and tlc comparison (3 solvent systems) to an authentic sample provided by Sankyo.[31]



Scheme 10

(i) ^{t}BuLi, 2.2eq., THF, -78°C, then (37), 84%; (ii) 6% Na/Hg, Na_2HPO_4, THF/MeOH, -40°C; (iii) PhCOCl, DMAP, Py, DCM, 27% from (38); (iv) TBAF, THF, reflux, 15 min, 91%; (v) TPAP, NMO, 4Å ground sieves, DCM, 76%; (vi) NaO_2Cl, 2-methyl-2-butene, KH_2PO_4, tBuOH/H_2O; (vii) NaOMe, MeOH; (viii) 2-chloro-1-methyl-pyridinium iodide, Et_3N, CH_3CN, reflux, 9h ,49% from (42).

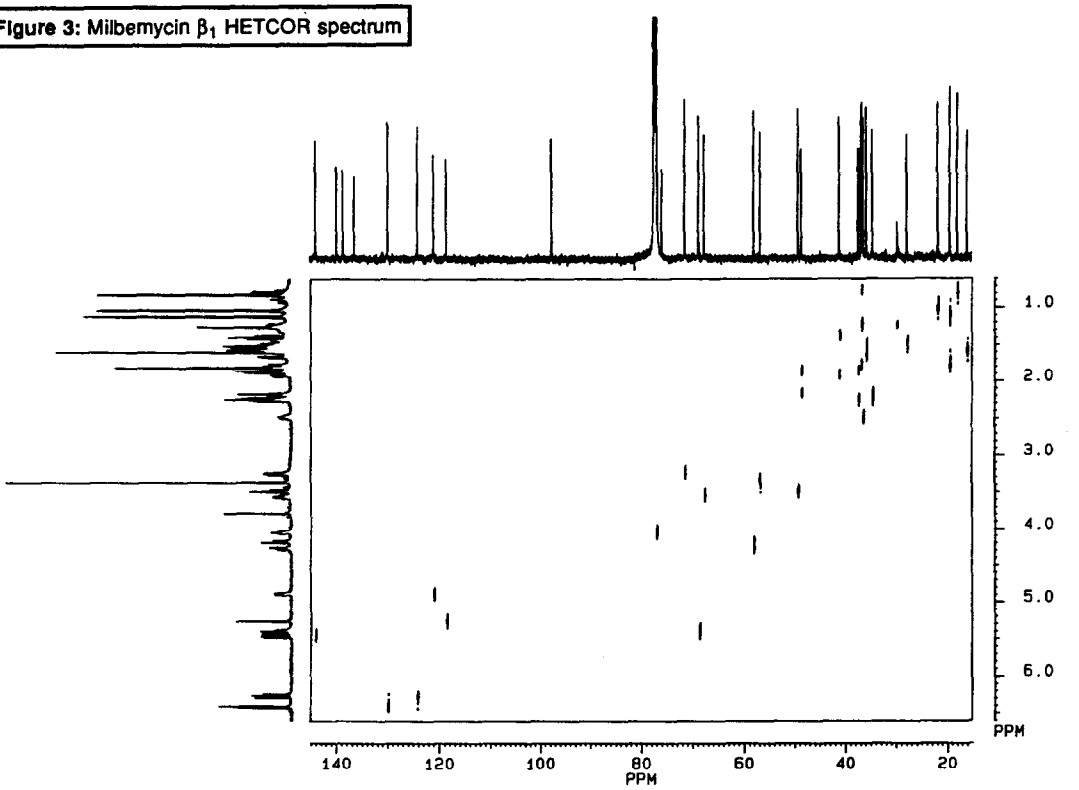


Scheme 11

(i) TPAP, NMO, 4Å ground sieves, DCM, 83%; (ii) TFA, DCM, 92%; (iii) 4eq. TBDMSOTf, 20eq. Et_3N, DCM, r.t., then PhSeCl, DCM, -78°C, 50%; (iv) 2-Benzenesulphonyl-3-(p-nitrophenyl)oxaziridine, $CDCl_3$, r.t., then $NaBH_4$, $CeCl_3$, MeOH, r.t.; (v) TPAP, 4Å ground sieves, DCM, then $NaBH_4$, $CeCl_3$, MeOH, r.t.; (vi) MeI, Ag_2O,))), 73%; (vii) HF, py, CH_3CN, 75%.

As ^{13}C data for the natural product have not been reported previously, a ^{13}C-^{1}H heteronuclear correlation study was undertaken as an aid to spectroscopic assignments. This correlation spectrum is reproduced in Figure 3.

Figure 3: Milbemycin β_1 HETCOR spectrum



We believe that the above synthesis vindicates the strategy shown in Scheme 1. Moreover, it demonstrates the versatility of our coupling approach which we hope to employ in the synthesis of other members of the avermectin and milbemycin series.

Acknowledgements

We thank the SERC, Pfizer Central Research and Merck, Sharp and Dohme for financial support. We also acknowledge Farmitalia Carlo-Erba, Milan, for study leave support (to M.G.B.) and the NATO for a research grant (to C.G.).

Experimental

^{1}H nmr spectra were recorded in $CDCl_3$ using a Varian EM-360A, Jeol FX 90Q, Bruker WM 250, Jeol GSX 270, Bruker WH 400 or Bruker AM-500 nmr spectrometer. ^{13}C nmr spectra were recorded in $CDCl_3$ at 22.5 MHz on a Jeol FX 90Q, 62.9 MHz on a Bruker WM 250 or at 125.8 MHz on a Bruker AM-500 spectrometer. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were recorded under EI conditions unless otherwise stated, using VG-7070B, VG 12-253 and VG ZAB-E instruments; microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity AA-1000 polarimeter. Sonication was carried out using a Semat 80W, 50kHz ultrasonic cleaning bath. Molecular modelling was performed using the MACROMODEL package,[32] on an Evans and Sutherland PS-390 graphics terminal. Column chromatography and MPLC were performed on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated; HPLC was performed on DYNAMAX 60A Si columns. Florisil refers to 200-300 U.S. mesh Florisil as supplied by BDH Ltd. Diethyl ether and tetrahydrofuran solvents were distilled from sodium-benzophenone ketyl; dichloromethane (DCM) from phosphorus pentoxide; toluene from sodium; acetonitrile from calcium hydride; dimethyl sulphoxide from calcium hydride. Petrol refers to petroleum ether b.p. 40-60°C which was distilled prior to use. Other solvents and reagents were purified by standard procedures as necessary. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised by ultra-violet light, acidic ammonium molybdate (IV) or iodine as appropriate. Numbering for ^{1}H nmr assignments follows the systematic (IUPAC) nomenclature until compound (40), when the natural product numbering system is adopted. Coupling constants are measured in Hertz.

(+)-(5S,6S)-Tetrahydro-5-methyl-6-[(phenylselenenyl)methyl]-2H-pyran-2-one **(7)**.- The acid (6) (9.0 g, 70.3 mmol) and tin (IV) chloride (7.0 ml of a 1M solution in DCM, 7.0 mmol) were dissolved in dry DCM (75 ml) under argon and heated to reflux. The heat source was removed and a solution of NPSP (23.4 g, 77.5 mmol) in dry DCM (250 ml) was added at such a rate as to maintain reflux. When the addition was complete the mixture was heated for a further 1.5h then cooled. The mixture was washed with 1M aqueous sodium hydroxide (3 x 75 ml) then dried ($MgSO_4$) and evaporated. Crystallisation of the residue from DCM/petrol afforded the *lactone* (7) (15.5 g, 78%) as a colourless solid, m.p. 106°; ν_{max} ($CHCl_3$) 2955, 1728 and 842 cm^{-1}; δ_H (250 MHz) 7.56 (2H, m, Ph), 7.27 (3H, m, Ph), 4.21 (1H, ddd, J 9.2, 5.5 and 3.4, H-6), 3.29 (1H, dd, J 12.5 and 3.4, CHSe), 3.15 (1H, dd, J 12.5 and 5.5, CHSe), 2.62 (1H, ddd, J 17.5, 11.2 and 4.5, H-3), 2.49 (1H, ddd, J 17.5, 9.5 and 6.7, H-3), 2.08-1.83 (2H, m), 1.55 (1H, m) and 0.95 (3H, d, J 6.7, Me); m/z 284 (M^+), 113 (M^+-CH_2SePh), 85, 55 and 43; found: C, 54.88; H, 5.71. $C_{13}H_{16}O_2Se$ requires C, 55.13; H, 5.69%.

(+)-(5S,6R)-Tetrahydro-5,6-dimethyl-2H-pyran-2-one **(8)**.- A mixture of the selenide (7) (0.50 g, 1.8 mmol), tri-n-butyltinhydride (0.77 g, 2.7 mmol), and AIBN (8 mg) in dry DME (10 ml) was heated to 80°C for 10 min then cooled to 0°C. Carbon tetrachloride (10 ml) was added and the mixture stirred at room temperature for 2h. Saturated aqueous potassium fluoride solution (5 ml) was added and the mixture filtered. The organic layer was washed with saturated aqueous KF (2 x 5 ml) then dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (50% ether-petrol) afforded the *lactone* (8) (0.20 g, 87%) as a colourless oil, $[\alpha]_D^{20}$ + 18.0° (*c* 1.2 in $CHCl_3$); ν_{max} (film) 2973, 1733, 1304, 1250, 1226 and 1095 cm^{-1}; δ_H (500 MHz) 4.04 (1H, dq, J 9.6 and 6.3, H-6), 2.62 (1H, ddd, J 17.9, 6.7 and 4.1, H-3), 2.48 (1H, ddd, J 17.9, 10.0 and 7.2, H-3), 1.89 (1H, m, H-5), 1.66-1.50 (2H, m, H_2-4), 1.36 (3H, d, J 6.3, Me-6) and 1.00 (3H, d, J 6.5, Me-5); m/z 128 (M^+, 10.5%), 113 (2.3, M^+-Me), 85 (6.3) and 56 (100); identical to literature material.[1b]

(5S,6R)-Tetrahydro-5,6-dimethyl-2H-pyran-2-ol.- A solution of the lactone (8) (0.46 g, 3.6 mmol) in dry toluene (2 ml) was added over 5 min to a solution of DIBAL (4.5 ml of a 1M solution in toluene, 4.5 mmol) at -78°C under argon. After 3h water (0.25 ml) was added and the mixture warmed to room temperature. Solid sodium hydrogencarbonate (3.8 g) was added and the mixture filtered through Florisil, washing with ethyl acetate (50 ml). Evaporation of the filtrate afforded the *lactol* (0.44 g, 94%) as a colourless oil (6:4 mixture of β:α anomers), ν_{max} (film) 3390, 2929, 2874, 1450, 1378, 1229, 1160, 1009, 965 and 943 cm^{-1}; δ_H (250 MHz) 5.29 (0.4H, br s, H-2α), 4.70 (0.6H, dd, J 9.0 and 1.5, H-2β), 4.28 (0.6H, br s, OHβ), 3.71 (0.4H, dq, J 9.0 and 6.0, H-6α), 3.53 (0.4H, br s, OHα), 3.19 (0.6H, dq, J 9.0 and 5.0, H-6β), 1.90-1.20 (5H, m, $C\underline{H}_2$, H-5α, H-5β), 1.21 (1.8H, d, J 6.5, 6β–Me), 1.13 (1.2H, d, J 6.5, 6α-Me), 0.84 (1.2H, d, J 6.5, 5α-Me) and 0.81 (1.8H, d, J 6.5, 5β-Me); m/z 130 (M^+, 4.1%), 112 (4.7, M^+-H_2O), 97 (4.5, M^+-H_2O-Me) and 44 (100); found: C, 64.38; H, 10.90. $C_7H_{14}O_2$ requires C, 64.58; H, 10.84%.

(2R,3S)-Tetrahydro-2,3-dimethyl-6-(phenylsulphonyl)-2H-pyran **(2)**.- A mixture of the lactol (1.29 g, 9.9 mmol), benzenesulphinic acid (2.81 g, 19.8 mmol) and 10-camphorsulphonic acid (11.5 mg, 0.05 mmol) in DCM (60 ml) was stirred at room temperature for 3h. The mixture was washed with saturated aqueous sodium hydrogencarbonate solution (2 x 25 ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed quickly on silica gel (50% ether-petrol) to afford the *sulphone* (2) (2.3 g, 91%, ca. 6:1 mixture of anomers) as a colourless solid. Crystallisation from ether/petrol (1:4) afforded an analytical sample of the major (α) anomer, m.p. 96-7°; ν_{max} ($CHCl_3$) 1302, 1291, 1150, 1082, 644 and 604 cm^{-1}; δ_H (250 MHz) 4.66 (1H, d, J 6.8, H-6), 4.18 (1H, dq, J 9.8 and 6.0, H-2), 2.70-1.27 (5H, m), 1.09 (3H, d, J 6.0, 2-Me) and 0.92 (3H, d, J 6.0, 3-Me); m/z 113 (95%, M^+-$PhSO_2$), 95 (100), 69 (60) and 41 (45); found: C, 61.52; H, 7.19. $C_{13}H_{18}SO_3$ requires C, 61.39; H, 7.13%.

(-)-(2R,4R)-1,2,4,5-Pentanetetrol-1,5-bis-(4-methylbenzenesulphonate) **(10)**.- Tetra-n-butylammonium fluoride (12 ml of a 1M soln. in THF, 12 mmol) was added to a solution of the triol (9) (3.74 g, 10 mmol) in THF (25 ml) under argon. After 1.5h the mixture was diluted with ether (30 ml) and extracted with water (30 ml). The aqueous extracts were neutralised by addition of Amberlyte IR 120(H^+) resin. The resin was removed by filtration, washing well with water and methanol. The filtrate was evaporated to leave a tan oil (1.5 g). This oil was taken up in pyridine (10 ml) at 0°C and treated under argon with *p*-toluenesulphonyl chloride (4.76 g, 25 mmol). After warming to room temperature the mixture was stirred for 4h then evaporated. Column chromatography of the residue on silica gel (40% ether-DCM) afforded the *bistosylate* (10) (2.88 g, 65%) as a colourless solid, m.p. 88-90°; $[\alpha]_D$ -8.5° (*c* 0.2 in EtOH); ν_{max} (film) 3419, 1596, 1353, 1173, 970, 815 and 667 cm^{-1}; δ_H (250 MHz) 7.78 (4H, d, J 7.0, Ar-H), 7.36 (4H, d, J 7.0, Ar-H), 4.12 (2H, m, H-2, H-4), 4.00 (2H, dd, J 10.0, 3.7, H-1), 3.90 (2H, dd, J 10.0, 7.2, H-5), 2.46 (6H, s, Ar-CH_3) and 1.63 (2H, dd, J 7.2, 5.5, H-3); δ_C (125.8 MHz) 145.1, 132.3, 129.8, 127.7, 73.5, 65.7, 34.7 and 21.4; m/z 172 (8%), 100 (9) and 91 (100); found: C, 51.14; H, 5.43. $C_{19}H_{24}O_8S_2$ requires C, 51.34; H, 5.44%.

(+)-(2R,2'R)-Methylenebis(oxirane) **(3)**.- The bistosylate (10) (3.90 g, 8.8 mmol) in DCM (30 ml) was treated with Amberlite IRA 400 (OH) resin (50 ml) at room temperature for 4h. The resin was removed by filtration, washing well with DCM (200 ml). The filtrate was dried (Na_2SO_4), filtered and the solvent removed by distillation *via* a Vigreux column. The residue was chromatographed on silica gel (20% ether-DCM) and appropriate fractions concentrated by distillation. The residue was distilled in a Kugelrohr apparatus to afford the *bisepoxide* (3) (0.52 g, 60%), b.p. 80° at 15 mmHg; $[\alpha]_D^{20}$ +47° (*c* 0.8 in $DCCl_3$); ν_{max} (film) 3054, 2994, 2923, 1419, 1256 and 844 cm^{-1}; δ_H (250 MHz) 3.10 (2H, m, H-2), 2.80 (2H, dd, J 5.0 and 4.9, H-3), 2.52 (2H,

dd, J 5.0 and 2.6, H-3) and 1.75 (2H, t, J 5.6, H-1); δ_C (22.5 MHz) 48.9, 46.3 and 35.6; m/z 100 (M^+, 1.8%), 69 (8.7, M^+-CH_2OH), 57 (7.3), 43 (20.8) and 42 (100); found: C, 60.00; H, 8.22. $C_5H_8O_2$ requires C, 59.98; H, 8.05%.

(+)-S-Methyl 3-(tert-Butyldiphenylsilyloxy)-2-methylpropionate.- tert-Butyldiphenylsilylchloride (21 ml, 80.8 mmol) was added to a solution of (+)-(S)-Methyl 3-hydroxy-2-methylpropionate (8.6 g, 73 mmol) and imidazole (11.0 g, 162 mmol) in DMF (15 ml), at r.t. under argon. After 3h the mixture was poured into water and extracted with ether. The combined organic extracts were washed sequentially with 1M HCl, saturated aqueous sodium hydrogencarbonate solution and brine, then dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (5% ether-petrol) afforded the *silyl ether* (25.4 g, 98%), as a colourless oil, $[\alpha]_D^{20}$ +23° (*c* 7.8 in MeOH); ν_{max} (film) 3071, 2934, 2858, 1741, 1200, 1112 and 823 cm^{-1}; δ_H (60 MHz) 7.60 (4H, m, Ph), 7.28 (6H, m, Ph), 3.85-3.60 (2H, m, H_2-3), 3.60 (3H, s, CO_2CH_3), 2.70 (1H, m, H-2), 1.20 (3H, d, J 6.5, Me) and 1.05 (9H, s, ^tBu); m/z 325 (M^+-OMe), 299 (M^+-^tBu), 269 (M^+-CH(Me)CO_2Me), 213 and 183; found: C, 70.87; H, 8.07. $C_{21}H_{28}O_3Si$ requires C, 70.74; H, 7.92%.

***(+)-(R)-3-(tert-Butyldiphenylsilyloxy)-2-methyl-1-propanol* (11).-** DIBAL (107 ml of a 1.5M solution in toluene, 160 mmol) was added dropwise to a solution of (+)-S-Methyl 3-(tert-Butyldiphenylsilyloxy)-2-methylpropionate (26.0 g, 73 mmol) in toluene (100 ml) at -78°C under argon. After 2h the mixture was quenched with saturated aqueous ammonium chloride solution (5 ml) and allowed to come to r.t. The suspension was diluted with ether (1l) and dried over $MgSO_4$. The inorganics were removed by filtration through Florisil. Evaporation followed by column chromatography of the residue on silica gel (30% ether-petrol) afforded the *alcohol* (11) (18.9 g, 79%), as a colourless oil, $[\alpha]_D^{20}$ +6.3° (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3370, 3070, 2931, 2859, 1112, 1035 and 823 cm^{-1}; δ_H (60 MHz) 7.70 (4H, m, Ph), 7.30 (6H, m, Ph), 3.80-3.40 (4H, m, H_2-1, H_2-3), 2.55 (1H, br s, OH), 1.95 (1H, m, H-2), 1.10 (9H, s, ^tBu) and 0.85 (3H, d, J 7.0, Me); m/z 271 (M^+-^tBu) and 199 (Ph_2SiOH); found: C, 72.98; H, 8.78. $C_{20}H_{28}O_2Si$ requires C, 73.12; H, 8.59%.

***(+)-R-5-(tert-Butyldiphenylsilyloxy)-4-methyl-1-pentyne* (12).-** A mixture of alcohol (11) (20.0 g, 60 mmol) and DMAP (11 mg, 90 μmol) in pyridine (105 ml) was cooled to 0°C and *p*-toluenesulphonyl chloride (12.6 g, 66 mmol) added portionwise over 15 min. The mixture was stirred at room temperature overnight. Water (100 ml) was added and the mixture extracted with ether (3 x 100 ml). The combined extracts were washed with 1M HCl (100 ml), saturated aqueous sodium hydrogencarbonate solution (100 ml) and brine (100 ml) then dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (15% ether-petrol) afforded the *tosylate* (25.3 g, 86%) as a colourless oil, $[\alpha]_D^{20}$ + 6.8° (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3070, 1598, 1428, 1189 and 1177 cm^{-1}; δ_H (60 MHz) 7.70-7.30 (10H, m, Ph), 3.90 (2H, m), 3.40 (2H, m), 2.30 (3H, s), 1.95 (1H, m), 1.05 (3H, d, J 7.0) and 1.00 (9H, s). To a solution of the tosylate (25.0 g, 52 mmol) in dry DMSO (120 ml) under argon was added lithium acetylide ethylenediamine complex (5.8 g of 90% (Aldrich), 57 mmol). The mixture was stirred for 3h when petrol (500 ml) and brine (200 ml) were carefully added. The organic layer was separated and washed with water (3 x 150 ml) and brine (150 ml) then dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (5% ether-petrol) to afford the *acetylene* (12) (14.6 g, 83%), $[\alpha]_D^{20}$ + 7.2° (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3305, 3070, 2958, 2929, 2857, 2118, 1558, 1112 and 702 cm^{-1}; δ_H (500 MHz) 7.68-7.66 (4H, m, Ph), 7.44-7.36 (6H, m, Ph), 3.59 (1H, dd, J 9.9 and 5.2, H-5), 3.54 (1H, dd, J 9.9 and 6.7, H-5) 2.40 (1H, ddd, J 16.6, 5.7 and 2.7, H-3), 2.20 (1H, ddd, J 16.6, 7.3 and 2.7, H-3), 1.96-1.89 (2H, m, H-1, H-4), 1.06 (9H, s, ^tBu) and 1.00 (3H, d, J 6.9, Me); m/z 279 (100%, M^+-^tBu) and 199 (32.3, Ph_2SiOH); found: C, 78.45; H, 8.46. $C_{22}H_{28}OSi$ requires C, 78.52; H, 8.39%.

(+)-(1E,4R)-5-(tert-Butyldiphenylsilyloxy)-1-iodo-2,4-dimethyl-1-pentene **(4)**.- To a solution of zirconocene dichloride (6.5 g, 22.7 mmol) in dry 1,2-dichloroethane (350 ml) under argon was added trimethylaluminium (133.5 ml of a 2M solution in hexanes, 267 mmol). After 30 min a solution of acetylene (12) (30.0 g, 89 mmol) in 1,2-dichloroethane (100 ml) was added. The mixture was stirred overnight at room temperature then cooled to -30°C. A solution of iodine (24.8 g, 97.9 mmol of I_2) in THF (175 ml) was added over 30 min. After 30 min the mixture was warmed to 0°C and saturated aqueous potassium carbonate solution (25 ml) was added slowly with vigorous stirring. After 30 min. $MgSO_4$ (50 g) was added and the mixture filtered, washing well with ether. The combined filtrate and washings were evaporated and the residue chromatographed on silica gel (2% ether-petrol) to afford the *vinyl iodide* (4) (38.0 g, 89%) as a colourless oil, $[\alpha]_D^{20}$ + 1.1° (*c* 4.5 in $CHCl_3$); ν_{max} (film) 3069, 2857, 1112 and 614 cm^{-1}; δ_H (250 MHz) 7.75-7.60 (4H, m, Ph), 7.50-7.30 (6H, m, Ph), 5.83 (1H, q, J 0.9, H-1), 3.48 (1H, dd, J 9.9 and 5.5, H-5), 3.42 (1H, dd, J 9.9 and 5.6, H-5), 2.45 (1H, ddd, J 13.3, 5.8 and 0.9, H-3), 1.98 (1H, ddd, J 13.3, 8.5 and 0.7, H-3), 1.81 (1H, m, H-4), 1.77 (3H, d, J 0.9, 2-Me), 1.06 (9H, s, ^{t}Bu) and 0.86 (3H, d, J 6.6, 4-Me); δ_C (62.9 MHz) 146.6 (C-2), 135.6 (Ar-C_{meta}), 133.9 (Ar-C_{ipso}), 129.6 (Ar-C_{para}), 127.6 (Ar-C_{ortho}), 75.5 (C-1), 68.1 (C-5), 43.5 (C-3), 34.0 (C-4), 27.0 (($\underline{C}H_3)_3CSi$), 23.8 (Me-2), 19.3 ($Si\underline{C}(CH_3)_3$) and 16.5 (Me-4); m/z 477 (0.1%, M^+-H), 463 (0.1, M^+-Me), 421 (80.2, M^+-^{t}Bu), 309 (37.2), 295 (37.1, MH^+-^{t}Bu-I) and 199 (100, Ph_2SiOH); observed: M^+-^{t}Bu, 421.0483. $C_{19}H_{22}OISi$ requires M-^{t}Bu, 421.0485.

1-Methoxy-4-methyl-1,4-cyclohexadiene **(13)**.- Freshly cut lithium pieces (5.28 g, 0.75 mol) were added to a vigorously stirred solution of 4-methyl anisole (30 g, 0.25 mol) in ether (60 ml) and liquid ammonia (200 ml), over 20 min. The resulting blue solution was stirred for 30 min before dropwise addition of methanol (60 ml). After the blue coloration was discharged, the ammonia was allowed to evaporate. The residue was treated cautiously with water (200 ml) and extracted with ether. Each extract was washed with brine and the combined extracts were dried ($MgSO_4$). Solvent evaporation at 0°C gave the *enol ether* (13) (27.8 g, 92%) as a colourless oil, ν_{max} (film) 2994, 2824, 1697, 1665 and 1217 cm^{-1}; δ_H (60 MHz) 5.35 (1H, m, H-5), 4.60 (1H, m, H-2), 3.59 (3H, s, OMe), 2.70 (4H, m) and 1.70 (3H, s, Me); m/z 124 (M^+).

5-Hydroxymethyl-4-methoxy-1-methyl-1,3-cyclohexadiene **(14)**.- Trimethylaluminium (707 ml of a 2.0M solution in hexanes, 1.41 mol) was added dropwise to a stirred mixture of paraformaldehyde (42.40 g, 1.41 mol) and the enol ether (13) (87.5 g, 0.705 mol) in DCM (1l) at 0°C under argon. After stirring at this temperature for 1h, the solution was diluted with ether (1l) and cautiously treated with water (400 ml). The aqueous phase was extracted exhaustively with ether, and each extract was washed with brine. The combined organic extracts were dried ($MgSO_4$) and evaporated. Rapid column chromatography on silica gel (30% ether-petrol) gave the *alcohol* (14) (69.3 g, 64%) as a colourless oil, ν_{max} (film) 3378, 2930, 1661, 1610 and 1216 cm^{-1}; δ_H (250 MHz) 5.51 (1H, m, H-2), 4.93 (1H, d, J 5.7, H-3), 3.70-3.50 (2H, m, $C\underline{H}_2OH$), 3.57 (3H, s, OMe), 2.52 (1H, m, H-5), 2.33 (1H, m, H-6), 2.14 (1H, m, H-6), 2.05 (1H, br s, OH) and 1.72 (3H, d, J 1.4, Me); m/z 154 (M^+); found: C, 69.96; H, 9.41. $C_9H_{14}O_2$ requires C, 70.08; H, 9.17%.

5-[(tert-Butyldiphenylsilyloxy)methyl]-4-methoxy-1-methyl-1,3-cyclohexadiene **(15)**.- *tert*-Butyldiphenylsilyl chloride (16.87 ml, 64.86 mmol) was added to a stirred solution of the alcohol (14) (10.0 g, 64.86 mmol), 4-dimethylaminopyridine (317 mg, 2.6 mmol) and triethylamine (10.85 ml, 77.8 mmol) in DCM (200 ml), under argon, at 0°C. After 18 h the reaction was poured into water and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated. Rapid column chromatography of the residue on silica gel (3% ether-petrol) afforded the *silyl ether* (15) (24.9 g, 98%) as a colourless oil, ν_{max}(film) 3071, 2931,

1663 and 1610 cm^{-1}; δ_H (250 MHz) 7.80-7.30 (10H, m, Ph), 5.51 (1H, m, H-2), 4.87 (1H, d, J 6.5, H-3), 3.70-3.56 (2H, m, CH_2OSi), 3.48 (3H, s, OMe), 2.51 (1H, m, H-5), 2.48-2.36 (2H, m, H_2-6), 1.75 (3H, s, Me) and 1.07 (9H, s, ^{t}Bu); m/z 392 (M^+); found: C, 76.35; H, 8.30. $C_{25}H_{32}O_2Si$ requires C, 76.47; H, 8.23%.

10-[(tert-Butyldiphenylsilyloxy)methyl]-8-methyl-1,4-dioxaspiro[4.5]dec-7-ene **(16)**.- A solution of the methyl enol ether (15) (1.0 g, 2.54 mmol), ethylene glycol (0.79 g, 12.7 mmol) and pyridinium-*p*-toluenesulphonate (63 mg, 0.25 mmol), in benzene (20 ml) was heated at reflux under Dean-Stark conditions for 16 h. The mixture was cooled and the solvent evaporated. Column chromatography of the residue on silica gel (15% ether-petrol) afforded the *dioxolane* (16) (0.945 g, 88%) as a colourless oil, ν_{max} (film) 3070, 2930, 1589 and 1248 cm^{-1}; δ_H (500 MHz) 7.66 (4H, m, Ph), 7.43-7.35 (6H, m, Ph), 5.25 (1H, m, H-7), 3.92-3.76 (5H, m, H_2-2, H_2-3, $CHOSi$), 3.55 (1H, t, J 9.6, $CHOSi$), 2.40 (1H, dd, J 17.9 and 5.4), 2.27 (1H, dd, J 17.5 and 5.9), 2.14 (1H, m), 2.09-2.08 (2H, m), 1.71 (3H, s, Me) and 1.05 (9H, s, ^{t}Bu); m/z 422 (M^+, 11.3%), 365 (100, M^+-^{t}Bu) and 199 (42.7, Ph_2SiOH); found: C, 74.09; H, 8.14. $C_{26}H_{34}O_3Si$ requires C, 73.87; H, 8.12%.

(7R*,8S*,10S*)-10-[(tert-Butyldiphenylsilyloxy)methyl]-8-methyl-1,4-dioxaspiro[4.5]decane-7,8-diol and ***(7R*,8S*,10R*)-10-[(tert-Butyldiphenylsilyloxy)methyl]-8-methyl-1,4-dioxaspiro[4.5]decane-7,8-diol*** **(17)**.- Osmium tetroxide (1.0 mg, 3.93 μmol) was added to a solution of N-methylmorpholine-N-oxide monohydrate (86 mg, 0.64 mmol) and the alkene (16) (200 mg, 0.47 mmol), in 10:3:1 t-butanol-THF-water (8 ml), at r.t. After 2h a slurry of dilute aqueous sodium sulphite solution and talc was added and, after 15 min further, the mixture filtered. The filtrate was extracted with ether and the combined extracts washed with brine, dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (75% ether-petrol) afforded the diols (17) (153 mg, 71%) and its C7, C8 epimer (8 mg, 4%), both as foams. Less polar, minor diastereoisomer, ν_{max} (film) 3482, 2931, 2887, 1654 and 702 cm^{-1}; δ_H (250 MHz) 7.71-7.64 (4H, m, Ph), 7.48-7.34 (6H, m, Ph), 4.00-3.51 (7H, m, H_2-2, H_2-3, CH_2OSi, H-7), 3.20 (1H, br s, 8-OH), 2.16-1.92 (3H, m, H_2-6, H-10), 1.78 (2H, m, H_2-9), 1.66 (1H, s, 7-OH), 1.29 (3H, s, Me) and 1.04 (9H, s, ^{t}Bu); m/z 399 (M^+-^{t}Bu), 381 (M^+-^{t}Bu-H_2O), 337 (M^+-^{t}Bu-H_2O-C_2H_4O), 205, 199 (Ph_2SiOH) and 183; observed: M^+-^{t}Bu, 399.1615. $C_{22}H_{27}O_5Si$ requires M-^{t}Bu, 399.1628.

More polar (17), ν_{max} (film) 3428, 2930, 2885, 1427, 1111, 1030 and 740 cm^{-1}; δ_H (250 MHz) 7.71-7.64 (4H, m, Ph), 7.48-7.34 (6H, m, Ph), 3.94-3.40 (7H, m, CH_2OSi, H_2-2, H_2-3, H-7), 2.33 (1H, m, H-10), 2.16 (1H, dd, J 14.0 and 5.0, H_{eq}-6), 1.94-1.70 (4H, m), 1.42 (1H, m), 1.30 (3H, s, Me) and 1.04 (9H, s, ^{t}Bu); m/z 441 (0.7%, M^+-Me), 399 (22.9, M^+-^{t}Bu), 381 (33.2, M^+-^{t}Bu-H_2O) and 199 (100, Ph_2SiOH); found: C, 68.14; H, 8.22. $C_{26}H_{36}O_5Si$ requires C, 68.39; H, 7.95%.

(-)-[1S(7S,8R,10S)4R]-[10-[(tert-Butyldiphenylsilyloxy)methyl]-8-hydroxy-8-methyl-1,4-dioxaspiro[4.5]decan-7-yl] 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate **(19)** and ***(-)-[1S(7R,8S,10R),4R]-[10-[(tert-Butyldiphenylsilyloxy)methyl]-8-hydroxy-8-methyl-1,4-dioxaspiro[4.5]decan-7-yl] 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate*** **(18)**.- Triethylamine (2.6 ml, 18.7 mmol) was added dropwise to a solution of the diol (17) (7.1 g, 15.5 mmol) in DCM (150 ml), at 0°C under argon, followed by 4-dimethylaminopyridine (19 mg, 0.16 mmol) in DCM (0.5 ml). After 10 min. a solution of 1-(S)-(-)-camphanic acid chloride (3.72 g, 17.2 mmol) in DCM (5 ml) was added dropwise. After a further 3h, the mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated. MPLC (50% ether-petrol) or HPLC (4% IPA-petrol) of the residue on silica gel afforded the esters (19) (4.3 g, 43%) and (18) (4.9 g, 49%), as colourless foams. Less polar (19) $[\alpha]_D^{20}$ -16.2° (*c* 3.2 in $CHCl_3$); ν_{max} (film) 3531, 3068, 2963, 2885, 1792, 1730 and 704 cm^{-1}; δ_H (250 MHz) 7.70-7.32 (10H, m, Ph), 4.91 (1H, dd, J 10.7 and 5.8, H-

7'), 3.97-3.82 (3H, m, H_2-2' and CHOSi), 3.80-3.63 (2H, m, H_2-3'), 3.46 (1H, dd, J 9.3 and 8.8, CHOSi), 2.55-2.38 (2H, m, H-10', H-6), 2.21 (1H, dd, J 14.2 and 4.2, H_{eq}-9'), 2.10-1.85 (4H, m, H_2-6', H-5, H-6), 1.78 (1H, br s, OH), 1.70 (1H, m, H-5), 1.48 (1H, t, J 13.3, H_{ax}-9'), 1.25 (3H, s, 8'-Me) and 1.15-0.93 (18H, m, ^{t}Bu, Me_3); m/z 579 (1.2%, M^+-^{t}Bu), 381 (100, M^+-^{t}Bu-$C_{10}H_{14}O_4$) and 199 (75.6, Ph_2SiOH); observed, M^+-^{t}Bu, 579.2411. $C_{32}H_{39}O_8Si$ requires M-^{t}Bu, 579.2414; found: C, 67.86; H, 7.73. $C_{36}H_{48}O_8Si$ requires C, 67.90; H, 7.60%.

More polar (18), $[\alpha]_D^{20}$ +2.4° (*c* 3.4 in $CHCl_3$); ν_{max} (film) 3536, 3069, 2965, 2877, 1791, 1750, 1737 and 704 cm^{-1}; δ_H (250 MHz) 7.70-7.32 (10H, m, Ph), 4.89 (1H, t, J 8.0, H-7'), 3.88 (3H, m, H_2-2', CHOSi), 3.70 (2H, m, H_2-3'), 3.47 (1H, t, J 9.2, CHOSi), 2.42 (2H, m, H-10', H-6), 2.21 (1H, dd, J 13.8 and 4.2, H_{eq}-9'), 2.17-1.87 (4H, m, H_2-6', H-5, H-6), 1.71 (1H, m, H-5), 1.48 (1H, t, J 13.8, H_{ax}-9'), 1.23 (3H, s, 8'-Me) and 1.15-0.95 (18H, m, ^{t}Bu, Me_3); m/z 579 (M^+-^{t}Bu), 381 (M^+-^{t}Bu-$C_{10}H_{14}O_4$) and 199 (Ph_2SiOH); found: C, 68.03; H, 7.77. $C_{36}H_{48}O_8Si$ requires C, 67.90; H, 7.60%.

(-)-[1S(7S,10S)4R]-[10-[(tert-Butyldiphenylsilyloxy)methyl]-8-methylene-1,4-dioxaspiro[4.5]decan-7-yl] 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate **(20).-** Thionyl chloride (0.10 ml, 1.37 mmol) was added dropwise to a stirred solution of the alcohol (19) (750 mg, 1.2 mmol) in pyridine (10 ml), at 0°C under argon. After 1 h the mixture was poured into saturated aqueous copper (II) sulphate solution and extracted with ether. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. HPLC (4% IPA-petrol) of the residue afforded the *allylic ester* (20) (260 mg, 36%), $[\alpha]_D^{20}$ -9.2° (*c* 10.4 in $CHCl_3$); ν_{max} (film) 2962, 2933, 2885, 1793, 1734 and 741 cm^{-1}; δ_H (250 MHz) 7.65-7.40 (10H, m, Ph), 5.42 (1H, dd, J 11.0 and 5.0, H-7'), 4.98 (1H, br. s, =CH), 4.92 (1H, br. s, =CH), 3.95-3.67 (5H, m, CHOSi, H_2-2', H_2-3'), 3.49 (1H, t, J 8.0, CHOSi), 2.81 (1H, dd, J 13.0 and 4.0, H-9'), 2.47 (1H, m, H-6), 2.28-1.85 (5H, m, H-9', H-10', H_2-6', H-6), 1.65 (2H, m, H_2-5'), 1.13 (3H, s, Me), 1.05 (12H, m, ^{t}Bu, Me) and 0.98 (3H, s, Me); m/z 618 (M^+), 561 (M^+-^{t}Bu), 421 (M^+-$C_{10}H_{13}O_4$), 363 (M^+-^{t}Bu-$C_{10}H_{14}O_4$), 319 (M^+-^{t}Bu-$C_{10}H_{14}O_4$-C_2H_4O), 241 (M^+-^{t}Bu-$C_{10}H_{14}O_4$-C_2H_4O-PhH) and 199 (Ph_2SiOH); observed: M^+-^{t}Bu, 561.2309. $C_{32}H_{37}O_7Si$ requires M-^{t}Bu, 561.2309.

(-)-(7S,8R,10S)-10-[(tert-Butyldiphenylsilyloxy)methyl]-8-methyl-1,4-dioxaspiro[4.5]decane-7,8-diol **(17).-** The ester (19) (16.5 g, 25.9 mmol) in methanol (220 ml) was added to a slurry of anhydrous potassium carbonate (17.9 g, 129.7 mmol) in methanol (250 ml), at r.t. After 1h the mixture was poured into water and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (70% ether-petrol) afforded the *diol* (17) (10.47 g, 88%), as an amorphous white solid, $[\alpha]_D^{20}$ -15.5° (*c* 1.3 in $CHCl_3$); spectral data identical to previously prepared racemic material.

(2'S,3a'S,6'S,7a'R)-6'-[(tert-Butyldiphenylsilyloxy)methyl]-tetrahydro-2'-methoxy-7a'-methyl spiro[1,3-dioxolane-2,5'(2'H,4'H)-1,3-benzo[d]dioxole] and its 2' epimer **(21).-** Pyridinium-*p*-toluenesulphonate (2.5 mg, 0.01mmol) was added to a solution of the diol (17) (100 mg, 0.22 mol), and trimethylorthoformate (0.12 ml, 1.1 mmol) in DCM (2 ml), under argon at r.t. After 20 min, the mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give the *methoxyacetals* (21) (110 mg, 100%) as a 2:1 mixture of diastereoisomers and as a clear oil, ν_{max} (film) 2933, 2886, 1428 and 704 cm^{-1}; δ_H (500 MHz) 7.71-7.63 (4H, m, Ph), 7.48-7.34 (6H, m, Ph), 5.74 (2/3H, s, H-2), 5.72 (1/3H, s, H-2), 4.12 (2/3H, t, J 6.3, CHOSi), 3.95-3.44 (19/3H, H_2-5, H_2-4, H-3a' and CH_2OSi), 3.41 (1H, s, OMe), 3.37 (2H, s, OMe), 2.57

(1/3H, dd, J 15.0 and 4.5, H-4'), 2.44 (1/3H, m, H-6'), 2.25 (4/3H, m, H-4', H-6'), 2.05 (2/3H, m, H-4', H-7'), 1.99-1.83 (4/3H, m, H-4', H-7'), 1.66 (1/3H, dd, J 15.0 and 12.8, H-7'), 1.55-1.38 (8/3H, m, H-7', 7a' Me), 1.31 (1H, s, 7a'Me) and 1.06 (9H, s, ^{t}Bu); m/z 498 (M^+), 497 (M^+-H), 467 (M^+-OMe), 441 (M^+-^{t}Bu), 409 (M^+-^{t}Bu-MeOH), 381 (M^+-^{t}Bu-MeO-CHO), 337 (M^+-^{t}Bu-MeO-CHO-C_2H_4O) and 199 (Ph_2SiOH); observed: M^+-^{t}Bu, 441.1724. $C_{24}H_{29}O_6Si$ requires M-^{t}Bu, 441.1733.

***(-)-(S)-10-[(tert-Butyldiphenylsilyloxy)methyl]-8-methyl-1,4-dioxaspiro[4.5]dec-7-ene* (16).-** The methoxy acetals (21) (10.80 g, 21.7 mmol) were dissolved in acetic anhydride (160 ml) and the solution heated at reflux under argon for 1h. The mixture was allowed to cool and the acetic anhydride evaporated off. The residue was azeotroped with toluene (3 x 20 ml). Column chromatography on silica gel (10% ether-petrol) afforded the *cyclohexene* (16) (8.62 g, 94%) as a colourless oil, $[\alpha]_D^{20}$ -21.1° (*c* 3.1 in $CHCl_3$); spectral data identical to previously prepared racemic material.

***(-)-(7R,8R,10S)-10-[(tert-Butyldiphenylsilyloxy)methyl]-8-methyl-1,4-dioxaspiro[4.5]decan-7-ol* (23) and *(-)-(7S,8S,10S)-10-[(tert-Butyl-diphenylsilyloxy)methyl]-8-methyl-1,4-dioxaspiro[4.5]decan-7-ol* (22).-** Borane-dimethyl sulphide complex (1.57 ml of a 10 M solution, 0.016 mol) was added dropwise to a stirred solution of the cyclohexene (16) (10.0 g, 0.024 mol), in THF (250 ml), at -10°C under argon. The mixture was allowed to warm to r.t. over 16h. Water (40 ml) was added, followed by 3M sodium hydroxide solution (200 ml). The mixture was cooled to 0°C and hydrogen peroxide (80 ml of a 30% solution in water) was added over 10 min. After 1h, water was added and the mixture extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (75% ether-petrol) afforded the *cyclohexanols* (23) (417 mg, 4%) and (22) (9.2 g, 88%), both as colourless oils. Less polar (23), $[\alpha]_D^{20}$ -17.0° (*c* 5.7 in $CHCl_3$); ν_{max} (film) 3422, 2930, 2887, 1427, 1360, 1112, 974 and 703 cm^{-1}; δ_H (250 MHz) 7.70-7.60 (4H, m, Ph), 7.45-7.30 (6H, m, Ph), 3.95-3.30 (7H, m, H_2-2, H_2-3, H-7, CH_2OSi), 2.34 (1H, br s, OH), 2.05-1.88 (2H, m, H-9, H-10), 1.79 (1H, dd, J 13.5 and 4.0, H_{eq}-6), 1.65-1.45 (3H, m, H-6, H-8, H-9), 1.04 (9H, s, ^{t}Bu) and 0.97 (3H, d, J 6.5, Me); m/z 440 (M^+, 0.1%), 439 (0.2, M^+-H), 423 (0.1, MH^+-H_2O), 407 (0.1, M^+-Me-H_2O), 383 (13.2, M^+-^{t}Bu), 365 (74.1, M^+-^{t}Bu-H_2O), 321 (51.1, M^+-^{t}Bu-H_2O-C_2H_4O) and 199 (100, Ph_2SiOH); observed: M^+-H, 439.2302. $C_{26}H_{35}O_4Si$ requires M-H, 439.2305; found: C, 70.71; H, 8.35. $C_{26}H_{36}O_4Si$ requires C, 70.87; H, 8.23%.

More polar (22), $[\alpha]_D^{20}$ -2.9° (*c* 1.4 in $CHCl_3$); ν_{max} (film) 3394, 3049, 2930, 2883, 1583, 1427, 1111 and 702 cm^{-1}; δ_H (250 MHz) 7.75-7.65 (4H, m, Ph), 7.47-7.33 (6H, m, Ph), 4.00-3.64 (5H, m, H_2-2, H_2-3, CHOSi), 3.45 (1H, t, J 9.3, CHOSi), 3.30 (1H, m, H-7), 2.23-1.97 (3H, m, H-10, H_2-6), 1.54 (1H, br s, OH), 1.45-1.20 (3H, m, H_2-9, H-8) and 1.08 (12H, m, Me, ^{t}Bu); m/z 440 (M^+, 0.1%), 439 (0.3, M^+-H), 423 (0.4, MH^+-H_2O), 383 (31.3, M^+-^{t}Bu), 365 (13.9, M^+-^{t}Bu-H_2O), 321 (63.0, M^+-H_2O-^{t}Bu-C_2H_4O) and 199 (100, Ph_2SiOH); found: C, 70.78; H, 8.40. $C_{26}H_{36}O_4Si$ requires C, 70.87; H, 8.23%.

***(-)-(2S,4S,5S)-2-[(tert-Butyldiphenylsilyloxy)methyl]-5-hydroxy-4-methylcyclohexanone* (24).-** Palladium (II) chloride-acetonitrile complex (50 mg, 0.19 mmol) was added to a stirred solution of the ketal (22) (8.40 g, 19.1 mmol), in acetone (200 ml), in the dark, under argon at r.t. After 7h, saturated sodium hydrogencarbonate solution (50 ml) was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (75% ether-petrol) afforded the *hydroxy ketone* (24) (7.41 g, 98%), as a colourless oil, $[\alpha]_D^{20}$ -7.4° (*c* 1.8 in $CHCl_3$); ν_{max} (film) 3425, 3067, 2931, 2860, 1708, 1588, 1460, 1389, 1111 and 703 cm^{-1}; δ_H (270 MHz) 7.71-7.61 (4H, m, Ph), 7.48-7.31 (6H, m, Ph), 3.98 (1H, dd, J 10.4 and 4.9, CHOSi), 3.63 (1H, dd, J 10.4 and 7.6, CHOSi), 3.31 (1H, m, H-5), 2.69

(1H, dd, J 13.2 and 4.9, H_{eq}-6), 2.56 (1H, m, H-2), 2.40 (1H, t, J 13.2, H_{ax}-6), 2.23 (1H, ddd, J 13.6, 6.0 and 3.9, H_{eq}-3), 1.88 (1H, d, J 6.0, OH), 1.80 (1H, m, H-4), 1.15 (4H, m, H_{ax}-3, Me) and 1.06 (9H, s, ^{t}Bu); m/z 396 (M^+), 378 (M^+-H_2O), 363 (0.5, M^+-H_2O-Me), 339 (13.8, M^+-^{t}Bu), 321 (100, M^+-^{t}Bu-H_2O) and 199 (100, Ph_2SiOH); found: C, 72.53; H, 8.21. $C_{24}H_{32}O_3Si$ requires C, 72.68; H, 8.13%.

(+)-(1S,3S,4S,6S)-6-[(tert-Butyldiphenylsilyloxy)methyl]-4-methyl-1-[1-methylene-3-(phenylthio)propyl]-1,3-cyclohexanediol **(25)**.- *tert*-Butyl-lithium (5.82 ml of a 1.7M solution in pentanes, 9.9 mmol) was added dropwise to a solution of 2-bromo-4-phenylthiobut-1-ene [22] (2.41 g, 9.9 mmol) in 1:1 ether/THF (75 ml), at -78°C, under argon. After 10 min the ketone (24) (1.31 g, 3.3 mmol), in 1:1 ether/THF (5 ml) was added dropwise. Saturated sodium hydrogencarbonate solution (100 ml) was added after 1h and the reaction allowed to warm to r.t. The mixture was poured into water and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Column chromatography (70% ether-petrol) of the residue on silica gel afforded the *hydroxysulphide* (25) (1.62 g, 87%) as a clear oil, $[\alpha]_D^{20}$ +9.3° (*c* 2.3 in $CHCl_3$); ν_{max} (film) 3467, 3069, 2929, 2858, 1585, 1465, 1427, 1113 and 703 cm^{-1}; δ_H (500 MHz) 7.67-7.61 (4H, m, Ph), 7.47-7.36 (6H, m, Ph), 7.30-7.13 (5H, m, Ph), 5.46 (1H, s, =CH), 5.06 (1H, s, =CH), 4.30 (1H, d, J 2.3, 1-OH), 3.88 (1H, dd, J 10.3 and 2.5, C<u>H</u>OSi), 3.69 (1H, dt, J 3.7 and 9.9, H-3), 3.43 (1H, dd, J 10.3 and 2.1, C<u>H</u>OSi), 3.09-3.03 (2H, m, H_2-3'), 2.32-2.27 (2H, m, H_2-2'), 1.97 (1H, m, H-5), 1.85 (1H, dd, J 13.0 and 4.6, H_{eq}-2), 1.61 (1H, m), 1.50 (1H, br s, 3-OH), 1.46-1.36 (3H, m), 1.10 (3H, d, J 6.2, Me) and 1.05 (9H, s, ^{t}Bu); m/z 560 (M^+, 0.1%), 542 (0.1, M^+-H_2O), 503 (40.0, M^+-^{t}Bu), 485 (2.0, M^+-^{t}Bu-H_2O) and 199 (100, Ph_2SiOH); observed: M^+-^{t}Bu, 503.2064. $C_{30}H_{35}O_3SSi$ requires M-^{t}Bu, 503.2076; found: C, 72.98; H, 8.13. $C_{34}H_{44}O_3SSi$ requires C, 72.81; H, 7.91%.

(+)-(1S,3S,4S,6S)-6-[(tert-Butyldiphenylsilyloxy)methyl]-4-methyl-1-[1-methylene-3-(phenylsulphonyl)propyl]-1,3-cyclohexanediol **(26)**.- A solution of mCPBA (1.79 g @ 85%, 8.8 mmol) in DCM (70 ml) was added dropwise to a solution of the sulphide (25) (4.69 g, 8.4 mmol) in DCM (180 ml), at 0°C. After 10 min, the mixture was washed with saturated aqueous sodium hydrogencarbonate solution (70 ml). The organic layer was evaporated and the crude sulphoxides taken up in methanol (180 ml) and THF (60 ml). Aqueous pH4 buffer solution (160 ml) was added. The mixture was cooled to 0°C before portionwise addition of oxone (11.58 g, 37.7 mmol), with vigorous stirring, over 2h. After 3h further, water was added and the mixture extracted with ether. The combined organic extracts were washed with saturated sodium hydrogencarbonate solution, brine, dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (ether) afforded the *sulphone* (26) (4.36 g, 88%) as a colourless foam, $[\alpha]_D^{20}$ +10.2° (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3462, 2929, 1445, 1427, 1307, 1150, 1112, 1087, 1066 and 740 cm^{-1}; δ_H (500 MHz) 7.90 (2H, m, Ph), 7.65-7.36 (13H, m, Ph), 5.32 (1H, br s, =CH), 4.88 (1H, s, =CH), 4.34 (1H, d, J 2.3, 1-OH), 3.80 (1H, dd, J 10.4 and 2.3, C<u>H</u>OSi), 3.65 (1H, br t, J 10.2, H-3), 3.44 (1H, dd, J 10.4 and 2.0, C<u>H</u>OSi), 3.25-3.22 (2H, m, H_2-3'), 2.45-2.41 (2H, m, H_2-2'), 1.93 (1H, q, J 13.2, H_{ax}-5), 1.80 (1H, dd, J 12.9 and 4.5, H_{eq}-2), 1.61 (1H, dd, J 12.5 and 2.8), 1.58 (1H, br s, 3-OH), 1.47-1.33 (3H, m), 1.09 (3H, d, J 6.1, Me) and 1.02 (9H, s, ^{t}Bu); m/z 535 (3.2%, M^+-^{t}Bu), 517 (2.6, M^+-^{t}Bu-H_2O), 505 (12.8, M^+-^{t}Bu-CH_2O), 487 (3.9, M^+-^{t}Bu-CH_2O-H_2O) and 199 (100, Ph_2SiOH); observed: M^+-^{t}Bu, 535.1972. $C_{30}H_{35}O_5SSi$ requires M-^{t}Bu, 535.1974; found: C, 69.00; H, 7.55. $C_{34}H_{44}O_5SSi$ requires C, 68.88; H, 7.48%.

(+)-[1S(1S),3S,4S,6S]-6-[(tert-Butyldiphenylsilyloxy)methyl]-1-[1-(hydroxymethyl)-3-(phenylsulphonyl)propyl]-4-methyl-1,3-cyclohexanediol **(28)** and ***(-)-[1S(1R),3S,4S,6S]-6-[(tert-Butyldiphenylsilyloxy)methyl]-1-[1-(hydroxymethyl)-3-(phenylsulphonyl)propyl]-4-methyl-1,3-cyclohexanediol*** **(27)**.- Borane-dimethylsulphide complex (0.306 ml of a 10M solution, 3.06

mmol) was added dropwise to a stirred solution of the alkene (26) (590 mg, 1.0 mmol) in THF (50 ml), under argon, at 0°C. The solution was allowed to warm to r.t. over 16h, whereupon water (0.27 ml), 3M aqueous sodium hydroxide (12 ml) and 30% aqueous hydrogen peroxide (5.3 ml) were added sequentially. After 30 min, water was added and the mixture extracted with ethyl acetate. Each organic extract was washed with brine, combined, dried ($MgSO_4$) and evaporated. Column chromatography (75% ethyl acetate-petrol) of the residue afforded the *triols* (28) (413 mg, 68%) and (27) (103 mg, 17%), both as clear oils. Less polar : (28), $[\alpha]_D^{20}$ +19.4° (*c* 2.2 in $CHCl_3$); ν_{max} (film) 3473, 3069, 2928, 1587, 1446, 1427, 1304, 1146, 1113, 1086, 998, 912, 822, 793, 736 and 704 cm^{-1}; δ_H (500 MHz) 7.93 (2H, m, Ph), 7.65-7.55 (7H, m, Ph), 7.46-7.37 (6H, m, Ph), 4.08 (1H, dd, J 10.8 and 2.8, C<u>H</u>OSi), 3.88 (1H, br s, 1-OH), 3.59-3.55 (3H, m, H-3, C<u>H</u>OSi, C<u>H</u>OH), 3.40 (1H, dd, J 11.1 and 6.5, C<u>H</u>OH), 3.33-3.31 (2H, m, H_2-3'), 2.26 (1H, m), 1.95-1.60 (6H, m), 1.34-1.24 (3H, m) and 1.15-1.00 (13H, m, H-5, Me and ^{t}Bu); m/z 523 (0.2%, M^+-^{t}Bu-CH_2O), 517 (0.5, M^+-^{t}Bu-$2H_2O$), 505 (1.2, M^+-^{t}Bu-CH_2O-H_2O), 487 (2.8, M^+-^{t}Bu-CH_2O-$2H_2O$) and 199 (100, Ph_2SiOH); found: C, 67.06; H, 7.70. $C_{34}H_{46}O_6SSi$ requires C, 66.85; H, 7.59%.

More polar (27), $[\alpha]_D^{20}$ -9.4° (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3432, 2927, 1445, 1427, 1305, 1146, 1112, 1085, 745 and 703 cm^{-1}; δ_H (500 MHz), 7.79 (2H, m, Ph), 7.69-7.39 (13H, m, Ph), 4.60 (1H, br d, J 1.4, 1-OH), 3.88-3.84 (2H, m, C<u>H</u>OSi, C<u>H</u>OH), 3.79 (1H, m, 3-OH), 3.64 (1H, dt, J 4.3 and 10.3, H-3), 3.55 (1H, dd, J 10.9 and 1.3, C<u>H</u>OSi), 3.46 (1H, m, C<u>H</u>OH), 3.07 (1H, ddd, J 13.9, 11.6 and 5.0, H-3'), 2.59 (1H, ddd, J 13.9, 11.3 and 4.8, H-3'), 2.05 (1H, dd, J 12.9 and 4.6, H_{eq}-2), 1.94 (1H, q, J 12.5, H_{ax}-5), 1.83 (1H, m), 1.58-1.50 (3H, m), 1.40-1.10 (4H, m), 1.08 (3H, d, J 6.2, Me) and 1.05 (9H, s, ^{t}Bu); m/z 553 (2.4%, M^+-^{t}Bu), 535 (0.5, M^+-^{t}Bu-H_2O), 517 (1.2, M^+-^{t}Bu-$2H_2O$), 505 (4.7, M^+-^{t}Bu-H_2O-CH_2O), 487 (2.5, M^+-^{t}Bu-$2H_2O$-CH_2O) and 199 (100, Ph_2SiOH); observed: M^+-^{t}Bu, 553.2072. $C_{30}H_{37}O_6SSi$ requires M-^{t}Bu, 553.2080.

(-)-(2S,5S,6S,8S,9S,11S)-11-[(tert-Butyldiphenylsilyloxy)methyl]-9-methyl-2-phenyl-5-[2-(phenylsulphonyl)ethyl]-1,3-dioxaspiro[5.5]undecan-8-ol **(29)** **and** ***(+)-(2R,5S,6S,8S,9S,11S)-11-[(tert-Butyldiphenylsilyloxy)methyl]-9-methyl-2-phenyl-5-[2-(phenylsulphonyl)ethyl]-1,3-dioxaspiro[5.5]undecan-8-ol*** **(30).**- A solution of the triol (28) (335 mg, 0.55 mmol), benzaldehyde (2.0 ml, 19.7 mmol) and pyridinium-*p*-toluene sulphonate (188 mg, 0.75 mmol) in benzene (60 ml) was heated at reflux under Dean-Stark conditions, under argon, for 1h. Saturated sodium hydrogencarbonate solution (20 ml) was added to the vigorously stirred hot solution. The mixture was allowed to cool to r.t. and extracted with ether. The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (90% ether-petrol) of the residue on silica gel afforded the *acetals* (29) (198 mg, 52%) and (30) (171 mg, 45%), both as colourless foams. Less polar: (29), $[\alpha]_D^{20}$ -0.8° (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3502, 2926, 1446, 1427, 1308, 1306, 1150, 1112, 1085, 1029, 822, 797, 743 and 702 cm^{-1}; δ_H (500 MHz) 7.91 (2H, m, Ph), 7.69-7.30 (18H, m, Ph), 5.34 (1H, s, H-2), 3.93 (1H, dd, J 9.7 and 3.5, C<u>H</u>OSi), 3.81 (1H, dd, J 11.6 and 5.6, H-4), 3.62 (2H, br t, J 9.2, H-8, C<u>H</u>OSi), 3.38 (1H, t, J 11.9, H-4), 3.09-2.91 (2H, m, H_2-2'), 2.05-1.87 (3H, m), 1.83 (2H, br dd, J 12.5 and 4.5), 1.55 (1H, dd, J 12.2 and 11.2), 1.45 (1H, m), 1.36-1.20 (3H, m), 1.08-1.04 (12H, m, Me, ^{t}Bu); m/z 641 (12.0%, M^+-^{t}Bu) and 199 (24.3, Ph_2SiOH); observed: M^+-^{t}Bu, 641.2390. $C_{37}H_{41}O_6SSi$ requires M-^{t}Bu, 641.2393.

More polar: (30), $[\alpha]_D^{20}$ +3.2 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3507, 3067, 2930, 1587, 1306, 1148, 1086, 934 and 702 cm^{-1}; δ_H (500 MHz) 7.91 (2H, m, Ph), 7.70-7.26 (18H, m, Ph), 5.86 (1H, s, H-2), 4.01 (1H, dd, J 10.4 and 4.5), 3.83 (1H, dd, J 10.4 and 6.0), 3.68-3.60 (2H, m), 3.38 (1H, dt, J 4.0 and 10.2, H-8), 3.03-2.93 (2H, m, H_2-2'), 2.26 (1H, dd, J 13.6 and 4.3, H_{eq}-7), 2.21 (1H, m, H-5), 1.98-1.92 (2H, m), 1.77 (1H, m), 1.67-1.56 (2H, m), 1.43 (1H, dd, J 13.3 and 11.1), 1.35-1.15 (2H, m), 1.06 (9H, s, ^{t}Bu) and 1.01 (3H, d, J 6.2, Me); m/z 683 (0.1%, M^+-Me), 641 (77.4, M^+-^{t}Bu), 535 (2.6, M^+-^{t}Bu-H_2O), 517 (5.0, M^+-^{t}Bu-H_2O-PhCHO) and 199

(100, Ph_2SiOH); found: C, 70.60; H, 7.32. $C_{41}H_{50}O_6SSi$ requires C, 70.45; H, 7.21%.

***(2R,5S,6S,8S,9S,11S)-11-[(tert-Butyldiphenylsilyloxy)methyl]-9-methyl-2-phenyl-5-[2-(phenylselenenyl)-2-(phenylsulphonyl)ethyl]-1,3-dioxaspiro[5.5]undecan-8-ol and its 5(2) epimer* (31).**- n-Butyllithium (0.943 ml of a 2.5M solution in hexanes, 2.36 mmol) was added dropwise to a stirred solution of the sulphone (30) (748 mg, 1.07 mmol) in THF (20 ml), under argon, at -78°C. After 15 min, phenylselenenyl chloride (513 mg, 2.68 mmol) in THF (7 ml) was added rapidly. A dark green coloration was observed approximately half-way through the addition.. After a further 1h at -78°C, the yellow solution was quenched with saturated aqueous ammonium chloride solution (5 ml) and allowed to come to r.t. The mixture was poured into water and extracted with DCM. The organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (70-100% ether-petrol) afforded the *selenides* (31a) (365 mg, 40%), (31b) (356 mg, 39%) and *starting sulphone* (30) (127 mg, 17%), all as colourless foams. Less polar (31a): $[\alpha]_D^{20}$ +0.38° (*c* 1.8 in $CHCl_3$); ν_{max} (film), 3390, 2929, 1446, 1306, 1148, 1111, 1082, 741 and 690 cm^{-1}; δ_H (500 MHz) 7.84 (2H, m, Ph), 7.70-7.19 (23H, m, Ph), 5.85 (1H, s, H-2), 3.99 (1H, dd, J 10.2 and 4.3), 3.88 (1H, dd, J 12.1 and 2.5), 3.67-3.62 (2H, m), 3.50 (1H, t, J 10.9), 3.36 (1H, dt, J 10.3, 4.0, H-8), 2.59 (1H, m), 2.30-2.23 (2H, m), 2.02-1.92 (2H, m), 1.77 (1H, m), 1.41 (1H, br s, 8-OH), 1.34 (1H, dd, J 13.6 and 11.0), 1.25 (1H, m), 1.17 (1H, m), 1.08 (9H, s, ^{t}Bu) and 1.00 (3H, d, J 6.2, Me). More polar (31b), $[\alpha]_D^{20}$ -18.7° (*c* 1.7 in $CHCl_3$); ν_{max} (film) 3432, 2929, 1446, 1389, 1306, 1147, 1111, 1082, 741 and 690 cm^{-1}; δ_H (500 MHz) 7.94 (2H, m, Ph), 7.70-7.16 (23H, m, Ph), 5.86 (1H, s, H-2), 4.00-3.95 (2H, m), 3.87 (1H, dd, J 10.4 and 5.6), 3.67 (1H, t, J 11.2), 3.62 (1H, dd, J 10.3 and 8.3), 3.32 (1H, m), 2.49 (1H, dt, J 15.4, 4.7), 2.40 (1H, m), 2.16 (1H, dd, J 13.6 and 4.3), 1.91 (1H, dd, J 9.7 and 3.8), 1.76-1.65 (2H, m), 1.34-1.15 (4H, m), 1.08 (9H, s, ^{t}Bu) and 0.99 (3H, d, J 5.6, Me); m/z 797 (0.4%, M^+-^{t}Bu), 691 (3.4, M^+-^{t}Bu-PhCHO), 673 (0.8, M^+-^{t}Bu-PhCHO-H_2O), 533 (11.7, M^+-^{t}Bu-PhCHO-PhSeH), 515 (2.6, M^+-^{t}Bu-PhCHO-H_2O-PhSeH) and 199 (100, Ph_2SiOH); found: C, 66.20; H, 6.57. $C_{47}H_{54}O_6SSeSi$ requires C, 66.10; H, 6.37%.

***(+)-(2R,5S(E),6S,8S,9S,11S)-11-[(tert-Butyldiphenylsilyloxy)methyl]-9-methyl-2-phenyl-5-[2-(phenylsulphonyl)ethenyl]-1,3-dioxaspiro[5.5]undecan-8-ol* (5).**- mCPBA (203 mg @ 85%, 1.0 mmol) was added portionwise to a vigorously stirred mixture of the selenides (31) (427 mg, 0.50 mmol) in DCM (14 ml) and saturated sodium hydrogencarbonate solution (5.5 ml), at 10°C. After 45 min, the mixture was poured into dilute aqueous sodium sulphite solution and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (ether) afforded the *vinyl sulphone* (5) (345 mg, 99%), as a colourless foam, $[\alpha]_D^{20}$ +14.7° (*c* 1.6 in $CHCl_3$); ν_{max}(film) 3463, 2926, 2854, 1446, 1427, 1390, 1307, 1147, 1111, 1086, 741 and 701 cm^{-1}; δ_H (500 MHz) 7.84 (2H, m, Ph), 7.75-7.20 (19H, m, Ph and H-1'), 6.41 (1H, d, J 15.0, H-2'), 5.87 (1H, s, H-2), 4.12 (1H, dd, J 10.4 and 4.9, CHOSi), 4.08 (1H, dd, J 10.9 and 4.9, H-4), 3.95 (1H, dd, J 10.9 and 8.2, H-4), 3.58 (1H, dd, J 10.4 and 7.6, CHOSi), 3.35 (1H, dt, J 3.7 and 10.4, H-8), 2.71 (1H, m, H-5), 2.51 (1H, dd, J 13.6 and 4.1, H_{eq}-7), 1.86 (1H, dt, J 13.6 and 3.9, H_{eq}-10), 1.81 (1H, m, H-11), 1.47 (1H, br s, OH), 1.37 (1H, dd, J 13.6 and 10.9), 1.29 (1H, m), 1.13 (1H, m), 1.09 (9H, s, ^{t}Bu) and 0.96 (3H, d, J 6.4, Me); m/z 639 (40.4, M^+-^{t}Bu), 533 (8.7, M^+-^{t}Bu-PhCHO), 391 (28.6, M^+-^{t}Bu-PhCHO-$PhSO_2H$), 373 (12.1, M^+-^{t}Bu-PhCHO-$PhSO_2H$-H_2O) and 199 (100, Ph_2SiOH); found: C, 70.97; H, 7.04. $C_{41}H_{48}O_6SSi$ requires C, 70.66; H, 6.94%.

***(2R*,5S*,6S*,8S*,9S*,11S*)-11-[(tert-Butyldiphenylsilyloxy)methyl]-9-methyl-2-phenyl-5-[2-(phenylsulphonyl)ethyl]-1,3-dioxaspiro[5.5]undecan-8-ol methanesulphonate* (32).**- Methanesulphonyl chloride (6µl, 77.5 µmol) was added dropwise to a stirred solution of the racemic alcohol (30) (38 mg, 54.4 µmol) and triethylamine (31 µl, 0.22 mmol) in DCM (5 ml), at -10°C under argon. After 5 min water

(5 ml) was added and the mixture allowed to warm to r.t. The two-phase mixture was extracted with DCM, the combined extracts dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (75% ether-petrol) afforded the ***mesylate*** (32) (38 mg, 90%) as cubes, mp 130-131°; ν_{max} (film) 2934, 1447, 1353, 1173, 1087 and 925 cm^{-1}; δ_H (500 MHz) 7.90 (2H, m, Ph), 7.75-7.50 (8H, m, Ph), 7.45-7.20 (10H, m, Ph), 5.83 (1H, s, H-2), 4.36 (1H, dt, J 4.3 and 11.0, H-8), 3.98 (1H, dd, J 10.5 and 4.0), 3.83 (1H, dd, J 10.5 and 3.0), 3.70-3.50 (2H, m), 3.10-2.85 (2H, m, H_2-2'), 2.99 (3H, s, SO_2CH_3), 2.58 (1H, dd, J 13.8 and 4.5), 2.16 (1H, m), 2.10-1.45 (6H, m), 1.25 (1H, m), 1.05 (9H, s, ^{t}Bu) and 1.00 (3H, d, J 7.0, Me); m/z 623 (M^+-^{t}Bu-$MeSO_3H$), 517 (M^+-^{t}Bu-$MeSO_3H$-PhCHO) and 199 (Ph_2SiOH); found: C, 64.87; H, 6.84. $C_{42}H_{52}O_8S_2Si$ requires C, 64.92; H, 6.75%.

(+)-α-[6-(tert-Butyldiphenylsilyloxy)-3,5-dimethyl-2-hexenyl]oxiraneethanol **(34)**.-To a solution of iodide (4) (0.62 g, 1.3 mmol) in ether (2.5 ml) at -120°C under argon was added *tert*-butyllithium (1.58 ml of a 1.7 M solution in pentanes, 2.7 mmol). The mixture was warmed to -78°C and stirred for 1h before transfer *via* cannula to a suspension of cuprous iodide (0.12 g, 0.65 mmol) in ether (0.5 ml) maintained at -25°C under argon. After 2h at -25°C the cuprate solution was cooled to -65°C and the bisepoxide (3) (0.050 g, 0.5 mmol) added. After 4h a mixture of saturated aqueous ammonium chloride and conc. ammonia (10 ml of 9:1 v/v) was added and the reaction warmed to room temperature. The mixture was extracted with ether (3 x 25 ml). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel (40% ether-petrol). Fractions containing the desired epoxy alcohol were evaporated and chromatographed again using a Dynamax Si column (5% IPA-petrol) to afford the *epoxy alcohol* (34) (0.120 g, 53%) as a colourless oil, $[\alpha]_D^{20}$ + 3.5° (*c* 2.0 in $CHCl_3$); ν_{max} (film) 3418, 2927, 2857, 1427, 1112, 824, 740 and 702 cm^{-1}; δ_H (400 MHz) 7.39-7.72 (10H, m, Ph), 5.13 (1H, t, J 7.5, H-2'), 3.81 (1H, m, H-α), 3.49 (1H, dd, J 10.0 and 5.5, C<u>H</u>OSi), 3.46 (1H, dd, J 10.0 and 6.0, C<u>H</u>OSi), 3.13 (1H, m, H-1), 2.82 (1H, dd, J 5.0 and 4.5, H-2), 2.58 (1H, dd, J 5.0 and 2.6, H-2), 2.28-1.56 (7H, m), 1.59 (3H, s, 3'-Me), 1.07 (9H, s, ^{t}Bu) and 0.88 (3H, d, J 6.5, 5'-Me); δ_C (22.5 MHz) 137.6, 135.5, 134.0, 129.5, 127.6, 121.0, 69.1, 68.7, 50.2, 46.9, 43.9, 38.6, 36.3, 33.7, 26.9, 19.3, 16.7 and 16.2; m/z 395 (M^+-^{t}Bu, 7%), 337 (24) and 199 (100); found: C, 73.98; H, 9.08. $C_{28}H_{40}O_3Si$ requires C, 74.28; H, 8.90%.

(+)-[2R(2E,4R),4S,6S,8R,9S]-2-[6-(tert-Butyldiphenylsilyloxy)-3,5-dimethyl-2-hexenyl]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol **(33)**.-To a solution of epoxy alcohol (34) (0.35 g, 0.77 mmol) in THF (6 ml) maintained at -20°C under argon was added titanium isopropoxide (0.35 ml, 1.16 mmol). The mixture was stirred for 30 min before addition *via* cannula to a solution prepared by reacting sulphone (2) (0.98 g, 3.87 mmol) in THF (18 ml) under argon at -78°C with n-butyllithium (1.5 ml of 2.6M, 3.9 mmol) for 15 min. The mixture was stirred overnight whilst being allowed to warm slowly to room temperature. Sulphuric acid (25 ml of 2N) and ether (40 ml) were added and the reaction stirred for 1h before extracting with ether (3 x 50 ml). The combined extracts were washed with saturated aqueous sodium hydrogencarbonate (2 x 50 ml) and brine (50 ml) then dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel (50% ether-petrol) afforded the *spiroketal* (33) (0.35 g, 80%) as a colourless oil, $[\alpha]_D^{20}$ + 33° (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3382, 3069, 2954, 2929, 2858, 1725, 1589, 1450, 1427, 1380, 1260, 1191, 1112, 991, 950, 823, 739 and 702 cm^{-1}; δ_H (400 MHz) 7.37-7.70 (10H, m, Ph), 5.18 (1H, t, J 7.0, H-2'), 4.09 (1H, tt, J 11.0 and 5.0, H-4), 3.54-3.44 (3H, m, C<u>H</u>$_2$OSi, H-7), 3.26 (1H, dq, J 10.0 and 6.5, H-8), 2.30-1.05 (17H, m), 1.10 (3H, d, J 6.5, 8-Me), 1.06 (9H, s, ^{t}Bu), 0.89 (3H, d, J 6.5, 5'-Me) and 0.82 (3H, d, J 6.5, 9-Me); m/z 507 (1%, M^+-^{t}Bu), 489 (1, M^+-^{t}Bu-H_2O), 337 (1), 199 (4) and 84 (100); observed: M^+-^{t}Bu, 507.2940. $C_{31}H_{43}O_4Si$ requires M-^{t}Bu, 507.2931; found: C, 74.48; H, 9.56. $C_{35}H_{52}O_4Si$ requires C, 74.42; H, 9.28%.

(+)-[2R(2E,4R),4S,6S,8R,9S]-2-[6-(tert-Butyldiphenylsilyloxy)-3,5-dimethyl-2-hexenyl]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol benzoate **(35)**.- A mixture of spiroacetal (33) (0.355 g, 0.63 mmol), DMAP (7.6 mg, 0.063 mmol) and benzoyl chloride (0.145 ml, 1.26 mmol) in dry pyridine (9 ml) was stirred under argon overnight then evaporated. Chromatography of the residue on silica gel (5% ether-petrol) afforded the *benzoate* (35) (0.36 g, 85%) as a colourless oil, $[\alpha]_D^{20}$ + 40° (*c* 1.1 in $CHCl_3$); ν_{max} (film) 2929, 1718, 1272 and 1112 cm^{-1}; δ_H (500 MHz) 8.03-8.00 (2H, m, Ph), 7.67-7.65 (4H, m, Ph), 7.54 (1H, tt, J 7.4 and 1.3, Ph), 7.44-7.31 (8H, m, Ph), 5.46 (1H, tt, J 11.4 and 4.9, H-4), 5.19 (1H, t, J 6.8, H-2'), 3.67 (1H, m, H-2), 3.50-3.44 (2H, m, CH_2OSi), 3.28 (1H, dq, J 9.8 and 6.2, H-8), 2.30-2.14 (5H, m), 2.11 (1H, ddd, J 12.2, 4.9 and 1.6), 1.83 (1H, m), 1.74-1.70 (2H, m), 1.59-1.45 (4H, m), 1.57 (3H, s, 3'-Me), 1.32 (1H, q, J 11.6, H_{ax}-3), 1.11 (3H, d, J 6.3, 8-Me), 1.05 (9H, s, ^tBu), 0.87 (3H, d, J, 7.0, 5'-Me) and 0.82 (3H, d, J 6.0 Hz, 9-Me); m/z 611 (1%, M^+-^tBu), 489 (14, M^+-^tBu-$PhCO_2H$), 330 (13) and 105 (100); found: C, 75.41; H, 8.71. $C_{42}H_{56}O_5Si$ requires C, 75.41; H, 8.44%.

(+)-[2R(3E,5R),4S,6S,8R,9S]-2-[6-Hydroxy-3,5-dimethyl-2-hexenyl]-8-9-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol benzoate (36).- To a solution of spiroacetal (35) (0.35 g, 0.52 mmol) in THF (5 ml) was added TBAF (1 ml of a 1M soln. in THF, 1 mmol). After stirring overnight at room temperature the mixture was evaporated and the residue chromatographed on silica gel (40% ether-petrol) to afford the *alcohol* (36) (0.215 g, 95%) as a colourless oil, $[\alpha]_D^{20}$ + 67.7° (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3426, 1716, 1273 and 713 cm^{-1}; δ_H (500 MHz) 8.02-8.00 (2H, m, Ph), 7.54 (1H, t, Ph), 7.44-7.40 (2H, m, Ph), 5.45 (1H, tt, J 11.4 and 4.8, H-4), 5.28 (1H, t, J 7.1, H-2'), 3.69 (1H, m, H-2), 3.51 (1H, dd, J 10.5 and 5.3, CHOSi), 3.42 (1H, dd, J 10.4 and 5.2, CHOSi), 3.28 (1H, dq, J 9.8 and 6.3, H-8), 2.25 (2H, t, J 6.7), 2.20 (1H, m), 2.13-2.06 (2H, m), 1.90-1.83 (2H, m), 1.72 (1H, m), 1.64 (3H, s, 3'-Me), 1.60-1.48 (6H, m), 1.34 (1H, q, J 11.6, H_{ax}-3), 1.14 (3H, d, J 6.3, 8-Me), 0.89 (3H, d, J 6.2 Hz, 5'-Me) and 0.83 (3H, d, J 6.5 Hz, 9-Me); m/z 430 (M^+, 0.1%), 308 (6, M^+-$PhCO_2H$) and 181 (100, $C_{11}H_{17}O_2$); found: C, 72.27; H, 9.07. $C_{26}H_{38}O_5$ requires C, 72.53; H, 8.90%.

(+)-[2R,4E,6(2R,4S,6S,8R,9S)]-6-(4-Benzoyloxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl)-2,4-dimethyl-4-hexenal **(37)**.- A mixture of the alcohol (36) (45.6 mg, 0.106 mmol), N-methylmorpholine-N-oxide (20 mg, 0.171 mmol) and ground 4Å sieves in DCM (2 ml) was stirred at r.t. under argon for 10 min. TPAP (catalytic amount) was then added. After 40 min, the mixture was filtered on a short pad of silica gel, washing well with ethyl acetate, and the filtrate evaporated. Column chromatography of the residue on silica gel (10% ether-petrol) afforded the *aldehyde* (37) (38.7 mg, 85%) as a clear oil, $[\alpha]_D^{20}$ + 48.4° (*c*.1.8 in $CHCl_3$); ν_{max} (film) 2929, 1717, 1449, 1380, 1313, 1272, 1221, 1195, 1177, 1113, 1069, 1026, 994 and 713 cm^{-1}; δ_H (500 MHz) 9.63 (1H, d, J 1.9, H-1), 8.01 (2H, m, Ph), 7.53 (1H, m, Ph), 7.42 (2H, m, Ph), 5.45 (1H, tt, J 11.3 and 5.0, H-4'), 5.30 (1H, br t, J 6.5, H-5), 3.68 (1H, m, H-2'), 3.26 (1H, dq, J 9.7 and 6.3, H-8'), 2.51 (1H, m, H-2), 2.45 (1H, dd, J 13.7 and 6.5, H-3), 2.24 (2H, m, H_2-6), 2.17 (1H, m, H_{eq}-3'), 2.11 (1H, ddd, J 12.2, 5.0 and 1.7, H_{eq}-5'), 2.00 (1H, dd, J 13.6 and 7.9, H-3), 1.70 (1H, dd, J 9.1 and 2.4, H_{eq}-11'), 1.63 (3H, s, 4-Me), 1.59-1.47 (4H, m, H_{ax}-11', H_2-10', H_{ax}-3'), 1.32 (1H, q, J 11.6, H_{ax}-3'), 1.25 (1H, m, H-9'), 1.13 (3H, d, J 6.3, 8'-Me), 1.05 (3H, d, J 6.9, 2-Me) and 0.83 (3H, d, J 6.6, 9'-Me); m/z 428 (M^+), 384 (0.3%, M^+-C_2H_4O), 327 (0.4, M^+-C_2H_4-C_3H_5O), 303 (11.4, $C_{18}H_{23}O_4$) and 181 (100, $C_{11}H_{17}O_2$); observed: M^+-C_2H_4O, 384.2303. $C_{24}H_{32}O_4$ requires M-C_2H_4O, 384.2301.

(+)-(2R,5E,6S,8S,9S,11S)-11-[(tert-Butyldiphenylsilyloxy)methyl]-9-methyl-2-phenyl-5-[2-(phenylsulphonyl)ethylidene]-1,3-dioxaspiro[5.5]undecan-8-ol **(39)** and ***(+)-[2R,5E[2E,4R,6E,8(2R,4S,6S,8R,9S)],6S,8S,9S,11S]-5-[(4-benzoyloxy-8,9-dimethyl-1,7-***

dioxaspiro[5.5]undecan-2-yl)-4,6-dimethyl-2,6-octadienylidene]-11-[(tert-butyldiphenylsilyloxy)methyl]-9-methyl-2-phenyl-1,3-dioxaspiro[5.5]undecan-8-ol benzoate **(40).**- *tert*-Butyllithium (0.415 ml of a 1.7M solution in pentanes, 0.706 mmol) was added dropwise to a stirred solution of the sulphone (5) (223 mg, 0.320 mmol) in THF (3.5 ml), under argon, at -78°C. After 10 min, the aldehyde (37) (121 mg, 0.285 mmol) in THF (5 ml) was added by cannula. After a further 1h, saturated ammonium chloride solution (3 ml) was added and the mixture allowed to warm to r.t. Water was added and the mixture extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography (70-100% ether-petrol) of the residue on silica gel gave unreacted aldehyde (37) (8.9 mg, 7%). HPLC (6% IPA-petrol) allowed separation of the *hydroxysulphones* (38) (268 mg, 84%) and the *allyl sulphone* (39) (35 mg, 16%), both as colourless foams. More polar (39), $[\alpha]_D^{20}$ +53.0° (*c* 1.3 in $CHCl_3$); ν_{max}(film) 2930, 1496, 1427, 1390, 1307, 1150, 1111, 1029, 739 and 702 cm^{-1}; δ_H (500 MHz) 7.82 (2H, m, Ph), 7.70-7.57 (8H, m, Ph), 7.44-7.20 (10H, m, Ph), 5.61 (1H, s, H-2), 5.05 (1H, m, H-1'), 4.19 (1H, d, J 14.9, H-4), 3.88-3.84 (2H, m, CHOSi, H-4), 3.63-3.58 (2H, m, CHOSi, H-2'), 3.39-3.35 (2H, m, H-8, H-2'), 2.66 (1H, dd, J 13.8 and 4.1, H_{eq}-7), 2.12 (1H, dt, J 13.4 and 3.8, H_{eq}-10), 2.01 (1H, m, H-11), 1.50-1.40 (2H, m, OH and H-9), 1.31 (1H, m, H_{ax}-10), 1.15 (1H, m, H_{ax}-7), 1.07 (3H, d, J 6.3, Me) and 1.03 (9H, s, ^{t}Bu); m/z 696 (M^+), 639 (1.0, M^+-^{t}Bu), 533 (3.0, M^+-^{t}Bu-PhCHO), 391 (16.9, M^+-^{t}Bu-PhCHO-$PhSO_2H$), 373 (10.7, M^+-^{t}Bu-PhCHO-$PhSO_2H$-H_2O) and 199 (100, Ph_2SiOH); found: C, 70.70; H, 6.60. $C_{41}H_{48}O_6SSi$ requires C, 70.66; H, 6.94%.

Powdered 6% sodium amalgam (890 mg, 2.32 mmol) was added to a vigorously stirred slurry of disodium hydrogenorthophosphate (1.2 g, 8.45 mmol) and the hydroxysulphones (38) (261 mg, 0.233 mmol) in THF: methanol, 3:1 (12 ml) under argon, at -40°C. After 70 min, the reaction was cooled to -78°C, ethyl acetate (7 ml) and powdered ammonium chloride were added and the mixture filtered rapidly through a pad of ammonium chloride and silica gel. The filtrate was evaporated. To the crude product and 4-dimethylaminopyridine (30 mg, 0.246 mmol) in DCM (3 ml) and pyridine (1 ml), at r.t. under argon, was added benzoyl chloride (0.220 ml, 1.90 mmol). After 1h, the mixture was poured into saturated aqueous $CuSO_4$ solution and extracted with ether. The organic extracts were washed with water, brine, dried ($MgSO_4$) and evaporated. Column chromatography (10% ether-petrol) of the residue on silica gel afforded the *E,E diene* (40) (67 mg, 27%) as a clear oil, $[\alpha]_D^{20}$ +43.9° (*c* 1.2 in $CHCl_3$); ν_{max} (film) 2929, 1714, 1450, 1270, 1176, 1112, 1068, 1026, 996 and 710 cm^{-1}; δ_H (500 MHz) 8.04-8.00 (4H, m, Ph), 7.68-7.28 (21H, m, Ph), 6.01 (1H, dd, J 14.9 and 11.1, H-10), 5.97 (1H, s, PhCH), 5.87 (1H, d, J 10.9, H-9), 5.54 (1H, dd, J 14.8 and 7.6, H-11), 5.45 (1H, tt, J 11.3 and 4.7, H-19), 5.23 (1H, br t, J 7.1, H-15), 4.85 (1H, dt, J 3.8 and 10.8, H-5), 4.66 (1H, d, J 14.4, H-8'), 4.54 (1H, d, J 14.3, H-8'), 4.11 (1H, dd, J 10.4 and 3.3, H-1), 3.69-3.62 (2H, m, H-1 and H-17), 3.28 (1H, dq, J 9.7 and 6.3, H-25), 3.10 (1H, dd, J 13.5 and 3.9, H_{eq}-6), 2.36-2.17 (8H, m), 2.10 (1H, dt, J 5.1 and 13.1), 1.88 (1H, dd, J 13.4 and 8.7), 1.70 (1H, m), 1.66-1.47 (5H, m), 1.59 (3H, s, 14-Me), 1.42-1.19 (3H, m), 1.13 (3H, d, J 6.2, Me), 1.05 (12H, m, ^{t}Bu, Me), 0.96 (3H, d, J 6.7, Me) and 0.83 (3H, d, J 6.6, Me); m/z (FAB from 3-nitrobenzylalcohol) 843 (2.1%, MH^+-$PhCO_2H$-PhCHO), 825 (2.6, MH^+-$PhCO_2H$-PhCHO-H_2O), 785 (0.3, M^+-^{t}Bu-$PhCO_2H$-PhCHO), 721 (2.2, MH^+-2$PhCO_2H$-PhCHO), 703 (4.2, MH^+-2$PhCO_2H$-PhCHO-H_2O), 663 (0.5, M^+-2$PhCO_2H$-PhCHO-^{t}Bu), 181 (37.6, $C_{11}H_{17}O_2$) and 153 (43.9, $C_{11}H_{17}O_2$-C_2H_4); found: C, 76.01; H, 7.69. $C_{68}H_{82}O_9Si$ requires C, 76.23; H, 7.71%.

(+)-[2R,5E[2E,4R,6E,8(2R,4S,6S,8R,9S)],6S,7S,9S,10S]-10-Benzoyloxy-5-[(4-benzoyloxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl)-4,6-dimethyl-2,6-octadienylidene]-9-methyl-2-phenyl-1,3-dioxaspiro[5.5]undecane-7-methanol **(41).**- Tetra-n-butylammonium fluoride (0.255 ml of a 1M solution in THF, 0.255 mmol) was added dropwise to a stirred solution of the silylether (40) (136 mg, 0.127

mmol) in THF (3 ml), under argon. The solution was heated at reflux for 15 min. Solvent evaporation followed by column chromatography on silica gel (30% ether-petrol) of the residue afforded the *alcohol* (41) (96 mg, 91%) as a clear oil, $[\alpha]_D^{20}$ +79.1° (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3501, 2926, 1713, 1449, 1381, 1313, 1272, 1177, 1113, 1069, 1026, 995 and 712 cm^{-1}; δ_H (500 MHz) 8.05-8.00 (4H, m, Ph), 7.57-7.52 (4H, m, Ph), 7.47-7.30 (7H, m, Ph), 6.11 (1H, dd, J 14.6 and 10.9, H-10), 6.06 (1H, s, PhC<u>H</u>), 5.93 (1H, d, J 10.9, H-9), 5.69 (1H, dd, J 14.8 and 7.3, H-11), 5.45 (1H, tt, J 11.4 and 4.8, H-19), 5.23 (1H, t, J 6.9, H-15), 4.92-4.88 (2H, m, H-5 and H-8'), 4.68 (1H, d, J 14.5, H-8'), 3.98 (1H, dd, J 11.1 and 4.7, H-1), 3.74 (1H, dd, J 11.1 and 2.8, H-1), 3.68 (1H, m, H-17), 3.28 (1H, dq, J 9.7 and 6.3, H-25), 3.17 (1H, dd, J 13.7 and 3.9, H_{eq}-6), 2.41 (1H, dt, J 13.9 and 6.9), 2.27 (1H, m), 2.21-2.17 (2H, m), 2.13-2.09 (3H, m), 1.94-1.79 (5H, m), 1.71-1.67 (1H, m), 1.60 (3H, s, 14-Me). 1.59-1.42 (4H, m), 1.32 (1H, q, J 11.6), 1.27-1.22 (2H, m), 1.14 (3H, d, J 6.3, Me), 1.05 (3H, d, J 6.2, Me), 0.98 (3H, d, J 6.7, Me) and 0.83 (3H, d, J 6.6, Me); m/z 604 (0.1%, M^+-$PhCO_2H$-PhCHO), 586 (7.3, M^+-$PhCO_2H$-PhCHO-H_2O), 482 (0.8, M^+-2$PhCO_2H$-PhCHO), 464 (3.7, M^+-2$PhCO_2H$-PhCHO-H_2O), 181 (71.8, $C_{11}H_{17}O_2$) and 153 (27.7, $C_{11}H_{17}O_2$-C_2H_4); found: C, 74.82; H, 7.87. $C_{52}H_{64}O_9$ requires C, 74.97; H, 7.74%.

(+)-[2R,5E[2E,4R,6E,8(2R,4S,6S,8R,9S)],6S,7S,9S,10S]-10-Benzoyloxy-5-[(4-benzoyloxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl)-4,6-dimethyl-2,6-octadienylidene]-9-methyl-2-phenyl-1,3-dioxaspiro[5.5]undecane-7-carboxaldehyde (42).- A mixture of the alcohol (41) (6.1 mg, 7.32 µmol), N-methyl morpholine-N-oxide monohydrate (1.5 mg, 11.1 µmol) and ground 4Å sieves, in DCM (0.5 ml) was stirred for 10 min at r.t., under argon. TPAP (cat. amount) was then added. After 5 min. the dark-green solution was diluted with DCM (3 ml), filtered on celite, and the filtrate concentrated. Column chromatography of the residue on silica gel (20% ether-petrol) afforded the *aldehyde* (42) (4.6 mg, 76%), as a colourless foam, $[\alpha]_D^{20}$ +82.1° (*c* 1.1 in $CHCl_3$); ν_{max} (film) 2926, 1713, 1450, 1271, 1176, 1111, 1069, 1026, 995 and 712 cm^{-1}; δ_H (500 MHz) 9.89 (1H, d, J 2.3, H-1), 8.05-8.00 (4H, m, Ph), 7.59-7.52 (4H, m, Ph), 7.45-7.35 (7H, m, Ph), 6.14 (1H, s, PhC<u>H</u>), 6.12 (1H, dd, J 15.3 and 10.7, H-10), 5.96 (1H, d, J 10.8, H-9), 5.72 (1H, dd, J 14.9 and 7.4, H-11), 5.45 (1H, tt, J 11.4 and 4.8, H-19), 5.22 (1H, t, J 6.9, H-15), 4.94-4.89 (2H, m, H-8', H-5), 4.65 (1H, d, J 14.3, H-8'), 3.67 (1H, m, H-17), 3.32-3.25 (2H, m, H-2 and H-25), 2.82 (1H, m), 2.40 (1H, dt, J 14.1 and 6.9), 2.28 (1H, m), 2.22-2.16 (2H, m), 2.12-2.05 (2H, m), 1.94-1.89 (3H, m), 1.81 (1H, t, J 13.1), 1.71 (1H, m), 1.59 (3H, s, 14-Me), 1.59-1.47 (4H, m), 1.41 (1H, dd, J 13.8 and 11.2), 1.32 (1H, q, J 11.6), 1.25 (1H, m), 1.14 (3H, d, J 6.3, Me), 1.05 (3H, d, J 6.1, Me), 0.97 (3H, d, J 6.7, Me) and 0.83 (3H, d, J 6.5, Me); m/z 602 (0.3, M^+-PhCHO-$PhCO_2H$), 584 (1.8, M^+-PhCHO-$PhCO_2H$-H_2O), 480 (1.2, M^+-PhCHO-2$PhCO_2H$), 462 (4.9, M^+-PhCHO-2$PhCO_2H$-H_2O), 181 (94.9, $C_{11}H_{17}O_2$) and 153 (14.1, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+-PhCHO-$PhCO_2H$, 602.3593. $C_{38}H_{50}O_6$ requires M-PhCHO-$PhCO_2H$, 602.3607.

(+)-5-O-Desmethyl-3,4S-dihydromilbemycin β_1 7,8'-R-Benzylidene acetal (43).- The aldehyde (42) (85 mg, 0.102 mmol) was dissolved in t-butanol (1.9 ml) and H_2O (1.9 ml). 2-methyl-2-butene (1.6 ml) was added, followed by potassium dihydrogenorthophosphate (320 mg, 2.35 mmol). To the stirred mixture at r.t. was added sodium chlorite (95 mg, 1.05 mmol). After 1.5h the mixture was cooled to 0°C before addition of saturated aqueous sodium sulphite solution (1 ml). Water was added and the mixture extracted with DCM (3 x 5 ml). The combined organics were dried ($MgSO_4$) and evaporated to give the crude *acid* as a pale yellow oil, ν_{max} (film) 3259, 2930, 1713, 1450, 1381, 1314, 1272, 1177, 1113, 1069, 1026, 994 and 714 cm^{-1}; δ_H (500 MHz) 8.05-7.95 (4H, m, Ph), 7.55-7.15 (11H, m, Ph), 6.26 (1H, s, PhC<u>H</u>), 6.15-6.07 (2H, m, H-9, H-10), 5.79 (1H, dd, J 14.1 and 7.5, H-11), 5.45 (1H, tt, J 11.3 and 4.8, H-19), 5.22 (1H, t, J 6.9, H-15), 4.98 (1H, d, J 14.2, H-8'), 4.93 (1H, dt, J 3.9 and 11.1, H-5), 4.61 (1H, d, J 14.1, H-8'), 3.67 (1H, m, H-17), 3.36 (1H, dd, J 14.1 and 3.8), 3.28 (1H, dq, J 9.6 and 6.3, H-25), 3.15 (1H, dd, J 12.8 and 4.1), 2.45-1.60 (10H, m), 1.59 (3H, s, 14-

Me), 1.60-1.14 (8H, m), 1.14 (3H, d, J 6.3, Me), 1.05 (3H, d, J 6.1, Me), 0.96 (3H, d, J 6.7, Me) and 0.82 (3H, d, J 6.6, Me); m/z 602 (0.3%, M^+-2PhCO$_2$H), 574 (2.0, M^+-PhCHO-PhCO$_2$H-CO$_2$), 556 (0.5, M^+-PhCHO-PhCO$_2$H-CO$_2$-H$_2$O), 452 (4.0, M^+-PhCHO-2PhCO$_2$H-CO$_2$), 181 (100, $C_{11}H_{17}O_2$) and 153 (22.1, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+-PhCHO-PhCO$_2$H-CO$_2$, 574.3670. $C_{37}H_{50}O_5$ requires M-PhCHO-PhCO$_2$H-CO$_2$, 574.3658.

To the crude acid in methanol (4 ml), at r.t. under argon, was added sodium methoxide (2.8 ml of a 2.9M solution in methanol, 8.1 mmol), portionwise over a period of 1.25 h. After a further 30 min., toluene (5 ml) was added, then solid ammonium chloride. The mixture was filtered on a pad of solid ammonium chloride and celite, and the solids washed exhaustively with ethyl acetate. Concentration gave the crude seco acid.

A solution of the seco acid and triethylamine (0.145 ml, 1.04 mmol) in acetonitrile (6 ml) was added (below the liquid surface) over 9h, to a solution of 2-chloro-1-methylpyridinium iodide (131 mg, 0.513 mmol), in acetonitrile (16 ml), at reflux, under argon. After a further 3h, the mixture was cooled to r.t., concentrated and filtered through a silica plug (ethyl acetate eluant). Evaporation followed by column chromatography (60% ether-petrol) of the residue on silica gel afforded the *macrolactone* (43) (31 mg, 49% from (42)) as a clear oil, $[\alpha]_D^{20}$ +3.8° (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3436, 2954, 2927, 2872, 1744, 1608, 1450, 1375, 1162, 1097, 1050, 1029 and 996 cm^{-1}; δ_H (500 MHz) 7.63 (2H, m, Ph), 7.39-7.32 (3H, m, Ph), 6.03 (1H, dd, J 15.2 and 10.3, H-10), 5.97 (1H, s, PhC<u>H</u>), 5.90 (1H, d, J 10.2, H-9), 5.74 (1H, dd, J 15.3 and 5.1, H-11), 5.46 (1H, tt, J 11.4 and 4.6, H-19), 4.87 (1H, br d, J 11.2, H-15), 4.84 (1H, d, J 13.8, H-8'), 4.54 (1H, d, J 13.8, H-8'), 3.67 (1H, m, H-17), 3.50 (1H, dt, J 4.7 and 11.5, H-5), 3.25 (1H, dq, J 9.8 and 6.2, H-25), 3.04 (1H, dd, J 3.8 and 4.2, H_{eq}-6), 2.90 (1H, dd, J 12.4 and 3.6, H-2), 2.57 (1H, m, H-12), 2.38-2.17 (3H, m), 2.05-1.68 (6H, m) 1.67 (3H, s, 14-Me), 1.57-1.12 (6H, m), 1.09-1.05 (6H, m, Me$_2$), 1.03 (3H, d, J 6.4, Me), 1.00-0.84 (3H, m) and 0.82 (3H, d, J 6.6, Me); m/z (FAB from 3-nitrobenzyl alcohol) 621 (MH^+, 1.2%), 602 (2.2, M^+-H$_2$O), 515 (17.2, MH^+-PhCHO), 497 (8.2, MH^+-PhCHO-H$_2$O), 479 (1.4, MH^+-PhCHO-2H$_2$O), 181 (35.2, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: MH^+, 621.3791. $C_{38}H_{53}O_7$ requires MH, 621.3791.

***(-)-5-Desmethoxy-3,4S-dihydro-5-oxomilbemycin β_1 7,8'-R-Benzylidene acetal* (44).-** A mixture of the alcohol (43) (8.6 mg, 13.8 μmol), N-methyl morpholine-N-oxide monohydrate (3.0 mg, 22.2 μmol) and ground 4Å sieves, in DCM (0.5 ml) was stirred for 10 min at r.t., under argon. TPAP (cat. amount) was then added. After 10 min. the dark-green solution was filtered on celite and the filtrate evaporated. Column chromatography of the residue on silica gel (25% ether-petrol) gave the *ketone* (44) (7.1 mg, 83%), as an amorphous colourless solid, $[\alpha]_D^{20}$ -49.5° (*c* 0.6 in $CHCl_3$); ν_{max} (film) 2929, 1743, 1716, 1449, 1377, 1252, 1197, 1160, 1095, 1026, 997 and 756 cm^{-1}; δ_H (500 MHz) 7.54 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 6.03 (1H, dd, J 15.1 and 10.3, H-10), 5.97 (1H, d, J 10.3, H-9), 5.92 (1H, s, PhC<u>H</u>), 5.77 (1H, dd, J 15.0 and 5.1, H-11), 5.49 (1H, tt, J 11.5 and 4.7, H-19), 4.88 (1H, d, J 11.0, H-15), 4.84 (1H, d, J 14.0, H-8'), 4.49 (1H, d, J 13.9, H-8'), 3.68 (1H, m, H-17), 3.49 (1H, d, J 14.3, H-6), 3.37 (1H, m, H-2), 3.25 (1H, dq, J 9.8 and 6.2, H-25), 2.59 (1H, m, H-12), 2.45-2.15 (8H, m), 2.00 (1H, m), 1.93 (1H, m), 1.68 (3H, s, 14-Me), 1.75-1.22 (5H, m), 1.08 (6H, d, J 6.2, Me$_2$), 1.03 (3H, d, J 6.5, Me), 0.96-0.85 (2H, m) and 0.82 (3H, d, J 6.6, Me); m/z: 618 (M^+, 0.3%), 600 (0.8, M^+-H$_2$O), 512 (2.9, M^+-PhCHO), 494 (1.2, M^+-PhCHO-H$_2$O), 476 (0.2, M^+-PhCHO-2H$_2$O), 181 (53, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+-PhCHO, 512.3127. $C_{31}H_{44}O_6$ requires M-PhCHO, 512.3138.

***(+)-5-Desmethoxy-3,4S-dihydro-5-oxomilbemycin β_1* (45).-** Trifluoroacetic acid was added by capillary to a stirred solution of the acetal (44) (7.1 mg, 11.5 μmol) in DCM (1 ml), at r.t. in an open flask. The reaction was monitored by tlc (75% ether-petrol; starting material R_f 0.69, product R_f 0.21). On completion, solid sodium hydrogencarbonate was added and the mixture filtered. Evaporation followed by column chromatography

of the residue on silica gel (75% ether-petrol) gave the *diol* (45) (5.6 mg, 92%), as an amorphous colourless solid, $[\alpha]_D^{20}$ +190.8° (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3482, 2926, 1714, 1449, 1376, 1289, 1235, 1180, 1096, 1054 and 993 cm^{-1}; δ_H (500 MHz) 6.26 (1H, d, J 11.1, H-9), 6.14 (1H, dd, J 14.7 and 11.1, H-10), 5.47 (1H, dd, J 14.7 and 9.7, H-11), 5.37 (1H, tt, J 11.5 and 4.7, H-19), 4.85 (1H, br d, J 10.2, H-15), 4.26 (2H, m, H_2-8'), 4.07 (1H, d, J 2.6, 7-OH), 3.58 (1H, m, H-17), 3.28-3.19 (2H, m, H-2 and H-25), 2.83 (1H, dd, J 14.1 and 2.1, H_{eq}-6), 2.47-2.39 (3H, m, incl. H-4, H-6), 2.29-2.02 (6H, m, incl. H_2-16), 1.87-1.82 (2H, m, incl H_{eq}-20), 1.78 (1H, m, H_{eq}-18), 1.67 (1H, m), 1.60 (3H, s, 14-Me), 1.55-1.48 (3H, m), 1.47 (1H, q, J 12.0), 1.32-1.14 (1H, m), 1.10 (6H, t, J 6.7, Me_2), 1.03 (3H, d, J 6.6, Me), 0.82 (3H, d, J 6.6, 24-Me) and 0.72 (1H, q, J 11.6, H_{ax}-18); m/z 530 (M^+, 2.4%), 512 (9.3, M^+-H_2O), 494 (3.2, M^+-$2H_2O$), 486 (1.2, M^+-CO_2), 468 (0.6, M^+-H_2O-CO_2), 450 (0.3, M^+-$2H_2O$-CO_2), 199 (5.8, $C_{11}H_{19}O_3$), 181 (94.6, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+, 530.3258. $C_{31}H_{46}O_7$ requires M, 530.3244.

(+)-8'O-(tert-Butyldimethylsilyl)-5-desmethoxy-3,4-dihydro-5-oxo-4-(phenylselenenyl)milbemycin β_1 **(46)**.- tert-Butyldimethylsilyl triflate (20 µl, 87.1 µmol) was added dropwise to a stirred mixture of the ketone (45) (8.9 mg, 16.8 µmol) and triethylamine (50 µl, 0.36 mmol) in DCM (2 ml), at r.t., under argon. After 1.5h the reaction was quenched with saturated aqueous sodium hydrogencarbonate solution and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was filtered on a short plug of silica gel (10% ether-petrol) and the eluant evaporated. To the crude enol ether in DCM (2 ml) at -78°C under argon was added phenylselenenyl chloride (7 mg, 36.5 µmol) in DCM (0.5 ml); the reaction mixture retained a slight yellow coloration. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution and allowed to come to r.t. The organic layer was separated and the aqueous layer further extracted with DCM. The combined organics were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (20% ether-petrol) afforded the *selenide* (46) (6.7 mg, 50%) as a colourless oil, $[\alpha]_D^{20}$ +84.5° (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3458, 2926, 1707, 1443, 1376, 1255, 1180, 1055, 997, 837, 774 and 740 cm^{-1}; δ_H (500 MHz) 7.45 (2H, m, Ph), 7.38 (1H, m, Ph), 7.32-7.23 (2H, m, Ph), 6.16-6.08 (2H, m, H-9, H-10), 5.42 (1H, dd, J 13.6 and 9.9, H-11), 5.34 (1H, tt, J 11.6 and 4.6, H-19), 4.88 (1H, br d, J 10.0, H-15), 4.44 (1H, d, J 12.1, H-8'), 4.33 (1H, d, J 2.7, 7-OH), 4.24 (1H, d, J 12.1, H-8'), 4.02 (1H, dd, J 14.7 and 2.8, H_{eq}-6), 3.66 (1H, dd, J 13.1 and 4.0, H-2), 3.59 (1H, m, H-17), 3.26 (1H, dq, J 9.6 and 6.3, H-25), 2.51 (1H, dd, J 14.6 and 13.2), 2.45 (1H, m, H-12), 2.37 (1H, d, J 14.8, H_{ax}-6), 2.29-2.12 (5H, m), 1.90-1.82 (2H, m), 1.72-1.63 (1H, m), 1.55 (3H, s, 14-Me), 1.54-1.45 (2H, m), 1.42 (3H, s, 4-Me), 1.38-1.26 (1H, m), 1.21 (1H, t, J 7.0), 1.12 (3H, d, J 6.3, Me), 1.03 (3H, d, J 6.6, Me), 0.97 (9H, s, ^{t}Bu), 0.84 (3H, d, J 6.6, Me), 0.76 (1H, q, J 11.7, H_{ax}-18), 0.18 (3H, s, MeSi) and 0.17 (3H, s, MeSi); m/z 743 (1.8%, M^+-^{t}Bu), 725 (0.6, M^+-^{t}Bu-H_2O), 668 (0.2, M^+-^{t}BuMe$_2$SiOH), 643 (0.5, M^+-PhSe), 626 (1.2, MH^+-PhSe-H_2O), 587 (2.8, MH^+-PhSe-^{t}Bu), 569 (1.2, MH^+-PhSe-^{t}Bu-H_2O), 550 (0.6, M^+-PhSe-^{t}Bu-$2H_2O$), 199 (2.2, $C_{11}H_{19}O_3$), 181 (22.4, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+-^{t}Bu, 743.2880. $C_{39}H_{55}O_7SeSi$ requires M-^{t}Bu, 743.2882.

(+)-5-epi-8'O-(tert-Butyldimethylsilyl)-5-O-desmethylmilbemycin β_1 **(48)**, ***(+)-8'O-(tert-Butyldimethylsilyl)-4'-dehydro-5-O-desmethyl-3-hydromilbemycin β_1*** **(47)**, and ***(+)-8'O-(tert-Butyldimethylsilyl)-5-O-desmethylmilbemycin β_1*** **(49)**.- The selenide (46) (11.7 mg, 14.6 µmol) was dissolved in $CDCl_3$ (1 ml), in an nmr tube. 2-(Phenylsulphonyl)-3-(p-nitrophenyl) oxaziridine was added portionwise and the reaction monitored by ^{1}H nmr. On completion of the reaction, integration of the signals at δ 6.28 (br s, H-3 of the *endo*-enone) and at 5.92 (br s, *exo*-methylene) and 5.22 (br s, *exo*-methylene) indicated that the *endo*- and *exo*- elimination products were formed in a 2:1 ratio, respectively. The reaction

mixture was poured into methanol (2 ml) and cerium (III) chloride heptahydrate (215 mg, 0.58 mmol) added. Sodium borohydride was added portionwise until tlc indicated consumption of the enone. The mixture was quenched with saturated aqueous ammonium chloride solution and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (30-50% ether-petrol) gave the allylic alcohols (48) (2.7 mg, 29%), (47) (2.4 mg, 25%), and (49) (2.5 mg, 27%), all as colourless oils. Least polar (48), $[\alpha]_D^{20}$ +110.0° (*c* 0.2 in $CHCl_3$); ν_{max} (film) 3424, 2926, 2856, 1699, 1450, 1377, 1255, 1180, 1113, 1055, 997 and 839 cm^{-1}; δ_H (500 MHz) 6.20 (1H, d, J 11.2, H-9), 6.13 (1H, dd, J 14.3 and 11.2, H-10), 5.43-5.36 (2H, m, H-11, H-19), 5.35 (1H, d, J 2.1, 7-OH), 5.14 (1H, t, J 1.5, H-3), 4.89 (1H, br d, J 9.0, H-15), 4.40 (1H, d, J 12.0, H-8'), 4.14 (1H, d, J 12.0, H-8'), 3.92 (1H, d, J 10.9, 5-OH), 3.89 (1H, dd, J 10.8 and 4.1, H-5), 3.62 (1H, br s, H-2), 3.59 (1H, m, H-17), 3.26 (1H, dq, J 9.8 and 6.2, H-25), 2.43 (1H, m, H-12), 2.27-2.15 (3H, m), 1.88 (3H, br s, 4-Me), 1.90-1.80 (3H, m), 1.68 (1H, m), 1.59-1.45 (5H, m), 1.56 (3H, s, 14-Me), 1.41 (1H, t, J 12.0), 1.31 (1H, m), 1.13 (3H, d, J 6.3, Me), 1.00 (3H, d, J 6.6, Me), 0.89 (9H, s, ^tBu), 0.83 (3H, d, J 6.6, Me), 0.76 (1H, q, J 11.8, H_{ax}-18) and 0.07 (6H, s, Me_2Si); m/z 644 (M^+, 0.9%), 627 (2.7, MH^+-H_2O), 587 (0.4, M^+-^tBu), 570 (5.3, MH^+-^tBu-H_2O), 512 (5.8, M^+-$^tBuMe_2SiOH$), 199 (4.4, $C_{11}H_{19}O_3$), 181 (41.4, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+-H_2O, 626.4018. $C_{37}H_{58}O_6Si$ requires M-H_2O, 626.4003.

More polar (47), $[\alpha]_D^{20}$ +158.8° (*c* 0.2 in $CHCl_3$); ν_{max} (film) 3457, 2926, 2854, 1699, 1463, 1377, 1256, 1180, 1056, 997, 837 and 774 cm^{-1}; δ_H (500 MHz) 6.17 (1H, d, J 11.1, H-9), 6.11 (1H, dd, J 14.0 and 11.1, H-10), 5.39 (1H, dd, J 14.2 and 9.9, H-11), 5.33 (1H, m, H-19), 5.02 (1H, br s, H-4'), 4.87 (1H, m, H-15), 4.86 (1H, br s, H-4'), 4.72 (1H, d, J 2.5, 7-OH), 4.60 (1H, m, H-5), 4.32 (1H, d, J 12.1, H-8'), 4.14 (1H, d, J 12.1, H-8'), 3.57 (1H, m, H-17), 3.26 (1H, dq, J 9.8 and 6.4, H-25), 2.96 (1H, dd, J 13.2 and 4.2), 2.65 (1H, t, J 13.2), 2.42 (1H, m, H-12), 2.35 (1H, dd, J 13.2 and 4.2), 2.32-2.12 (4H, m), 1.87-1.75 (4H, m), 1.67 (1H, m), 1.64-1.45 (4H, m), 1.57 (3H, s, 14-Me), 1.41 (1H, t, J 12.0), 1.22 (1H, m), 1.12 (3H, d, J 6.2, Me), 1.01 (3H, d, J 6.6, Me), 0.89 (9H, s, ^tBu), 0.83 (3H, d, J 6.6, Me), 0.72 (1H, q, J 11.8, H_{ax}-18) and 0.06 (6H, s, Me_2Si); m/z 645 (MH^+), 626 (0.3%, M^+-H_2O), 587 (0.1, M^+-^tBu), 569 (0.1, M^+-^tBu-H_2O), 512 (0.1, M^+-$^tBuMe_2SiOH$), 199 (1.4, $C_{11}H_{19}O_3$), 181 (3.8, $C_{11}H_{17}O_2$) and 153 (12.6, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+-H_2O, 626.4018. $C_{37}H_{58}O_6Si$ requires M-H_2O, 626.4003.

Most polar (49), $[\alpha]_D^{20}$ +77.0° (*c* 0.1 in $CHCl_3$); ν_{max} (film) 3452, 2953, 2925, 2854, 1701, 1450, 1377, 1337, 1255, 1182, 1116, 1055, 996 and 663 cm^{-1}; δ_H (500 MHz) 6.25 (1H, d, J 11.2, H-9), 6.14 (1H, dd, J 14.5 and 11.2, H-10), 5.41-5.34 (2H, m, H-11, H-19), 5.17 (1H, br d, J 1.5, H-3), 4.89 (1H, br d, J 10.0, H-15), 4.73 (1H, d, J 1.9, 7-OH), 4.50 (1H, m, H-5), 4.40 (1H, d, J 11.9, H-8'), 4.16 (1H, d, J 12.0, H-8'), 3.71 (1H, dd, J 4.8 and 2.5, H-2), 3.57 (1H, m, H-17), 3.26 (1H, dq, J 9.7 and 6.3, H-25), 2.42 (1H, m, H-12), 2.27-2.14 (4H, m), 1.98 (1H, m), 1.89-1.75 (3H, m), 1.83 (3H, br s, 4-Me), 1.67 (1H, m), 1.56 (3H, s, 14-Me), 1.55-1.47 (5H, m), 1.39 (1H, t, J 12.0), 1.30 (1H, m), 1.12 (3H, d, J 6.3, 25-Me), 1.00 (3H, d, J 6.6, 12-Me), 0.90 (9H, s, ^tBu), 0.83 (3H, d, J 6.6, 24-Me), 0.77 (1H, q, J 11.8, H_{ax}-18) and 0.08 (6H, s, Me_2Si); m/z 644 (M^+, 2.6%), 626 (1.7, M^+-H_2O), 587 (0.4, M^+-^tBu), 569 (3.1, M^+-^tBu-H_2O), 512 (9.9, M^+-$^tBuMe_2SiOH$), 199 (3.9, $C_{11}H_{19}O_3$), 181 (31.5, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+, 644.4067. $C_{37}H_{60}O_7Si$ requires M, 644.4108.

(+)-8'O-(tert-Butyldimethylsilyl)milbemycin β_1 **(50).**- The alcohol (49) (2.1 mg, 3.26 μmol) and freshly prepared silver (I) oxide (90 mg, 0.39 mmol) were dissolved in methyl iodide (1ml), in the dark. The mixture was stirred at r.t. for 36h, with periodic sonication. The mixture was filtered on celite and the filtrate evaporated. Column chromatography of the residue on silica gel (20-60% ether-petrol) afforded the *methyl ether* (50) (1.6 mg, 73%) as a colourless oil, $[\alpha]_D^{20}$ +86.5° (*c* 0.3 in $CHCl_3$); ν_{max} (film) 3461, 2926, 2856, 1703, 1450, 1377, 1338, 1256, 1183, 1116, 1096, 1056 and 997 cm^{-1}; δ_H (500 MHz) 6.27 (1H, d, J 11.2, H-9), 6.15

(1H, dd, J 14.6 and 11.2, H-10), 5.41-5.35 (2H, m, H-11, H-19), 5.19 (1H, br d, J 1.5, H-3), 4.88 (1H, br d, J 9.0, H-15), 4.67 (1H, d, J 1.9, 7-OH), 4.36 (1H, d, J 11.9, H-8'), 4.18 (1H, d, J 11.9, H-8'), 4.10 (1H, m, H-5), 3.68 (1H, dd, J 4.8 and 2.5, H-2), 3.57 (1H, m, H-17), 3.36 (3H, s, OMe), 3.25 (1H, dq, J 9.7 and 6.3, H-25), 2.43 (1H, m, H-12), 2.32-2.14 (4H, m), 1.95 (1H, m), 1.88-1.75 (3H, m), 1.79 (3H, s, 4-Me), 1.67 (1H, m), 1.56 (3H, s, 14-Me), 1.56-1.47 (3H, m), 1.39 (1H, t, J 12.0), 1.30 (1H, m), 1.12 (3H, d, J 6.2, 25-Me), 1.00 (3H, d, J 6.6, 12-Me), 0.90 (9H, s, ^{t}Bu), 0.83 (3H, d, J 6.6, 24-Me), 0.77 (1H, q, J 11.8, H_{ax}-18) and 0.08 (6H, s, Me_2Si); m/z 658 (M^+, 0.6%), 640 (0.5, M^+-H_2O), 626 (0.5, M^+-MeOH), 601 (0.8, M^+-^{t}Bu), 569 (4.4, M^+-^{t}Bu-MeOH), 526 (11.7, M^+-^{t}BuMe$_2$SiOH), 199 (3.2, $C_{11}H_{19}O_3$), 181 (32.3, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+, 658.4268. $C_{38}H_{62}O_7Si$ requires M, 658.4265.

***Milbemycin β_1* (1).**- 40% Aqueous hydrofluoric acid was added periodically to a stirred solution of the silyl ether (50) (2.6 mg, 3.95 μmol) and pyridine (65 μl) in acetonitrile (400 μl), at r.t., the reaction being monitored by tlc (ether; starting material R_f 0.83, product R_f 0.57). On completion of the reaction, saturated aqueous sodium hydrogencarbonate solution was added and the mixture extracted with DCM. The combined extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (75% ether-petrol) afforded *milbemycin β_1* (1) (1.6 mg, 75%) as a clear oil, $[\alpha]_D^{20}$ +129.1° (*c* 0.3 in $CHCl_3$); ν_{max} (film) 3452, 2926, 1707, 1450, 1377, 1336, 1272, 1181, 1166, 1096, 1055, 997, 947 and 854 cm^{-1}; δ_H (500 MHz) 6.41 (1H, d, J 11.3, H-9), 6.25 (1H, dd, J 14.7 and 11.3, H-10), 5.45 (1H, dd, J 14.7 and 9.8, H-11), 5.39 (1H, tt, J 11.5 and 4.7, H-19), 5.25 (1H, br. s, H-3), 4.87 (1H, m, H-15), 4.26 (1H, dd, J 12.1 and 6.1, H-8'), 4.17 (1H, dd, J 12.1 and 4.6, H-8'), 4.04 (1H, m, H-5), 3.78 (1H, d, J 1.6, 7-OH), 3.55 (1H, m, H-17), 3.48 (1H, m, H-2), 3.36 (3H, s, OMe), 3.24 (1H, dq, J 9.7 and 6.2, H-25), 2.47 (1H, m, H-12), 2.27-2.16 (4H, m, H_2-16, H-13, H-6), 1.93-1.75 (4H, m, H-6, H-13, H_{eq}-18, H_{eq}-20), 1.80 (3H, s, 4-Me), 1.64 (1H, m, H-22), 1.59 (3H, s, 14-Me), 1.56-1.42 (4H, m, incl. H_2-23, H-22), 1.39 (1H, t, J 11.9, H-20), 1.25-1.19 (1H, m, H-24), 1.11 (3H, d, J 6.3, 25-Me), 1.03 (3H, d, J 6.3, 12-Me), 0.82 (3H, d, J 6.6, 24-Me) and 0.77 (1H, q, J 11.6, H_{ax}-18); δ_C (125.8 MHz) 173.6 (C-1), 143.9 (C-11), 139.8, 138.5, 136.4 (C-7, C-8, C-14), 129.7 (C-9), 124.0 (C-10), 120.8 (C-15), 118.4 (C-3), 97.6 (C-21), 75.8 (C-5), 71.3 (C-25), 68.6 (C-19), 67.5 (C-17), 57.9 (C-8'), 56.6 (OMe), 49.1 (C-2), 48.5 (C-6 or C-13), 41.1 (C-20), 37.3 (C-6 or C-13), 36.7 (C-18), 36.6 (C-24), 36.3 (C-12), 35.7 (C-23), 34.5 (C-16), 27.7 (C-22), 21.7 (Me-12), 19.3 (Me-25 and Me-4), 17.8 (Me-24) and 15.9 (Me-14); m/z 544 (M^+, 8.3%), 526 (2.5, M^+-H_2O), 512 (1.0, M^+-MeOH), 494 (1.6, M^+-H_2O-MeOH), 476 (0.7, M^+-2H_2O-MeOH), 402 (1.5, $C_{25}H_{38}O_4$), 199 (12.9, $C_{11}H_{19}O_3$), 181 (57.7, $C_{11}H_{17}O_2$) and 153 (100, $C_{11}H_{17}O_2$-C_2H_4); observed: M^+, 544.3401. $C_{32}H_{48}O_7$ requires M, 544.3400. Data identical to an authentic sample.[31]

Crystal data for (20)[33]: $C_{36}H_{46}O_7Si$, *M*=618.8, monoclinic, *a*=11.360(4), *b*=9.992(4), *c*=15.106(5)Å, β=97.91(3)°, *V*=1698Å^3, space group $P2_1$, *Z*=2, D_c= 1.21 gcm^{-3}, Cu radiation, λ=1.54178Å, μ (Cu-K_α)= 10 cm^{-1}, *F*(000)=664. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 2449 independent reflections ($2\theta \leq 116°$) were measured, of which 2127 had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, *U* (H) = 1.2 U_{eq} (C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. The absolute configuration of the molecule was determined by refinement of a free variable η which multiplies all f''. Refinement was by block-cascade full-matrix least-squares to $R = 0.058$, R_w = 0.063 [$w^{-1} = \sigma^2(F) + 0.00233F^2$]. The maximum and minimum residual electron densities in the final ΔF map

were 0.50 and -0.29eÅ^{-3}, respectively. The mean and maximum shift / error in the final refinement were 0.008 and 0.036 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL[34] program system.

Crystal data for (32)[33]: $C_{42}H_{50}O_8S_2Si.[C_2H_6O_2]_{.25}$, M=790.6, monoclinic, a=40.573(41), b=11.249(13), c=20.051(13)Å, β=95.20(8)°, V=9114Å^3, space group $C2/c$, Z=8, D_c= 1.15 gcm^{-3}, Cu radiation, λ=1.54178Å, μ (Cu-K_α)= 17 cm^{-1}, F(000)=3364. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 4684 independent reflections (2θ ≤ 100°) were measured, of which 3474 had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. A ΔF map revealed the presence of a disordered solvent fragment. The positions of the hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U (H) = 1.2 U_{eq} (C), and allowed to ride on their parent carbon atoms. The solvent hydrogen atoms were not located. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares to R = 0.152, R_w = 0.154 [$w^{-1} = \sigma^2(F) + 0.00050F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.84 and -0.43eÅ^{-3}, respectively. The mean and maximum shift / error in the final refinement were 0.046 and 0.281 respectively. The high final value for R is a consequence of the poor crystal quality, disorder in the OTBDPS unit, and the presence of included solvent. The stereochemistry is, however, definitive. Computations were carried out on an Eclipse S140 computer using the SHELXTL[34] program system.

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1436 and 690 cm^{-1}; δ_H (90 MHz) 7.40-7.10 (5H, m, Ph), 5.58 (1H, dt, J 1.5 and 1.0, H-1), 5.42 (1H, d, J 1.5, H-1), 3.08 (2H, m, H_2-3) and 2.70 (2H, m, H_2-4); m/z 244 (M^+), 163 (M^+-Br), 123 ($PhSCH_2$) and 45 (SCH); observed: M^+, 241.9761. $C_{10}H_{11}BrS$ requires M, 241.9765; found: C, 49.32; H, 4.55. $C_{10}H_{11}BrS$ requires C, 49.39; H, 4.56%.

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