Total Synthesis of the Anthelmintic Macrolide Avermectin B1a

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A highly convergent total synthesis of the anthelmintic macrolide avermectin B1a **1** is described. The key features of this synthesis include the introduction of the C(11)–C(15) portion by selective ring opening of a symmetrical 1,4-bis-epoxide **4** followed by reaction with the anion derived from the 3-methyl-2-(1-methylpropyl)-6-phenylsulphonylpyran **3** to afford the 'northern' C(11)–C(25) fragment **39**. Coupling of the derived C(11)–C(25) aldehyde unit **42** with a C(1)–C(10) 'southern' fragment **2** was achieved *via* a novel deconjugative vinyl sulphone anion sequence. Macrolactonisation and subsequent introduction of the 3,4-double bond gave the aglycone portion **51**. The oleandrosyloleandrose disaccharide was introduced by a novel silver-mediated coupling between the 5-acetylated aglycone **70** and the thiocarbonylimidazolide **69**. Final deacetylation was accomplished using Super-Hydride to give the natural product **1**.

The discovery of the avermectins from an actinomycete designated *Streptomyces avermitilis* MA 4680 (NRRL 8165) in 1978[1] heralded a new era in the control of parasitic disease. Since this time, the 22,23-dihydroavermectin, Ivermectin, has been marketed internationally, and many new avermectin and related milbemycin natural products have been discovered which have exemplified a major new class of biologically active molecules.[2]

Not surprisingly, an enormous amount of interest in the synthesis of these compounds has been generated, culminating in the preparation of avermectins A1a,[3] B1a[4,5] and milbemycins β_3,[6] β_1[7] and E.[8] A synthesis of the avermectin B1a aglycone has also been reported recently.[9] Other work has concentrated on the preparation of the northern spiroacetal fragment[10] and the southern hydrobenzofuran portion,[11] while relatively little has been reported concerning the synthesis of the bis-oleandrose carbohydrate unit of the avermectins.[12,13] Along with these studies, important degradation reactions of the natural products and recoupling strategies have been reported.[14] In this paper we describe in full[4] the total synthesis of avermectin B1a, **1**, the central and most active member of the series, harnessing new synthetic methods developed by our group.

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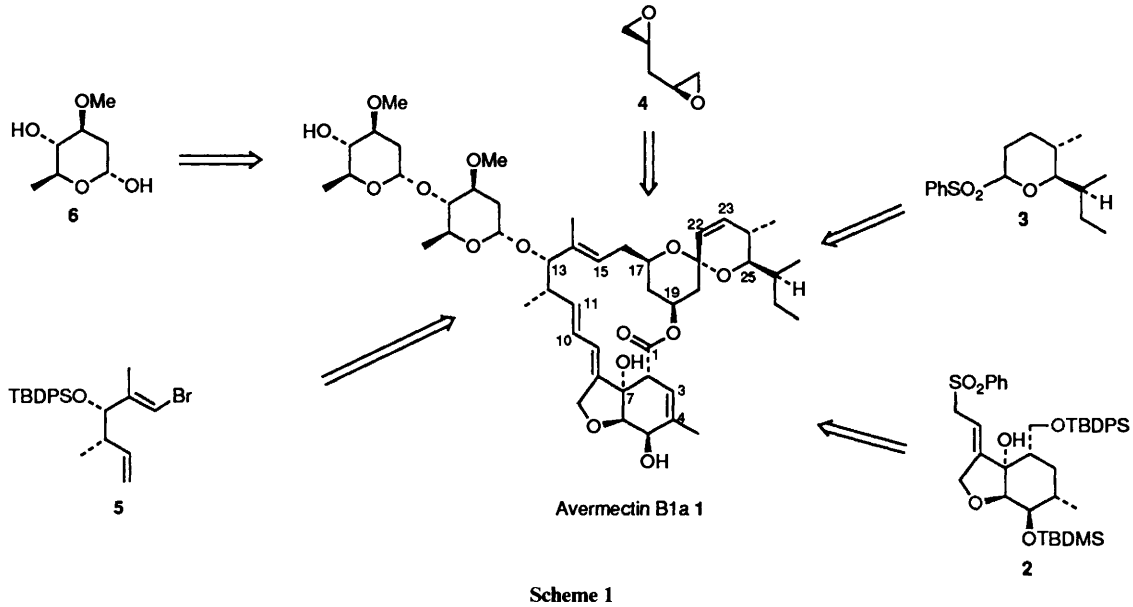
Results and Discussion

Construction of a molecule such as **1**, with its 20 stereogenic centres, 5 specifically substituted olefinic units and array of chemically sensitive functional groups, requires careful synthetic planning. Furthermore, we wished to devise a route which could also be applied to the synthesis of the milbemycins, since these related compounds are of growing biological importance.[15] The highly convergent approach shown in Scheme 1 brings together five key structural elements. The general concepts follow the route that we established during the total synthesis of milbemycin β_1.[7]

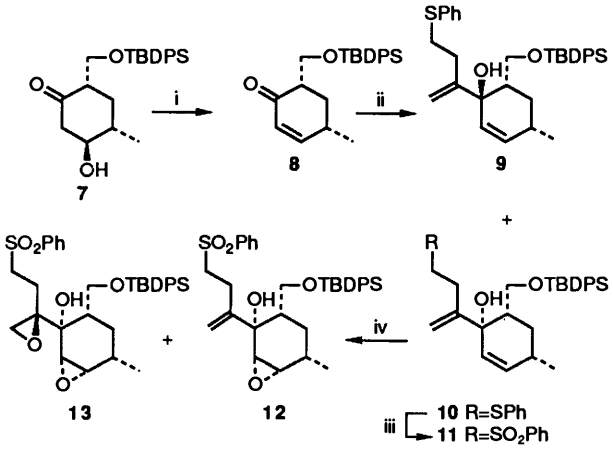
The C(1)–C(10) hydrobenzofuran fragment **2** was designed to act as a nucleophilic coupling partner following deprotonation α to the phenylsulphonyl substituent. Introduction of the 3,4 double bond at a late stage in the synthesis was envisaged in



Scheme 1

order to avoid possible problems, noted by other workers, of migration of this double bond into conjugation with a C(1)-carbonyl group.[16] Use of the 2-phenylsulphonylpyran unit **3** employs new methodology introduced by our group for the preparation of saturated[17] and unsaturated[18] spiroacetals following facile deprotonation and coupling with epoxides. The choice of the bis-epoxide **4** as a double electrophile in this work considerably shortens the synthetic sequence to the northern hemisphere spiroacetal fragments of these molecules since it facilitates introduction of the relevant side chains and contains the C-17 and C-19 stereocentres common to *all* milbemycins and avermectins. Regioselective opening of this bis-epoxide by an organometallic reagent derived from the *E*-alkenyl bromide **5** establishes the required *E*-geometry of the C(14)–C(15) double bond of the natural product and avoids difficulties associated with other sequences.[6a,6b,6d] Finally, the bis-oleandrosyl portion of avermectin B1a **1** was to be derived from appropriate coupling[3,12,13] of oleandrose **6** which, in turn, we believed could be prepared from π-allyltricarbonyliron lactone complexes using methodology developed in our laboratories.[19]

Synthesis of the southern C(1)–C(10) hydrobenzofuran fragment **2** started from the hydroxycyclohexanone **7** which was prepared previously in optically pure form and used during our milbemycin β_1 synthesis.[7] This is consistent with our goal of devising a unified strategy towards several members of this series of natural products. Dehydration of **7** by treatment with methanesulphonyl chloride and triethylamine in dichloromethane gave the enone **8** in essentially quantitative yield. Addition of 2-lithio-4-phenylthiobut-1-ene[7] to **8** at −78 °C gave **9** and **10** in 44 and 50% yields respectively. We were able to solve this problem of poor stereoselectivity during the addition reaction by an alternative approach which is discussed later; however, this route did allow us to determine the stereochemical consequences of this and later reactions. Oxidation of **10** using Oxone gave the sulphone **11**. Various attempts at selective olefin functionalisation of **11** met with no success, but hydroxy group-directed epoxidation using vanadyl acetylacetonate and *tert*-butyl hydroperoxide[20] gave the α-epoxide **12** as the major product (69%), along with 22% of the bis-epoxide **13** (Scheme 2).



Scheme 2 *Reagents and conditions:* i, MsCl, Et_3N, CH_2Cl_2, 0 °C to room temp. (100%); ii, $PhSCH_2CH_2C(CH_2)Li$, THF/Et_2O, −78 °C, 5 min (94%); iii, Oxone, THF/MeOH/pH 4 buffer, room temp., 2 h (89%); iv, $VO(acac)_2$, TBHP, CH_2Cl_2, 0 °C to room temp., 10 h (91%)

Fortunately, a racemic sample of **13** proved crystalline, allowing structure determination by X-ray crystallography (Fig. 1). These data are important in confirming the relative stereochemistry at the C-5 and C-7 positions. Re-exposure of **12** to the same epoxidation conditions slowly afforded **13**, thus confirming the stereochemistry of **12**.

In an alternative approach it was found that the enone

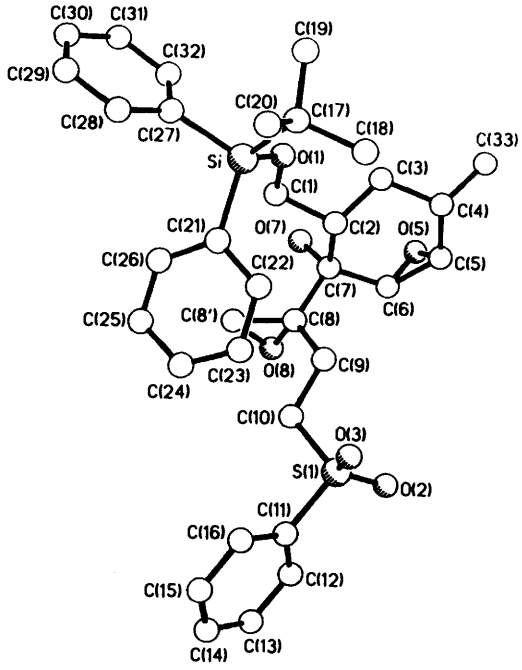
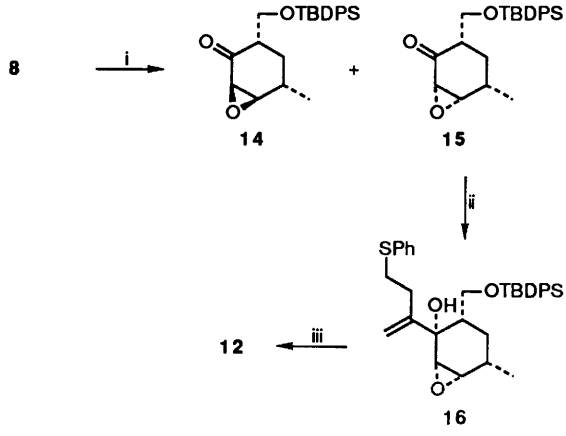


Fig. 1 The X-ray crystal structure of **13**

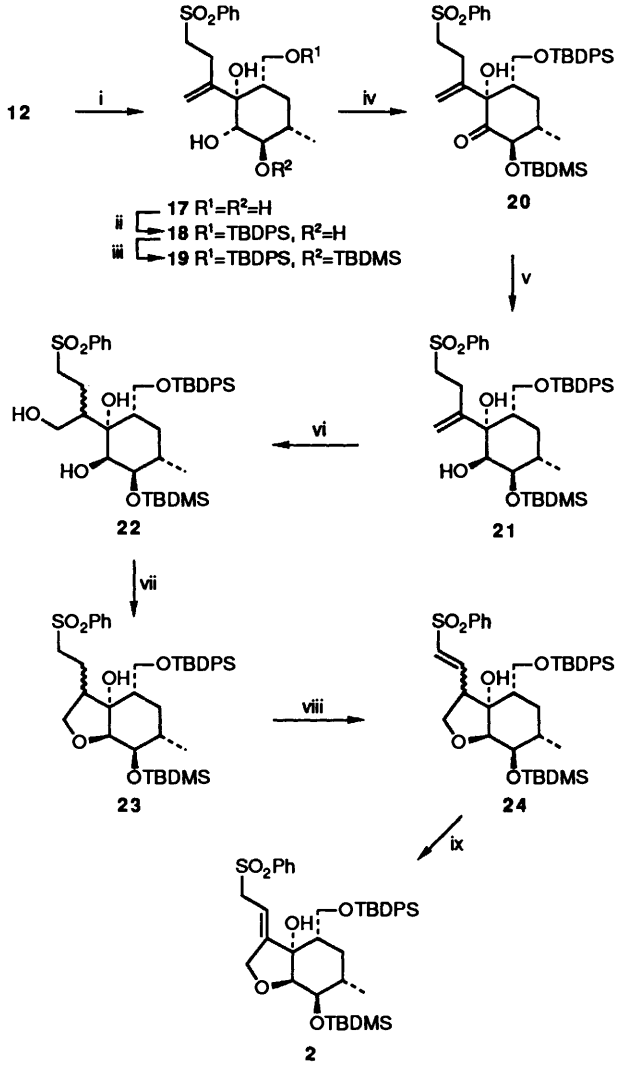
8 underwent stereoselective epoxidation using dimethyldioxirane[21–23] to give a readily separable mixture of β and α epoxides **14** and **15** in 12 and 64% yields, respectively. All other attempts to effect this epoxidation failed owing to the ready β-elimination of *tert*-butyldiphenylsilanol from **8** under basic conditions. The reason for the selectivity observed in this epoxidation reaction is not apparent. Proof of the stereochemical outcome follows from correlation with compound **13**, prepared previously, the structure of which was rigorously determined. Addition of 2-lithio-4-phenylthiobut-1-ene to **15** proceeded well, giving **16** as the only diastereoisomer detected by ^1H NMR. Oxidation of **16** with Oxone gave the same sulphone **12** prepared earlier (Scheme 3). The yield to **12** from **7** using this new sequence was an excellent 54% overall. While several routes to convert **12** into the benzohydrofuran fragment **2** are conceivable only the successful procedure is reported here. Stereoselective ring opening of the epoxide **12** with 15% aqueous sulphuric acid in tetrahydrofuran (THF) at 60 °C gave the tetraol **17**. All attempts to open the epoxide ring without removal of the 1-silyl group failed. Nevertheless, **17** could be regioselectively reprotected with *tert*-butyldiphenylsilyl



Scheme 3 *Reagents and conditions:* i, Me_2CO_2, CH_2Cl_2, room temp., 40 h (75%); ii, $PhSCH_2CH_2C(CH_2)Li$, THF, −78 °C, 10 min (95%); iii, Oxone, THF/MeOH/pH 4 buffer, room temp., 3.5 h (88%)

chloride and imidazole to give **18**. This also underwent highly selective silylation on the 5-hydroxy group (*tert*-butyldimethylsilyl triflate, triethylamine, CH_2Cl_2) to give **19** in excellent yield. In order to invert the C-6 configuration, **19** was oxidised to the ketone **20** using oxalyl chloride/DMSO,[24] followed by stereoselective (6:1) reduction with sodium borohydride to give **21** (58% yield over the two steps). The methylene group in **21** was then subjected to hydroboration using borane–dimethyl sulphide followed by basic hydrogen peroxide to give the alcohols **22** as a 2:1 ratio of C-8 isomers. Whilst separation was possible, and the remaining steps of the synthesis were performed initially on the separate isomers, it was more convenient to perform the reaction on the mixture since both isomers converge in the later steps of the synthesis.

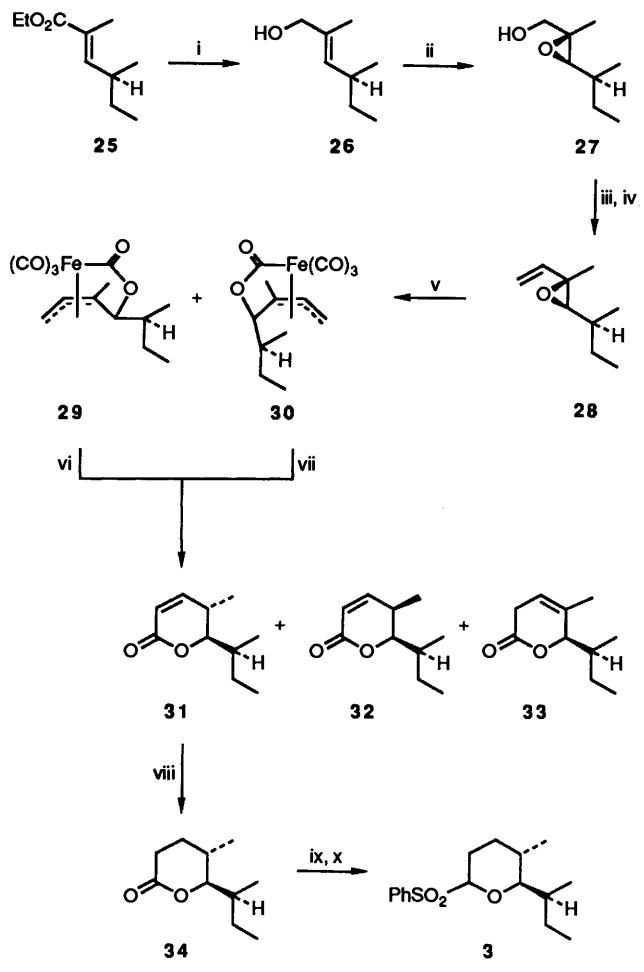
Closure of the alcohols **22** to the furans **23** proceeded in 78% yield simply using toluene-*p*-sulphonyl chloride and pyridine at 60 °C. The major component of the furan mixture was assigned the 8*S* stereochemistry on the basis of nuclear Overhauser difference experiments; in particular, irradiation of 2-H resulted in a 6.3% enhancement of 8-H. The final steps to the required southern zone fragment **2** involved selenenylation of **23** by treatment with 2.2 equiv. of butyllithium in THF at −78 °C, quenching with benzeneselenenyl chloride, followed by oxidation of the selenides with *m*-chloroperbenzoic acid (*m*CPBA) and *syn*-elimination of the resulting selenoxides to afford the vinyl sulphones **24**. This mixture was converted cleanly and stereoselectively into the *E*-allylic sulphone fragment **2** by deconjugation using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at room temperature[25] (Scheme 4). The synthetic compound **2** was identical by ^{1}H NMR, IR, MS, $[\alpha]_D$ and TLC comparisons to a sample obtained by degradation and manipulation of the natural product avermectin B1a.[26]



Scheme 4 *Reagents and conditions*: i, H_2SO_4, THF/H_2O, 60 °C, 12 h (80%); ii, TBDPSCl, imidazole, DMF, room temp., 1 h (91%); iii, TBDMSOTf, Et_3N, CH_2Cl_2, room temp., 15 min (86%); iv, Me_2SO, $(COCl)_2$, THF, −35 °C; Et_3N, −78 °C to room temp. (73%); v, $NaBH_4$, MeOH, room temp. (79%); vi, BH_3·Me_2S, THF, room temp., 64 h; H_2O_2, NaOH (66%); vii, TsCl, pyr., room temp., 16 h; 60 °C, 20 h (78%); viii, Bu^{t}Li, THF, −78 °C, 5 min; PhSeCl, THF, 10 min, −78 °C (65%); *m*CPBA, CH_2Cl_2, room temp., 15 min (100%); ix, DBU, MeCN, room temp., 12 h (77%)

This phase of work completes the preparation of the C-1 to C-10 carbon framework of the target molecule **1**. The next section describes the synthesis of the remaining C-11 to C-25 portion following the general plan outlined in Scheme 1. Construction of the 2-phenylsulphonyltetrahydropyran **3** employed the use of π-allyltricarbonyliron lactone complexes for the preparation of unsaturated lactones following our previously established methods.[27] Reaction of (*S*)-2-methylbutanal[28] with ethoxycarbonylethylidenetriphenylphosphorane in dichloromethane gave **25** which, on reduction with diisobutylaluminium hydride (DIBAL) in toluene, afforded the allylic alcohol **26**. Sharpless epoxidation[29] [titanium(IV) isopropoxide, *tert*-butyl hydroperoxide, and D-(−)-diethyl tartrate] at −23 °C gave the epoxide **27**. In order to prepare the key π-allyltricarbonyliron complexes, **27** was oxidised with oxalyl chloride and DMSO under the Swern conditions and then subjected to a Wittig methylenation to prepare the precursor alkenyl epoxide **28** for complex formation. Treatment of **28** with diiron nonacarbonyl in THF gave a 74% yield of the separable diastereoisomeric iron complexes **29** and **30** in a 1:1 ratio. These π-allytricarbonyliron lactone complexes were individually carbonylated at high pressure to afford δ-lactone products (Scheme 5). Reaction of **29** under 240 atm of carbon monoxide at 140 °C in benzene gave **31**, **32** and **33** in 40, 7 and 57% yields, respectively. The complex **30** underwent carbonylation at lower temperature, 50 °C, to give the same lactones **31**, **32** and **33**, but in more favourable yields (65, 24 and 10%). The combination of these experiments therefore provided the required lactone **31** in 52% yield. Catalytic hydrogenation of **31** gave the saturated lactone **34**. This was readily transformed to the 2-phenylsulphonyltetrahydropyran **3** by reduction to the lactol with DIBAL in toluene followed by treatment with benzenesulphinic acid in CH_2Cl_2 (Scheme 5). This series of experiments completes the preparation of another key fragment proposed in our initial plan towards avermectin B1a.

Preparation of the northern C(11)–C(15) fragment **5** started from the hydroxyvinyl bromide **35**. This, in turn, was obtained from prop-2-yn-1-ol by treatment with trimethylaluminium and bis(cyclopentadienyl)zirconium dichloride followed by a stereospecific quench of the resulting aluminium species with bromine.[30] Oxidation of **35** using tetrapropylammonium perruthenate (TPAP)[31] afforded the unstable aldehyde which was immediately reacted with (+)-(*E*)-crotyldiisopinocampheylborane[32] to give **36** with excellent optical- and stereo-control. Protection using *tert*-butyldiphenylsilyl chloride at 50 °C in DMF gave **5**. Metal exchange of the bromide in **5** was achieved by treatment with *tert*-butyllithium at −78 °C followed by addition of trimethylaluminium and warming to 0 °C to give an intermediate alanate species. This was treated with the bis-epoxide (+)-(2*R*,2′*R*)-methylenebis(oxirane) **4** at −30 °C to give an epoxy alcohol which was stabilised by protection as its *tert*-butyldimethylsilyl ether **37** using *tert*-butyldimethylsilyl chloride in the presence of triethylamine and 4-*N*,*N*-dimethylaminopyridine (DMAP) (Scheme 6). The preparation of the bis-epoxide **4** was reported earlier during studies on the synthesis of

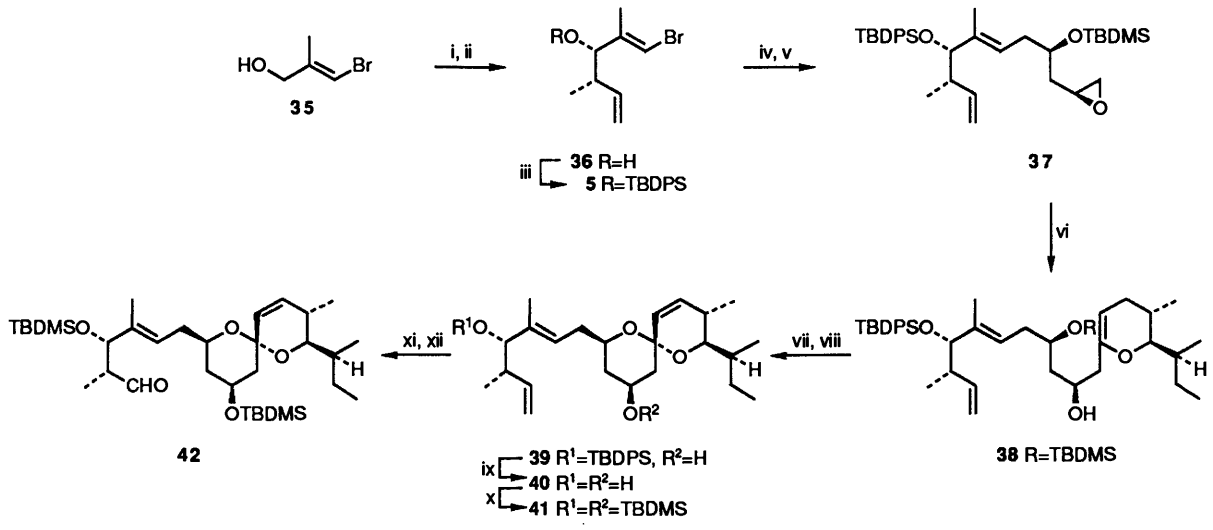


Scheme 5 *Reagents and conditions:* i, DIBAL, PhMe, −78 °C (91%); ii, $Ti(OPr^i)_4$, D-(−)-DET, CH_2Cl_2, TBHP, −20 °C, 16 h (81%); iii, Me_2SO, $(COCl)_2$, CH_2Cl_2, −78 °C, 30 min; Et_3N, −78 °C to room temp. (80%); iv, $Ph_3P{=}CH_2$, THF, −20 °C to room temp. (85%); v, $Fe_2(CO)_9$, THF, 1 h (99%); vi, CO (240 atm), PhH, 50 °C, 3 days (100%); vii, CO (240 atm), PhH, 140 °C, 42 h (99%); viii, H_2, PtO_2, EtOAc, 15 h (100%); ix, as for i (93%); x, $PhSO_2H$, CSA, CH_2Cl_2, 0 °C, 4 h (71%)

milbemycin β_1.[7] Deprotonation of the sulphone **3**, prepared earlier, with butyllithium at −78 °C in THF followed by reaction with the protected epoxide **37** in the presence of boron trifluoride-diethyl ether gave the sensitive enol ether **38**. This process follows methodology we developed previously for the preparation of spiroacetals through intermediate enol ethers.[17,33] Compound **38** was immediately subjected to reaction with benzeneselenenyl chloride in methanol[34] to afford the saturated spiroacetal C-22 phenyl selenides in 66% yield after deprotection and spirocyclisation using camphorsulphonic acid in dichloromethane. Oxidation with *p*-nitrophenyl-*N*-sulphonyloxaziridine (Davis oxaziridine)[35] rapidly afforded the selenoxides which underwent *syn*-elimination in $CHCl_3$ at 50 °C to give the unsaturated spiroacetal **39** (77%). Attempts to prepare **39** by coupling of an unsaturated 2-phenylsulphonyl-hydropyran derived from the lactone **31** were not successful. In order to link with material derived from degradation of the natural product avermectin B1a, **39** was treated with tetrabutylammonium fluoride (TBAF) to give the diol **40** which was reprotected as the bis-*tert*-butyldimethylsilyl ether **41** in the usual manner. Finally, **41** was converted into the northern hemisphere C(11)–C(25) coupling fragment **42** by selective oxidative cleavage of the terminal vinyl substituent by glycolation with catalytic OsO_4[36] followed by periodate cleavage (Scheme 6). This compound **42** was identical by IR, ^1H NMR and $[\alpha]_D$ comparisons to an authentic sample which was derived from degradation of the natural product.

We were now in a position to investigate coupling of the C(1)–C(10) and C(11)–C(25) units, and the subsequent elaboration to avermectin B1a **1**. Reaction of **2** with 2.2 equiv. of *tert*-butyllithium at −78 °C afforded the corresponding dianion which reacted with the northern fragment **42** to give the hydroxy sulphones **43** in excellent yield (74%), as a mixture of diastereoisomers. Reductive elimination of **43** using 6% sodium amalgam in THF–MeOH at −30 °C gave the diene **44** in 34% yield, as a *ca.* 7:1 *E*:*Z* mixture at the newly formed C(10)–C(11) double bond.[37] The low yield in this reaction is due to competitive formation of the reduced product where the phenylsulphonyl group is removed without elimination of the 11-functionality occurring. The next step of the synthesis involved complete removal of all the protecting groups in **44** by reaction with TBAF to afford the pentaol **45** (94%). This is a bold move during the synthesis of such a polyoxygenated natural product, but we believed that we could exploit the reactivity difference of the various hydroxy groups in the molecule and thus avoid the need for further protection. This turned out to be the case and we were able to progress a further nine steps to the aglycone of avermectin B1a. Selective oxidation of the primary 1-hydroxy group using the Oshima system[38] afforded the aldehyde, which was further oxidised to the acid **46** using sodium chlorite.[39] No epimerisation or oxidation of other groups was observed. The seco-acid **46** was subjected to macrolactonisation using the Mukaiyama method[40] (2-chloro-1-methylpyridinium iodide and triethylamine in acetonitrile at reflux) to afford selectively the 16-membered ring macrolide **47** (Scheme 7). It was now necessary to achieve selective oxidation of the secondary 5-hydroxy group in the presence of the allylic alcohol at C-13. The preferred conformation of the macrolide is known to prevent overlap of the C(14)–C(15) π-system with the C(13)–O bond. The 13-hydroxy group therefore lacks the extra reactivity usually associated with allylic alcohols.[41] The oxidation was attempted using the TPAP reagent, since this is known to be sensitive, in part, to steric constraints. Pleasingly, at 0 °C in CH_2Cl_2, selective oxidation of **47** to the ketone **48** was achieved in 60% yield. The carbonyl group at C-5 now gave access to the C-4 position for introduction of the important C(3)–C(4) double bond. Thus, reaction of **48** with an excess of trimethylsilyl triflate afforded the silyl enol ether which, after quenching with benzeneselenenyl chloride, gave the α and β selenides **49** and **50** in a 1:1 ratio. The structure of the α-selenide **49** was proved by X-ray crystallography (Fig. 2). After removal of the trimethylsilyl ethers from **49** with HF–pyridine, oxidation with Davis oxaziridine gave the selenoxides, which rapidly underwent *syn*-elimination. In order to avoid possible aromatisation, the products were immediately reduced with sodium borohydride in the presence of cerium(III) chloride[42] to give avermectin B1a aglycone **51** as the major product together with some (23%) of the *exo*-methylene product **52** (Scheme 7). The synthetic aglycone **51** was identical (^1H NMR, IR, MS and $[\alpha]_D$) with an authentic sample derived by removal of the oleandrosyl-oleandrose residue from avermectin B1a.

After a number of experiments, the route to the aglycone utilising the α-selenide with free hydroxy groups at C-7 and C-13 was found to be optimum. If oxidation and *syn*-elimination were performed prior to removal of the trimethylsilyl ethers, the α-selenide gave a 1:3 *endo*:*exo* mixture. The β-selenide, with or without the trimethylsilyl ethers, gave a 1:5 *endo*:*exo* mixture. The use of different oxidants failed to alter the tendency for *exo*-elimination to prevail. Neither enantiomer of camphorsulphonyl oxaziridine gave any improvement in the *endo*:*exo* ratio, and oxidations with these reagents were slow, allowing side-reactions to occur. Attempts at hydroxy-directed oxidation with *m*-chloroperbenzoic acid, over a range of temperatures



Scheme 6 *Reagents and conditions:* i, TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, room temp., 4 h (94%); ii, (+)-$IPC_2BCH_2CHCHMe$, BF_3·OEt_2, THF, −78 °C, 12 h (75%); iii, TBDPSCl, imidazole, DMAP, DMF, 50 °C, 4 days (92%); iv, Bu^{t}Li, Et_2O, −78 °C, 30 min; Me_3Al, −78 to 0 °C; **4**, −30 to 0 °C, 2 h (82%); v, TBDMSCl, DMAP, Et_3N, DMF, room temp., 15 h (94%); vi, **3**, BuLi, THF, −78 °C, 2 min; BF_3·OEt_2, −78 °C, 2 h (45%); vii, PhSeCl, THF, room temp., 3 min; MeOH, Et_3N, 0 °C, 30 min; CSA, MeOH, room temp., 3 h (66%); viii, Davis oxaziridine, $CHCl_3$, 10 min; Et_3N, 50 °C, 3 h (76%); ix, TBAF, THF, reflux, 5 min (98%); x, TBDMSCl, imidazole, DMF, room temp., 16 h (95%); xi, OsO_4, NMO, Bu^{t}OH/THF/H_2O, room temp., 100 h (77%); xii, $NaIO_4$, KH_2PO_4, MeOH/H_2O, room temp., 3 h (86%)

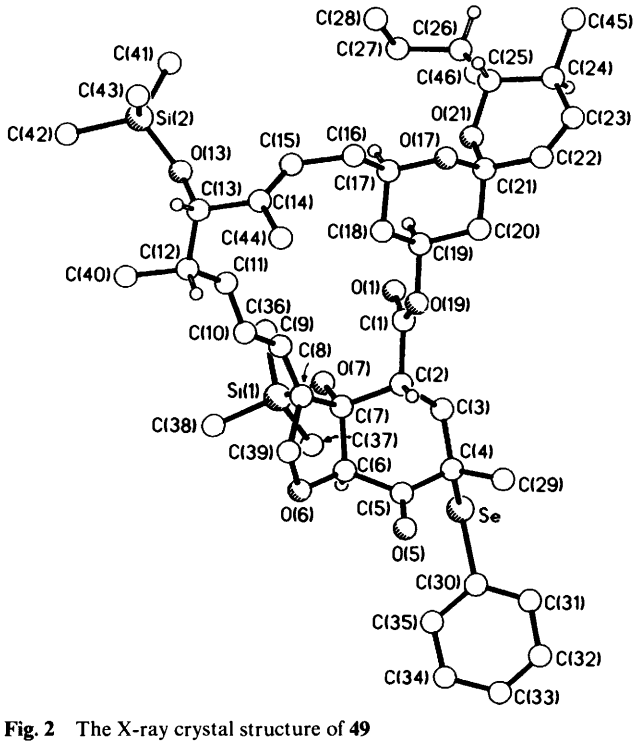
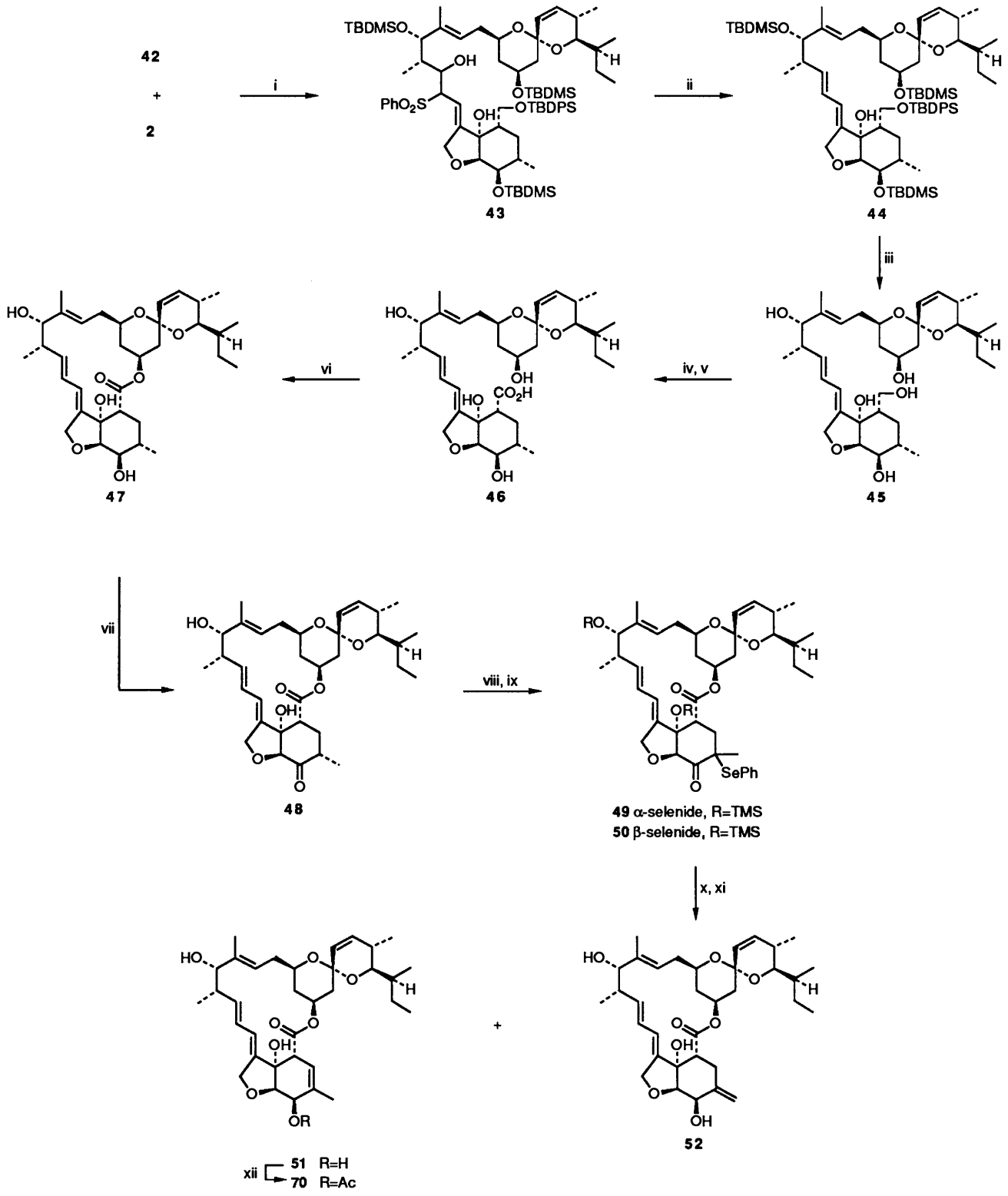


Fig. 2 The X-ray crystal structure of **49**

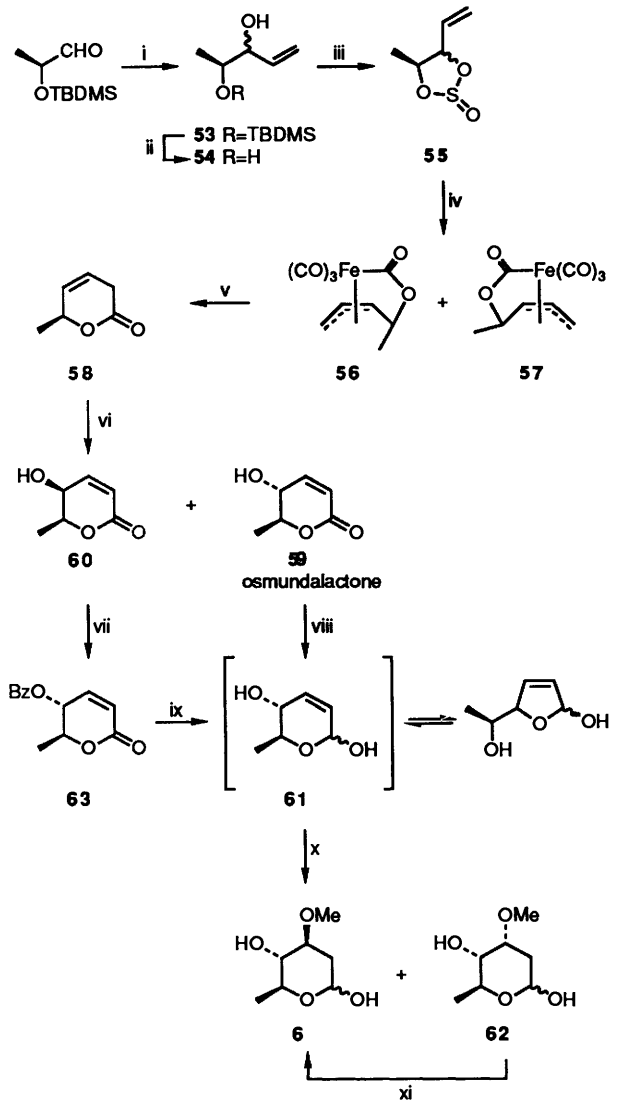
(−60 °C to room temperature), were also unsuccessful. These experiments never gave better than a 1:1 ratio. Further studies on the introduction of the 3,4-double bond are underway at present. With the preparation of the aglycone in hand we required a synthesis of the disaccharide unit and a new method to effect its coupling to complete the total synthesis of avermectin B1a **1**. For this work the preparation of the monosaccharide oleandrose **6** became the first goal. Since this system contains a pyran ring there is an opportunity once again to employ the use of π-allyltricarbonyliron lactone complexes for its synthesis. To this end, vinyl magnesium bromide was treated with (*S*)-2-hydroxypropanal-*tert*-butyldimethylsilyl ether[43] to give **53** as a 5:1 mixture of diastereoisomers. These were deprotected with toluene-*p*-sulphonic acid in methanol to give **54**, which was converted into the cyclic sulphites **55** in essentially quantitative yield using thionyl chloride. Reaction of **55**[44] with diiron nonacarbonyl in benzene under ultrasonic conditions[45] gave a 65% yield of the diastereoisomeric iron complexes **56** and **57** in an approximately 3:2 ratio. These were carbonylated at 230 atm of carbon monoxide at 70 °C in benzene, in the presence of acrolein to act as a carbonyliron scavenger. This was essential in order to minimise migration of the double bond into conjugation. In the best experiment, a 98% yield of the β,γ-unsaturated lactone **58** was realised. However, 50% yields were more typically obtained, due partly to the volatility of the product. In the next step, **58** was epoxidised using dimethyldioxirane at 0 °C. The unstable intermediate epoxides were not isolated, but were treated with 2% triethylamine in pyridine to give the ring-opened allylic alcohols **59** and **60** in 26 and 49% yields respectively (Scheme 8). These products were also unstable and required separation on a silica gel column doped with pyridine. The compound **59** is a natural product, osmundalactone, which has been synthesised previously.[46] Both the alcohols **59** and **60** may be further elaborated to oleandrose **6**, but for **60** an additional step is required in order to invert the hydroxy group configuration. Reduction of **59** with DIBAL, using THF as solvent owing to the insolubility of **59** in toluene, gave an unstable intermediate, presumably **61**. This was isolated by quenching of the excess of DIBAL with methanol and filtration through a pad of silica. After evaporation, the crude product was immediately treated with DBU in methanol at room temperature. Overnight equilibration afforded a mixture of oleandrose **6** and cymarose **62**[47,48] in 40 and 15% yields, respectively, from **59**. These carbohydrate derivatives were readily separated on Florisil. These products, clearly the result of ring opening of the lactol, conjugate addition of methanol and reclosure, were formed as an 70:30 equilibrium mixture. Re-equilibration of cymarose **62** in a separate experiment with DBU–MeOH gave a further 60% isolated yield of oleandrose **6**. The other hydroxy lactone isomer **60** reacted under the Mitsunobu conditions[49] with benzoic acid, triphenylphosphine and diethyl azodicarboxylate to give the inverted benzoate **63** in 97% yield. This, on similar treatment with DIBAL in toluene, gave the same intermediate **61**, which, upon reaction with DBU in methanol, afforded **6** and **62** in 47 and 19% yields from the benzoate **63** (Scheme 8). As we have to use this convergent route to oleandrose **6** it is more appropriate



Scheme 7 *Reagents and conditions:* i, Bu^{t}Li, −78 °C, 10 min; **42**, 1 h (74%); ii, Na/Hg, Na_2HPO_4, THF/MeOH, −40 °C, 2 h (34%); iii, TBAF, THF, heat under reflux, 36 h (93%); iv, $(Ph_3P)_3RuCl_2$, PhH, CH_2Cl_2, room temp., 48 h; v, $NaClO_2$, Bu^{t}OH/H_2O, Me_2CCHMe, room temp., 1 h (32%); vi, 2-Cl-1-$MeC_5H_3N^+I^-$, MeCN, heat under reflux, Et_3N (47%); vii, TPAP, NMO, 4 Å molecular sieves, room temp., 1 h (61%); viii, TMSOTf, Et_3N, 0 °C, CH_2Cl_2, 4 h (88%); ix, PhSeCl, CH_2Cl_2, −78 °C, 2 h (91%); x, HF, pyr., room temp., 36 h (87%); xi, Davis oxaziridine, $CHCl_3$, room temp., 30 min; $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 15 min (92%); xii, AcCl, pyr, DMAP, room temp., 90 min (97%)

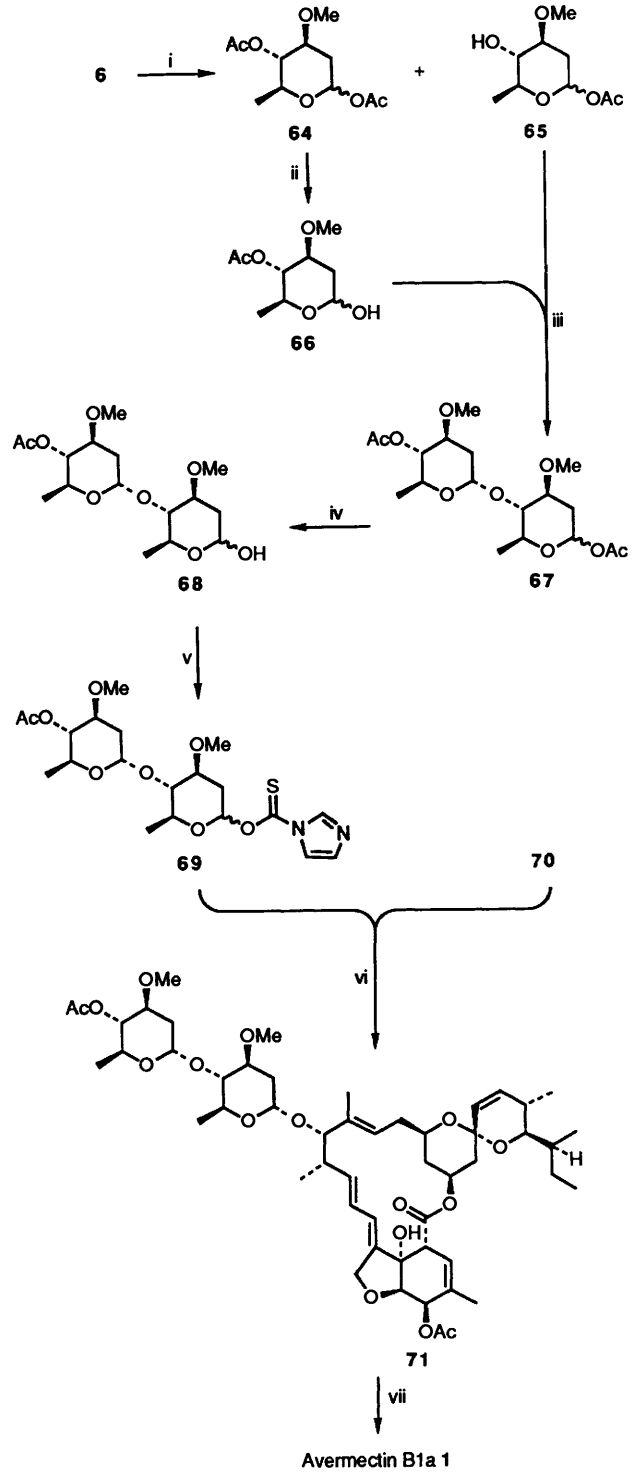
to describe the combined yield from the lactone **58** to **6** as 40% following one recycle of the cymarose. Syntheses of oleandrose have been described previously,[3,12,13,48,50] but the new route reported here demonstrates further applications of the tricarbonyliron lactone complexes, and additionally allows the preparation of other natural products.

With supplies of **6** now available we were in a position to study its dimerisation to a disaccharide derivative using a new glycosidation sequence we have developed[51] and examine a similar coupling strategy for attachment to the aglycone. We preferred to use our new glycosidation procedures rather than simply adopt existing sequences.[3,5,12,13,52] Indeed, we believe



Scheme 8 *Reagents and conditions:* i, $CH_2CHMgBr$, THF, −60 °C to room temp., 4 h (74%); ii, TsOH, MeOH, room temp., 15 h (91%); iii, $SOCl_2$, CCl_4, reflux, 30 min (100%); iv, $Fe_2(CO)_9$, PhH, ultrasonication, 17 h (65%); v, CO (230 atm), PhH, acrolein, 70 °C, 18 h (92%); vi, Me_2CO_2, Et_2O, Me_2CO, 0 °C to room temp. (75%); vii, DEAD, Ph_3P, $PhCO_2H$, THF, room temp., 4 h (92%); viii, DIBAL, THF, −78 °C, 90 min; ix, DIBAL, PhMe, −78 °C, 6 h; x, DBU, MeOH, room temp., 15 h (55% from **59**, 66% from **63**); xi, DBU, MeOH, room temp., 15 h (60%)

our new route does have practical advantages and has proved to be both efficient and reliable. We found that oleandrose **6** reacts with acetic acid activated by carbonyldiimidazole in CH_2Cl_2 to give a readily separable 1:1 mixture of the diacetate **64** and the C(1) monoacetate **65** in 93% combined yield. Treatment of the diacetate **64** with 2.5 equiv. of Super-Hydride ($LiBEt_3H$) at −78 °C gave a 95% yield of the other (C-4) monoacetate **66** suitable for coupling to **65**. Accordingly **66**, *via* its imidazolylcarbonyl glycoside and activated by addition of silver perchlorate, was coupled with **65** at 40 °C in diethyl ether to give the disaccharide diacetate **67** in 62% yield after separation of a small amount (11%) of the C-1′ β-anomer. Once again the selective Super-Hydride deprotection of **67** to give **68** worked extremely well. In contrast to the previous coupling, compound **68** was converted into the imidazolyl-thiocarbonyl glycoside **69** by treatment with thiocarbonylidiimidazole in THF. This was an important modification to our glycosidation procedure which provided a suitable fragment for coupling to the B1a aglycone C-5 monoacetate **70**. Compound **70** was



Scheme 9 *Reagents and conditions:* i, CDI, AcOH, CH_2Cl_2, room temp., 26 h (93%); ii, $LiBHEt_3$, THF, −78 °C, 2 h (95%); iii, **66**, CDI, CH_2Cl_2, room temp., 1 h; **65**, THF, $AgClO_4$, 50 °C, 45 min (62%); iv, $LiBHEt_3$, THF, −78 °C, 2 h (98%); v, $(Imid)_2C{=}S$, THF, room temp., 44 h (57%); vi, **70**, $CaCO_3$, $AgClO_4$, THF, room temp., 10 min (64%); vii, $LiBHEt_3$, THF, −78 °C, 2 h (90%)

obtained in 97% yield by selective monoacetylation of the aglycone **51** using acetyl chloride and pyridine. Pleasingly, coupling of freshly prepared **69** with **70**, in the presence of silver perchlorate and $CaCO_3$ in THF–toluene at 20 °C, proceeded in 64% yield. The contaminating β-anomer, which is always produced in these coupling reactions with avermectin B1a aglycones, was easily removed by silica gel chromatography. Finally, removal of the two acetate groups from C-5 and C-4″

was effected by treatment with an excess of Super-Hydride at −78 °C to give the macrolide anthelmintic agent avermectin B1a **1** (Scheme 9), identical in all respects with the natural product (^{1}H NMR, ^{13}C NMR, HPLC, IR, MS, microanalysis and $[\alpha]_D$).

In conclusion, we have described a novel route to avermectin B1a. The general strategy is also applicable to the synthesis of the related milbemycin structures and potentially useful for novel analogue preparation. Furthermore, we have been able to show applications of new synthetic methods developed in these laboratories towards a challenging and important synthetic problem.

Experimental

General.—^{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 NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 983G spectrometer. *J* Values are in Hz. 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. M.p.s 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, 50 KHz ultrasonic cleaning bath. Molecular modelling was performed using the MACROMODEL package,[53] 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 (referred to throughout as ether) and tetrahydrofuran were distilled from sodium–benzophenone ketyl; dichloromethane (DCM) from phosphorus pentoxide; toluene from sodium; acetonitrile from calcium hydride; and dimethyl sulphoxide from calcium hydride. Petroleum refers to light petroleum 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 $60F_{254}$) and visualised by UV light, acidic ammonium molybdate(IV) or iodine as appropriate.

Crystal Data for [1S,2R(R),3S,5S,6S]-3-[(tert-*Butyldiphenylsilyloxy)methyl*]-5-*methyl*-2-{2-[2-(*phenylsulphonyl)ethyl*]-*oxiran*-2-*yl*}-7-*oxabicyclo*[4.1.0]*heptan*-2-*ol* **13**.—Single crystals of **13**, suitable for X-ray crystallography, were grown at room temperature from diethyl ether and had a m.p. of 150–151 °C. $C_{34}H_{42}O_6SSi$, M = 606.9, triclinic, a = 8.377(2), b = 14.143(3), c = 14.373(3) Å, α = 97.37(2), β = 102.89(2), γ = 100.17(2)°, U = 1609 Å^3, space group $P\bar{1}$, Z = 2, D_c = 1.25 g cm^{-3}, Cu radiation, λ = 1.541 78 Å, μ(Cu-Kα) = 16 cm^{-1}, F(000) = 648. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. 4347 Independent reflections were measured ($2\theta \leqslant 116°$), of which 4217 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 cyclopropyl and hydroxy protons on C(5), C(6), C(8′) and O(7) were located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C–H = 0.96 Å, 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. Refinement was by block-cascade, full-matrix least-squares to R = 0.066, R_w = 0.086 [$w^{-1} = \sigma^2(F) + 0.000\,75F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 1.28 and −0.32 eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.009 and 0.045 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL[54] program system.

Crystal Data for (4S)-5-*Dehydroxy*-3,4-*dihydro*-5-*oxo*-4-(*phenylselenenyl*)-7,13-*di*-O-(*trimethylsilyl*)*avermectin B1a Aglycone* **49**.—Single crystals of **49**, suitable for X-ray crystallography, were grown at room temperature from diethyl ether and had a m.p. of 186–190 °C. $C_{46}H_{68}O_8SeSi_2$, M = 884.2, orthorhombic, a = 9.885(1), b = 21.300(3), c = 23.574(4) Å, U = 4964 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.18 g cm^{-3}, Cu radiation, λ = 1.541 78 Å, μ(Cu-Kα) = 19 cm^{-1}, F(000) = 1880. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. 3775 Independent reflections were measured ($2\theta \leqslant 116°$), of which 3231 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 = 0.96 Å, 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 = 0.054, R_w = 0.059 [$w^{-1} = \sigma^2(F) + 0.002\,14F^2$], residual electron density in difference map within 0.56 and −0.24 eÅ^{-3}. The mean and maximum shift/error in the final refinement were 0.028 and 0.340 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL[54] program system.

(4S,6S)-6-[(tert-*Butyldiphenylsilyloxy)methyl*]-4-*methylcyclohex*-2-*enone* **8**.—Methanesulphonyl chloride (3.9 ml, 50.4 mmol) was added to a solution of the hydroxy ketone **7** (10.5 g, 26.5 mmol) and triethylamine (33 ml, 240 mmol) in CH_2Cl_2 (300 ml), at 0 °C under argon. The reaction was allowed to come to room temperature. After 30 min, the mixture was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the *enone* **8** (10.0 g, 100%) as a clear oil, $[\alpha]_D^{20}$ −13.5 (*c* 1.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3069, 3047, 3025, 2957, 2930, 1675, 1217, 1113, 1081 and 703; δ_H(500 MHz) 7.75–7.69 (4 H, m, Ph), 7.46–7.39 (6 H, m, Ph), 6.77 (1 H, dd, *J* 10.0 and 1.7, 5-H), 5.97 (1 H, dd, *J* 10.0 and 2.8, 6-H), 4.06 (1 H, dd, *J* 10.3 and 3.9, CHOSi), 3.95 (1 H, dd, *J* 10.3 and 6.8, CHOSi), 2.63 (1 H, m, 4-H), 2.51 (1 H, m, 2-H), 2.36 (1 H, m, 3-H), 1.62 (1 H, q, *J* 11.3, 3-H), 1.20 (3 H, d, *J* 7.2, Me) and 1.09 (9 H, s, Bu^t); δ_C(125.8 MHz) 199.1 (s), 155.7 (d), 135.5 (d), 135.4 (d), 133.5 (s), 133.3 (s), 129.5 (d), 128.7 (d), 127.5 (d), 62.6 (t), 48.3 (d), 34.5 (t), 31.6 (d), 26.7 (q), 21.0 (q) and 19.1 (s); *m/z* 363 (M^+ − Me), 321 (M^+ − Bu^t) and 199 (Ph_2SiOH) (Found: C, 76.3; H, 8.25. $C_{24}H_{30}O_2Si$ requires C, 76.13; H, 7.99%).

(1R,4S,6S)-6-[(tert-*Butyldiphenylsilyloxy)methyl*]-4-*methyl*-1-[1-*methylene*-3-(*phenylthio)propyl*]*cyclohex*-2-*enol* **9** *and* (1S,4S,6S)-6-[(tert-*Butyldiphenylsilyloxy)methyl*]-4-*methyl*-1-[1-*methylene*-3-(*phenylthio)propyl*]*cyclohex*-2-*enol* **10**.—*tert*-Butyllithium (1.7 mol dm^{-3} solution in pentanes; 16 ml, 27.2

Table 1 Atom co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses for compound **13**

Atom	*x*	*y*	*z*
Si	3 903(1)	6 245(1)	2 521(1)
O(1)	2 918(3)	7 084(1)	2 843(1)
C(1)	1 550(4)	7 367(2)	2 231(2)
C(2)	2 036(3)	8 453(2)	2 200(2)
C(3)	2 360(4)	9 055(2)	3 202(2)
C(4)	3 207(4)	10 104(2)	3 242(2)
C(5)	2 332(4)	10 517(2)	2 428(2)
O(5)	575(3)	10 437(1)	2 335(2)
C(6)	1 131(4)	9 904(2)	1 587(2)
C(7)	723(3)	8 795(2)	1 469(2)
O(7)	−861(2)	8 465(1)	1 654(1)
C(8)	680(3)	8 377(2)	409(2)
O(8)	−895(2)	8 377(2)	−253(1)
C(8′)	−481(4)	7 467(2)	−57(2)
C(9)	2 233(3)	8 745(2)	70(2)
C(10)	1 944(3)	8 432(2)	−1 020(2)
S(1)	3 509(1)	9 120(1)	−1 472(1)
O(2)	3 345(3)	10 121(1)	−1 400(2)
O(3)	5 094(3)	8 927(2)	−1 049(2)
C(11)	2 937(4)	8 569(2)	−2 718(2)
C(12)	2 052(4)	9 010(3)	−3 392(2)
C(13)	1 622(4)	8 571(3)	−4 367(2)
C(14)	2 091(5)	7 717(3)	−4 646(3)
C(15)	2 979(6)	7 273(3)	−3 969(3)
C(16)	3 411(4)	7 707(3)	−2 990(3)
C(17)	6 065(4)	6 611(2)	3 382(2)
C(18)	6 854(6)	7 693(3)	3 394(3)
C(19)	5 849(5)	6 527(3)	4 399(2)
C(20)	7 209(5)	5 962(4)	3 107(4)
C(21)	3 831(4)	6 143(2)	1 200(2)
C(22)	4 893(4)	6 805(3)	841(2)
C(23)	4 723(5)	6 753(3)	−167(3)
C(24)	3 500(6)	6 048(3)	−796(3)
C(25)	2 407(6)	5 402(3)	−471(3)
C(26)	2 586(5)	5 453(3)	522(2)
C(27)	2 778(3)	5 060(2)	2 728(2)
C(28)	3 106(4)	4 164(2)	2 387(3)
C(29)	2 302(5)	3 302(2)	2 607(3)
C(30)	1 146(5)	3 306(3)	3 117(3)
C(31)	766(6)	4 181(3)	3 451(3)
C(32)	1 585(4)	5 046(2)	3 250(3)
C(33)	3 317(6)	10 745(3)	4 205(3)

mmol) was added dropwise to a stirred solution of 2-bromo-4-phenylthiobut-1-ene (6.47 g, 26.6 mmol) in ether–THF (1:1; 100 ml), at −78 °C under argon. After 5 min, the enone **8** (5.03 g, 13.3 mmol) in ether–THF (1:1; 100 ml) was added by cannula. After a further 5 min, saturated aqueous sodium hydrogen carbonate was added and the mixture allowed to come to room temperature. Water was added and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (10% ether–petroleum) afforded the *sulphides* **9** (3.19 g, 44%) and **10** (3.64 g, 50%), as clear oils. Less-polar **9**, $[\alpha]_D^{20}$ +20.9 (*c* 2.6 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3506, 2954, 2927, 1585, 1427, 1113, 1046, 739 and 702; δ_H(500 MHz) 7.72–7.68 (4 H, m, Ph), 7.48–7.15 (11 H, m, Ph), 5.63 (1 H, d, *J* 9.9, 6-H or 5-H), 5.43 (1 H, dd, *J* 10.0 and 2.5, 5-H or 6-H), 5.16 (1 H, s, C=CH), 5.07 (1 H, s, C=CH), 4.38 (1 H, s, OH), 3.59 (1 H, t, *J* 10.5, CHOSi), 3.49 (1 H, dd, *J* 10.5 and 4.5, CHOSi), 3.26 (1 H, ddd, *J* 12.5, 10.8 and 5.0, PhSCH), 3.04 (1 H, ddd, *J* 12.5, 10.5 and 5.7, PhSCH), 2.78 (1 H, ddd, *J* 14.9, 10.9 and 4.9, $PhSCH_2CH$), 2.50 (1 H, m, $PhSCH_2CH$), 2.30 (1 H, m, 4-H), 2.23 (1 H, m, 2-H), 1.34 (1 H, m, 3-H), 1.09 (9 H, s, Bu^t), 0.94 (3 H, d, *J* 7.1, Me) and 0.87 (1 H, q, *J* 13.4, 5-H); δ_C(125.8 MHz) 149.9, 135.6, 135.5, 132.7, 132.5, 131.7, 129.9, 129.9, 128.8, 127.8, 125.6, 115.1, 78.3, 67.1, 47.2, 33.7, 33.0, 30.7, 29.9, 26.9, 21.3 and 18.9; *m/z* 542 (M^+), 524 ($M^+ - H_2O$), 485 (M^+ − Bu^t), 467 (M^+ − Bu^t − H_2O), 375 (M^+ − Bu^t − PhSH), 357 (M^+ − Bu^t − H_2O − PhSH) and 199 (Ph_2SiOH) (Found: C, 75.45; H, 7.9. $C_{34}H_{42}O_2SSi$ requires C, 75.23; H, 7.80%).

More polar **10**, $[\alpha]_D^{20}$ −53.4 (*c* 3.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3469, 2930, 1584, 1427, 1113, 1059, 822, 739 and 702; δ_H(500 MHz) 7.66 (4 H, d, *J* 7.0, Ph), 7.46–7.14 (11 H, m, Ph), 5.70 (1 H, d, *J* 9.8, 6-H or 5-H), 5.50 (1 H, s, C=CH), 5.45 (1 H, dd, *J* 9.8 and 2.5, 5-H or 6-H), 5.06 (1 H, s, C=CH), 3.88 (1 H, dd, *J* 10.4 and 4.1, CHOSi), 3.67 (1 H, s, OH), 3.63 (1 H, dd, *J* 10.4 and 2.4, CHOSi), 3.04–2.99 (2 H, m, $PhSCH_2$), 2.23–2.18 (3 H, m, 4-H, $PhSCH_2CH_2$), 1.77–1.63 (3 H, m, H_2-3, 2-H), 1.08 (3 H, d, *J* 7.3, Me) and 1.07 (9 H, s, Bu^t); *m/z* 542 (M^+), 524 ($M^+ - H_2O$), 485 (M^+ − Bu^t), 467 (M^+ − Bu^t − H_2O), 375 (M^+ − Bu^t − PhSH), 357 (M^+ − Bu^t − H_2O − PhSH) and 199 (Ph_2SiOH) (Found: C, 75.1; H, 7.8. $C_{34}H_{42}O_2SSi$ requires C, 75.23; H, 7.80%).

(1S,4S,6S)-6-[(tert-*Butyldiphenylsilyloxy*)*methyl*]-4-*methyl*-1-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]*cyclohex*-2-*enol* **11**.—Oxone (3.70 g, 12.0 mmol $KHSO_5$) was added to a solution of the sulphide **10** (1.65 g, 3.04 mmol) in THF–MeOH–pH 4 aqueous buffer (1:1:1; 90 ml). After 2 h the mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the *sulphone* **11** (1.56 g, 89%), as a colourless oil, $[\alpha]_D^{20}$ −39.3 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3493, 2954, 2929, 1446, 1427, 1389, 1308, 1151, 1112, 1087 and 704; δ_H(500 MHz) 7.89–7.87 (2 H, m, Ph), 7.65–7.37 (13 H, m, Ph), 5.66 (1 H, dd, *J* 9.8 and 1.5, 6-H or 5-H), 5.40 (1 H, s, C=CH), 5.33 (1 H, dd, *J* 9.8 and 2.6, 5-H or 6-H), 4.87 (1 H, s, C=CH), 3.79 (1 H, dd, *J* 10.4 and 3.9, CHOSi), 3.74 (1 H, br s, OH), 3.57 (1 H, dd, *J* 10.5 and 2.9, CHOSi), 3.21–3.17 (2 H, m, $PhSO_2CH_2$), 2.35–2.31 (2 H, m, $PhSO_2CH_2CH_2$), 2.17 (1 H, m, 4-H), 1.69–1.57 (3 H, m, 3-H_2 and 2-H), 1.06 (3 H, d, *J* 7.1, Me) and 1.03 (9 H, s, Bu^t); *m/z* 556 ($M^+ - H_2O$), 517 (M^+ − Bu^t), 499 (M^+ − Bu^t − H_2O), 487 (M^+ − Bu^t − CH_2O) and 199 (Ph_2SiOH) (Found: C, 70.95; H, 7.55. $C_{34}H_{42}O_4SSi$ requires C, 71.04; H, 7.36%).

(1S,2S,3S,5S,6S)-3-[(tert-*Butyldiphenylsilyloxy*)*methyl*]-5-*methyl*-2-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]-7-*oxabicyclo*[4.1.0]*heptan*-2-*ol* **12** *and* (1S,2R(R),3S,5S,6S)-3-[(tert-*Butyldiphenylsilyloxy*)*methyl*]-5-*methyl*-2-[2-[2-(*phenylsulphonylethyl*)*oxiran*-2-*yl*]-7-*oxabicyclo*[4.1.0]*heptan*-2-*ol* **13**.—*tert*-Butyl hydroperoxide (3 mol dm^{-3} solution in toluene; 1 ml, 3.0 mmol) was added to a solution of the olefin **11** (1.56 g, 2.72 mmol) and vanadyl acetylacetonate (36 mg, 0.14 mmol) in CH_2Cl_2 (40 ml), at 0 °C under argon. The mixture was allowed to come to room temperature. After 4.5 h, more *tert*-butyl hydroperoxide (3 mol dm^{-3} solution in toluene; 0.18 ml, 0.54 mmol) was added. After a further 5 h, the mixture was poured into saturated aqueous sodium sulphite and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the *epoxides* **12** (1.14 g, 69%) and **13** (367 mg, 22%), both as white foams.

Less polar **12**, $[\alpha]_D^{20}$ −23.2 (*c* 2.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3502, 3067, 2930, 2857, 1587, 1446, 1308, 1150, 1113, 1088 and 704; δ_H(500 MHz) 7.88 (2 H, d, *J* 7.5, Ph), 7.64–7.52 (7 H, m, Ph), 7.45–7.33 (6 H, m, Ph), 5.07 (1 H, s, C=CH), 4.85 (1 H, s, C=CH), 3.55 (1 H, dd, *J* 10.4 and 3.6, CHOSi), 3.44 (1 H, dd, *J* 10.3 and 7.9, CHOSi), 3.22 (1 H, d, *J* 3.4, 6-H or 5-H), 3.19–3.15 (2 H, m, $PhSO_2CH_2$), 2.94 (1 H, d, *J* 3.7, 5-H or 6-H), 2.75 (1 H, s, OH), 2.44 (2 H, br t, *J* 8.3, $PhSO_2CH_2CH_2$), 1.94 (1 H, m, 4-H), 1.65 (1 H, m, 3-H), 1.54 (1 H, m, 2-H), 1.15 (3 H, d, *J* 6.8, Me), 1.06 (1 H, m, 3-H) and 1.01 (9 H, s, Bu^t); δ_C(125.8 MHz) 148.7, 139.1, 135.5, 133.6, 133.4, 129.6, 129.2, 127.9, 127.6, 112.5, 72.7, 63.7, 60.4, 60.1, 55.6, 45.6, 30.9, 26.8, 25.5, 25.2, 19.1 and 18.5; *m/z*

Table 2 Atom co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses for compound **49**

Atom	*x*	*y*	*z*
C(1)	594(6)	1876(2)	−1440(2)
O(1)	−373(5)	1576(2)	−1302(2)
C(2)	809(6)	2167(2)	−2031(2)
C(3)	−276(7)	2635(3)	−2185(3)
C(4)	269(7)	3054(3)	−2656(3)
C(5)	1273(7)	2715(3)	−3015(2)
O(5)	2208(5)	2973(2)	−3244(2)
C(6)	1081(7)	2017(3)	−3078(2)
O(6)	2144(6)	1715(2)	−3368(2)
C(7)	906(6)	1668(2)	−2501(2)
O(7)	−261(4)	1296(2)	−2480(2)
C(8)	2198(6)	1292(2)	−2459(2)
C(9)	2468(6)	862(2)	−2061(2)
C(10)	3701(6)	509(2)	−1976(2)
C(11)	3895(6)	92(2)	−1576(2)
C(12)	5153(6)	−287(3)	−1491(2)
C(13)	5381(6)	−447(3)	−858(2)
O(13)	4374(5)	−874(2)	−673(2)
C(14)	5402(6)	142(2)	−487(2)
C(15)	4507(7)	234(3)	−82(2)
C(16)	4357(8)	822(3)	271(2)
C(17)	3036(7)	1159(3)	152(2)
O(17)	2973(4)	1687(2)	536(2)
C(18)	2927(7)	1380(3)	−458(2)
C(19)	1641(7)	1747(3)	−533(2)
O(19)	1645(4)	1997(2)	−1113(1)
C(20)	1589(7)	2281(3)	−124(2)
C(21)	1761(7)	2055(3)	487(2)
O(21)	615(4)	1701(2)	619(1)
C(22)	1940(8)	2598(3)	882(2)
C(23)	1165(9)	2679(3)	1327(2)
C(24)	118(8)	2221(3)	1507(2)
C(25)	422(7)	1599(2)	1216(2)
C(26)	−633(8)	1086(3)	1275(3)
C(27)	−130(11)	466(3)	1046(3)
C(28)	960(16)	173(4)	1333(5)
C(29)	887(9)	3664(3)	−2458(4)
Se	−1319(1)	3226(1)	−3154(1)
C(30)	−544(8)	3791(4)	−3711(3)
C(31)	−525(9)	4417(4)	−3609(4)
C(32)	−17(10)	4815(4)	−4032(4)
C(33)	370(11)	4603(5)	−4530(4)
C(34)	349(11)	3967(6)	−4637(4)
C(35)	−133(10)	3543(5)	−4219(4)
Si(1)	−1117(2)	844(1)	−2906(1)
C(36)	−2129(9)	345(4)	−2441(4)
C(37)	−2359(11)	1333(5)	−3326(5)
C(38)	−42(11)	381(4)	−3362(4)
C(39)	3079(7)	1476(3)	−2954(3)
C(40)	5151(8)	−883(3)	−1846(3)
Si(2)	4597(2)	−1537(1)	−328(1)
C(41)	3210(13)	−1578(5)	190(4)
C(42)	4548(14)	−2204(3)	−822(4)
C(43)	6243(12)	−1553(5)	34(5)
C(44)	6504(8)	605(3)	−632(3)
C(45)	87(11)	2149(4)	2156(3)
C(46)	−1989(8)	1270(4)	994(3)

533 ($M^+ - Bu^t$), 515 ($M^+ - Bu^t - H_2O$), 503 ($M^+ - Bu^t - CH_2O$), 485 ($M^+ - Bu^t - CH_2O - H_2O$) and 199 ($Ph_2SiOH$) (Found: C, 68.95; H, 7.15. $C_{34}H_{42}O_5SSi$ requires C, 69.12; H, 7.16%).

More polar **13**, $[\alpha]_D^{20}$ −20.5 (*c* 2.2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3492, 3068, 2957, 2931, 1446, 1427, 1308, 1149, 1112, 1088 and 705; δ_H(500 MHz) 7.90–7.88 (2 H, m, Ph), 7.69–7.55 (7 H, m, Ph), 7.47–7.36 (6 H, m, Ph), 3.69 (1 H, dd, *J* 10.4 and 4.8, CHOSi), 3.47 (1 H, dd, *J* 10.4 and 6.8, CHOSi), 3.23 (1 H, d, *J* 3.6, 6-H or 5-H), 3.14 (1 H, d, *J* 3.7, 5-H or 6-H), 3.10 (1 H, ddd, *J* 13.7, 11.5 and 4.3, $PhSO_2CH$), 2.86 (1 H, d, *J* 4.4, 8′-H), 2.80 (1 H, ddd, *J* 13.6, 11.7 and 5.4, $PhSO_2CH$), 2.45 (1 H, s, OH), 2.27 (1 H, d, *J* 4.4, 8′-H), 2.25–2.17 (2 H, m, $PhSO_2CH_2CH_2$), 1.92 (1 H, m, 4-H), 1.54–1.45 (2 H, m, 2-H, 3-H), 1.14 (3 H, d, *J* 6.8, Me), 1.07 (1 H, m, 3-H) and 1.03 (9 H, s, Bu^t); *m/z* 549 ($M^+ + Bu^t$), 531 ($M^+ - Bu^t - H_2O$), 519 ($M^+ - Bu^t - CH_2O$) and 199 (Ph_2SiOH) (Found: C, 67.15; H, 7.0. $C_{34}H_{42}O_6SSi$ requires C, 67.29; H, 6.98%).

A sample of racemic **13** crystallised on slow evaporation of a solution in ether, m.p. 150–151 °C, allowing proof of relative stereochemistry by X-ray crystallography (see Fig. 1).

(1R,3S,5S,6R)-3-[(tert-*Butyldiphenylsilyloxy)methyl*]-5-*methyl*-7-*oxabicyclo*[4.1.0]*heptan*-2-*one* **14** *and* (1S,3S,5S,6S)-3-[(tert-*Butyldiphenylsilyloxy)methyl*]-5-*methyl*-7-*oxabicyclo*-[4.1.0]*heptan*-2-*one* **15**.—Dimethyldioxirane (*ca.* 0.1 mol dm^{-3} solution in acetone; 20 ml, 2.0 mmol) was added to a stirred solution of the enone **8** (676 mg, 1.79 mmol) in CH_2Cl_2 (15 ml). After 20 h, a further portion of the dioxirane solution (20 ml, 2.0 mmol) was added and reaction continued for 20 h before the mixture was concentrated. Column chromatography of the residue on silica gel (15% ether–petroleum) gave the *epoxy ketones* **14** (78 mg, 11%) and **15** (451 mg, 64%), both as colourless oils.

Less polar **14**, $[\alpha]_D^{20}$ −12.6 (*c* 2.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3068, 2957, 2930, 1711, 1588, 1458, 1426, 1389, 1113 and 703; δ_H(500 MHz) 7.70–7.64 (4 H, m, Ph), 7.45–7.37 (6 H, m, Ph), 3.95 (1 H, dd, *J* 10.5 and 4.6, CHOSi), 3.60 (1 H, dd, *J* 10.5 and 7.6, CHOSi), 3.31 (1 H, dd, *J* 3.8 and 1.7, 5-H), 3.22 (1 H, d, *J* 3.6, 6-H), 3.02 (1 H, m, 2-H), 2.46 (1 H, m, 4-H), 2.34 (1 H, m, 3-H), 1.35 (1 H, m, 3-H), 1.14 (3 H, d, *J* 7.3, Me) and 1.06 (9 H, s, Bu^t); *m/z* 379 ($M^+ - Me$), 361 ($M^+ - Me - H_2O$), 337 ($M^+ - Bu^t$) and 199 (Ph_2SiOH) (Found: C, 72.9; H, 7.8. $C_{24}H_{30}O_3Si$ requires C, 73.05; H, 7.66%).

More polar **15**, $[\alpha]_D^{20}$ −86.1 (*c* 2.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2958, 2930, 2857, 1707, 1457, 1427, 1388, 1236, 1112 and 703; δ_H(500 MHz) 7.69–7.67 (4 H, m, Ph), 7.46–7.38 (6 H, m, Ph), 3.97 (1 H, dd, *J* 10.0 and 6.0, CHOSi), 3.85 (1 H, dd, *J* 10.1 and 3.6, CHOSi), 3.40 (1 H, d, *J* 3.8, 6-H or 5-H), 3.25 (1 H, d, *J* 3.8, 5-H or 6-H), 2.21–2.15 (2 H, m, 2-H, 4-H), 1.83 (1 H, q, *J* 12.6, 3-H), 1.72 (1 H, m, 3-H), 1.29 (3 H, d, *J* 6.9, Me) and 1.08 (9 H, s, Bu^t); *m/z* 379 ($M^+ - Me$), 337 ($M^+ - Bu^t$), 319 ($M^+ - Bu^t - H_2O$) and 199 (Ph_2SiOH) (Found: C, 72.9; H, 7.85. $C_{24}H_{30}O_3Si$ requires C, 73.05; H, 7.66%).

(1S,2S,3S,5S,6S)-3-[(tert-*Butyldiphenylsilyloxy)methyl*]-5-*methyl*-2-[1-*methylene*-3-(*phenylthio)propyl*]-7-*oxabicyclo*-[4.1.0]*heptan*-2-*ol* **16**.—*tert*-Butyllithium (1.7 mol dm^{-3} solution in pentanes; 750 μl, 1.28 mmol) was added dropwise to a stirred solution of 2-bromo-4-phenylthiobut-1-ene (296 mg, 1.22 mmol) in THF (5 ml), at −78 °C under argon. After 10 min, the epoxy ketone **15** (309 mg, 0.78 mmol) in THF (3 + 1 + 1 ml) was added by cannula. After a further 10 min, saturated aqueous ammonium chloride (5 ml) was added and the mixture allowed to come to room temperature before addition of water and extraction with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (10% ether–petroleum) afforded the *sulphide* **16** (417 mg, 95%), as a colourless oil, $[\alpha]_D^{20}$ −23.7 (*c* 2.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3541, 3069, 2929, 2856, 1585, 1459, 1426, 1112, 1090 and 703; δ_H(500 MHz) 7.65–7.62 (4 H, m, Ph), 7.44–7.26 (10 H, m, Ph), 7.18 (1 H, t, *J* 7.2, Ph), 5.25 (1 H, s, C=CH), 4.98 (1 H, s, C=CH), 3.67 (1 H, dd, *J* 10.4 and 3.5, CHOSi), 3.54 (1 H, dd, *J* 10.3 and 8.2, CHOSi), 3.20 (1 H, d, *J* 3.5, 5-H or 6-H), 3.03 (1 H, d, *J* 3.7, 6-H or 5-H), 3.02–2.98 (2 H, m, $PhSCH_2$), 2.79 (1 H, s, OH), 2.27 (2 H, t, *J* 7.9, $PhSCH_2CH_2$), 1.92 (1 H, m, 4-H), 1.70 (1 H, m, 3-H), 1.56 (1 H, m, 2-H), 1.17 (3 H, d, *J* 6.8, Me), 1.15 (1 H, q, *J* 12.6, 3-H) and 1.05 (9 H, s, Bu^t); *m/z* 501 ($M^+ - Bu^t$), 483 ($M^+ - Bu^t - H_2O$), 471 ($M^+ - Bu^t - CH_2O$) and 199 (Ph_2SiOH) (Found: $M^+ - Bu^t$,

501.1920. $C_{30}H_{33}O_3SSi$ requires M − Bu^t, 501.1920) (Found: C, 73.25; H, 7.7. $C_{34}H_{42}O_3SSi$ requires C, 73.07; H, 7.58%).

(1S,2S,3S,5S,6S)-3-[(tert-*Butyldiphenylsilyloxy*)*methyl*]-5-*methyl*-2-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]-7-*oxabicyclo*[4.1.0]*heptan*-2-*ol* **12**.—Oxone (890 mg, 2.90 mmol $KHSO_5$) was added to a solution of the sulphide **16** (404 mg, 0.72 mmol) in THF–MeOH–pH4 aqueous buffer (1:1:1; 18 ml). After 3.5 h the mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (50% ether–petroleum) afforded the sulphone **12** (376 mg, 88%); spectroscopically identical with previously prepared material, see above.

(1S,2S,3R,4S,6S)-6-(*Hydroxymethyl*)-4-*methyl*-1-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]*cyclohexane*-1,2,3-*triol* **17**.—The epoxide **12** (1.14 g, 1.93 mmol) was dissolved in THF (60 ml) and 15% aqueous sulphuric acid (60 ml). The mixture was heated at 60 °C for 12 h, then allowed to cool before addition of aqueous NaOH (3 mol dm^{-3}; 50 ml). Solid sodium hydrogen carbonate was then added until effervescence ceased. Water was added and the mixture extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (7% methanol–CH_2Cl_2) afforded the *tetraol* **17** (0.572 g, 80%), as a white foam, $[\alpha]_D^{20}$ +3.4 (*c* 2.6 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3334, 2923, 1445, 1305, 1146, 1085 and 1055; δ_H(500 MHz) 7.93–7.91 (2 H, m, Ph), 7.70–7.66 (1 H, m, Ph), 7.61–7.58 (2 H, m, Ph), 5.44 (1 H, br s, C=CH), 5.14 (1 H, s, C=CH), 3.74 (1 H, br d, *J* 9.7), 3.54 (1 H, m), 3.46–3.26 (5 H, m), 2.66 (1 H, br s, OH), 2.53 (2 H, br s), 2.20 (1 H, br s, OH), 2.04 (1 H, m, OH), 1.76 (1 H, q, *J* 12.9, 3-H), 1.68 (1 H, br dd, *J* 12.5 and 3.0), 1.58–1.54 (2 H, m) and 1.11 (3 H, d, *J* 6.2, Me); *m/z* (ACE, NH_3) 371 (MH^+) and 335 ($MH^+ - 2H_2O$) (Observed (CI, NH_3): MH^+, 371.1597. $C_{18}H_{27}O_6S$ requires MH, 371.1528) (Found: C, 58.1; H, 7.05. $C_{18}H_{26}O_6S$ requires C, 58.36; H, 7.07%). A racemic sample of **17** crystallised as needles from ethyl acetate, m.p. 171–172 °C.

(1S,2S,3R,4S,6S)-6-[(tert-*Butyldiphenylsilyloxy*)*methyl*]-4-*methyl*-1-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]*cyclohexane*-1,2,3-*triol* **18**.—*tert*-Butyldiphenylsilyl chloride (445 μl, 1.71 mmol) was added to a stirred solution of the alcohol **17** (572 mg, 1.55 mmol) and imidazole (420 mg, 6.17 mmol) in dry DMF (2 ml), at room temperature under argon. After 1 h, the mixture was poured into water and extracted with ether. The ethereal extract was washed twice with water then with brine, dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (50% ethyl acetate–CH_2Cl_2) afforded the *triol* **18** (857 mg, 91%), as a white foam, $[\alpha]_D^{20}$ +2.6 (*c* 3.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3456, 3068, 2929, 1588, 1427, 1307, 1149, 1112, 1036 and 703; δ_H(500 MHz) 7.89–7.87 (2 H, m, Ph), 7.65–7.31 (13 H, m, Ph), 5.53 (1 H, br s, C=CH), 5.07 (1 H, s, C=CH), 4.18 (1 H, br s, OH), 3.72 (1 H, br s), 3.49–3.34 (3 H, m), 3.19 (2 H, br s), 2.46 (1 H, br s, OH), 2.36 (3 H, br s), 1.80 (1 H, br q, *J* 12.2, 3-H), 1.62 (1 H, br d, *J* 12.5), 1.55–1.44 (2 H, m), 1.11 (3 H, d, *J* 6.2, Me) and 1.04 (9 H, s, Bu^t); *m/z* 551 (M^+ − Bu^t), 533 (M^+ − Bu^t − H_2O), 521 (M^+ − Bu^t − CH_2O), 503 (M^+ − Bu^t − CH_2O − H_2O) and 199 (Ph_2SiOH) (Found: M^+ − Bu^t, 551.1913. $C_{30}H_{35}O_6SSi$ requires M^+ − Bu^t, 551. 1923).

(1S,2S,3R,4S,6S)-3-(tert-*Butyldimethylsilyloxy*)-6-[(tert-*butyldiphenylsilyloxy*)*methyl*]-4-*methyl*-1-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]*cyclohexane*-1,2-*diol* **19**.—*tert*-Butyldimethylsilyl triflate (0.49 ml, 2.13 mmol) was added to a solution of the alcohol **18** (857 mg, 1.41 mmol) and triethylamine (1.0 ml, 7.17 mmol) in CH_2Cl_2 (25 ml), at room temperature under argon. After 15 min, the reaction was quenched with water (1 ml) and then poured into saturated aqueous sodium hydrogen carbonate. The CH_2Cl_2 layer was separated and the aqueous phase re-extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (35% ether–petroleum) afforded the *silyl ether* **19** (876 mg, 86%), as a white foam, $[\alpha]_D^{20}$ +2.6 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3488, 3068, 2953, 2928, 1587, 1460, 1307, 1150, 1104 and 703; δ_H(500 MHz) 7.90–7.87 (2 H, m, Ph), 7.65–7.37 (13 H, m, Ph), 5.56 (1 H, br s, C=CH), 4.99 (1 H, s, C=CH), 3.99 (1 H, s), 3.66 (1 H, br s), 3.46 (1 H, dd, *J* 10.3 and 2.3), 3.44 (1 H, m), 3.34 (1 H, br s), 3.17 (2 H, br t, *J* 7.2), 2.34 (2 H, br s), 2.01 (1 H, d, *J* 5.9), 1.76 (1 H, m), 1.60 (1 H, dd, *J* 12.3 and 2.6), 1.46 (2 H, br dd, *J* 10.3 and 3.3), 1.05–1.02 (12 H, m, Bu^t, Me), 0.92 (9 H, s, Bu^t) and 0.11 (6 H, s, Me_2Si); *m/z* 665 (M^+ − Bu^t), 647 (M^+ − Bu^t − H_2O) and 199 (Ph_2SiOH) (Found: M^+ − Bu^t, 665.2788. $C_{36}H_{49}O_6SSi_2$ requires M − Bu^t, 665.2788) (Found: C, 66.45; H, 8.2. $C_{40}H_{58}O_6SSi_2$ requires C, 66.44; H, 8.08%).

(2S,3S,5S,6R)-6-(tert-*Butyldimethylsilyloxy*)-3-[(tert-*butyldiphenylsilyloxy*)*methyl*]-2-*hydroxy*-5-*methyl*-2-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]*cyclohexanone* **20**.—Dimethyl sulphoxide (1.03 ml, 14.5 mmol) was added to a solution of oxalyl chloride (0.635 ml, 7.28 mmol) in dry THF (15 ml), at −78 °C under argon. After 5 min, the alcohol **19** (876 mg, 1.21 mmol) was added in THF (10 + 5 + 5 + 5 ml), and the mixture warmed to −35 °C. After a further 20 min, the solution was re-cooled to −78 °C before the addition of triethylamine (3.4 ml, 24.4 mmol). The mixture was allowed to come to room temperature, filtered through a silica pad (ether eluent) and evaporated. Column chromatography of the residue on silica gel (25% ether–petroleum) afforded the *ketone* **20** (642 mg, 73%), as a white foam, $[\alpha]_D^{20}$ +34.2 (*c* 1.6 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3437, 2929, 2856, 1732, 1446, 1427, 1308, 1254, 1152, 1089 and 703; δ_H(500 MHz) 7.88–7.86 (2 H, m, Ph), 7.63–7.38 (13 H, m, Ph), 5.34 (1 H, br s, C=CH), 5.16 (1 H, s, C=CH), 4.89 (1 H, s, OH), 4.57 (1 H, d, *J* 11.0, 5-H), 3.88 (1 H, br d, *J* 9.5, CHOTBDPS), 3.55 (1 H, dd, *J* 10.5 and 1.9), CHOTBDPS), 3.44 (1 H, m, $PhSO_2CH$), 3.18 (1 H, m, $PhSO_2CH$), 2.39–2.28 (3 H, m), 1.85 (1 H, m), 1.71 (1 H, m, 4-H), 1.51 (1 H, m), 1.17 (3 H, d, *J* 6.4, Me), 1.05 (9 H, s, Bu^t), 0.91 (9 H, s, Bu^t), 0.06 (3 H, s, MeSi) and −0.02 (3 H, s, MeSi); *m/z* 720 (M^+), 663 (M^+ − Bu^t), 645 (M^+ − Bu^t − H_2O) and 199 (Ph_2SiOH); (Found: M^+ − Bu^t, 663.2624. $C_{36}H_{47}O_6SSi_2$ requires M − Bu^t, 663.2632) (Found: C, 66.4; H, 8.05. $C_{40}H_{56}O_6SSi_2$ requires C, 66.62; H, 7.83%).

(1S,2R,3R,4S,6S)-3-(tert-*Butyldimethylsilyloxy*)-6-[(tert-*butyldiphenylsilyloxy*)*methyl*]-4-*methyl*-1-[1-*methylene*-3-(*phenylsulphonyl*)*propyl*]*cyclohexane*-1,2-*diol* **21**.—Sodium borohydride (50 mg, 1.32 mmol) was added to a solution of the ketone **20** (460 mg, 0.64 mmol) in methanol (15 ml) at room temperature. The mixture was poured into saturated aqueous ammonium chloride and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. ^1H NMR analysis of the crude mixture indicated that a 5.8:1 mixture of 2*R*:2*S* alcohols had been formed. Column chromatography on silica gel (25% ether–petroleum) afforded the *alcohol* **21** (366 mg, 79%), as a colourless oil, $[\alpha]_D^{20}$ +14.0 (*c* 2.1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3468, 2929, 2857, 1307, 1152, 1113 and 703; δ_H(500 MHz) 7.89–7.87 (2 H, m, Ph), 7.62–7.36 (13 H, m, Ph), 5.34 (1 H, s, C=CH), 5.00 (1 H, s, C=CH), 4.25 (1 H, s, OH), 3.84 (1 H, br d, *J* 8.7, CHOTBDPS), 3.70 (1 H, dd, *J* 10.2 and 3.1, 5-H), 3.50–3.43 (2 H, m, CHOTBDPS, $PhSO_2CH$), 3.23 (1 H, d, *J* 3.1, 6-H), 3.16 (1 H, dt, *J* 4.1 and 13.0, $PhSO_2CH$), 2.70 (1 H, m, $PhSO_2CH_2CH$), 2.44–2.38 (2 H, m, OH, $PhSO_2CH_2CH$), 2.02 (1 H, br d, *J* 12.2, 2-H), 1.89 (1 H, q, *J* 12.7, 3-H), 1.73 (1 H,

m, 4-H), 1.31 (1 H, dt, *J* 12.9 and 3.6, 3-H), 1.00 (9 H, s, Bu^t), 0.97 (3 H, d, *J* 6.4, Me), 0.89 (9 H, s, Bu^t), 0.11 (3 H, s, MeSi) and 0.07 (3 H, s, MeSi); *m/z* 665 (M^+ – Bu^t), 647 (M^+ – Bu^t – H_2O) and 199 (Ph_2SiOH) (Found: M^+ – Bu^t, 665.2800. $C_{36}H_{49}O_6SSi_2$ requires M – Bu^t, 665.2788).

[1R(R),2R,3R,4S,6S]-3-(tert-*Butyldimethylsilyloxy*)-6-[(tert-*butyldiphenylsilyloxy*)*methyl*]-1-[1-*hydroxymethyl*-3-(*phenylsulphonyl*)*propyl*]-4-*methylcyclohexane*-1,2-*diol* **22a** *and* [1R(S),2R,3R,4S,6S]-3-(tert-*Butyldimethylsilyloxy*)-6-[(tert-*butyldiphenylsilyloxy*)*methyl*]-1-[1-*hydroxymethyl*-3-(*phenylsulphonyl*)*propyl*]-4-*methylcyclohexane*-1,2-*diol* **22b**.—Borane–methyl sulphide complex (10 mol dm^{-3}; 720 μl, 7.2 mmol) was added to a stirred solution of the alcohol **21** (519 mg, 0.72 mmol) in THF (15 ml), at room temperature under argon. After 24 h, more borane–methyl sulphide complex (10 mol dm^{-3}; 720 μl, 7.2 mmol) was added and the mixture stirred for 40 h. Water (2 ml) was added and the reaction cooled to 0 °C before addition of aqueous sodium hydroxide (3 mol dm^{-3}; 55 ml), then hydrogen peroxide (27.5% aqueous solution; 25 ml). After being allowed to come to room temperature, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (45–50% ether–petroleum) afforded the *alcohols* **22a** (118 mg, 22%), as a colourless oil, and **22b** (235 mg, 44%), as a white foam.

Less polar **22a**, $[\alpha]_D^{20}$ −9.2 (*c* 2.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3481, 3068, 2952, 2927, 2856, 1587, 1459, 1446, 1427, 1306, 1253, 1146, 1113, 1083 and 704; δ_H(500 MHz) 7.77–7.36 (15 H, m, Ph), 4.51 (1 H, s, O), 3.84 (1 H, t, *J* 9.5), 3.72 (2 H, dd, *J* 10.8 and 1.8), 3.69 (1 H, d, *J* 3.3, 6-H), 3.67–3.55 (3 H, m), 3.08 (1 H, ddd, *J* 13.8, 12.1 and 4.7), 2.44–2.37 (2 H, m), 1.88–1.60 (6 H, m), 1.26 (1 H, d, *J* 3.1), 1.05 (9 H, s, Bu^t), 0.98 (3 H, d, *J* 6.5, Me), 0.90 (9 H, s, Bu^t), 0.11 (3 H, s, MeSi) and 0.10 (3 H, s, MeSi); *m/z* 683 (M^+ – Bu^t), 665 (M^+ – Bu^t – H_2O), 647 (M^+ – Bu^t – $2H_2O$) and 199 (Ph_2SiOH) (Found: M^+ – Bu^t, 683.2878. $C_{36}H_{51}O_7SSi_2$ requires M – Bu^t, 683.2894).

More polar **22b**, $[\alpha]_D^{20}$ +40.8 (*c* 3.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3473, 3068, 2927, 2856, 1461, 1426, 1306, 1254, 1147, 1113, 1073 and 703; δ_H(500 MHz) 7.96–7.94 (2 H, m, Ph), 7.65–7.36 (13 H, m, Ph), 3.97 (1 H, br d, *J* 10.5, CHOH), 3.88 (1 H, dd, *J* 10.8 and 2.5, CHOTBDPS), 3.81 (1 H, s, OH), 3.65 (1 H, dd, *J* 10.2 and 3.2, 5-H), 3.60 (1 H, dd, *J* 10.8 and 1.4, CHOTBDPS), 3.51 (1 H, d, *J* 11.0, CHOH), 3.35 (1 H, d, *J* 3.1, 6-H), 3.34–3.25 (2 H, m, OH, $PhSO_2CH$), 3.06 (1 H, m, $PhSO_2CH$), 2.95 (1 H, br s, OH), 2.27 (1 H, m, $PhSO_2CH_2CH$ or $CHCH_2OH$), 1.96 (1 H, br d, *J* 14.0, 2-H), 1.91–1.80 (3 H, m, 3-H, $PhSO_2CH_2CH$, $CHCH_2OH$ or $PhSO_2CH_2CH$), 1.66 (1 H, m, 4-H), 1.27 (1 H, m, 3-H), 1.06 (9 H, s, Bu^t), 0.96 (3 H, d, *J* 6.5, Me), 0.89 (9 H, s, Bu^t), 0.12 (3 H, s, MeSi) and 0.07 (3 H, s, MeSi); *m/z* 665 (M^+ – Bu^t – H_2O), 647 (M^+ – Bu^t – $2H_2O$) and 199 (Ph_2SiOH) (Found: C, 64.63; H, 8.31. $C_{40}H_{60}O_7SSi_2$ requires C, 64.82; H, 8.16%).

(3S,3aR,4S,6S,7R,7aR)-7-(tert-*Butyldimethylsilyloxy*)-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methyl*-3-[2-(*phenylsulphonyl*)*ethyl*]*benzofuran*-3a-*ol* **23a**.—Pyridine (5 ml) was added to a mixture of the alcohol **22b** (90.4 mg, 0.12 mmol) and toluene-*p*-sulphonyl chloride (140 mg, 0.73 mmol), at room temperature under argon. The mixture was stirred for 14 h before being added to ether, washed several times with saturated aqueous $CuSO_4$, then once each with water and brine. The organic extract was dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (50% ether–petroleum) afforded the *furan* **23a** (74.1 mg, 84%), as a white foam, and recovered starting alcohol **22b** (7.3 mg, 8%).

Less polar **23a**, $[\alpha]_D^{20}$ +31.7 (*c* 2.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3452, 2928, 2855, 1469, 1446, 1427, 1388, 1306, 1251, 1148, 1113 and 704; δ_H(500 MHz) 7.93–7.90 (2 H, m, Ph), 7.66–7.38 (13 H, m, Ph), 4.46 (1 H, s, OH), 4.08–4.05 (2 H, m, 8′-H, CHOTBDPS), 3.66 (1 H, dd, *J* 10.9 and 2.5, CHOTBDPS), 3.50 (1 H, dd, *J* 10.1 and 3.5, 5-H), 3.45 (1 H, d, *J* 3.6, 6-H), 3.40 (1 H, dd, *J* 9.6 and 4.5, 8′-H), 3.24 (1 H, ddd, *J* 13.9, 10.5 and 5.6, $PhSO_2CH$), 3.01 (1 H, ddd, *J* 14.0, 10.6 and 4.7, $PhSO_2CH$), 2.18 (1 H, m, $PhSO_2CH_2CH$), 2.04 (1 H, m, 8-H), 1.81 (1 H, m, 4-H), 1.73 (1 H, q, *J* 12.6, 3-H), 1.67 (1 H, m, $PhSO_2CH_2CH$), 1.40 (1 H, br dd, *J* 12.6 and 2.6, 2-H), 1.32 (1 H, dt, *J* 13.0 and 3.0, 3-H), 1.04 (9 H, s, Bu^t), 0.98 (3 H, d, *J* 6.3, Me), 0.90 (9 H, s, Bu^t), 0.09 (3 H, s, MeSi) and 0.08 (3 H, s, MeSi); *m/z* 707 (M^+ – Me), 665 (M^+ – Bu^t), 647 (M^+ – Bu^t – H_2O) and 199 (Ph_2SiOH) (Found: C, 66.3; H, 8.15. $C_{40}H_{58}O_6SSi_2$ requires C, 66.44; H, 8.08%).

[3S(E),3aR,4S,6S,7R,7aR]-7-(tert-*Butyldimethylsilyloxy*)-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methyl*-3-[2-(*phenylsulphony*)*vinyl*]*benzofuran*-3a-*ol* **24a**.—*tert*-Butyllithium (1.6 mol dm^{-3} solution in hexanes; 210 μl, 0.34 mmol) was added dropwise to a stirred solution of the sulphone **23a** (72.2 mg, 0.10 mmol) in THF (2 ml), at −78 °C under argon. After 10 min, benzeneselenenyl chloride (50 mg, 0.26 mmol) in THF (1 ml) was added rapidly. After a further 10 min, saturated aqueous ammonium chloride (1 ml) was added and the mixture allowed to come to room temperature. Water was added and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the selenides (73.5 mg, 84%), and recovered starting sulphone **23a** (8.7 mg, 12%). To a solution of the selenides (72.5 mg, 82.6 μmol) in CH_2Cl_2 (2 ml) at room temperature was added *m*CPBA (80%; 36 mg, 167 μmol). After 15 min the solvent was evaporated. Column chromatography of the residue on silica gel (50% ether–petroleum) afforded the *vinyl sulphone* **24a** (55.2 mg, 93%), $[\alpha]_D^{20}$ +34.1 (*c* 2.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3442, 2951, 2927, 2855, 1468, 1445, 1426, 1319, 1251, 1147, 1113 and 703; δ_H(500 MHz) 7.95–7.92 (2 H, m, Ph), 7.59–7.29 (13 H, m, Ph), 7.22 (1 H, dd, *J* 15.0 and 9.5, $PhSO_2CH{=}CH$), 6.23 (1 H, d, *J* 15.0, $PhSO_2CH{=}C$), 4.55 (1 H, s, OH), 4.09 (1 H, dd, *J* 9.8 and 8.0), 4.03 (1 H, dd, *J* 10.9 and 2.1), 3.73 (1 H, dd, *J* 9.9 and 4.6), 3.68 (1 H, d, *J* 3.6, 6-H), 3.66 (1 H, dd, *J* 10.9 and 2.6), 3.55 (1 H, dd, *J* 9.8 and 3.5), 2.89 (1 H, m, 8-H), 1.85 (1 H, m, 4-H), 1.77 (1 H, q, *J* 12.6, 3-H), 1.53 (1 H, br dd, *J* 12.5 and 2.5, 2-H), 1.40 (1 H, dt, *J* 13.0 and 3.2, 3-H), 1.01 (3 H, d, *J* 6.4, Me), 0.98 (9 H, s, Bu^t), 0.91 (9 H, s, Bu^t), 0.11 (3 H, s, MeSi) and 0.10 (3 H, s, MeSi); δ_C(125.8 MHz) 146.2, 140.6, 135.6, 135.4, 133.2, 131.8, 131.5, 131.1, 130.2, 129.2, 127.9, 127.9, 127.6, 83.8, 82.4, 75.2, 70.3, 65.6, 48.7. 41.3, 33.8, 32.7, 26.7, 25.9, 18.9, 18.8, 18.2, −4.3 and −4.7; *m/z* 663 (M^+ – Bu^t), 645 (M^+ – Bu^t – H_2O) and 199 (Ph_2SiOH) (Found: C, 66.45; H, 7.85. $C_{40}H_{56}O_6SSi_2$ requires C, 66.62; H, 7.83%).

(3E,3aS,4S,6S,7R,7aR)-7-(tert-*Butyldimethylsilyloxy*)-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methyl*-3-[2-(*phenylsulphonyl*)*ethylidene*]*benzofuran*-3a-*ol* **2**.—DBU (3 drops) was added to a stirred solution of the sulphone **24** (55.2 mg, 76.6 mmol) in acetonitrile (2 ml) at room temperature under argon. After 3.5 h, the mixture was evaporated. Column chromatography of the residue on silica gel (50% ether–petroleum) afforded the *allylic sulphone* **2** (44.3 mg, 80%), $[\alpha]_D^{20}$ +9.8 (*c*, 2.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3444, 2928, 2855, 1587, 1460, 1427, 1388, 1321, 1307, 1250, 1148, 1113, 1022 and 704; δ_H(500 MHz) 7.79 (2 H, d, *J* 7.6, Ph), 7.71–7.41 (13 H, m, Ph), 5.46 (1 H, tt, *J* 8.0 and 2.5, $PhSO_2CH_2CH{=}C$), 5.15 (1 H, s, OH), 4.04 (1 H, dd, *J* 10.6 and 2.1, CHOTBDPS), 3.88 (1 H, dd, *J* 14.5 and 2.1, 8′-H), 3.80 (1 H, dd, *J* 14.5 and 2.4, 8′-H), 3.73 (1 H, dd, *J* 14.0 and 8.0, $PhSO_2CH$), 3.58 (1 H, dd, *J* 14.1 and

8.5, $PhSO_2CH$), 3.55–3.52 (2 H, m, 5-H, C*H*OTBDPS), 3.40 (1 H, d, *J* 3.5, 6-H), 1.81–1.73 (2 H, m, 3-H, 4-H), 1.35 (1 H, dd, *J* 10.1 and 3.0), 1.24 (1 H, dd, *J* 14.2 and 2.4), 1.11 (9 H, s, Bu^t), 0.99 (3 H, d, *J* 5.9, Me), 0.89 (9 H, s, Bu^t), 0.09 (3 H, s, MeSi) and 0.07 (3 H, s, MeSi); δ_C(125.8 MHz) 153.8 (s), 138.2 (s), 135.7 (d), 135.6 (d), 133.8 (d), 131.8 (s), 130.2 (d), 130.1 (d), 129.0 (d), 128.4 (d), 128.1 (d), 127.8 (d), 107.1 (C-9), 82.9 (C-6), 82.2 (s), 74.9 (C-5), 66.6 (C-8′), 64.9 (C-1), 56.6 (C-10), 38.8 (C-2), 33.9 (C-4), 32.8 (C-3), 26.7 (q), 25.9 (q), 19.1 (s), 18.8 (4-Me), 18.2 (s), −4.4 (q) and −4.7 (q); *m/z* 663 (M^+ − Bu^t), 645 (M^+ − Bu^t − H_2O) and 199 (Ph_2SiOH) (Found: M^+ − Bu^t, 663.2632. $C_{36}H_{47}O_6SSi_2$ requires M − Bu^t, 663.2617) (Found: C, 66.4; H, 7.95. $C_{40}H_{56}O_6SSi_2$ requires C, 66.62; H, 7.83%).

(3R,3aR,4S,6S,7R,7aR)-7-(tert-*Butyldimethylsilyloxy*)-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methyl*-3-[2-(*phenylsulphonyl*)*ethyl*]*benzofuran*-3a-*ol* **23b**.—Pyridine (2.5 ml) was added to a mixture of the alcohol **22a** (50.2 mg, 67.8 μmol) and toluene-*p*-sulphonyl chloride (65 mg, 0.34 mmol), at room temperature under argon. The mixture was stirred for 12 h before addition of more toluene-*p*-sulphonyl chloride (25 mg, 0.13 mmol). After a further 12 h, the reaction was added to ether, washed several times with saturated aqueous $CuSO_4$, then once with water and then brine. The organic extract was dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40–50% ether–petroleum) afforded the intermediate *tosylate* (28.5 mg, 47%) as a white foam, and the *furan* **23b** (5.2 mg, 11%) as a colourless oil. Less polar, the tosylate, $[\alpha]_D^{20}$ +8.1 (*c* 2.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3468, 2929, 2857, 1597, 1459, 1426, 1361, 1306, 1189, 1176, 1113, 1080 and 704; δ_H(500 MHz) 7.76–7.73 (4 H, m, Ph), 7.64–7.43 (5 H, m, Ph), 7.42–7.36 (8 H, m, Ph), 7.32 (2 H, d, *J* 7.9, Ph), 4.52 (1 H, dd, *J* 9.3 and 3.0), 4.17 (1 H, dd, *J* 9.3 and 7.2), 4.04 (1 H, s, OH), 3.63 (1 H, dd, *J* 10.9 and 1.5), 3.54–3.50 (2 H, m), 3.23 (1 H, d, *J* 3.2, 6-H), 3.19 (1 H, ddd, *J* 13.9, 12.2 and 5.2, $PhSO_2CH$), 2.45 (3 H, s, Ar-Me), 2.31 (1 H, ddd, *J* 14.1, 11.7 and 4.2, $PhSO_2CH$), 2.22 (1 H, s, OH), 2.02 (1 H, m), 1.89–1.63 (5 H, m), 1.26 (1 H, m), 1.02 (9 H, s, Bu^t), 0.94 (3 H, d, *J* 6.5, Me), 0.87 (9 H, s, Bu^t), 0.08 (3 H, s, MeSi) and 0.02 (3 H, s, MeSi); *m/z* 665 (M^+ − Bu^t − TsOH), 647 (M^+ − Bu^t − TsOH − H_2O) and 199 (Ph_2SiOH) (Found: C, 62.95; H, 7.3. $C_{47}H_{69}O_9S_2Si_2$ requires C, 63.05; H, 7.43%).

More polar **23b**, $[\alpha]_D^{20}$ −3.3 (*c* 1.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3454, 3068, 2953, 2928, 2856, 1587, 1459, 1446, 1427, 1388, 1307, 1250, 1147, 1113, 1041 and 703; δ_H(500 MHz) 7.81–7.79 (2 H, m, Ph), 7.68–7.60 (5 H, m, Ph), 7.50–7.40 (8 H, m, Ph), 4.90 (1 H, s, OH), 4.18 (1 H, dd, *J* 11.0 and 2.5, CHOTBDPS), 4.03 (1 H, t, *J* 8.7, 8′-H), 3.64–3.61 (2 H, m, 6-H, CHOTBDPS), 3.45 (1 H, dd, *J* 10.0 and 3.1, 5-H), 3.37 (1 H, dd, *J* 10.6 and 8.7, 8′-H), 3.06–2.93 (2 H, m, $PhSO_2CH_2$), 2.41 (1 H, m, 8-H), 2.19 (1 H, m, $PhSO_2CH_2CH$), 1.80 (1 H, m, 4-H), 1.71 (1 H, q, *J* 12.7, 3-H), 1.66–1.57 (2 H, m, 4-H, $PhSO_2CH_2CH$, 1.25 (1 H, dt, *J* 12.9 and 3.3, 3-H), 1.08 (9 H, s, Bu^t), 0.93 (3 H, d, *J* 6.4, Me), 0.90 (9 H, s, Bu^t) and 0.09 (6 H, s, MeSi); *m/z* 704 (M^+ − H_2O), 689 (M^+ − Me − H_2O), 665 (M^+ − Bu^t), 647 (M^+ − Bu^t − H_2O) and 199 (Ph_2SiOH) (Found: M^+ − Bu^t, 665.2782. $C_{36}H_{49}O_6SSi_2$ requires M − Bu^t, 665.2788).

[3R(E),3aR,4S,6S,7R,7aR]-7-(tert-*Butyldimethylsilyloxy*)-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methyl*-3-[2-(*phenylsulphonyl*)*vinyl*]*benzofuran*-3a-*ol* **24b**.—*tert*-Butyllithium (1.6 mol dm^{-3} solution in hexanes; 50 μl, 80 μmol) was added dropwise to a stirred solution of the sulphone **23b** (18.0 mg, 24.9 μmol) in THF (1 ml), at −78 °C under argon. After 5 min, benzeneselenenyl chloride (12 mg, 62.7 μmol) in THF (0.5 ml) was added rapidly. After a further 10 min, saturated aqueous ammonium chloride (0.5 ml) was added and the mixture allowed to come to room temperature. Water was added and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the selenides (16.4 mg, 75%), and recovered starting sulphone **23b** (3.3 mg, 18%).

To a solution of the selenides (16.4 mg, 18.7 μmol) in CH_2Cl_2 (1 ml) at room temperature was added *m*CPBA (80%; 8 mg, 37.1 μmol). After 15 min the solvent was evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the *vinyl sulphone* **24b** (12.6 mg, 94%), as a colourless oil, $[\alpha]_D^{20}$ −26.1 (*c* 1.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3435, 2928, 2855, 1459, 1427, 1320, 1251, 1148, 1113 and 703; δ_H(500 MHz) 7.74–7.38 (15 H, m, Ph), 7.04 (1 H, dd, *J* 15.1 and 8.5, $PhSO_2CH$=CH), 6.32 (1 H, dd, *J* 15.1 and 1.1, $PhSO_2CH$=C), 5.45 (1 H, s, OH), 4.17 (1 H, dd, *J* 11.2 and 1.4, CHOTBDPS), 4.08 (1 H, t, *J* 8.9, 8′-H), 3.74–3.70 (2 H, m, 8′-H, 6-H), 3.55–3.49 (2 H, m, 5-H, CHOTBDPS), 3.22 (1 H, q, *J* 8.4, 8-H), 1.83 (1 H, m, 4-H), 1.74–1.64 (2 H, m, 2-H, 3-H), 1.15 (1 H, m, 3-H), 1.09 (9 H, s, Bu^t), 0.93 (3 H, d, *J* 6.5, Me), 0.91 (9 H, s, Bu^t) and 0.11 (6 H, s, MeSi); *m/z* 720 (M^+), 705 (M^+ − Me), 663 (M^+ − Bu^t), 645 (M^+ − Bu^t − H_2O) and 199 (Ph_2SiOH) (Found: M^+ − Bu^t, 663.2630. $C_{36}O_{47}O_6SSi_2$ requires M − Bu^t, 663.2632).

(3E,3aS,4S,6S,7R,7aR)-7-(tert-*Butyldimethylsilyloxy*)-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methyl*-3-[2-(*phenylsulphonyl*)*ethylidene*]*benzofuran*-3a-*ol* **2**.—DBU (3 drops) was added to a stirred solution of the vinyl sulphone **24b** (10.1 mg, 14.0 μmol) in acetonitrile (0.75 ml) at room temperature under argon. After 20 h, the mixture was evaporated. Column chromatography of the residue on silica gel (50% ether–petroleum) afforded the allylic sulphone **2** (8.3 mg, 82%); spectroscopically identical with previously prepared material, see above.

Cyclisation of a 2:1 *Mixture of the Alcohols* **22a** *and* **22b**.—A 2:1 mixture of the alcohols **22b** and **22a** (172 mg, 0.23 mmol) and toluene-*p*-sulphonyl chloride (270 mg, 1.42 mmol) was stirred in pyridine (9 ml), under argon, for 16 h at room temperature followed by a further 20 h at 60 °C. The mixture was allowed to cool and then added to ether. The ether layer was washed several times with saturated aqueous $CuSO_4$, then once with water, and then brine. The organic extract was dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the furans **23** (131.5 mg, 78%). ^1H NMR indicated that the product consisted of a 2:1 mixture of the furans **23a** and **23b**.

Preparation of the Mixture of Vinyl Sulphones **24a** *and* **24b**.—*tert*-Butyllithium (1.6 mol dm^{-3} solution in hexanes; 250 μl, 0.40 mmol) was added dropwise to a stirred solution of the sulphones **23a** and **23b** (131.5 mg, 0.18 mmol) in THF (4 ml), at −78 °C under argon. After 5 min, benzeneselenenyl chloride (90 mg, 0.47 mmol) in THF (2 ml) was added rapidly. After a further 10 min, saturated aqueous ammonium chloride (3 ml) was added and the mixture allowed to come to room temperature. Water was added and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the selenides (103.3 mg, 65%), and recovered starting sulphone **23** (38.8 mg, 30%).

To a solution of the selenides (103.3 mg, 0.18 mmol) in CH_2Cl_2 (3 ml) at room temperature was added *m*CPBA (80%; 30 mg, 0.14 mmol). After 15 min the solvent was evaporated. Column chromatography of the residue on silica gel (40% ether–petroleum) afforded the vinyl sulphones **24** (85 mg, 100%).

(3E,3aS,4S,6S,7R,7aR)-7-(tert-*Butyldimethylsilyloxy*)-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methyl*-3-[2-(*phenylsulphonyl*)*ethylidene*]*benzofuran*-3a-*ol* **2**.—DBU (5 drops) was added to a stirred solution of the mixture of the vinyl sulphones **24** (85 mg, 0.12 mmol) in acetonitrile (4 ml) at room temperature under argon. After 12 h, the mixture was evaporated. Column chromatography of the residue on silica gel (50% ether–petroleum) afforded the allylic sulphone **2** (65 mg, 77%); this was spectroscopically identical with a previously prepared sample, see above.

(2E,4S)-*Ethyl* 2,4-*Dimethylhex*-2-*enoate* **25**.—1-Ethoxycarbonylethylidenetriphenylphosphorane (70 g, 191.9 mmol) was added at room temperature to a solution of (*S*)-2-methylbutanal[28] (15.0 g, 174.2 mmol) in CH_2Cl_2 (1 l) and the solution stirred overnight. The solvent was removed by distillation and the crude product purified by column chromatography on silica gel (2% ether–petroleum) to give, less polar, the Z-*isomer* (0.2 g, 0.9%) as a white solid, and, more polar, the E-*ester* **25** (25.1 g, 85%), as a colourless oil. Less polar, *Z*-isomer, m.p. 79–80 °C; ν_{max}(film)/cm^{-1} 2960, 2937, 1710, 1479, 1274, 1227, 1177, 1095 and 1027; δ_H(270 MHz, systematic numbering) 5.65 (1 H, dq, *J* 10.0 and 1.2, 3-H), 4.20 (2 H, q, *J* 7.0, $CO_2CH_2CH_3$), 3.03 (1 H, m, 4-H), 1.91 (3 H, d, *J* 1.2, 2-Me), 1.31 (3 H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.40–1.20 (2 H, m, 5-H), 0.98 (3 H, d, *J* 6.8, 4-Me) and 0.86 (3 H, t, *J* 7.3, 6-Me); *m*/*z* 170 (M^+), 155 ($M^+ - Me$), 141 ($M^+ - C_2H_7$) and 97 ($M^+ - C_3H_5O_2$).

More polar **25**, $[\alpha]_D^{20}$ +23.4 (*c* 1.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2962, 2929, 1709, 1458, 1273, 1154 and 1098; δ_H(400 MHz, systematic numbering) 6.53 (1 H, dq, *J* 10.0 and 1.5, 3-H), 4.19 (2 H, q, *J* 7.0, $CO_2CH_2CH_3$), 2.41 (1 H, m, 4-H), 1.83 (3 H, d, *J* 1.5, 2-Me), 1.40–1.20 (2 H, m, 5-H_2), 1.30 (3 H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.00 (3 H, d, *J* 6.5, 4-Me) and 0.86 (3 H, t, *J* 7.5, 5-Me); *m*/*z* 170 (M^+), 141 ($M^+ - C_2H_7$) and 97 ($M^+ - C_3H_5O_2$); (Found: M^+, 170.1310. $C_{10}H_{18}O_2$ requires M, 170.1307) (Found: C, 70.45; H, 10.85. $C_{10}H_{18}O_2$ requires C, 70.59; H, 10.59%).

(2E,4S)-2,4-*Dimethylhex*-2-*enol* **26**.—Diisobutylaluminium hydride (1.5 mol dm^{-3} solution in toluene; 78 ml, 118 mmol) was added dropwise *via* a syringe pump to a stirred solution of the ester **25** (8.0 g, 47.1 mmol) in dry toluene (800 ml) under argon at −78 °C. The solution was stirred for 0.5 h, quenched with water (10 ml) and allowed to warm to room temperature. Upon gelling (*ca.* 0.5–1 h), the slurry was stirred with solid $NaHCO_3/Na_2SO_4$ and an excess of ether. The mixture was stirred vigorously until, upon standing, the solution cleared. The ether was decanted and filtered through a pad of Celite. The filtrate was evaporated and purified by column chromatography on silica gel (15% ether–petroleum), to give the *alcohol* **26** (5.5 g, 91%) as a liquid, $[\alpha]_D^{20}$ +37.3 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3432, 2962, 2873, 1459, 1382, 1074 and 1037; δ_H(270 MHz, systematic numbering) 5.18 (1 H, dq, *J* 10.0 and 1.5, 3-H), 4.00 (2 H, s, 1-H_2), 2.28 (1 H, m, 4-H), 1.68 (3 H, d, *J* 1.5, 2-Me), 1.50 (1 H, br s, OH), 1.42–1.22 (2 H, m, 5-H_2), 0.93 (3 H, d, *J* 6.5, 4-Me) and 0.84 (3 H, t, *J* 7.5, 5-Me); *m*/*z* 128 (M^+) and 97 ($M^+ - CH_2OH$) (Found: M^+, 128.1201. $C_8H_{16}O$ requires M, 128.1201).

[2R,3R(S)]-2-*Methyl*-3-(1-*methylpropyl*)*oxiran*-2-*ylmethanol* **27**.—To dry CH_2Cl_2 (120 ml) at −20 °C under argon was added titanium tetraisopropoxide (5.1 ml, 17.2 mmol) and D-(−)-diethyl tartrate (3.6 g, 17.2 mmol). The mixture was stirred for 5 min before the addition of the alcohol **26** (2.2 g, 17.2 mmol) in CH_2Cl_2 (10 ml) and *tert*-butyl hydroperoxide (3.5 mol dm^{-3} solution in toluene; 10 ml, 35.0 mmol). The mixture was stirred overnight at −20 °C, after which 10% aqueous tartaric acid (60 ml) was added. The mixture was stirred for 30 min at −15 °C and then for 1 h at room temperature or until the aqueous phase cleared. The organic phase was washed with water, dried (Na_2SO_4), and evaporated to afford the crude product contaminated with *tert*-butyl hydroperoxide. The oil was diluted with ether (30 ml), cooled to 5 °C and stirred with NaOH (1 mol dm^{-3} aqueous solution; 50 ml) for 30 min at 5 °C. The organic phase was washed with brine, dried (Na_2SO_4), evaporated and purified by column chromatography on silica gel (20% ether–petroleum) to give the *epoxide* **27** (2.0 g, 81%) as a colourless liquid, $[\alpha]_D^{20}$ +32.4 (*c* 1.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3432, 2962, 2873, 1459, 1382, 1074 and 1037; δ_H(270 MHz, systematic numbering) 3.60 (1 H, dd, *J* 12.2 and 3.4, 1′-H), 3.50 (1 H, dd, *J* 12.2 and 6.7, 1′-H), 2.65 (1 H, d, *J* 9.0, 3-H), 2.58 (1 H, br s, OH), 1.40–1.20 (3 H, m, 4-H, 2″-H_2), 1.24 (3 H, s, 2-Me), 1.01 (3 H, d, *J* 6.1, 1″-Me) and 0.85 (3 H, t, *J* 7.2, 2″-Me); *m*/*z* 145 (MH^+), 126 ($M^+ - H_2O$) and 97 ($M^+ - Bu^t$) (Found: $M^+ - H_2O$, 126.1045. $C_8H_{14}O$ requires $M - H_2O$, 126.1045).

[2R,3R(S)]-2-*Methyl*-3-(1-*methylpropyl*)-2-*vinyloxirane* **28**.—Dimethyl sulphoxide (1.6 ml, 22.7 mmol) was added dropwise to a solution of oxalyl chloride (1.0 ml, 11.4 mmol) in dry CH_2Cl_2 (30 ml) at −78 °C. The mixture was stirred for 5 min and then the alcohol **27** (1.5 g, 10.4 mmol) in CH_2Cl_2 (10 ml) was added. The solution was stirred for a further 30 min at −78 °C, after which triethylamine (7.2 ml, 52.0 mmol) was added and the reaction allowed to warm to room temperature. The mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated and the residue purified by column chromatography on silica gel (10% ether–petroleum) to give [2R,3R(S)]-2-*methyl*-3-(1-*methylpropyl*)*oxirane*-2-*carbaldehyde* (1.12 g, 80%) as a colourless liquid, $[\alpha]_D^{20}$ +11.8 (*c* 0.2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2965, 2875, 1725, 1461, 1389, 1080, 1010 and 878; δ_H(270 MHz, systematic numbering) 8.87 (1 H, s, CHO), 2.83 (1 H, d, *J* 9.0, 3-H), 1.41 (3 H, s, 2-Me), 1.50–1.20 (3 H, m, 1′-H, 2′-H_2), 1.16 (3 H, d, *J* 6.1, 1′-Me) and 0.88 (3 H, t, *J* 7.0, 2″-Me); *m*/*z* 142 (M^+), 127 ($M^+ - Me$), 113 ($M^+ - CHO$) and 85 ($M^+ - Bu^s$) (Found: $M^+ - Me$, 127.0763. $C_7H_{11}O_2$ requires M − Me, 127.0760).

Hexamethyldisilazane (7.5 ml, 35.8 mmol) was added to a suspension of KH [35% by weight paraffin oil dispersion; 4.1 g, 35.8 mmol, washed with THF (3 × 20 ml)] in THF (30 ml) and stirred for 30 min under argon. The resulting solution of potassium hexamethyldisilazide was allowed to settle, then added dropwise to methyltriphenylphosphonium bromide (12.8 g, 35.8 mmol) in toluene (30 ml) at −20 °C. The mixture was allowed to warm to room temperature and then cooled back to −20 °C to allow complete formation of the yellow ylide. [2*R*,3*R*(*S*)]-2-Methyl-3-(1-methylpropyl)oxirane-2-carbaldehyde (0.94 g, 6.6 mmol) in THF (15 ml) was added dropwise, the mixture was warmed to room temperature, poured into brine and extracted with ether. The extract was dried ($MgSO_4$) and evaporated and the residue purified by column chromatography on silica gel (10% ether–petroleum) to give the alkene **28** (0.79 g, 85%) as a colourless liquid; ν_{max}(film)/cm^{-1} 2957, 2925, 2855, 1639, 1461, 1379, 1070, 986, 916 and 885; δ_H(270 MHz, systematic numbering) 5.76 (1 H, dd, *J* 17.3 and 10.5, 1′-H), 5.34 (1 H, dd, *J* 17.3 and 1.2, 2′-H), 5.19 (1 H, dd, *J* 10.5 and 1.2, 2′-H), 2.52 (1 H, d, *J* 9.0, 1″-H), 1.42 (3 H, s, 2-Me), 1.30–1.20 (3 H, m, 1″-H, 2″-H_2), 1.15 (3 H, d, *J* 6.1, 1″-Me) and 0.92 (3 H, t, *J* 7.1, 2″-Me); *m*/*z* 140 (M^+) and 83 ($M^+ - Bu^s$). This compound was unstable and was used immediately in the next reaction.

(exo,4R,5S)-1,2,3-η^3-(3,5-*Dimethylhepten*-4-*yloxycarbonylato*)*tricarbonyliron* **29** *and* (endo,4R,5S)-1,2,3-η^3-(3,5-*Dimethylhepten*-4-*yloxycarbonylato*)*tricarbonyliron* **30**.—Nona-

carbonyldiiron (4.14 g, 11.9 mmol) was added to a solution of alkene **28** (1.0 g, 7.1 mmol) in dry tetrahydrofuran (100 ml). The mixture was stirred for 1 h and then evaporated and purified by column chromatography on silica gel (30% ether–petroleum) to give the endo-*ferrilactone* **30** (0.8 g, 49%) as a colourless solid, and the exo-*ferrilactone* **29** (0.9 g, 50%), also as a colourless solid. Less polar, the *endo* isomer **30**, m.p. 102–103 °C (decomp); ν_{max}(film)/cm^{-1} 2959, 2931, 2079, 2022, 1663, 1044 and 1017; δ_H(270 MHz, C_6D_6, systematic numbering) 4.08 (1 H, br s, 4-H), 3.88 (1 H, dd, *J* 12.8 and 8.7, 2-H), 2.80 (1 H, dd, *J* 8.7 and 2.1, 1-H), 2.52 (1 H, dd, *J* 12.8 and 2.1, 1-H), 1.32 (3 H, s, 3-Me), 0.79 (3 H, t, *J* 7.0, 7-Me) and 0.70 (3 H, d, *J* 5.4, 5-Me); *m/z* 308 (M^+), 280 (M^+ – CO), 252 (M^+ – 2CO), 224 (M^+ – 3CO), 196 (M^+ – $Fe(CO)_2$), 168 (M^+ – $Fe(CO)_3$) and 139 (M^+ – $Fe(CO)_2$ – Bu^s) (Found: C, 60.0; H, 5.4. $C_{13}H_{16}FeO_5$ requires C, 50.67; H, 5.19%).

More polar, the *exo* isomer **29**, m.p. 104–105 °C (decomp); ν_{max}(film)/cm^{-1} 2960, 2081, 2022, 1654, 1383, 1043, 892, 774 and 754; δ_H(270 MHz, C_6D_6, systematic numbering) 4.04 (1 H, dd, *J* 12.5 and 8.5, 2-H), 3.62 (1 H, br s, 4-H), 2.61 (1 H, dd, *J* 8.5 and 1.2, 1-H), 2.45 (1 H, dd, *J* 12.5 and 1.2, 1-H), 1.36 (3 H, s, 3-Me), 1.00 (3 H, d, *J* 5.4, 5-Me) and 0.76 (3 H, t, *J* 7.0, 7-Me); *m/z* 308 (M^+), 280 (M^+ – CO), 252 (M^+ – 2CO), 196 (M^+ – $Fe(CO)_2$), 168 (M^+ – $Fe(CO)_3$) and 95 (Found: C, 50.6; H, 5.15. $C_{13}H_{16}FeO_5$ requires C, 50.67; H, 5.19%).

[6R(S)]-3,6-*Dihydro*-5-*methyl*-6-(1-*methylpropyl*)*pyran*-2-*one* **33**, [5S,6R(S)]-5,6-*Dihydro*-5-*methyl*-6-(1-*methylpropyl*)-*pyran*-2-*one* **31**, *and* [5R,6R(S)]-5,6-*Dihydro*-5-*methyl*-6-(1-*methylpropyl*)*pyran*-2-*one* **32**.—The ferrilactone **29** (0.1 g, 0.32 mmol) in dry benzene (25 ml) was heated at 50 °C for 3 days under a pressure of 240 atm of carbon monoxide in a high pressure bomb. The mixture was then filtered through a cotton wool plug, evaporated and purified by column chromatography on silica gel (10% ether–petroleum) to give the *β,γ-unsaturated lactone* **33** (31.1 mg, 57%), the *α,β-unsaturated lactone* **32** (1.6 mg, 3%), and the *α,β-unsaturated lactone* **31** (21.8 mg, 40%), all as oils. Least polar, the *β,γ*-unsaturated lactone **33**, $[\alpha]_D^{20}$ −51.7 (*c* 1.4 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2975, 2872, 1728, 1642, 1609, 1445, 1381, 1113 and 713; δ_H(270 MHz) 5.54 (1 H, m, 23-H), 4.82 (1 H, m, 25-H), 3.05 (2 H, m, 22-H), 1.72 (3 H, m, 24-Me), 1.80–1.40 (3 H, m, 26-H, 27-H_2), 0.97 (3 H, t, *J* 7.3, 27-Me) and 0.82 (3 H, d, *J* 6.9, 26-Me); *m/z* 168 (M^+), 112 (M^+ – Bu^s) and 82 (M^+ – Bu^s – CO) (Found: M^+, 168.1150. $C_{10}H_{16}O_2$ requires M, 168.1150) (Found: C, 71.55; H, 9.5. $C_{10}H_{16}O_2$ requires C, 71.43; H, 9.52%).

More polar, the *α,β*-unsaturated lactone **32**, $[\alpha]_D^{20}$ −180.0 (*c* 1.1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2956, 1714, 1673, 1606, 1455, 1380, 989 and 772; δ_H(500 MHz) 6.96 (1 H, dd, *J* 9.6 and 6.5, 23-H), 5.96 (1 H, d, *J* 9.6, 22-H), 4.01 (1 H, dd, *J* 10.2 and 3.1, 25-H), 2.50 (1 H, m, 24-H), 1.78 (1 H, m, 26-H), 1.46 (1 H, m, 27-H), 1.10 (1 H, m, 27-H), 1.10 (3 H, d, *J* 6.5, 24-Me), 1.02 (3 H, d, *J* 7.0, 26-Me) and 0.94 (3 H, t, *J* 7.4, 27-Me); *m/z* 168 (M^+), 112 (M^+ – Bu^s) and 82 (M^+ – Bu^s – CO) (Found: M^+, 168.1150. $C_{10}H_{16}O_2$ requires M, 169.1150).

Most polar, the *α,β*-unsaturated lactone **31**, $[\alpha]_D^{20}$ +48.0 (*c* 0.75 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2930, 1713, 1605, 1461, 1381, 1239, 1007 and 813; δ_H(270 MHz) 6.65 (1 H, dd, *J* 9.8 and 2.2, 23-H), 5.95 (1 H, d, *J* 9.8, 22-H), 4.05 (1 H, dd, *J* 10.5 and 2.4, 25-H), 2.63 (1 H, m, 24-H), 1.71–1.39 (3 H, m, 26-H, 27-H_2), 1.09 (3 H, d, *J* 7.3, 24-Me), 0.97 (3 H, d, *J* 6.6, 26-Me) and 0.93 (3 H, t, *J* 7.3, 27-Me); *m/z* 168 (M^+), 112 (M^+ – Bu^s) and 82 (M^+ – Bu^s – CO) (Found: M^+, 168.1150. $C_{10}H_{16}O_2$ requires M, 168.1150).

Ferrilactone **30** (0.1 g, 0.32 mmol) in dry benzene (25 ml) was heated at 140 °C for 42 h under a pressure of 240 atm of carbon monoxide in a high pressure bomb. Following the same procedure as before the lactones **32** (13 mg, 24%), **33** (5.0 mg, 10%) and **31** (35 mg, 65%), were isolated.

[5S,6R(S)]-*Tetrahydro*-5-*methyl*-6-(1-*methylpropyl*)*pyran*-2-*one* **34**.—The *α,β*-unsaturated lactone **31** (25 mg, 0.15 mmol) was stirred vigorously in ethyl acetate (5 ml) with catalytic PtO_2 under an atmosphere of H_2 overnight. The mixture was filtered through Celite, evaporated and purified by column chromatography on silica gel (40% ether–petroleum) to give the *lactone* **34** (25 mg, 100%) as a colourless oil, $[\alpha]_D^{20}$ +47.7 (*c* 1.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2962, 1735, 1459, 1380, 1248, 1107 and 1003; δ_H(270 MHz) 3.93 (1 H, dd, *J* 10.5 and 2.0, 25-H), 2.62 (1 H, ddd, *J* 17.9, 6.9 and 3.9, 22-H), 2.44 (1 H, m, 22-H), 1.95–1.30 (6 H, m, 23-H_2, 24-H, 26-H, 27-H_2), 0.97 (3 H, d, *J* 6.3, 24-Me), 0.92 (3 H, t, *J* 7.3, 27-Me) and 0.89 (3 H, d, *J* 6.8, 26-Me); *m/z* 170 (M^+), 142 (M^+ – CO), 112 (M^+ – Bu^s) and 82 (M^+ – Bu^s – CO) (Found: M^+, 170.1312. $C_{10}H_{18}O_2$ requires M, 170.1307).

[2S,5S,6R(S)]- *and* [2R,5S,6R(S)]-*Tetrahydro*-3-*methyl*-2-(1-*methylpropyl*)-6-(*phenylsulphonyl*)-2H-*pyran* **3**.—Diisobutylaluminium hydride (1.5 mol dm^{-3} solution in toluene; 0.91 ml, 1.37 mmol) was added dropwise to a stirred suspension of the lactone **34** (155 mg, 0.91 mmol) in toluene (2 ml) at −78 °C under argon. The mixture was stirred at this temperature for 1 h after which acetic acid (0.5 ml) was added dropwise, followed by water (0.5 ml); the mixture was then warmed slowly to room temperature. Sodium hydrogen carbonate and magnesium sulphate were added until a thick paste had formed, which was extracted with ethyl acetate (3 × 15 ml). The extracts were filtered through Celite, washing with ethyl acetate, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel (50% ether–petroleum) to give [2RS,5S,6R(S)]-*tetrahydro*-5-*methyl*-6-(1-*methylpropyl*)-*pyran*-2-*ol* (145 mg, 93%, 1:1 mixture of anomers), $[\alpha]_D^{20}$ +76.8 (*c* 1.1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3408, 2961, 1458, 1378, 1228, 1122, 1052, 997 and 930; δ_H(400 MHz) 5.30 (0.5 H, br s, 22-H), 4.65 (0.5 H, br m, 22-H), 3.60 (0.5 H, dd, *J* 9.0 and 2.0, 26-H), 3.05 (0.5 H, br s, OH), 3.03 (0.5 H, dd, *J* 10.0 and 2.0, 26-H), 2.40 (0.5 H, br s, OH), 1.95–1.15 (8 H, m, 23-H_2, 24-H_2, 25-H, 26-H, 27-H_2) and 1.00–0.70 (9 H, m, 3 × Me); *m/z* 172 (M^+), 154 (M^+ – H_2O), 115 (M^+ – Bu^s), 97 (M^+ – Bu^s – H_2O) and 87 ($C_5H_{11}O$) (Found: C, 69.55; H, 11.85. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%).

Sodium benzenesulphinate (3.5 g, 21.3 mmol) was added to aqueous sulphuric acid (7%; 60 ml, 42.9 mmol) and the solution extracted with CH_2Cl_2 (3 × 30 ml). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give benzenesulphinic acid. The sulphinic acid (2.7 g, 19.0 mmol) was added to a solution of [2*RS*,5*S*,6*R*(*S*)]-tetrahydro-5-methyl-6-(1-methylpropyl)pyran-2-ol (1.64 g, 9.52 mmol) in CH_2Cl_2 (50 ml) at 0 °C, followed by camphorsulphonic acid (30 mg, 0.12 mmol). The mixture was stirred for 4 h. Saturated aqueous sodium hydrogen carbonate (30 ml) was added and the mixture stirred vigorously for 2 min. The organic layer was separated and the aqueous phase extracted with ether (3 × 30 ml). The combined organic layers were washed with brine (30 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The solid residue was recrystallised from petroleum to give the *axial sulphone* **3** (2.0 g, 71%, <5% of other diastereoisomers by ^{1}H NMR) as plates, m.p. 67 °C (from petroleum); $[\alpha]_D^{20}$ +144.8 (*c* 1.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2961, 2935, 2867, 1454, 1302, 1144, 725 and 689; δ_H(270 MHz) 7.92–7.90 (2 H, m, Ph), 7.65 (1 H, m, Ph), 7.62–7.50 (2 H, m, Ph), 4.76 (1 H, dd, *J* 6.6 and 2.0, 22-H), 4.00 (1 H, dd, *J* 9.8 and 2.2, 26-H), 2.62 (1 H, m), 2.05–1.75 (2 H, m), 1.70–1.45 (3 H, m), 1.25 (1 H, m), 1.04 (1 H, m), 0.88 (3 H, d, *J* 6.3, 24-Me or 26-Me), 0.87 (3 H, t, *J* 7.3, 27-Me) and 0.70 (3 H, d, *J* 7.1, 24-Me or 26-Me); *m/z* 239 (M^+ – Bu^s), 155 (M^+ –

$PhSO_2$) and 142 ($PhSO_2H$) (Found: C, 65.0; H, 8.2. $C_{16}H_{24}O_3S$ requires C, 64.83; H, 8.16%).

3-Bromo-2-methylprop-2-en-1-ol **35**.—In a 5 l three-neck round-bottom flask was dissolved $Zr(cp)_2Cl_2$ (39 g, 133 mmol) in dry CH_2Cl_2 (1 l). After addition of trimethylaluminium (2 mol dm^{-3} solution in hexane; 800 ml, 1.6 mol), prop-2-ynyl alcohol (29.9 g, 533 mmol) was added in CH_2Cl_2 (250 ml) at 0 °C. The yellow solution was stirred for 20 h at room temperature and then cooled to −30 °C and bromine (41.2 ml, 800 mmol) added in CH_2Cl_2 (250 ml). After the mixture had been stirred for 3 h its temperature was allowed to rise to 0 °C and saturated aqueous K_2CO_3 (50 ml) was added, the internal temperature being maintained in the range 0–5 °C. A mixture of $MgSO_4$ and Na_2SO_4 (1:1; 500 g) was then added and the mixture stirred for 2 h. The mixture was filtered through a Celite pad and the solvent evaporated. The residue was purified by column chromatography on silica gel (50% ether–petroleum) to give the *vinyl bromide* **35** (39.5 g, 49%), as a colourless liquid; ν_{max}(film)/cm^{-1} 3315, 2918, 1633, 1290, 1068, 1014, 783 and 716; δ_H(270 MHz, systematic numbering) 6.26 (1 H, m, 3-H), 4.09 (2 H, m, 1-H) and 1.82 (3 H, d, *J* 1.4, 2-Me); *m/z* 150 and 152 (M^+), 135 and 133 ($M^+ - H_2O$), 71 ($M^+ - Br$) and 53 ($M^+ - Br - H_2O$).

(1E,3S,4S)-*1-Bromo-2,4-dimethylhexa-1,5-dien-3-ol* **36**.—Anhydrous *N*-methylmorpholine *N*-oxide (12.0 g, 89.4 mmol) and tetrapropylammonium perruthenate (2.0 g, 5.7 mmol) were added to a stirred solution of the alcohol **35** (9.0 g, 60.0 mmol) in dry CH_2Cl_2 (500 ml) over 4 Å molecular sieves (3.0 g). The mixture was stirred for 4 h, washed with aqueous $CuSO_4$, filtered through a Celite pad, washed with water and brine, dried ($MgSO_4$) and evaporated and the residue purified by column chromatography on silica gel (5% ether–petroleum) to give 3-bromo-2-methylprop-2-enal (8.4 g, 94%) as a colourless oil, ν_{max}(film)/cm^{-1} 3062, 2967, 2925, 2827, 2726, 1688 and 1607; δ_H(270 MHz, systematic numbering) 9.49 (1 H, s, CHO), 7.43 (1 H, q, *J* 1.5, 3-H) and 1.90 (3 H, d, *J* 1.5, 2-Me); *m/z* 150 and 148 (M^+), 69 ($M^+ - Br$) and 41 ($M^+ - Br - CO$). This aldehyde was unstable and was used immediately in the next step.

To a stirred mixture of potassium *tert*-butoxide (8.0 g, 71.4 mmol) and (*E*)-but-2-ene (13.3 ml, 143 mmol) in THF (100 ml) was added butyllithium (2.5 mol dm^{-3} solution in hexanes; 28.8 ml, 72.0 mmol). After complete addition, the mixture was stirred at −45 °C for 10 min. The resulting bright yellow solution was recooled to −78 °C and methoxydiisopinocampheylborane [25 g, 78 mmol, derived from (+)-α-pinene] was added in ether (30 ml). After the reaction mixture had been stirred at −78 °C for 30 min, boron trifluoride–ether (9.6 ml, 78 mmol) was added dropwise. 3-Bromo-2-methylprop-2-enal (9.7 g, 65.0 mmol) in THF (100 ml) was added *via* a cannula at −78 °C. The mixture was then stirred at −78 °C for 12 h, quenched with brine and left to warm to room temperature. The aqueous phase was extracted with ether and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in ether and 2-hydroxyethylamine (5.9 ml, 97 mmol) was added. A precipitate appeared and was filtered off. The filtrate was evaporated and the residue purified by column chromatography on silica gel (30% ether–petroleum) to give the *alcohol* **36** (8.3 g, 75%) as a colourless oil, $[\alpha]_D^{20}$ −11.5 (*c* 2.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3406, 3075, 2969, 2926, 1628, 1377, 1283, 1010 and 720; δ_H(270 MHz) 6.21 (1 H, m, 15-H), 5.72 (1 H, ddd, *J* 17.8, 10.0 and 8.3, 11-H), 5.18 (1 H, dm, *J* 17.8, 10-H), 5.17 (1 H, dm, *J* 10.0, 10-H), 3.79 (1 H, dd, *J* 8.3, 2.9, 13-H), 2.35 (1 H, m, 12-H), 1.97 (1 H, d, *J* 2.9, OH), 1.78 (3 H, d, *J* 1.2, 14-Me) and 0.92 (3 H, d, *J* 6.8, 12-Me); δ_C(125.8 MHz) 141.9 (C-14), 140.0 (C-11), 117.1 (C-10), 105.7 (C-15), 79.3 (C-13), 42.1 (C-12), 16.5 (14-Me) and 14.5 (12-Me); *m/z* 165 and 163 ($M^+ - 41$), 151 and 149 ($M^+ - C_4H_7$) (Found: $M^+ - OH + NH_4$, 206.0367. $C_8H_{16}BrN$ requires $M - OH + NH_4$, 206.0363).

(1E,3S,4S)-*1-Bromo-3-(tert-butyldiphenylsilyloxy)-2,4-dimethylhexa-1,5-diene* **5**.—*tert*-Butyldiphenylsilyl chloride (30.6 g, 117.3 mmol) was added to a solution of imidazole (15.2 g, 222.6 mmol) and 4-dimethylaminopyridine (1.4 g, 11.1 mmol) in DMF (10 ml). The stirred solution was heated for 1 h at 50 °C before addition of the vinyl bromide **36** (7.6 g, 37.1 mmol) in DMF (10 ml). After 4 days at 50 °C, the mixture was diluted with ether and washed three times with water and brine, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel (1% ether–petroleum) gave the *silyl ether* **5** (15.1 g, 92%), as a colourless oil, $[\alpha]_D^{20}$ −50.5 (*c* 4.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2959, 2930, 1628, 1589, 1426, 1111, 1072 and 702; δ_H(270 MHz) 7.70–7.30 (10 H, m, Ph), 5.35 (1 H, m, 15-H), 5.70 (1 H, ddd, *J* 17.0, 10.3 and 8.0, 11-H), 4.97 (1 H, dm, *J* 17.0, 10-H), 4.95 (1 H, dm, *J* 10.3, 10-H), 3.91 (1 H, d, *J* 7.4, 13-H), 2.38 (1 H, m, 12-H), 1.64 (3 H, d, *J* 1.2, 14-Me), 1.06 (9 H, s, Bu^t) and 0.78 (3 H, d, *J* 7.0, 12-Me); δ_C(125.8 MHz) 141.9 (C-14), 141.0 (C-11), 136.2 (2 C, d, Ph), 136.1 (2 C, d, Ph), 133.7 (s, Ph), 133.1 (s, Ph), 129.1 (2 C, d, Ph), 114.9 (C-10), 105.9 (C-15), 81.5 (C-13), 42.7 (C-12), 27.1 (3 C, q, Bu^t), 19.5 (s, Bu^t), 15.7 (12-Me) and 15.4 (14-Me); *m/z* 443 (M^+), 429 ($M^+ - Me$), 387 ($M^+ - Bu^t$), 239 (15), 159 (23) and 135 (79) (Found: C, 65.1; H, 7.25. $C_{24}H_{31}OSi$ requires C, 65.01; H, 7.00%).

[2S(2R,4E,6S,7S)]-2-[2-(tert-*Butyldimethylsilyloxy*)-6-(tert-*butyldiphenylsilyloxy*)-5,7-*dimethylnona*-4,8-*dienyl*]*oxirane* **37**.—*tert*-Butyllithium (1.7 mol dm^{-3} solution in pentane; 3.7 ml, 6.3 mmol) was added at −78 °C to a solution of the vinyl bromide **5** (1.3 g, 2.8 mmol) in ether (10 ml) and the mixture stirred for 0.5 h. Trimethylaluminium (2.0 mol dm^{-3} solution in hexanes; 1.7 ml, 3.8 mmol) was added and the reaction was stirred for 0.5 h at −78 °C; it was then allowed to warm to 0 °C and left for an additional 0.5 h. The reaction mixture was then cooled down to −30 °C and the bis-epoxide **4** (190 mg, 1.9 mmol) was added. The reaction was left to warm to 0 °C. After 2 h, water (0.3 ml) was added and the mixture left to warm to room temperature. A mixture of $NaHCO_3$ and Na_2SO_4 (1:1; 2 g) was added and the reaction mixture stirred for 2 h. It was then filtered, washed with ether and evaporated. The residue was purified by column chromatography on silica gel (30% ether–petroleum) to afford [αR(2E,4S,5S]-α-[4-(tert-*butyldiphenylsilyloxy*)-3,5-*dimethylhepta*-2,6-*dienyl*]*oxiran*-2-*ylethanol* (1.1 g, 82%) as a colourless oil, $[\alpha]_D^{20}$ −14.0 (*c* 0.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3446, 3069, 2927, 1388, 1110, 1055, 1006, 740 and 703; δ_H(500 MHz) 7.66 (2 H, dd, *J* 8.1 and 1.4, *ortho*-Ph), 7.64 (2 H, dd, *J* 8.1 and 1.4, *ortho*-Ph), 7.40–7.30 (6 H, m, *meta*-Ph, *para*-Ph), 5.75 (1 H, ddd, *J* 17.4, 10.3 and 7.6, 11-H), 5.01 (1 H, t, *J* 7.1, 15-H), 4.95 (1 H, dm, *J* 17.4, 10-H), 4.94 (1 H, dm, *J* 10.3, 10-H), 3.90 (1 H, d, *J* 7.2, 13-H), 3.64 (1 H, m, 17-H), 3.06 (1 H, m, 19-H), 2.79 (1 H, t, *J* 4.7, 20-H), 2.52 (1 H, dd, *J* 4.7 and 2.8, 20-H), 2.37 (1 H, m, 12-H), 2.05–1.98 (2 H, m, 16-H), 1.71 (1 H, d, *J* 4.1, OH), 1.70 (1 H, m, 18-H), 1.52 (3 H, s, 14-Me), 1.42 (1 H, ddd, *J* 14.4, 6.6 and 3.5, 18-H), 1.05 (9 H, s, Bu^t) and 0.79 (3 H, d, *J* 6.9, 12-Me); *m/z* 464 (M^+), 409 ($M^+ - Bu^t$), 351, 349, 265, 239, 199 and 135 (Found: $M^+ - Bu^t$, 409.2202. $C_{25}H_{31}O_3Si$ requires $M - Bu^t$, 409.2202) (Found: C, 75.15; H, 8.85. $C_{29}H_{40}O_3Si$ requires C, 75.00; H, 8.62%).

4-Dimethylaminopyridine (21 mg, 0.17 mmol) and triethylamine (0.64 ml, 0.46 mmol) were added to a solution of *tert*-butyldimethylsilyl chloride (104 mg, 0.69 mmol) in DMF (0.5 ml) under argon at room temperature. After 10 min the solution was added to [αR(2E,4S,5S),2S]-α[4-(*tert*-butyldiphenylsilyloxy)-

3,5-dimethylhepta-2,6-dienyl]oxiran-2-ylethanol (270 mg, 0.58 mmol) and stirred overnight. The reaction mixture was diluted with ether and washed with aqueous hydrochloric acid (2 mol dm^{-3}; 2 × 20 ml), saturated aqueous sodium hydrogen carbonate (25 ml) and water (25 ml). The ethereal phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2% ether–petroleum) to give the *silyl ether* **37** (313 mg, 94%) as a colourless oil, $[\alpha]_D^{20}$ −30.4 (*c* 1.03 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3069, 2955, 2929, 2890, 2856, 1636, 1589, 1255, 1110, 1069, 912, 835, 775, 740, 702 and 690; δ_H(500 MHz) 7.66 (2 H, dd, *J* 7.9 and 1.4, *ortho*-Ph), 7.59 (2 H, dd, *J* 7.9 and 1.4, *ortho*-Ph), 7.42–7.29 (6 H, m, *meta*- and *para*-Ph), 5.70 (1 H, ddd, *J* 17.4, 10.3 and 7.6, 11-H), 5.01 (1 H, t, *J* 7.0, 15-H), 4.92 (1 H, dm, *J* 17.4, 10-H), 4.89 (1 H, dm, *J* 10.3, 10-H), 3.83 (1 H, d, *J* 7.4, 13-H), 3.79 (1 H, m, 17-H), 2.95 (1 H, m, 19-H), 2.75 (1 H, dd, *J* 5.1 and 4.0, 20-H), 2.37 (1 H, dd, *J* 5.1 and 2.8, 20-H), 2.32 (1 H, m, 12-H), 2.07 (1 H, ddd, *J* 14.0, 7.5 and 4.0, 18-H), 1.98 (1 H, m, 16-H), 1.49 (3 H, s, 14-Me), 1.48 (1 H, m, 16-H), 1.35 (1 H, ddd, *J* 14.0, 7.0 and 3.4, 18-H), 1.04 (9 H, s, Bu^t – TBDPS), 0.87 (9 H, s, Bu^t – TBDMS), 0.75 (3 H, d, *J* 6.9, 12-Me), 0.05 (3 H, s, MeSi) and 0.04 (3 H, s, MeSi); *m/z* 523 ($M^+ - C_4H_7$), 389, 265, 201 and 73 (Found: $M^+ - C_4H_7$, 523.3063. $C_{31}H_{47}O_3Si_2$ requires M – C_4H_7, 523.3064) (Found: C, 72.45; H, 9.4. $C_{35}H_{54}O_3Si_2$ requires C, 72.61; H, 9.40%).

[αS(2R,4E,6S,7S),2R(S),3S]-α-[4-(tert-*Butyldimethylsilyloxy*)-6-(tert-*butyldiphenylsilyloxy*)-5,7-*dimethylnona*-4,8-*dienyl*]-3,4-*dihydro*-3-*methyl*-2-(1-*methylpropyl*)-2H-*pyran*-2-*ylethanol* **38**.—Butyllithium (2.5 mol dm^{-3} solution in hexane;) 2.52 μl, 6.3 mmol) was added to a solution of the sulphone **3** (1.7 g, 5.7 mmol) in THF (12 ml) at −78 °C. After the mixture had been stirred for 30 min, the epoxide **37** (0.52 g, 0.89 mmol) was added in THF (2 ml) at −78 °C. The solution was stirred at − 78 °C for 2 min before addition of boron trifluoride–ether (165 μl, 1.34 mmol) and left at that temperature for 2 h before being allowed to warm up slowly to room temperature (12 h). After the reaction mixture had been cooled to −78 °C, saturated aqueous sodium carbonate (5 ml) was added and the mixture was left to warm to room temperature. The mixture was extracted with ether and the extract dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (3% ether–petroleum) gave the *enol ether* **38** (295 mg, 45%) as a colourless liquid, $[\alpha]_D^{20}$ −4.0 (*c* 0.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3450, 2956, 2865, 1725, 1675, 1460, 1426, 1377, 1256, 1187, 1110, 1071, 836, 776, 740 and 702; δ_H(500 MHz) 7.66 (2 H, dd, *J* 7.9 and 1.4, *ortho*-Ph), 7.58 (2 H, dd, *J* 7.9 and 1.4, *ortho*-Ph), 7.42–7.29 (6 H, m, *meta*- and *para*-Ph), 5.71 (1 H, ddd, *J* 17.5, 10.3 and 7.5, 11-H), 5.03 (1 H, t, *J* 6.9, 15-H), 4.94 (1 H, dm, *J* 17.5, 10-H), 4.90 (1 H, dm, *J* 10.3, 10-H), 4.46 (1 H, m, 22-H), 3.94 (1 H, m, 19-H), 3.89 (1 H, m, 17-H), 3.83 (1 H, d, *J* 7.5, 13-H), 3.39 (1 H, dd, *J* 9.0, 2.7, 25-H), 2.80 (1 H, d, *J* 2.7, OH), 2.32 (1 H, m, 12-H), 2.30–1.50 (8 H, m, 16-H_2, 18-H_2, 20-H_2, 23-H_2), 1.50–1.10 (4 H, m, 24-H, 26-H, 27-H_2), 1.48 (3 H, s, 14-Me), 1.04 (9 H, s, Bu^t – TBDPS), 0.87 (9 H, s, Bu^t – TBDMS), 0.90–0.80 (9 H, m, 24-Me, 26-Me, 28-Me), 0.74 (3 H, d, *J* 6.9, 12-Me), 0.05 (3 H, s, MeSi) and 0.04 (3 H, s, MeSi); *m/z* 659 ($M^+ - C_4H_7 - H_2O$), 657 (M^+ – Bu^t – H_2O), 527, 377, 199 and 191 (Found: $M^+ - C_4H_7 - H_2O$, 657.4162. $C_{31}H_{47}O_3Si_2$ requires M – C_4H_7 – H_2O, 657.4159).

[2R(2E,4S,5S),4S,6S,8R(S),9S]-2-[4-tert-*Butyldiphenylsilyloxy*-3,5-*dimethylhepta*-2,6-*dienyl*]-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*[5.5]*undec*-10-*en*-4-*ol* **39**.—Benzeneselenenyl chloride (94 mg, 0.5 mmol) was added at room temperature to a solution of the enol ether **38** (0.3 g, 0.4 mmol) in THF, to give an orange solution that faded after 3 min. Methanol (0.17 ml, 4.1 mmol) was then added at room temperature and the mixture was stirred for a further 3 min before addition of triethylamine (0.07 ml, 1.0 mmol) at 0 °C to give a white precipitate. The mixture was stirred for 30 min, saturated aqueous sodium hydrogen carbonate (3 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 4 ml). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The oil was dissolved in methanol (5 ml) and a catalytic amount of camphorsulphonic acid added. After the solution had been stirred at room temperature for 3 h, saturated aqueous sodium hydrogen carbonate (2 ml) was added and the mixture extracted with CH_2Cl_2 (4 × 10 ml). The extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (20% ether–petroleum) to give [2R(2E,4S,5S),4S,6S,8*R*(*S*),9*S*,11*RS*]-2-[4-*tert*-(butyldiphenylsilyloxy)-3,5-dimethylhepta-2,6-dienyl]-9-methyl-8-(1-methylpropyl)-11-(phenylselenenyl)-1,7-dioxaspiro[5.5]undecan-4-ol (0.21 g, 66%) as a colourless oil, ν_{max}(film)/cm^{-1} 3415, 3069, 1639, 1577, 1472, 1456, 1435, 1426, 1378, 1111, 1041, 910, 822, 740 and 702; δ_H(500 MHz) 7.67–7.23 (15 H, m, Ph), 5.75 (1 H, m, 11-H), 5.01 (1 H, t, *J* 6.9, 15-H), 4.98–4.90 (2 H, m, 10-H), 4.01 (1 H, m, 19-H), 3.85 (0.5 H, d, *J* 7.3, 13-H), 3.84 (0.5 H, d, *J* 7.2, 13-H), 3.45 (1 H, m, 17-H), 3.25 (0.5 H, t, *J* 3.1, 22-H), 3.15 (0.5 H, dd, *J* 10.1 and 1.9, 25-H), 3.12 (0.5 H, dd, *J* 12.0 and 1.6, 25-H), 2.96 (0.5 H, dd, *J* 11.5 and 6.5, 22-H), 2.67 (0.5 H, br d, *J* 3.0, OH), 2.64 (0.5 H, br d, *J* 3.0, OH), 2.40–2.05 (3 H, m, 12-H, 16-H_2), 2.00–1.65 (4 H, m, 18-H_2, 20-H_2), 1.52 (1.5 H, s, 14-Me), 1.48 (1.5 H, s, 14-Me), 1.55–1.00 (6 H, m, 23-H_2, 24-H, 25-H, 26-H_2), 1.05 (4.5 H, s, Bu^t – TBDPS), 1.03 (4.5 H, s, Bu^t – TBDPS) and 0.95–0.72 (12 H, m, 12-Me, 24-Me, 26-Me, 27-Me); *m/z* 716 (M^+ – Bu^t), 563, 523, 509, 435, 407, 379, 277, 199 and 149.

2-(Phenylsulphonyl)-3-(*p*-nitrophenylsulphonyl)oxaziridine (78.4 mg, 0.26 mmol) was added to a stirred solution of the [2R(2E,4S,5S),4S,6S,8R(S),9S,11RS]-2-[4-(*tert*-butyldiphenylsilyloxy)-3,5-dimethylhepta-2,6-dienyl]-9-methyl-8-(1-methylpropyl)-11-(phenylselenenyl)-1,7-dioxaspiro[5.5]undecan-4-ol (90 mg, 0.12 mmol) in $CHCl_3$ (3 ml), causing the formation of a white precipitate after 10 min. Triethylamine (40 μl, 0.6 mmol) was added and the mixture heated at 50 °C for 3 h, causing the precipitate to dissolve slowly. The solution was allowed to cool to room temperature and the solvent was evaporated. Chromatography of the residue on silica gel (20% ether–petroleum) gave the *unsaturated spiroacetal* **39** (54 mg, 76%) as a colourless oil, $[\alpha]_D^{20}$ +41.0 (*c* 0.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3390, 2968, 2926, 1459, 1426, 1379, 1111, 1040, 997, 910, 822, 738, 702 and 690; δ_H(500 MHz) 7.65 (2 H, dd, *J* 8.0 and 1.3, *ortho*-Ph), 7.60 (2 H, dd, *J* 8.1 and 1.4, *ortho*-Ph), 7.47–7.30 (6 H, m, *meta*- and *para*-Ph), 5.74 (1 H, ddd, *J* 17.4, 10.3 and 7.6, 11-H), 5.69 (1 H, dd, *J* 9.9 and 1.7, 22-H), 5.52 (1 H, dd, *J* 9.9 and 2.6, 23-H), 4.96 (1 H, dm, *J* 17.4, 10-H), 4.95 (1 H, t, *J* 7.0, 15-H), 4.92 (1 H, dm, *J* 10.3, 10-H), 4.02 (1 H, m, 19-H), 3.84 (1 H, d, *J* 7.5, 13-H), 3.61 (1 H, m, 17-H), 3.36 (1 H, dd, *J* 10.0 and 1.7, 25-H), 2.33 (1 H, m, 12-H), 2.21 (1 H, m, 24-H), 2.15 (1 H, m, 16-H), 1.95 (1 H, ddd, *J* 12.1, 4.5 and 1.8, 20-H_{eq}), 1.88 (1 H, m, 16-H), 1.75 (1 H, m, 18-H_{eq}), 1.54 (3 H, s, 14-Me), 1.50–1.00 (5 H, m, 20-H_{ax}, 18-H_{ax}, 26-H, 27-H_2), 1.04 (9 H, s, Bu^t), 0.90–0.84 (9 H, m, 24-Me, 26-Me, 28-Me) and 0.76 (3 H, d, *J* 6.9, 12-Me); *m/z* 561 ($M^+ - C_4H_7$), 559 (M^+ – Bu^t), 543 ($M^+ - C_4H_7 - H_2O$), 541 (M^+ – Bu^t – H_2O), 475, 393, 351, 287, 265, 239, 199 and 197 (Found: $M^+ - C_4H_7$, 561.3409. $C_{35}H_{47}O_4Si$ requires M – C_4H_7, 561.3400).

[2R(2E,4S,5S),4S,6S,8R(S),9S]-2-[4-*Hydroxy*-3,5-*dimethylhepta*-2,6-*dienyl*]-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*-[5.5]*undec*-10-*en*-4-*ol***40**.—Tetrabutylammoniumfluoride(1mol dm^{-3} solution in THF; 130 μl, 0.13 mmol) was added drop-

wise to a stirred solution of the silyl ether **39** (20 mg, 0.03 mmol) in THF (3 ml) under argon. The solution was heated at reflux for 5 min. Solvent evaporation followed by column chromatography of the residue on silica gel (40% ether–petroleum) afforded the *alcohol* **40** (12 mg, 98%), $[\alpha]_D^{20}$ +36 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3382, 2960, 2927, 1636, 1453, 1379, 1281, 1150, 1124, 1073, 994, 911, 862, 760 and 733; δ_H(500 MHz, $CDCl_3$, avermectin numbering) 5.78–5.70 (2 H, m, 11-H, 23-H), 5.56 (1 H, dd, *J* 9.8 and 2.6, 22-H), 5.42 (1 H, t, *J* 7.0, 15-H), 5.19–5.13 (2 H, m, 10-H_2), 4.12 (1 H, tt, *J* 11.2 and 4.6, 19-H), 3.79 (1 H, m, 17-H), 3.65 (1 H, d, *J* 8.7, 13-H), 3.40 (1 H, dd, *J* 10.0 and 1.8, 25-H), 2.39–2.29 (2 H, m, 12-H, 16-H), 2.25–2.18 (2 H, m, 16-H, 24-H), 2.02–1.96 (2 H, m, 18-H, 20-H), 1.74 (1 H, br s, OH), 1.62 (3 H, d, *J* 0.9, 14-Me), 1.58 (1 H, m, 26-H), 1.46–1.31 (4 H, m, 20-H, 27-H_2, OH), 1.14 (1 H, q, *J* 11.7, 18-H), 0.92 (3 H, t *J* 7.2, 27-Me), 0.90 (3 H, d, *J* 7.2, Me), 0.88 (3 H, d, *J* 6.8, Me) and 0.86 (3 H, d, *J* 6.9, Me); *m/z* 378 (0.4%, M^+), 360 ($M^+ - H_2O$), 323 ($M^+ - C_4H_7$), 305 ($M^+ - C_4H_7 - H_2O$), 292, 239, 221, 167, 109 and 55 [Found (CI, NH_3): MH^+, 379.2848. $C_{23}H_{39}O_4$ requires MH, 379.2848] (Found: C, 72.85; H, 10.4. $C_{23}H_{38}O_4$ requires C, 72.98; H, 10.12%).

[2R(2E,4S,5S),4S,6S,8R(S),9S]-4-(tert-*Butyldimethylsilyloxy*)-2-[4-tert-*butyldimethylsilyloxy*)-3,5-*dimethylhepta*-2,6-*dienyl*]-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*[5.5]-*undec*-10-*ene* **41**.—The diol **40** (3.5 mg, 0.009 mmol), imidazole (25 mg, 0.37 mmol) and *tert*-butyldimethylsilyl chloride (36 mg, 0.24 mmol) were combined at room temperature under argon and then taken up in DMF (100 μl). After 16 h, the mixture was partitioned between petroleum and water. The aqueous layer was extracted with petroleum (×3). The combined extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on silica gel (gradient elution, 2–5% ether–petroleum) afforded the *bis-silyl ether* **41** (5.3 mg, 95%), $[\alpha]_D^{20}$ +45 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3075, 2957, 2929, 2886, 2857, 1636, 1460, 1380, 1360, 1254, 1213, 1155, 1118, 1068, 997, 939, 911, 874, 836, 774 and 733; δ_H(500 MHz) 5.84 (1 H, ddd, *J* 17.5, 10.5 and 7.3, 11-H), 5.69 (1 H, dd, *J* 9.9 and 1.8, 23-H), 5.55 (1 H, dd, *J* 9.9 and 2.6, 22-H), 5.26 (1 H, t, *J* 7.1, 15-H), 4.99–4.94 (2 H, m, 10-H_2), 4.10 (1 H, tt, *J* 11.1 and 4.6, 19-H), 3.75 (1 H, m, 17-H), 3.66 (1 H, d, *J* 7.6, 13-H), 3.41 (1 H, dd, *J* 9.9 and 1.7, 25-H), 2.33–212 (4 H, m, 12-H, 24-H, 16-H_2), 1.88–1.83 (2 H, m, 18-H_{eq}, 20-H_{eq}), 1.55 (3 H, d, *J* 0.5, 14-Me), 1.54 (1 H, m, 26-H), 1.47–1.34 (3 H, m, 20-H_{ax}, 27-H_2), 1.16 (1 H, q, *J* 11.8, 18-H_{ax}), 0.93 (3 H, t, *J* 7.5, 27-Me), 0.90 (3 H, d, *J* 7.2, Me), 0.88 (9 H, s, Bu^t), 0.87 (9 H, s, Bu^t), 0.86 (3 H, d, *J* 6.9, Me), 0.83 (3 H, d, *J* 6.8, Me), 0.05 (6 H, s, MeSi), 0.00 (3 H, s, MeSi) and −0.05 (3 H, s, MeSi); *m/z* 591 (M^+ − Me), 551, 549, 419, 385, 353, 221, 187 and 49 (Found (CI, NH_3): MH^+, 607.4578. $C_{35}H_{67}O_4Si$ requires MH, 607.4578) (Found: C, 69.35; H, 11.05. $C_{35}H_{66}O_4Si_2$ requires C, 69.25; H, 10.96%).

[2S,3S,4E,6[2R,4S,6S,8R(S),9S]]-3-(tert-*Butyldimethylsilyloxy*)-6-[4-tert-*butyldimethylsilyloxy*)-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*[5.5]*undec*-10-*en*-2-*yl*]-2,4-*dimethylhex*-4-*enal* **42**.—Osmium tetroxide (2.5 wt% solution in *tert*-butyl alcohol; 15 μl, 0.001 mmol) was added to a stirred solution of the alkene **41** (38 mg, 0.063 mmol) and *N*-methylmorpholine *N*-oxide (7.5 mg, 0.064 mmol) in *tert*-butyl alcohol–THF–H_2O (10:3:1; 1 ml) at room temperature. After 100 h, the reaction was cooled to 0 °C and a slurry of saturated aqueous sodium sulphite and talc was added. The mixture was stirred for a further 16 h, after which it was filtered through a pad of Celite, the latter being washed thoroughly with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (×3) and then the combined extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on silica gel [gradient elution, 10% ether–petroleum; ether–petroleum–methanol (50:49:1)] afforded {2RS,3S,4S,5E,7[2R,4S,6S,8R(S),9S]}-4-(tert-*butyldimethylsilyloxy*)-7-[4-(tert-*butyldimethylsilyloxy*)-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*[5.5]*undec*-10-*en*-2-*yl*]-3,5-*dimethylhept*-5-*ene*-1,2-*diol* (7:3 mixture of diastereoisomers) (31 mg, 77% as a colourless oil, ν_{max}(film)/cm^{-1} 3436, 2956, 2929, 2884, 2856, 1462, 1381, 1254, 1213, 1154, 1118, 1070, 1000, 873, 836, 775 and 733; δ_H(500 MHz) 5.69 (0.3 H, dd, *J* 9.9 and 1.7, 23-H), 5.68 (0.7 H, dd, *J* 9.9 and 1.7, 23-H), 5.54 (0.3 H, dd, *J* 9.9 and 2.6, 22-H), 5.53 (0.7 H, dd, *J* 9.9 and 2.6, 22-H), 5.44 (0.3 H, t, *J* 7.1, 15-H), 5.33 (0.7 H, t, *J* 6.8, 15-H), 4.57 (0.7 H, br s), 4.14–4.08 (1 H, m, 19-H), 4.01 (0.3 H, d, *J* 6.0), 3.97 (0.3 H, m), 3.90 (0.7 H, d, *J* 7.2), 3.81–3.75 (1 H, m, 17-H), 3.71–3.60 (1.7 H, m), 3.57–3.48 (1 H, m), 3.39 (0.3 H, dd, *J* 10.0 and 1.6, 25-H), 3.36 (0.7 H, dd, *J* 10.0 and 1.5, 25-H), 3.29 (0.3 H, d, *J* 4.0), 2.38–2.29 (1 H, m), 2.23–2.13 (2.7 H), 1.97 (0.3 H, dd, *J* 8.4 and 3.8), 1.88–1.77 (3 H, m), 1.59–1.55 [4 H, m (inc. 14-Me at 1.57)], 1.45–1.34 (3 H, m), 1.19 (1 H, q, *J* 11.7, 18-H_{ax}), 0.94–0.84 (28 H, m, Me), 0.67 (2 H, d, *J* 6.9, Me), 0.11 (2 H, s, MeSi), 0.09 (1 H, s, MeSi), 0.05 (6 H, s, MeSi), 0.02 (2 H, s, MeSi) and 0.00 (1 H, s, MeSi); *m/z* 640 (M^+), 622 ($M^+ - H_2O$), 583, 565, 551, 353, 285, 187, 73 and 57 [Found (FAB from 3-nitrobenzyl alcohol): MNa^+, 663.445. $C_{35}H_{68}NaO_{46}Si_2$ requires MNa, 663.447] (Found: C, 65.45; H, 10.95. $C_{35}H_{68}O_6Si_2$ requires C, 65.57; H, 10.69%).

Sodium periodate (14.0 mg, 0.065 mmol) was added to a stirred solution of {2*RS*,3*S*,4*S*,5*E*,7[2*R*,4*S*,6*S*,8*R*(*S*),9*S*]}-4-(*tert*-butyldimethylsilyloxy)-7-[4-(*tert*-butyldimethylsilyloxy)-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undec-10-en-2-yl]-3,5-dimethylhept-5-ene-1,2-diol (7:3 mixture of diastereoisomers) (14.0 mg, 0.022 mmol) and potassium dihydrogen orthophosphate (100 mg) in methanol–water (4:1) (1 ml) at room temperature. After 3 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (×3). The combined extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on silica gel (gradient elution: 5–10% ether–petroleum) afforded the *aldehyde* **42** (12.0 mg, 86%) as a colourless oil, $[\alpha]_D^{20}$ +31 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2957, 2929, 2856, 1726, 1461, 1381, 1253, 1213, 1155, 1117, 1068, 998, 918, 873, 836, 775 and 733; δ_H(500 MHz) 9.75 (1 H, d, *J* 2.8, 11(H), 5.69 (1 H, dd, *J* 9.9 and 1.8, 23-H), 5.54 (1 H, dd, *J* 9.8 and 2.6, 22-H), 5.39 (1 H, t, *J* 6.7, 15-H), 4.11 (1 H, tt, *J* 11.0 and 4.6, 19-H), 4.09 (1 H, d, *J* 8.8, 13-H), 3.77 (1 H, m, 17-H), 3.38 (1 H, dd, *J* 9.9 and 1.7, 25-H), 2.55 (1 H, m, 12-H), 2.33 (1 H, m, 16-H), 2.26–2.16 (2 H, m, 16-H, 24-H), 1.87 (1 H, ddd, *J* 12.2, 4.5 and 1.9, 20-H_{eq}), 1.82 (1 H, m, 18-H_{eq}), 1.59 (3 H, s, 14-Me), 1.57 (1 H, m, 26-H), 1.46–1.34 (3 H, m, 20-H_{ax}, 27-H_2), 1.19 (1 H, q, *J* 11.7, 18-H_{ax}), 0.93 (3 H, t, *J* 7.4, 27-Me), 0.90–0.85 (27 H, m, 2 × Bu^t (0.88 and 0.85), 12-Me, 24-Me, 26-Me), 0.05 (6 H, s, MeSi), 0.03 (3 H, s, MeSi) and −0.03 (3 H, s, MeSi); *m/z* (CI, NH_3) 609 (MH^+), 551, 477, 353, 311 and 229 (Found: MH^+, 609.4370. $C_{34}H_{65}O_5Si_2$ requires MH, 609.4371) (Found: C, 66.9; H, 10.85. $C_{34}H_{64}O_5Si_2$ requires C, 67.05; H, 10.59%).

(3E{2E,4S,5S,6E,8[2R,4S,6S,8R(S),9S]}-3aS,4S,7R,7aR)-7-(tert-*Butyldimethylsilyloxy*)-3-[5-(tert-*butyldimethylsilyloxy*)-8-[tert-*butyldimethylsilyloxy*)-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*[5.5]*undec*-10-*en*-2-*yl*]-4,6-*dimethylocta*-2,6-*dienylidene*]-4-[(tert-*butyldiphenylsilyloxy*)*methyl*]*octahydro*-6-*methylbenzofuran*-3a-*ol* **44**.—*tert*-Butyllithium (1.7 mol dm^{-3} solution in pentane; 0.192 ml, 0.326 mmol) was added dropwise to a stirred solution of the sulphone **2** (106.6 mg, 0.148 mmol) in THF (2 ml), under argon, at −78 °C. After 10 min, a solution of the aldehyde **42** in THF (3 ml) was added by cannula. After a further 1 h, saturated aqueous ammonium chloride (1 ml) was added and the mixture allowed to warm to room temperature. Water was added and the mixture extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on silica gel (10–25–

50% ether–petroleum) gave unchanged aldehyde **42** (21.3 mg, 24%), the hydroxy sulphones **43** (140.8 mg, 74%), and the starting sulphone **2** (29.2 mg, 27%).

Powdered 6% sodium amalgam (397 mg, 1.04 mmol) was added to a vigorously stirred slurry of disodium hydrogen orthophosphate (0.54 g, 3.80 mmol) and the hydroxy sulphones **43** (140.8 mg, 0.11 mmol) in THF–methanol (3:1; 4 ml) under argon at −40 °C. After 90 min, a further portion of powdered sodium amalgam (397 mg, 1.04 mmol) was added. After a further 45 min, the reaction mixture was cooled to −78 °C, ethyl acetate (5 ml) and powdered ammonium chloride were added and the mixture filtered rapidly through a pad of ammonium chloride and silica gel. The filtrate was concentrated. Column chromatography of the residue on silica gel (10% ether–petroleum) afforded the *diene* **44** (42.2 mg, 34%) as a clear oil and as a 7:1 mixture of Δ^{10} *E*:*Z* mixture, $[\alpha]_D^{20}$ +64 (*c* 0.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3467, 3070, 2929, 2855, 1459, 1154, 1003 and 775 cm^{-1}; δ_H(500 MHz) 7.70–7.68 (2 H, m, Ph), 7.65–7.63 (2 H, m, Ph), 7.48–7.39 (6 H, m, Ph), 5.98 (1 H, br d, *J* 11.1, 9-H), 5.82 (1 H, dd, *J* 14.8 and 11.3, 10-H), 5.70 (1 H, dd, *J* 10.0 and 1.8, 23-H), 5.59 (1 H, dd, *J* 14.8 and 8.0, 11-H), 5.55 (1 H, dd, *J* 10.0 and 2.5, 22-H), 5.28 (1 H, t, *J* 6.8, 15-H), 5.04 (1 H, s, 7-OH), 4.58 (1 H, dd, *J* 14.4 and 2.2, 8′-H), 4.45 (1 H, dd, *J* 14.4 and 2.2, 8′-H), 4.15 (1 H, dd, *J* 10.5 and 2.5, 1-H), 4.11 (1 H, tt, *J* 11.0 and 4.5, 19-H), 3.77 (1 H, m, 17-H), 3.65–3.58 (4 H, m, 1-H, 5-H, 6-H, 13-H), 3.41 (1 H, dd, *J* 9.9 and 1.7, 25-H), 2.36–2.20 (3 H, m, 12-H, 16-H, 24-H), 2.15 (1 H, dt, *J* 14.6 and 7.3, 16-H), 1.93–1.77 (4 H, m, 3-H, 4-H, 18-H, 20-H), 1.60–1.54 (4 H, m, 14-Me at 1.54, 26-H), 1.50–1.35 (5 H, m, 2-H, 3-H, 20-H, 27-H_2), 1.18 (1 H, q, *J* 11.8, 18-H), 1.11 (9 H, s, Bu^t), 1.01 (3 H, d, *J* 6.4, Me), 0.94 (3 H, t, *J* 7.5, 27-Me), 0.92 (9 H, s, Bu^t), 0.90 (3 H, d, *J* 6.9, Me), 0.89 (9 H, s, Bu^t), 0.87 (3 H, d, *J* 6.9, Me), 0.81 (3 H, d, *J* 6.8, Me), 0.76 (9 H, s, Bu^t), 0.11 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.06 (3 H, s, $SiCH_3$), 0.06 (3 H, s, $SiCH_3$), −0.10 (3 H, s, $SiCH_3$) and −0.12 (3 H, s, $SiCH_3$); *m*/*z* 1152 ($M^+ - H_2O$), 1096 ($MH^+ + H_2O$ + Bu^t) and 1020 ($M^+ - H_2O$ − TBDMSOH) (Found: C 69.9; H, 10.05. $C_{68}H_{114}O_8Si_4$ requires C, 69.69; H, 9.81%).

(3E{2E,4S,5S,6E,8[2R,4S,6S,8R(S),9S]},3aS,4S,6S,7R,7aR)-*Octahydro*-4-(*hydroxymethyl*)-3-{5-*hydroxy*-8-[4-*hydroxy*-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*[5.5]*undec*-10-*en*-2-*yl*]-4,6-*dimethylocta*-2,6-*dienylidene*}-6-*methylbenzofuran*-3a,7-*diol* **45**.—Tetrabutylammonium fluoride (1.0 mol dm^{-3} solution in THF; 500 μl, 0.50 mmol) was added to a stirred solution of the silyl ether **44** (101 mg, 0.086 mmol) in THF at room temperature under argon. The solution was then heated to reflux. After 36 h the mixture was allowed to cool, then concentrated under reduced pressure. Column chromatography of the residue on the minimum amount of silica gel [gradient elution, ethyl acetate–CH_2Cl_2–MeOH (79:2:1) ethyl acetate–CH_2Cl_2–MeOH (77:20:3)] afforded the *pentol* **45** (47.1 mg, 93%) as a white solid, $[\alpha]_D^{20}$ +41 (*c* 0.67 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3380, 2960, 2880, 1452, 1379, 1018 and 756; δ_H(500 MHz 6.04 (1 H, dt, *J* 11.0 and 2.4, 9-H), 5.95 (1 H, dd, *J* 14.9 and 11.1, 10-H), 5.72 (1 H, dd, *J* 9.8 and 1.8, 23-H), 5.69 (1 H, dd, *J* 15.0 and 8.1, 11-H), 5.55 (1 H, dd, *J* 9.7 and 2.6, 22-H), 5.38 (1 H, t, *J* 7.0, 15-H), 4.61 (1 H, dd, *J* 14. 4 and 2.2, 8′-H), 4.54 (1 H, dd, *J* 14.4 and 2.3, 8′-H), 4.13–4.06 (3 H, m, 1-H, OH, 19-H), 3.83–3.78 (2 H, m, 13-H, 17-H), 3.68 (1 H, d, *J* 3.7, 6-H), 3.62 (1 H, br d, *J* 11.0, 1-H), 3.46– (1 H, td, *J* 10.2 and 3.6, 5-H), 3.40 (1 H, dd, *J* 10.0 and 1.7, 25-H), 2.80 (1 H, br s, OH), 2.45 (1 H, sextet, *J* 7.1, 12-H), 2.37 (1 H, dt, *J* 12.0 and 6.0, 16-H), 2.26–2.18 (2 H, m, 16-H, 24-H), 2.01–1.91 (4 H, m, 18-H_{eq}, 20-H_{eq}, OH, OH), 1.84 (1 H, m, 4-H), 1.75 (1 H, br s, OH), 1.69 (1 H, q, *J* 13.0, 2-H), 1.61 (3 H, s, 14-Me), 1.58–1.52 (3 H, m, 3-H_2, 26-H), 1.45–1.34 (3 H, m, 20-H_{ax}, 27-H_2), 1.11–1.06 (4 H, m, 18-H_{ax}, 4-Me), 0.96 (3 H, d, *J* 6.8, 12-Me), 0.92 (3 H, t, *J* 7.0, 27-Me), 0.90 (3 H, d, *J* 7.1, 24-Me) and 0.86 (3 H, d, *J* 6.8, 26-Me); *m*/*z* 572 ($M^+ - H_2O$), 554 ($M^+ - 2H_2O$), 323, 249, 239, 221 and 43 (Found: $M^+ - 2H_2O$, 554.3609. $C_{34}H_{50}O_6$ requires $M - 2H_2O$, 554.3607) (Found: C, 68.8; H, 9.5. $C_{34}H_{54}O_8$ requires C, 69.09; H, 9.21%).

(3E{2E,4S,5S,6E,8[2R,4S,6S,8R(S),9S]},3aS,4R,6S,7R,7aR)-*Octahydro*-3a,7-*dihydroxy*-3-{5-*hydroxy*-8-[4-*hydroxy*-9-*methylpropyl*)-1,7-*dioxaspiro*[5.5]*undec*-10-*en*-2-*yl*]-4,6-*dimethylocta*-2,6-*dienylidene*}-6-*methylbenzofuran*-4-*carboxylic Acid* **46**.—Tris(triphenylphosphine)ruthenium(II) chloride (75 mg, mmol) was added to a stirred solution of the pentol **45** (65.0 mg, 0.058 mmol) in benzene–CH_2Cl_2 (6:1; 12 ml) at room temperature. After 48 h, the reaction mixture was evaporated. Column chromatography of the residue on the minimum amount of Florisil (20% CH_2Cl_2–ethyl acetate) afforded (3E{2E,4S,5S,6E,8[2R,4S,6S,8R(S),9S]}3aS,4S,6S,7R,7aR)-*octahydro*-3a,7-*dihydroxy*-3-{5-*hydroxy*-8-[4-*hydroxy*-9-*methyl*-8-(1-*methylpropyl*)-1,7-*dioxaspiro*[5.5]*undec*-10-*en*-2-*yl*]-4,6-*dimethylocta*-2,6-*dienylidene*}-6-*methylbenzofuran*-4-*carbaldehyde* contaminated with triphenylphosphine oxide (51 mg) as a grey foam. A pure sample of aldehyde was obtained by reverse phase HPLC (20% H_2O–MeOH), $[\alpha]_D^{20}$ +18 (*c* 0.57 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3390, 2958, 2926, 1718, 1453, 1378, 1268, 1113, 1044, 997 and 733; δ_H(500 MHz) 9.78 (1 H, d, *J* 1.1, 1-H), 6.06 (1 H, dt, *J* 11.0 and 2.5, 9-H), 5.94 (1 H, dd, *J* 15.0 and 11.1, 10-H), 5.72 (1 H, dd, *J* 9.9 and 1.7, 23-H), 5.69 (1 H, dd, *J* 15.0 and 8.0, 11-H), 5.55 (1 H, dd, *J* 9.9 and 2.6, 22-H), 5.40 (1 H, t, *J* 7.1, 15-H), 4.66 (2 H, m, 8′-H_2), 4.11 (1 H, tt, *J* 11.0 and 4.5, 19-H), 3.82–3.76 (2 H, m, 13-H, 17-H), 3.70 (1 H, d, *J* 3.7, 6-H), 3.45 (1 H, m, 5-H), 3.40 (1 H, dd, *J* 9.9 and 1.7, 25-H), 2.80 (1 H, br s, OH), 2.58 (1 H, dd, *J* 12.8 and 2.5, 2-H), 2.43 (1 H, m, 12-H), 2.35 (1 H, m, 16-H), 2.26–2.20 (2 H, m, 16-H, 24-H), 2.02–1.94 (2 H, m, 18-H_{eq}, 20-H_{eq}), 1.86–1.80 (3 H, m), 1.62 (3 H, s, 14-Me), 1.60–1.50 (2 H, m), 1.46–1.33 (5 H, m), 1.14–1.08 (4 H, m, 18-H_{ax}, Me) and 0.94–0.85 (12 H, m, Me); δ_C(125.8 MHz, $CDCl_3$) 203.8 (d, C-1), 142.9 (s), 139.2 (d), 137.1 (s), 135.6 (d), 128.3 (d), 125.9 (d), 124.0 (d), 120.5 (d), 95.6 (s, C-21), 83.4 (d), 81.3 (d), 79.3 (s, C-7), 75.2 (d), 73.8 (d), 68.7 (d), 68.1 (t, C-8′), 65.0 (d), 51.8 (d), 44.3 (t), 40.9 (d), 40.0 (t), 35.3 (d), 34.1 (t), 33.6 (d), 30.6 (d), 29.1 (t), 27.7 (t), 18.0 (q), 16.8 (q), 16.5 (q), 12.7 (q), 12.3 (q) and 11.6 (q); *m*/*z* 570 ($M^+ - H_2O$), 552 ($M^+ - 2H_2O$), 534, 323, 247, 239, 236, 221 and 79 (Found: $M^+ - H_2O$, 570.3569. $C_{34}H_{52}O_8$ requires $M - H_2O$, 570.3557). Sodium chlorite (85%; 117 mg, 1.11 mmol) was added to a stirred solution of the crude aldehyde (51 mg) and 2-methylbut-2-ene (2 ml) in *tert*-butyl alcohol–water (1:1; 4 ml) at room temperature. After 1 h, saturated aqueous sodium sulphite (1 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (×3). The combined extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on the minimum amount of silica gel (94:5:1 [ethyl acetate–MeOH–AcOH (94:5:1)] afforded the *acid* **46** (21.4 mg, 32%) as white foam, $[\alpha]_D^{20}$ +120 (*c* 0.57 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3386, 3000–2100br (CO_2H), 2959, 2922, 1705, 1583, 1455, 1379, 998 and 732; δ_H(500 MHz) 5.90 (1 H, br d, *J* 11.1, 9-H), 5.81 (1 H, dd, *J* 14.8 and 11.1, 10-H), 5.75 (1 H, dd, *J* 9.9 and 1.6, 23-H), 5.61 (1 H, dd, *J* 14.9 and 9.0, 11-H), 5.55 (1 H, dd, *J* 9.9 and 2.5, 22-H), 5.29 (1 H, m, 15-H), 4.65 (1 H, dd, *J* 14.4 and 2.2, 8′-H), 4.60 (1 H, dd, *J* 14.4 and 2.2, 8′-H), 4.26 (1 H, tt, *J* 11.4 and 4.5, 19-H), 3.91 (1 H, br s, 13-H), 3.85 (1 H, m, 17-H), 3.81 (1 H, d, *J* 3.8, 6-H), 3.50 (1 H, dd, *J* 10.0 and 3.8, 5-H), 3.43 (1 H, dd, *J* 10.0 and 1.5, 25-H), 2.61 (1 H, dd, *J* 13.1 and 3.0, 2-H), 2.49 (1 H, m), 2.38 (1 H, m), 2.27–2.20 (2 H, m), 2.02 (1 H, ddd, *J* 12.2, 4.6 and 1.5, 20-H_{eq}), 1.97 (1 H, br d, *J* 12.0, 18-H_{eq}), 1.83–1.77 (2 H, m), 1.66–1.54 ([5 H, m (inc. Me at 1.55)], 1.47–1.35

(3 H, m), 1.08–1.03 (7 H, m, 18-H_{ax}, Me) and 0.93–0.87 (9 H, m, Me); *m/z* 604 (M^+), 586 ($M^+ - H_2O$), 568, 550, 532, 323, 305 and 86 (Found: C, 67.35; H, 8.6. $C_{34}H_{52}O_9$ requires C, 67.50; H, 8.70%).

(4S)-3,4-*Dihydroavermectin B1a Aglycone* **47**.—To a stirred solution of 2-chloro-1-methylpyridinium iodide (59 mg, 0.23 mmol) in MeCN (7 ml), at reflux under argon, was added a solution of the acid **46** (35 mg, 0.058 mmol) and triethylamine (65 μl, 0.46 mmol) in MeCN (3.5 ml), below the liquid surface, over 9 h, *via* a syringe pump. Upon complete addition heating was continued for a further 4 h. The reaction mixture was allowed to cool and then evaporated. Column chromatography of the residue on silica gel (50% ethyl acetate–petroleum) afforded the macrolactone **47** (16 mg, 47%) as a white foam, $[\alpha]_D^{20}$ +223 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3462, 2959, 2927, 1703, 1453, 1377, 1269, 1160, 1043, 999 and 754; δ_H(500 MHz) 5.76 (1 H, dd, *J* 10.0 and 1.5, 23-H), 5.75 (3 H, m, 9-H), 10-H, 11-H), 5.55 (1 H, dd, *J* 10.0 and 2.5, 22-H), 5.41 (1 H, tt, *J* 11.5 and 5.0, 19-H), 5.30 (1 H, br d, *J* 10.0, 15-H), 4.63 (1 H, dd, *J* 14.0 and 2.0, 8′-H), 4.63 (1 H, s, OH), 4.56 (1 H, dd, *J* 14.0 and 2.0, 8′-H), 3.99 (1 H, br s, 13-H), 3.87 (1 H, m, 17-H), 3.82 (1 H, d, *J* 3.5, 6-H), 3.51 (1 H, ddd, *J* 11.0, 9.0 and 3.5, 5-H), 3.46 (1 H, dd, *J* 10.0 and 2.5, 25-H), 2.45 (1 H, dd, *J* 9.5 and 6.5, 2-H), 2.50 (1 H, m, 12-H), 2.33–2.24 (3 H, m, 16-H_2, 24-H), 1.91 (1 H, ddd, *J* 12.0, 5.0 and 2.0, 20-H_{eq}), 1.80 (1 H, d, *J* 9.0, OH), 1.75–1.69 (2 H, m, 4-H), 18-H_{eq}), 1.65–1.58 (4 H, m, 3-H_2, 26-H, OH), 1.53–1.45 (3 H, m, 20-H_{ax}, 27-H_2), 1.50 (3 H, s, 14-Me), 1.17 (3 H, d, *J* 7.0, 12-Me), 1.07 (3 H, d, *J* 7.0, 4-Me), 0.96 (3 H, t, *J* 7.0, 27-Me), 0.91 (3 H, d, *J* 7.0, 24-Me), 0.89 (3 H, d, *J* 7.0, 26-Me) and 0.84 (1 H, q, *J* 12.0, 18-H_{ax}); δ_C(125.8 MHz) 174.6 (C-1), 141.0 (C-8), 138.6 (C-14), 136.6 (C-11 or C-10), 136.2 (C-23), 127.8 (C-22), 124.8 (C-10 or C-11), 119.3 (C-9), 117.0 (C-15), 95.6 (C-21), 81.3 (C-6), 78.3 (C-7), 77.6 (C-13), 75.2 (C-25), 68.3 (C-17), 68.0 (C-8′), 67.5 (C-19), 46.5 (C-2), 40.4 (C-20), 40.1 (C-12), 36.7 (C-18), 35.2 (C-26), 34.5 (C-16), 34.3 (C-4), 31.1 (C-3), 30.5 (C-24), 27.5 (C-27), 19.1 (12-Me), 17.9 (4-Me), 14.5 (14-Me), 12.8 (26-Me) and 12.1 (27-Me); *m/z* 586 (M^+), 568 ($M^+ - H_2O$), 550. 305, 221, 169 and 105 (Found: C, 69.5; H, 8.4. $C_{34}H_{50}O_8$ requires C, 69.60; H, 8.59%).

(4S)-5-*Dehydroxy*-3,4-*dihydro*-5-*oxoavermectin B1a Aglycone* **48**.—A solution of *N*-methylmorpholine *N*-oxide (5.3 mg, 0.045 mmol) in CH_2Cl_2 (1 ml) was added over 1.5 h *via* a syringe pump to a stirred solution/suspension of the alcohol **47** (24.0 mg, 0.041 mmol), tetrapropylammonium perruthenate (1.5 mg, 0.004 mmol) and powdered 4 Å sieves (250 mg) at room temperature under argon. Upon complete addition stirring was continued for a further 60 min. The reaction mixture was filtered through a pad of Florisil, eluting with ethyl acetate. The filtrate was evaporated. Column chromatography of the residue on Florisil (gradient elution, 30-50% ethyl acetate–petroleum) afforded the ketone **48** (8.7 mg, 61%) and recovered alcohol (9.1 mg). Less polar **48**, $[\alpha]_D^{20}$ +190 (*c* 0.57 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3472, 3029, 2962, 2930, 1721, 1453, 1379, 1350, 1180, 1161, 1073 and 997 cm^{-1}; δ_H(500 MHz) 5.82–5.72 (4 H, m, 9-H, 10-H, 11-H, 23-H), 5.64 (1 H, dd, *J* 10.0 and 2.5, 22-H), 5.42 (1 H, tt, *J* 11.5 and 5.0, 19-H), 5.31 (1 H, m, 15-H), 4.76 (1 H, dd, *J* 14.0 and 2.5, 8′-H), 4.65 (1 H, dd, *J* 14.0 and 2.5, 8′-H), 4.55 (1 H, s, OH), 4.00 (1 H, br s, 13-H), 3.89 (1 H, m, 17-H), 3.76 (1 H, s, 6-H), 3.46 (1 H, dd, *J* 10.0 and 1.5, 25-H), 3.01 (1 H, dd, *J* 13.0 and 4.0, 2-H), 2.79 (1 H, m, 4-H), 2.51 (1 H, m, 12-H), 2.34–2.24 (3 H, m, 16-H_2, 24-H), 2.07 (1 H, q, *J* 13.0, 3-H), 1.93 (1 H, ddd, *J* 12.0, 5.0 and 1.5, 20-H_{eq}), 1.75 (1 H, m, 18-H_{eq}), 1.62–1.45 (5 H, m, 20-H_{ax}, 26-H, 27-H_2, OH), 1.52 (3 H, s, 14-Me), 1.17 (3 H, d, *J* 7.0, 12-Me), 1.09 (3 H, d, *J* 7.0, 4-Me), 0.96 (3 H, t, *J* 7.5, 27-Me), 0.91 (3 H, d, *J* 7.0, 26-Me), 0.90 (3 H, d, *J* 7.0, 24-Me) and 0.85 (1 H, q, *J* 12.0, 18-H_{az}); *m/z* 584 (M^+), 566, 498, 305, 221, 193, 169, 105 and 74 (Found: M^+, 584.3358. $C_{34}H_{48}O_8$ requires M, 584.3349).

(4S)-5-*Dehydroxy*-3,4-*dihydro*-5-*oxo*-4-(*phenylselenenyl*)-7,13-*di*-O-(*trimethylsilyl*)*avermectin B1a Aglycone* **49** *and* (4R)-5-*Dehydroxy*-3,4-*dihydro*-5-*oxo*-4-(*phenylselenenyl*)-7,13-*di*-O-(*trimethylsilyl*)*avermectin B1a Aglycone* **50**.—Trimethylsilyl triflate (2.50 ml, 11.4 mmol) was added dropwise to a stirred solution of the ketone **48** (390 mg, 0.67 mmol) and triethylamine (4.0 ml, 28.7 mmol) at 0 °C under argon in CH_2Cl_2 (6 ml). After 4 h, saturated aqueous sodium hydrogen carbonate (10 ml) was added and stirring continued for a further 20 min at 0 °C. The mixture was then poured into saturated aqueous sodium hydrogen carbonate and extracted with CH_2Cl_2 (×3). The combined extracts were concentrated under reduced pressure (to ~10 ml), then filtered through a pad of Florisil, eluting with ether. The filtrate was evaporated. Column chromatography of the residue on Florisil (gradient elution, 5–10% ether–petroleum) afforded 5-*dehydro*-3-*hydro*-5,7,13-*tri*-O-(*trimethylsilyl*)*avermectin B1a aglycone* (473 mg, 88%) as a white foam, $[\alpha]_D^{20}$ +111 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2958, 1740, 1683, 1404, 1374, 1316, 1250, 1227, 1215, 1198, 1157, 1036, 996, 963, 884 and 843; δ_H(500 MHz) 5.80 (1 H, br d, *J* 11.0, 9-H), 5.72 (1 H, dd, *J* 9.9 and 1.6, 23-H), 5.68 (1 H, dd, *J* 15.0 and 10.8, 10-H), 5.61 (1 H, dd, *J* 14.9 and 9.5, 11-H), 5.52 (1 H, dd, *J* 9.9 and 2.5, 22-H), 5.28–5.20 (2 H, m, 15-H, 19-H), 4.57 (1 H, dd, *J* 14.2 and 2.2, 8′-H), 4.49 (1 H, dd, *J* 14.2 and 2.2, 8′-H), 3.89 (1 H, br s, 13-H), 3.84 (1 H, m, 17-H), 3.68 (1 H, s, 6-H), 3.48 (1 H, d, *J* 10.0, 25-H), 2.69 (1 H, dd, *J* 16.5 and 12.2, 3-H), 2.57 (1 H, dd, *J* 12.0 and 4.1, 2-H), 2.44 (1 H, m, 12-H), 2.28–2.22 (3 H, m, 16-H_2, 24-H), 1.96 (1 H, ddd, *J* 12.4, 5.0 and 1.0, 20-H_{eq}), 1.92 (1 H, dd, *J* 16.8 and 4.2, 3-H), 1.75 (1 H, br d, *J* 15.0, 18-H_{eq}), 1.60 (3 H, s, Me), 1.58 (1 H, m, 27-H), 1.50–1.46 ([4 H, m, 27-H, Me (at 1.49)], 1.35 (1 H, t, *J* 11.7, 20-H_{ax}), 1.30 (1 H, m, 26-H), 1.06 (3 H, d, *J* 6.8, 12-Me), 0.95 (3 H, t, *J* 7.2, 27-Me), 0.91 (3 H, d, *J* 6.2, Me), 0.90 (3 H, d, *J* 6.2, Me), 0.76 (1 H, q, *J* 12.2, 18-H_{ax}), 0.18 (9 H, s, Me_3Si), 0.11 (9 H, s, Me_3Si) and 0.08 (9 H, s, Me_3Si); δ_C(125.8 MHz) 170.6, 140.1, 139.4, 137.7, 136.9, 136.0, 128.3, 124.9, 121.7, 118.3, 116.5, 95.8, 80.6, 80.5, 79.1, 74.6, 68.7, 67.6. 66.1 45.7, 41.2, 40.9, 36.3, 35.2, 34.2, 30.6, 29.9, 27.4, 19.8, 16.4, 15.8, 14.6, 13.1, 12.0, 2.0, 0.6 and 0.1; *m/z* (CI, NH_3) 800 (M^+), 711 (M^+ – TMSOH), 495, 377 and 221 (Found: M^+, 800.4535. $C_{43}H_{72}O_8Si_3$ requires M, 800.4535) (Found: C, 64.2; H, 9.3. $C_{43}H_{72}O_8Si_3$ requires C, 64.45; H, 9.06%).

A solution of benzeneselenenyl chloride (113 mg, 0.59 mmol) in CH_2Cl_2 (10 ml) was added *via* a cannula to a stirred solution of 5-dehydro-3-hydro-5,7,13-tri-*O*-(trimethylsilyl)avermectin B1a aglycone (413 mg, 0.52 mmol) in CH_2Cl_2 at −78 °C under argon. After 2 h, saturated aqueous sodium hydrogen carbonate (10 ml) was added and the reaction mixture was warmed to room temperature. The mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with CH_2Cl_2 (×3). The combined extracts were dried (Na_2SO_4), filtered and evaporated. Column chromatography of the residue on Florisil (gradient elution, 10–30% ether petroleum) afforded the *β-selenide* **50** (215 mg, 47%) as a colourless oil and the *α-selenide* **49** (200 mg, 44%), as a white solid. Less polar, *β-selenide* (4R) **50**, $[\alpha]_D^{20}$ +69 (*c* 0.75 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2958, 2925, 1739, 1695, 1452, 1375, 1252, 1208, 1159, 1101, 1088, 1037, 995, 883, 842, 741 and 690; δ_H(500 MHz) 7.54–7.52 (2 H, m, Ph), 7.40 (1 H, br t, *J* 7.5, Ph), 7.30 (2 H, br t, *J* 7.6, Ph), 5.80–5.66 (4 H, m, 9-H, 10-H, 11-H, 23-H), 5.57 (1 H, dd, *J* 9.9 and 2.5, 22-H), 5.28 (1 H, t, *J* 7.8, 15-H), 5.15 (1 H, tt, *J* 11.5 and 4.7, 19-H), 4.82 (1 H, dd, *J* 14.0 and 2.1, 8′-H), 4.65 (1 H, dd, *J* 14.0 and 2.1, 8′-H), 3.93 (1 H, br s, 13-H), 3.88 (1 H, s, 6-H), 3.86 (1 H, m, 17-H), 3.50 (1 H, d, *J* 9.8, 25-H), 3.35 (1 H, dd, *J* 13.0 and 2.5, 2-H), 2.60 (1 H, dd, *J* 15.2 and 13.1, 3-H), 2.50 (1 H, m, 12-H), 2.32–2.22 (3 H, m, 16-H_2, 24-H), 2.10 (1 H, br dd,

J 12.0 and 5.0, 20-H_{eq}), 2.02 (1 H, dd, *J* 15.3 and 2.5, 3-H), 1.81 (1 H, br d, *J* 12.0, 18-H_{eq}), 1.64–1.56 (2 H, m), 1.52–1.41 (8 H, m, inc. methyl singlets at 1.51 and 1.44), 1.09 (3 H, d, *J* 6.9, 12-Me), 0.98–0.85 (10 H, m, Me, 18-H_{ax}), 0.12 (9 H, s, Me_3Si) and 0.06 (9 H, s, Me_3Si); δ_C(125.8 MHz) 200.5, 169.5, 138.4, 138.3, 137.9, 137.6, 136.1, 129.6, 128.9, 128.2, 126.6, 124.5, 122.4, 118.2, 95.8, 84.2, 84.0, 78.9, 74.6, 69.0, 68.0. 67.2, 51.4, 44.5, 41.4, 41.0, 36.1, 35.2, 34.1, 30.6, 27.4, 25.2, 19.7, 16.4, 14.6, 14.1, 13.1, 12.0, 2.0 and 0.1; *m/z* 884 (M^+), 794 (M^+ – TMSOH), 728, 638, 377, 305 and 221 (Found: C, 62.25; H, 7.85. $C_{46}H_{68}O_8SeSi_2$ requires C, 62.49; H, 7.75%).

More polar, *α-selenide* **49**, m.p. 186–190 °C; $[\alpha]_D^{20}$ +109 (*c* 1.60 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2958, 1740, 1713, 1453, 1374, 1251, 1158, 1103, 1035, 996, 874, 842, 741 and 690; δ_H(500 MHz) 7.49–7.47 (2 H, m, Ph), 7.38 (1 H, br t, *J* 7.4, Ph), 7.29 (2 H, br t, *J* 7.6, Ph), 5.85 (1 H, br d, *J* 9.0, 9-H), 5.76–5.67 (3 H, m, 10-H, 11-H, 23-H), 5.51 (1 H, dd, *J* 9.9 and 2.5, 22-H), 5.28 (1 H, br dd, *J* 11.5 and 5.5, 15-H), 5.23 (1 H, tt, *J* 11.5 and 4.8, 19-H), 5.03 (1 H, s, 6-H), 4.65 (1 H, dd, *J* 13.6 and 2.0, 8′-H), 4.46 (1 H, dd, *J* 13.6 and 2.1, 8′-H), 3.92 (1 H, br s, 13-H), 3.84 (1 H, m, 17-H), 3.49 (1 H, d, *J* 9.9, 25-H), 2.89 (1 H, t, *J* 13.7, 3-H), 2.49 (1 H, m, 12-H), 2.31–2.22 (4 H, m, 2-H, 16-H_2, 24-H), 2.02–1.98 (2 H, m, 3-H, 20-H_{eq}), 1.78 (1 H, m, 18-H_{eq}), 1.61–1.54 (2 H, m), 1.49 (1 H, m), 1.46 (3 H, s, Me), 1.41 (3 H, s, Me), 1.36 (1 H, t, *J* 11.8, 20-H_{ax}), 1.07 (3 H, d, *J* 6.9, 12-Me), 0.96 (3 H, t, *J* 7.1, 27-Me), 0.92 (3 H, d, *J* 6.6, Me), 0.90 (3 H, d, *J* 7.4, Me), 0.78 (1 H, q, *J* 12.4, 18-H_{ax}), 0.22 (9 H, s, Me_3Si) and 0.11 (9 H, s, Me_3Si); δ_C(125.8 MHz) 203.6, 168.8, 139.2, 138.0, 137.9, 137.7, 136.1, 129.6, 129.0, 128.1, 127.1, 124.6, 118.3, 95.8, 85.3, 84.4, 78.5, 74.7, 68.7, 68.5, 67.0, 49.1, 48.3, 40.9, 40.8, 36.3, 36.2, 35.2, 34.0, 30.6, 27.4, 25.3, 19.7, 16.4, 14.4, 13.1, 12.0, 2.2 and 0.1; *m/z* 884 (M^+), 728 (M^+ – PhSeH), 638, 377, 314, 305 and 221 (Found: C, 62.55; H, 7.85. $C_{46}H_{68}O_8SeSi_2$ requires C, 62.49; H, 7.75%).

Avermectin B1a Aglycone **51**, and *4′-Dehydro-3-hydroavermectin B1a Aglycone* **52**.—Hydrofluoric acid (40 wt% in water; 20 drops) was added to a stirred solution of the silyl ether **49** (34.0 mg, 0.038 mmol) and pyridine (500 μl) in MeCN (5 ml) at 0 °C. The reaction was allowed to come room temperature. After 36 h, saturated aqueous sodium hydrogen carbonate (5 ml) was added dropwise. The mixture was then extracted with CH_2Cl_2 (×3). The combined extracts were dried (Na_2SO_4), filtered and evaporated. Column chromatography of the residue on silica gel (30% ethyl acetate–petroleum) afforded (4S)-5-*dehydroxy*-3,4-*dihydro*-5-*oxo*-4-(*phenylselenenyl*)-*avermectin B1a aglycone* (24.0 mg, 87%) as a white solid, $[\alpha]_D^{20}$ +148 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3488, 2961, 2929, 1706, 1459, 1374, 1180, 1073, 998, 908 and 733; δ_H(500 MHz) 7.50–7.48 (2 H, m, Ph), 7.37 (1 H, m, Ph), 7.31–7.27 (2 H, m, Ph), 5.88 (1 H, m, 9-H), 5.78–5.71 (3 H, m, 10-H, 11-H, 23-H), 5.53 (1 H, dd, *J* 9.9 and 2.5, 22-H), 5.42 (1 H, tt, *J* 11.4 and 4.7, 19-H), 5.31 (1 H, br d, *J* 10.0, 15-H), 4.85 (1 H, s, 6-H), 4.67 (1 H, dd, *J* 13.8 and 2.1, 8′-H), 4.51 (1 H, dd, *J* 13.9 and 2.4, 8′-H), 4.39 (1 H, br s, OH), 4.00 (1 H, br s, 13-H), 3.88 (1 H, m, 17-H), 3.46 (1 H, dd, *J* 9.9 and 2.1, 25-H), 2.85 (1 H, t, *J* 13.9, 3-H), 2.54–2.50 (2 H, m, 2-H, 12-H), 2.31–2.22 (3 H, m, 16-H_2, 24-H), 2.10 (1 H, dd, *J* 14.4 and 3.7, 3-H), 1.90 (1 H, ddd, *J* 12.0, 4.8 and 1.7, 20-H_{eq}), 1.76 (1 H, ddd, *J* 12.6, 4.5 and 2.3, 18-H_{eq}), 1.65–1.54 (3 H, m), 1.52–1.42 (8 H, m, inc. methyl singlets at 1.50 and 1.46), 1.17 (3 H, d, *J* 7.0, Me), 0.96 (3 H, t, *J* 7.4, 27-Me), 0.91 (3 H, d, *J* 7.3, Me), 0.90 (3 H, d, *J* 6.7, Me) and 0.81 (1 H, q, *J* 11.8, 18-H_{ax}); *m/z* 740 (M^+), 564 (M^+ – PhSeH – H_2O), 480, 305 and 221 (Found (FAB from 3-nitrobenzyl alcohol): MH^+ 741.2906. $C_{40}H_{53}O_8Se$ requires MH, 741.2905).

2-(Phenylsulphonyl)-3-(*p*-nitrophenylsulphonyl)oxaziridine (55 mg, 0.18 mmol) was added to a stirred solution of (4S)-5-dehydroxy-3,4-dihydro-5-oxo-4-(phenylselenenyl)avermectin B1a aglycone (38.0 mg, 0.051 mmol) in $CHCl_3$ (5 ml) at room temperature. After 30 min the reaction was poured into a solution of cerium(III) chloride heptahydrate (150 mg, 0.40 mmol) in MeOH at 0 °C. Sodium borohydride (41 mg, 1.07 mmol) was then added portionwise. After 15 min, saturated aqueous ammonium chloride was added and the mixture was extracted with CH_2Cl_2 (×3). The combined extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated. Column chromatography of the residue on silica gel (40% ethyl acetate–petroleum) afforded the allylic alcohols **51** and **52** (27.0 mg, 92%) as a 1:1 mixture (*endo*:*exo*). The alcohols were separated by reverse phase HPLC (85% MeOH–H_2O) to give *avermectin B1a aglycone* **51**, retention time of 17.2 min (13.0 mg, 43%), $[\alpha]_D^{20}$ +158 (*c* 1.2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3678, 3464, 3019, 2960, 2928, 1707, 1601, 1454, 1377, 1339, 1310, 1182, 1160, 1117, 1074, 1036, 993, 966, 948, 906 and 866; δ_H(500 MHz) 5.83 (1 H, dt, *J* 10.7 and 2.2, 9-H), 5.79–5.68 (3 H, m, 10-H, 11-H, 23-H), 5.54 (1 H, dd, *J* 9.8 and 2.6, 22-H), 5.41 (1 H, br s, 3-H), 5.40–5.31 (2 H, m, 15-H, 19-H), 4.70 (1 H, dd, *J* 14.3 and 2.3, 8′-H), 4.66 (1 H, dd, *J* 14.3 and 2.3, 8′-H), 4.29 (1 H, t, *J* 6.9, 5-H), 4.01 (1 H, br s, 13-H), 3.98 (1 H, s, OH), 3.97 (1 H, d, *J* 6.2, 6-H), 3.86 (1 H, m, 17-H), 3.46 (1 H, dd, *J* 9.9 and 1.7, 25-H), 3.27 (1 H, q, *J* 2.2, 2-H), 2.52 (1 H, m, 12-H), 2.34–2.24 (4 H, m, 16-H_2, 24-H, OH), 2.01 (1 H, ddd, *J* 12.0, 4.8 and 1.9, 20-H_{eq}), 1.87 (3 H, t, *J* 1.6, 4-Me), 1.76 (1 H, ddd, *J* 13.0, 5.0 and 2.5, 18-H_{eq}), 1.61–1.57 (2 H, m), 1.52 (3 H, s, 14-Me), 1.51–1.44 (3 H, m), 1.17 (3 H, d, *J* 7.0, 12-Me), 0.96 (3 H, t, *J* 7.4, 27-Me), 0.91 (6 H, d, *J* 7.0, 24-Me, 26-Me) and 0.87 (1 H, q, *J* 12.3, 18-H_{ax}); δ_C(125.8 MHz) 173.1 (C-1), 139.4 (C-8), 138.6 (C-14), 137.4 (C-4), 137.0 (C-11), 136.0 (C-23), 127.7 (C-22), 124.5 (C-10), 120.3 (C-9), 118.0 (C-3), 117.0 (C-15), 95.6 (C-21), 80.1 (C-7), 79.2 (C-6), 77.3 (C-13), 75.0 (C-25), 68.24 (C-17 or C-8′ or C-19), 68.2 (C-17 or C-8′ or C-19), 68.1 (C-17 or C-8′ or C-19), 67.5 (C-5), 45.5 (C-2), 40.5 (C-20), 39.9 (C-12), 36.3 (C-18), 35.1 (C-26), 34.2 (C-24), 30.4 (C-16), 27.4 (C-27), 19.7 (4-Me), 19.1 (12-Me), 16.2 (24-Me or 26-Me), 14.4 (14-Me), 12.7 (26-Me or 24-Me) and 12.0 (12-Me); *m/z* 585 (MH^+), 549, 305, 193 and 169 (Found: MH^+, 585.3427. $C_{34}H_{49}O_8$ requires MH, 585.3427) (Found: C, 70.0; H, 8.4. $C_{34}H_{48}O_8$ requires C, 69.84; H, 8.27%); and the exo *methylene isomer* **52**, retention time of 19.7 min, (12.0 mg, 39%), $[\alpha]_D^{20}$ +135 (*c* 0.02 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3581, 2922, 2852, 1715, 1653, 1596, 1456, 1377, 1160, 1121, 1075 and 997; δ_H(500 MHz) 5.78–5.70 (4 H, m, 9-H, 10-H, 11-H, 23-H), 5.55 (1 H, dd, *J* 10.0 and 2.5, 22-H), 5.42 (1 H, tt *J* 11.0 and 5.0, 19-H), 5.31 (1 H, br d, *J* 10.0, 15-H), 5.20 (1 H, m, 4′-H), 503 (1 H, m, 4′-H), 4.66 (1 H, s, OH), 4.59 (2 H, m, 8′-H_2), 4.45 (1 H, m, 5-H), 4.00 (1 H, br s, 13-H), 3.92 (1 H, d, *J* 4.5, 6-H), 3.87 (1 H, m, 17-H), 3.47 (1 H, dd, *J* 10.0 and 2.5, 25-H), 2.63 (1 H, dd, *J* 14.0 and 13.0, 3-H), 2.55 (1 H, dd, *J* 14.0 and 3.0, 3-H), 2.50 (1 H, m, 12-H), 2.39 (1 H, dd, *J* 13.0 and 3.0, 2-H), 2.32–2.24 (3 H, m, 16-H_2, 24-H), 2.12 (1 H, d, *J* 3.5, OH), 1.94 (1 H, ddd, *J* 12.0, 5.0 and 2.0, 20-H_{eq}), 1.72 (1 H, m, 18-H_{eq}), 1.50 (3 H, s, 14-Me), 1.60–1.45 (5 H, m, OH, 20-H_{ax}, 26-H, 27-H_2), 1.17 (3 H, d, *J* 7.0, 12-Me), 0.96 (3 H, t, *J* 7.0, 27-Me), 0.91 (3 H, d, *J* 7.0, 24-Me), 0.90 (3 H, d, *J* 7.0, 26-Me) and 0.85 (1 H, q *J* 12.0, 18-H_{ax}); *m/z* 584 (M^+), 566 (M^+ – H_2O), 541, 305, 221 and 169 (Found: M^+, 584.3358. $C_{34}H_{48}O_8$ requires M, 584.3349).

5-O-*Acetylavermectin B1a Aglycone* **70**.—Avermectin B1a aglycone **51** (32 mg, 0.054 mmol) and DMAP (3.5 mg, 0.029 mmol) were dissolved in pyridine (0.5 ml) under an argon atmosphere, and acetyl chloride (10 μl, 11 mg, 0.14 mmol) was added dropwise at room temperature. After 1.5 h the reaction was diluted with CH_2Cl_2, and the solution was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel (25% ether–petroleum) gave the *monoacetate* **70**) as a white foam (33 mg, 97%), $[\alpha]_D^{20}$ +118.9 (*c* 0.93 in $CHCl_3$);

ν_{max}(film)/cm^{-1} 3468, 2957, 2923, 1738, 1670, 1453, 1370, 1159, 1032 and 994; δ_H(500 MHz) 5.81 (1 H, dt, *J* 10.0 and 2.5, 9-H), 5.77–5.68 (2 H, m, 10-H, 11-H), 5.73 (1 H, dd, *J* 10.0 and 1.5, 23-H), 5.56–5.52 (3 H, m, 3-H, 5-H, 22-H), 5.37–5.30 (2 H, m, 15-H, 19-H), 4.66 (1 H, dd, *J* 14.0 and 2.5, 8′-H), 4.58 (1 H, dd, *J* 14.0 and 2.5, 8′-H), 4.06 (1 H, d, *J* 6.0, 6-H), 3.99 (1 H, br s, 13-H), 3.90 (1 H, s, 7-OH), 3.87 (1 H, m, 17-H), 3.46 (1 H, dd, *J* 10.0 and 1.5, 25-H), 3.33 (1 H, dd, *J* 5.0 and 2.5, 2-H), 2.52 (1 H, m, 12-H), 2.34–2.17 (4 H, m, 13-OH, 16-H_2, 24-H), 2.15 (3 H, s, 5-OAc), 2.04 (1 H, ddd, *J* 12.0, 4.5 and 2.0, 20-H_{eq}), 1.77 (1 H, m, 18-H_{eq}), 1.75 (3 H, s, 4-Me), 1.58 (1 H, m, 26-H), 1.52 (3 H, s, 14-Me), 1.51–1.47 (2 H, m, 27-H_2), 1.45 (1 H, d, *J* 12.0, 20-H_{ax}), 1.17 (3 H, d, *J* 7.0, 12-Me), 0.96 (3 H, t, *J* 7.0, 27-Me), 0.91 (6 H, d, *J* 7.0, 24-Me, 26-Me) and 0.86 (1 H, m, 18-H_{ax}); *m/z* 626 (M^+), 608 ($M^+ - H_2O$), 566 (M^+ – AcOH), 548 (M^+ – AcOH – H_2O), 320 ($C_{20}H_{32}O_3$), 305 [$C_{19}H_{29}O_3$, C(13)–C(28) fragment], 221 ([$C_{14}H_{21}O_2$, C(1)–C(12) fragment], 199 ($C_{12}H_{23}O_2$), 193 ($C_{13}H_{21}O$), 169 ($C_{10}H_{17}O_2$), 151 ($C_{10}H_{15}O$), 123 ($C_8H_{11}O$), 109 (C_7H_9O) and 95 (C_6H_7O) [Found (CI, NH_3): MH^+, 627.3533. $C_{36}H_{51}O_9$ requires MH, 627.3533] (Found: C, 68.95; H, 8.05. $C_{36}H_{50}O_9$ requires C, 68.99; H, 8.04%).

(4S)-4-tert-*Butyldimethylsilyloxypent*-1-*en*-3-*ol* **53**.—Vinylmagnesium bromide (1.0 mol dm^{-3} solution in THF; 38.6 ml, 38.6 mmol) was added dropwise to a stirred solution of (2*S*)-2-*tert*-butyldimethylsilyloxypropanal[43] (6.6 g, 35.0 mmol) in THF (100 ml) at −60 °C. The mixture was allowed to warm to room temperature after which it was stirred for 4 h and then quenched by addition of saturated aqueous ammonium chloride (20 ml) and water (10 ml). This mixture was extracted with ether (3 × 50 ml) and the combined organic extracts were washed with brine (30 ml), dried ($MgSO_4$) and evaporated. Column chromatography of the residue (6.6 g) on silica gel (10% ether–petroleum) gave the *alcohol* **53** (5.62 g, 74%) as an oil; ν_{max}(film)/cm^{-1} 3418, 2904, 2930, 2807, 1461, 1376, 1264, 1096, 1005, 938, 835 and 776; δ_H(500 MHz) 5.85–5.71 (0.17 H, m, CH=CH_2 minor isomer), 5.81 (0.83 H, ddd, *J* 6.3, 10.6 and 17.3, CH=CH_2 major isomer), 5.32 (0.17 H, d, *J* 17, C=CH*H* minor isomer), 5.28 (0.83 H, d, *J* 17.3, C=CH*H* major isomer), 5.19 (1 H, d, *J* 10.6, C=CH*H*), 4.00–4.04 (0.83 H, m, C*H*OH major isomer), 3.84 (0.83 H, dq, *J* 3.7 and 6.3, C*H*Me major isomer), 3.81 (0.17 H, br q, *J* 5, C*H*OH minor isomer), 3.68 (0.17 H, p, *J* 6.1, C*H*Me minor isomer), 2.57 (0.17 H, br d, *J* 5, OH minor isomer), 2.29 (0.83 H, br d, *J* 4, OH major isomer), 1.15 (0.5 H, d, *J* 6.1, MeC minor isomer), 1.07 (2.5 H, d, *J* 6.3, MeC major isomer) and 0.08 (6 H, s, Me_2Si), 0.90 (9 H, s, Bu^t); *m/z* 202 ($M^+ - CH_2$), 201 (M^+ – Me), 199 (M^+ – OH), 185 ($M^+ - CH_2$ – OH), 183 (M^+ – Me – H_2O), 173 (M^+ – Me – C_2H_4), 159, 115, 101, 75 and 73 (Found: C, 61.4; H, 11.3 $C_{11}H_{24}O_2Si$ requires C, 61.1; H, 11.2%).

(2S)-*Pent*-4-*ene*-2,3-*diol* **54**.—A solution of 4-*tert*-butyldimethylsilyloxypent-1-en-3-ol **53** (3.0 g, 13.9 mmol) and toluene-*p*-sulphonic acid (100 mg) in methanol (50 ml) was stirred for 15 h. The solvent was evaporated and the residue purified by column chromatography on silica gel (60% ether–petroleum) to give the *diol* **54** (1.29 g, 91% as an oil, ν_{max}(film)/cm^{-1} 3386; δ_H(500 MHz) 5.90 (0.83 H, ddd, *J* 6.5, 10.5, 17.3, C*H*=CH_2 major isomer), 5.85 (0.17 H, ddd, *J* 6.5, 10.5 and 17.2, CH=CH_2 minor isomer), 5.36 (0.17 H, dt, *J* 17.2 and 1.3, C=C*H*H minor isomer), 5.34 (0.83 H, dt *J* 17.2 and 1.4, C=CH*H* major isomer, 5.28 (0.83 H, dt, *J* 10.5 and 1.4, C=CH*H* major isomer), 5.25 (0.17 H, dt, *J* 10.5 and 1.3, C=CH*H* minor isomer), 4.11–4.07 (0.83 H, m, MeCHCH major isomer), 3.91–3.85 (1 H, m, C*H*Me major isomer and MeCHCH minor isomer), 3.65 (0.17 H, br p, *J* 7, CH Me minor isomer), 2.30–2.20 (0.17 H, br s, OH minor isomer), 2.10–1.90 (0.33 H, m, 2 × OH major isomer), 1.65–1.60 (0.17 H, br s, OH minor isomer), 1.18 (0.5 H, d, *J* 6.3, Me minor isomer) and 1.15 (2.5 H, d, *J* 6.5, Me major isomer); *m/z* 101 (M^+ – H), 85 (M^+ – OH), 58 ($M^+ - CHCH_2$ – OH), 45 and 43 (Found: C, 59.1; H, 10.2. $C_5H_{10}O_2$ requires C, 58.8; H, 9.9%).

(5S)-5-*Methyl*-4-*vinyl*-1,3,2-*dioxathiolane* S-*Oxide* **55**.—Thionyl chloride (350 mg, 214 μl, 2.9 mmol) was added to a solution of (2*S*)-pent-4-ene-2,3-diol **54** (200 mg, 2.0 mmol) in dry CCl_4 (3 ml). Gas evolution was immediately observed. The reaction was stirred at room temperature for 30 min, heated under reflux for 30 min, and then cooled to room temperature. The mixture was poured into water (30 ml) and extracted with ether (2 × 30 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (20 ml), dried ($MgSO_4$) and evaporated. Column chromatography of the residue on silica gel (25% ether–petroleum) gave the *thiolane* S-*oxide* **55** (291 mg, 100%) as an oil; ν_{max}(film)/cm^{-1} 2988, 2937, 1430, 1385, 1210, 934, 829, 763 and 726; δ_H(500 MHz) 6.13–6.04 (0.17 H, m, CH=CH_2 isomer C), 5.95–5.88 (0.08 H, m, CH=CH_2 isomer B), 5.82–5.68 (0.75 H, m, CH=CH_2 isomers A and D), 5.60–5.40 (2 H, m, $CHCH_2$), 5.27 (0.67 H, t, *J* 6.7, C=CCHO isomer A), 5.11 (0.67 H, br p, *J* 6.5, MeCH O isomer A), 4.95–4.90 (0.25 H, m, C=CCHO isomers B and C), 4.77–4.72 (0.25 H, m, MeCHO isomers B and C), 4.38–4.33 (0.07 H, m, C=CCHO isomer D), 4.22–4.17 (0.07 H, m, MeCH O isomer D), 1.55 (0.22 H, d, *J* 6.3, Me isomer D), 1.50 (0.5 H, d, *J* 6.7, Me isomer C), 1.47 (0.25 H, d, *J* 6.1, Me isomer B) and 1.30 (2 H, d, *J* 6.4, Me isomer A); *m/z* 194 (M^+), 118, 104, 92, 55, 48 and 43 (Found: C, 40.5; H, 5.3. $C_5H_8SO_3$ requires C, 40.5; H, 5.4%).

(2S)-exo-3,4,5-η^3-(2-*Formyloxypent*-4-*en*-3-*ylato*)*tricarbonyliron* **57**[55] *and* (2S)-endo-3,4,5-η^3-(2-*Formyloxypent*-4-*en*-3-*ylato*)*tricarbonyliron* **56**.[55]—A mixture of nonacarbonyldiiron (0.5 g, 1.3 mmol) and the thiolane *S*-oxide **55** (100 mg, 0.67 mmol) was sonicated for 17 h in dry benzene (10 ml) under argon. The green reaction mixture was filtered through talc, washing with toluene (5 ml) and ether. The ether and benzene were removed under reduced pressure to give a solution in toluene. This solution was applied to a column of silica (10 g) and purified by gradient elution with petroleum–ether mixtures ranging from 95:5 to pure ether to give the ferrilactones **56** and **57** (110 mg, 65%) as a gum; ν_{max}(film)/cm^{-1} 2090, 2079, 2028, 2003 and 1655; δ_H(270 MHz, C_6D_6) 3.85 (1 H, dt, *J* 12.8 and 8.1, 3-H *exo* isomer), 3.80 (1 H, br p, *J* 6.4, 1-H *endo* isomer), 3.68 (1 H, q, *J* 6.4, 1-H *exo* isomer), 3.67–3.56 (2 H, m, 2-H, 3-H *endo* isomer), 3.55 (1 H, d, *J* 8.1, 2-H *exo* isomer), 2.84–2.72 (2 H, m, 4-H_{endo}, 4-H_{exo} *endo* isomer), 2.78 (1 H, dt, *J* 8.1 and 1.4, 4-H_{exo} *exo* isomer), 2.61 (1 H, dd, *J* 12.8 and 1.4, 4-H_{endo} *exo* isomer), 0.95 (3 H, d, *J* 6.4, CH_3 *exo* isomer) and 0.93 (3 H, d, *J* 6.4, CH_3 endo isomer).

(S)-3,6-*Dihydro*-6-*methyl*-2H-*pyran*-2-*one* **58** *and* (S)-5,6-*Dihydro*-6-*methyl*-2H-*pyran*-2-*one*.—A solution of the tricarbonyliron lactones **56** and **57** (0.7 g, 2.8 mmol) and acrolein (10 ml) in dry benzene (40 ml) was heated at 70 °C under an atmosphere of carbon monoxide at 230 atm for 18 h. The resulting mixture was filtered through talc, washing with ether, and the solvent was removed under reduced pressure at 10–15 °C. The resulting gum was purified by flash chromatography on silica (50 g) eluting with ether–petroleum (8:92 then 15:85, 50:50 and finally 100:0) to give a slightly impure mixture of the δ-lactones (287 mg, 92%) as an oil. This oil was further purified by silica gel chromatography (33% ether–petroleum) to give, less polar, the *β,γ-unsaturated lactone*, followed by, more polar, the *α,β-unsaturated isomer*, parasorbic acid,[56] both as pale yellow oils. The less polar, β,γ-unsaturated lactone **58**, $[\alpha]_D^{20}$ +38.1 (*c*

1.09 in $CHCl_3$) (lit.,[57] +88, *c* 1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2979, 1736, 1375, 1226, 1120, 1094 and 1043; δ_H(500 MHz, systematic numbering) 5.83 (2 H, s, 4-H, 5-H), 5.08 (1 H, m, 6-H), 3.10–2.99 (2 H, m, 3-H_2) and 1.45 (3 H, d, *J* 6.5, 6-Me); *m/z* 112 (M^+), 111 ($M^+ - H$), 97 ($M^+ - Me$), 84 ($M^+ - C_2H_4$), 69 (C_4H_5O) and 43 (C_2H_3O) (Found: $M^+ - H$, 111.0446. $C_6H_7O_2$ requires M − H, 111.0446).

The more polar, α,β-unsaturated isomer, parasorbic acid,[56,58] $[\alpha]_D^{20}$ +208 (*c* 1.07 in $CHCl_3$) (lit.,[56] +126.3, *c* 2.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2979, 2936, 1722, 1386, 1247, 1109, 1054, 955 and 849; δ_H(500 MHz, systematic numbering) 6.87 (1 H, ddd, *J* 10.0, 6.0 and 2.5, 2-H), 6.02 (1 H, ddd, *J* 9.5, 2.5 and 1.0, 3-H), 4.78 (1 H, dqd, *J* 11.0, 6.5 and 4.5, 6-H), 2.37 (1 H, dddd, *J* 18.5, 5.5, 4.5 and 1.0, 5-H), 2.29 (1 H, ddt, *J* 18.5, 11.0 and 2.5, 5-H) and 1.45 (3 H, d, *J* 6.5, 6-Me); *m/z* 112 (M^+), 97 ($M^+ - Me$), 84 ($M^+ - C_2H_4$) and 68 (C_4H_4O) (Found: M^+, 122.0524. $C_6H_8O_2$ requires M, 112.0524).

Osmundalactone **59**[59,60] *and* 4-epi-*Osmundalactone* **60**.[60]—The β,γ-unsaturated lactone **58** (410 mg, 3.66 mmol) was dissolved in ether (5 ml), and the solution cooled to 0 °C and treated with dimethyldioxirane[21–23] (*ca.* 0.1 mol dm^{-3} solution in acetone; 50 ml, *ca* 5 mmol); it was then stirred overnight and allowed to warm slowly to room temperature. Since TLC indicated remaining alkene, the solvent was removed under reduced pressure and further dimethyldioxirane (*ca.* 0.1 mol dm^{-3} solution in acetone; 28 ml, *ca.* 2.8 mmol) was added at 0 °C. The reaction mixture was stirred for 20 h, allowed to warm to room temperature, and then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then treated with a 2% solution of triethylamine in pyridine and stirred at room temperature overnight. The triethylamine and pyridine were removed under reduced pressure by azeotroping with toluene. The residue was purified by column chromatography on silica gel (2% pyridine–49% petroleum–49% ethyl acetate) to give the two unsaturated hydroxy lactones, the less polar, osmundalactone **59** (121 mg, 26%) and the more polar, 4-*epi*-osmundalactone **60** (231 mg, 49%). Less polar, osmundalactone **59**, as a pale yellow solid, m.p. 77–80 °C (lit.,[59] 82–82.5 °C); $[\alpha]_D^{30}$ −47.9 (*c* 1.01 in H_2O) (lit.,[59] $[\alpha]_D^{20}$ −70.6, *c* 2.0 in H_2O); ν_{max}(film)/cm^{-1} 3408, 1722, 1384, 1240, 1104, 1068, 1024 and 813; δ_H(500 MHz, systematic numbering) 6.85 (1 H, dd, *J* 10.0 and 2.0, 3-H), 5.97 (1 H, dd, *J* 10.0 and 2.0, 2-H), 4.37 (1 H, dq, *J* 9.0 and 6.5, 5-H), 4.25 (1 H, dt, 9.0 and 2.0, 4-H) and 1.50 (3 H, d, *J* 6.5, 5-Me); *m/z* (CI, NH_3) 146 (MNH_4^+) and 129 (MH^+) [Found (CI, NH_3): MH^+, 129.0552. Calc. for $C_6H_9O_3$: MH, 128.0473].

More polar **60**, as an orange solid, m.p. 48–53 °C; $[\alpha]_D^{33}$ +230.6 (*c* 0.51 in H_2O) (lit.,[60] $[\alpha]_D^{20}$ +142.8 *c*, 0.53 in H_2O); ν_{max}(film)/cm^{-1} 3391, 1705, 1384, 1265, 1114, 1059, 1018, 987, 967 and 829; δ_H(500 MHz, systematic numbering) 7.00 (1 H, dd, *J* 9.5 and 5.5, 3-H), 6.07 (1 H, d, *J* 9.5, 2-H), 4.53 (1 H, qd, *J* 6.5 and 3.0, 5-H), 4.05 (1 H, dd, *J* 5.5 and 3.0, 4-H), 1.50 (3 H, d, *J* 6.5, 5-Me); *m/z* (CI, NH_3) 146 (MNH_4^+) and 129 (MH^+); [Observed (CI, NH_3): MNH_4^+, 146.0817. Calc. for $C_6H_9O_3$: MNH_4, 146.0817] (Found: C, 56.0; H, 6.3. Calc. for $C_6H_8O_3$: C, 56.25; H, 6.29%).

4-O-*Benzoylosmundalactone* **63**.—4-*epi*-Osmundalactone **60** (30 mg, 0.234 mmol) was dissolved in THF (4 ml) together with triphenylphosphine (129 mg, 0.492 mmol) and benzoic acid (64 mg, 0.524 mmol). Diethyl azodicarboxylate (100 μl, 111 mg, 0.635 mmol) was added dropwise *via* a syringe, and the reaction mixture was stirred at room temperature for 4 h, before being concentrated under reduced pressure. The residue was purified by chromatography on silica gel (gradient elution, 10–20% ether–petroleum) to give the *benzoate* **63**, contaminated with ethyl benzoate (60 mg, 5:1 by NMR, therefore 0.215 mmol, 92%) as a white solid, $[\alpha]_D^{20}$ −205.1 (*c* 1.04 in $CHCl_3$, allowing for contaminant); ν_{max}(film)/cm^{-1} 1722, 1257, 1105 and 711; δ_H(500 MHz, systematic numbering) 8.05 (2 H, dd, *J* 8.5 and 1.5, *m*-Ph-H), 7.62 (1 H, tt, *J* 7.5 and 1.5, *p*-Ph-H), 7.48 (2 H, t, *J* 7.5, *o*-Ph-H), 6.90 (1 H, dd, *J* 10.0 and 3.5, 3-H), 6.17 (1 H, dd, *J* 10.0 and 1.5, 2-H), 5.54 (1 H, ddd, *J* 7.0, 3.5 and 1.5, 4-H), 4.77 (1 H, quintet, *J* 6.5, 5-H) and 1.51 (3 H, d, *J* 6.5, 5-Me); *m/z* 232 (M^+), 188 ($M - CO_2^+$), 122 ($PhCO_2H^+$), 105 ($PhCO^+$) and 77 (Ph^+) [Found (CI, NH_3): MH^+, 233.0814. $C_{13}H_{13}O_4$ requires MH, 233.0814].

Oleandrose **6** *from Osmundalactone* **59**.—DIBAL (1.5 mol dm^{-3} solution in toluene; 500 μl, 0.750 mmol) was added to a solution of osmundalactone **59** (65 mg, 0.507 mmol) in THF (10 ml) at −78 °C under argon. After 5 h, further DIBAL (1.5 mol dm^{-3} solution in toluene; 500 μl, 0.750 mmol) was added and stirring was continued. After 1.5 h the reaction was quenched at −78 °C with a 10% solution of methanol in CH_2Cl_2. The resulting mixture was filtered through a short pad of silica gel washing with further 10% methanol–CH_2Cl_2. The solution was concentrated under reduced pressure, and the residue was dissolved in dry methanol (15 ml) under argon, and treated with DBU (150 μl). This solution was stirred at room temperature overnight. The pH was then adjusted to *ca* 6 with acetic acid, and the solution was concentrated. The residue was purified by chromatography on Florisil (gradient elution, 70–80% ethyl acetate–petroleum) to give the less polar oleandrose **6** (33 mg, 40%), and the more polar cymarose **62**[47,48] (12.0 mg, 0.074 mmol, 15%).

The less polar oleandrose **6** as a colourless oil and a mixture of anomers (α:β, 2:1), $[\alpha]_D^{20}$ +10.4 (*c* 1.25 in H_2O) (lit.,[12] $[\alpha]_D^{20}$ +10.8, *c* 1.23 in H_2O); ν_{max}(film)/cm^{-1} 3384, 2970, 2934, 1445, 1379, 1259, 1200, 1146, 1079, 991, 922, 896, 826 and 770; δ_H(500 MHz, systematic numbering) 5.37 (0.7 H, br s, major isomer 1-H_{eq}), 4.83 (0.3 H, ddd, *J* 9.5, 6.5 and 2.0, minor 1-H_{ax}), 3.93 (0.7 H, dq, *J* 9.3 and 6.0, major 5-H), 3.53 (0.7 H, ddd, *J* 11.5, 9.0 and 5.0, major 3-H), 3.41 (1 H, s, minor 3-OMe), 3.40 (2 H, s, major 3-OMe), 3.38 (0.3 H, dq, *J* 9.0 and 6.0, minor 5-H), 3.21 (0.3 H, ddd, *J* 11.0, 8.5 and 4.5, minor 3-H), 3.17 (0.7 H, td, *J* 9.0 and 2.0, major 4-H), 3.16 (0.3 H, td, *J* 8.5 and 2.0, minor 4-H), 3.03 (0.3 H, d, *J* 6.5, minor 1-OH), 2.51 (0.3 H, d, *J* 2.0, minor 4-OH), 2.48 (1.4 H, d, *J* 2.5, major 1-OH, major 4-OH), 2.43 (0.3 H, ddd, *J* 12.5, 4.5 and 2.0, minor 2-H_{eq}), 2.31 (0.7 H, ddd, *J* 13.0, 5.0 and 1.5, major 2-H_{eq}), 1.50 (0.7 H, ddd, *J* 13.0, 11.5 and 2.0, major 2-H_{ax}), 1.41–1.37 (0.3 H, m, minor 2-H_{ax}), 1.35 (1 H, d, *J* 6.0, minor 5-Me) and 1.29 (2 H, d, *J* 6.5, major 5-Me); *m/z* 162 (M^+), 160 ($M^+ - H_2$), 145 ($M^+ - OH$), 130 ($M^+ - CH_3OH$), 118 ($M^+ - C_2H_4O$), 105 ($M^+ - C_3H_5O$), 86 ($C_4H_6O_2$), 74 ($C_3H_6O_2$), 71 (C_4H_7O) and 57 (C_3H_5O) (Found (CI, NH_3): MNH_4^+, 180.1236. Calc. for $C_7H_{14}O_4$: MNH_4, 180.1236) (Found: C, 51.65; H, 8.95. Calc. for $C_7H_{14}O_4$, C, 51.84; H, 8.70%).

The less polar 3-*epi*-compound, the natural product cymarose **62**[47,48] (12.0 mg, 0.074 mmol, 15%), was not characterised. Instead, this material was redissolved in dry methanol and treated with DBU to re-equilibrate the 3-position. Stirring overnight, followed by isolation as before, gave a further portion of oleandrose **6** (60%).

Oleandrose **6** *from* 4-O-*Benzoylosmundalactone* **63**.—DIBAL (1.5 mol dm^3 solution in toluene; 1.10 ml, 1.65 mmol) was added to a solution of 4-*O*-benzoylosmundalactone **63** (contaminated with ethyl benzoate, 1.63:1 molar ratio, 87 mg, 0.268 mmol of **63** in toluene (8 ml) at −78 °C under argon. The reaction was stirred at −78 °C for 6 h and then quenched at −78 °C with a 10% solution of methanol in CH_2Cl_2. The resulting mixture was filtered through a short pad of silica gel washing with further 10% methanol–CH_2Cl_2. The solution was concentrated under reduced pressure and the residue was

dissolved in dry methanol (10 ml) under an argon atmosphere, and treated with DBU (100 μl). This solution was stirred at room temperature overnight. The pH was then adjusted to *ca.* 6 with acetic acid, and the solution was concentrated under reduced pressure. The residue was purified by chromatography on Florisil (gradient elution, 70–80% ethyl acetate–petroleum) to give the oleandrose **6** (20 mg, 47%) as a mixture of anomers (α:β, 2:1), spectroscopically identical with that prepared from the osmundalactone **59**. Further elution additionally gave cymarose **62** (8.1 mg, 19%), which could be re-equilibrated as described above.

1,4-*Di*-O-*acetyloleandrose* **64** *and* 1-O-*Acetyloleandrose* **65**.—Carbonyldiimidazole (324 mg, 2.00 mmol) and acetic acid (115 μl, 121 mg, 2.0 mmol) were premixed in dry CH_2Cl_2 (4 ml) and stirred at room temperature under a nitrogen atmosphere for 1 h. Oleandrose **6** (163 mg, 1.01 mmol) was then added as a solution in dry CH_2Cl_2 (2 ml) and the mixture was stirred at room temperature for 26 h. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (gradient elution, 60–80% ether–pentane) to give the less polar 1,4-*di*-O-*acetyloleandrose* **64** (100 mg, 40%, followed by the more polar 1-*O*-acetyloleandrose **65** (108 mg, 0.529 mmol, 53%), both as colourless oils. Less polar, 1,4-di-*O*-acetyloleandrose **64**, mixture of anomers (α:β, 1:5); ν_{max}(film)/cm^{-1} 2937, 1747, 1371, 1226, 1158, 1110, 1079, 1047 and 992; δ_H(500 MHz, systematic numbering) 6.19 (0.17 H, t, *J* 2.0, minor isomer 1-H_{eq}), 5.70 (0.83 H, dd, *J* 10.0 and 2.5, major 1-H_{ax}), 4.73 (0.17 H, t, *J* 9.5, minor 4-H), 4.68 (0.83 H, t, *J* 9.0, major 4-H), 3.84 (0.17 H, dq, *J* 10.0 and 6.0, minor 5-H), 3.63 (0.83 H, dq, *J* 9.0 and 6.0, major 5-H), 3.63 (0.17 H, ddd, *J* 11.5, 9.5 and 5.0, minor 3-H), 3.41 (0.83 H, ddd, *J* 11.0, 9.0 and 5.0, major 3-H), 3.35 (0.5 H, s, minor 3-OMe), 3.34 (2.5 H, s, major 3-OMe), 2.37 (0.83 H, ddd, *J* 12.5, 5.5 and 2.0, major 2-H_{eq}), 2.28 (0.17 H, ddd, *J* 13.0, 5.0 and 1.5, minor 2-H_{eq}), 2.11 (3 H, s, 1-OAc), 2.10 (3 H, s, 4-OAc), 1.77 (0.17 H, ddd, *J* 13.5, 11.5 and 3.5, minor 2-H_{ax}), 1.67 (0.83 H, ddd, *J* 12.0, 12.0 and 10.0, major 2-H_{ax}), 1.21 (2.5 H, d, *J* 6.0, major 5-Me) and 1.15 (0.5 H, d, *J* 6.5, minor 5-Me); *m/z* 187 (M^+ – AcO), 126 (M^+ – AcOH – AcOH), 116 ($C_5H_8O_3$), 100 ($C_5H_8O_3$), 87 ($C_4H_7O_2$), 74 ($C_3H_6O_2$), 59 ($C_2H_3O_2$) and 43 (C_2H_3O) (Found: M^+ – AcO, 187.0970. $C_9H_{15}O_4$ requires M – AcO, 187.09706) (Found: C, 53.6; H, 7.5. $C_{11}H_{18}O_6$ requires C, 53.65; H, 7.37%).

More polar, 1-*O*-acetyloleandrose **65**, mixture of anomers (α:β, 1:5); ν_{max}(film)/cm^{-1} 3463, 2934, 1751, 1370, 1229, 1197, 1113, 1081, 1049 and 991; δ_H(500 MHz, systematic numbering) 6.20 (0.17 H, dd, *J* 3.5 and 1.0, minor isomer 1-H_{eq}), 5.71 (0.83 H, dd, *J* 10.0 and 2.5, major 1-H_{ax}), 3.78 (0.17 H, dq, *J* 9.5 and 6.0, minor 5-H), 3.50 (0.17 H, ddd, *J* 11.5, 9.0 and 5.0, minor 3-H), 3.46 (0.83 H, dq, *J* 9.0 and 6.0, major 5-H), 3.41 (3 H, s, 3-OMe), 3.26 (0.83 H, ddd, *J* 11.5, 8.5 and 4.5, major 3-H), 3.22 (0.17 H, td, *J* 9.0 and 1.5, minor 4-H), 3.18 (0.83 H, td, *J* 9.0 and 1.5, major 4-H), 2.53 (1 H, d, *J* 2.0, 4-OH), 2.38 (0.83 H, ddd, *J* 12.0, 4.5 and 2.5, major 2-H_{eq}), 2.29 (0.17 H, ddd, *J* 13.5, 5.0 and 1.5, minor 2-H_{eq}), 2.11 (2.5 H, s, major 1-OAc), 2.10 (0.5 H, s, minor 1-OAc), 1.64 (0.17 H, ddd, *J* 13.5, 11.5 and 3.5, minor 2-H_{ax}), 1.54 (0.83 H, ddd, *J* 12.0, 11.5 and 10.5, major 2-H_{ax}), 1.36 (2.5 H, d, *J* 6.0, major 5-Me) and 1.30 (0.5 H, d, *J* 6.0, minor 5-Me); *m/z* 203 (M^+), 145 (M^+ – AcO), 1.27 (M^+ – AcOH – H_2O), 117 ($C_5H_9O_3$), 113 (M^+ – AcOH – MeOH), 100 ($C_5H_8O_2$), 95 (C_6H_7O), 87 ($C_4H_7O_2$), 74 ($C_3H_6O_2$), 59 ($C_2H_3O_2$) and 43 (C_2H_3O) (Found: M^+ – H, 203.0919. $C_9H_{15}O_5$ requires M – H, 203.09196 (Found: C, 52.65; H, 7.95. $C_9H_{16}O_5$ requires C, 52.93; H, 7.90%).

4-O-*Acetyl*-L-*oleandrose* **66**.—To a solution of the diacetate **64** (970 mg, 3.94 mmol) in THF (80 ml) at −78 °C under argon, was added dropwise $LiBHEt_3$ (1 mol dm^{-3} solution in THF; 9.85 ml, 9.85 mmol). The resulting solution was stirred for 2 h and acetic acid (568 μl, 9.85 mmol) was added. After the mixture had been allowed to warm to room temperature the solvent was removed under reduced pressure. Chromatography on silica gel (gradient elution, 50–100% ether–petroleum) gave the *monoacetate* **66** (as a colourless oil (764 mg, 95%), $[\alpha]_D^{20}$ −32.2 (*c* 1.1 in MeOH); ν_{max}(film)/cm^{-1} 3416, 2935 and 1740; δ_H(500 MHz, systematic numbering) 5.37 (0.75 H, d, *J* 2.6, 1-H), 4.83 (0.25 H, dd, *J* 9.5 and 1.9, 1-H), 4.68 (0.75 H, t, *J* 9.5, 4-H), 4.67 (0.25 H, t, *J* 9.2, 4-H), 4.01 (0.75 H, dq, *J* 9.7 and 6.2, 5-H), 3.70 (0.75 H, ddd, *J* 11.4, 9.2 and 5.0, 3-H), 3.45 (0.25 H, dq, *J* 9.7 and 6.2, 5-H), 3.38 (0.25 H, ddd, *J* 11.6, 9.1 and 5.0, 3-H), 3.35 (2.25 H, s, 3-OMe), 3.34 (0.75 H, s, 3-OMe), 2.51 (1 H, br s, 1-OH), 2.43 (0.25 H, ddd, *J* 12.5, 4.9 and 2.1, 2-H), 2.43 (0.75 H, ddd, *J* 13.1, 5.0 and 1.5, 2-H), 2.10 (3 H, s, 4-OAc), 1.64 (0.75 H, ddd, *J* 13.1, 11.4 and 3.6, 2-H), 1.53 (0.25 H, ddd, *J* 12.5, 11.6 and 9.6, 2-H), 1.21 (0.75 H, d, *J* 6.2, 5-Me) and 1.16 (2.25 H, d, *J* 6.3, 5-Me); *m/z* 203 (M^+ – H), 187, 144, 129, 74 and 43 (Found: M^+ – H, 203.0919. $C_9H_{15}O_5$ requires M – H, 203.0919) (Found: C, 53.15; H, 8.20. $C_9H_{16}O_5$ requires C, 52.93; H, 7.90%).

(1-O-*Acetyl*-L-*oleandrosyl*)-(4-O-*acetyl*-L-*oleandroside*) **67**.—Carbonyldiimidazole (0.4 mol dm^{-3} solution in THF; 650 μl, 0.26 mmol) was added to a 4-*O*-acetyloleandrose **66** (50 mg, 0.253 mmol) under argon, and the mixture stirred for 1 h. The reaction was then diluted with CH_2Cl_2 (10 ml), washed with pH 7.5 buffer, dried (Na_2SO_4), evaporated and azeotroped with toluene. 1-*O*-Acetyloleandrose (100 mg, 0.506 mmol) was then added to the residue and the mixture was dissolved in THF (400 μl) under argon. A solution of anhydrous silver perchlorate (52.5 mg, 0.253 mmol) in THF (400 μl) was then added and the reaction warmed to 50 °C, in the dark, for 45 min. The reaction mixture was cooled, a suspension of silica in CH_2Cl_2 (1 ml) added and the solvents removed under reduced pressure. The residue was then chromatographed on silica gel (gradient elution, 10–20% ether–CH_2Cl_2) to give the desired 1″-α-*disaccharide* **67** (43.6 mg, 62%), and its 1″-β-epimer (7.9 mg, 11%), along with recovered 4-*O*-acetyloleandrose (7.0 mg), and 1-*O*-acetyloleandrose (63.3 mg), $[\alpha]_D^{20}$ (1′-α) −86.9 (*c* 0.7 in $CHCl_3$); $[\alpha]_D^{20}$ (1′-β) −88.7 (*c* 0.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2980, 2934 and 1743; δ_H(500 MHz) 6.18 (0.5 H, m, 1′-H), 5.69 (0.5 H, dd, *J* 8.5 and 3.0, 1′-H), 5.39 (1 H, m, 1″-H), 4.68 (0.5 H, t, *J* 8.0, 4″-H), 4.67 (0.5 H, t, *J* 8.0, 4″-H), 3.80 (1 H, m, 5″-H), 3.56 (1 H, m, 3″-H), 3.44 (1 H, dq, *J* 8.0 and 6.0, 5′-H), 3.38–3.32 (7 H, m, 3-OMe_2, 3′-H), 3.27 (1 H, t, *J* 8.0, 4′-H), 2.38 (1 H, ddd, *J* 11.0, 5.0 and 3.0, 2′-H), 2.27 (1 H, ddd, *J* 13.0, 5.0 and 2.0, 2″-H), 2.12–2.09 (6 H, m, 1′-OAc, 4″-OAc), 1.66 (1 H, ddd, *J* 13.0, 10.0 and 4.0, 2″-H), 1.57 (1 H, ddd, *J* 11.0, 10.0 and 1.0, 2′-H), 1.34 (1.5 H, d, *J* 6.0, 5-Me), 1.30 (1.5 H, d, *J* 6.0, 5-Me), 1.14 (1.5 H, d, *J* 6.0, 5-Me) and 1.13 (1.5 H, d, *J* 6.0, 5-Me); *m/z* (CI, NH_3) 408 (MNH_4^+), 348, 330, 299, 286, 270, 256, 247, 230, 213, 203, 187, 171, 155, 143, 127, 116, 111, 99, 95, 87, 83, 74, 71, 67, 59, 55 and 43 (Found: MNH_4^+, 408.2234. $C_{18}H_{34}O_9N$ requires MNH_4, 408.2233).

(4-O-*Acetyl*-L-*oleandrosyl*)*oleandroside* **68**.—To a solution of the diacetate **67** (144 mg, 0.48 mmol) in THF (8 ml) under argon at −78 °C was added dropwise $LiBHEt_3$ (1 mol dm^{-3} solution in THF; 923 μl, 0.923 mmol). After 2 h the reaction mixture was quenched with acetic acid (53 μl, 0.923 mmol) and allowed to warm to room temperature. After concentration under reduced pressure, the residue was chromatographed on silica gel (gradient elution, 50–100% ethyl acetate–petroleum) to give the *mono-acetate* **68** (126 mg, 98%), as an oil, which crystallised from ether, m.p. 136–137.5 °C (ether); $[\alpha]_D^{20}$ −110.5 (*c* 1.03 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3462, 2962, 1735 and 1452; δ_H(500 MHz) 5.39 (1 H, m, 1″-H), 5.30 (0.86 H, br s, 1′-H), 4.79 (0.14 H, ddd, *J* 9.0, 6.6 and 2.0, 1′-H), 4.67 (1 H, t, *J* 9.4, 4″-H), 3.93 (1 H,

dq, *J* 9.4 and 6.3, 5″-H), 3.85 (1 H, m, 5′-H), 3.66 (0.86 H, ddd, *J* 11.3, 8.8 and 4.9, 3′-H), 3.62–3.53 (1.14 H, m, 3″-H, 3′-H), 3.36 (3 H, s, 3-OMe), 3.35 (2.58 H, s, 3-OMe), 3.34 (0.42 H, s, 3-OMe), 3.25 (0.14 H, t, *J* 8.8, 4′-H), 3.24 (0.86 H, t, *J* 9.0, 4′-H), 3.00 (0.14 H, d, *J* 6.6, 1′-OH), 2.48 (0.86 H, t, *J* 2.6, 1′-OH), (0.14 H, ddd, *J* 12.4, 4.8 and 2.0, 2′-H), 2.34–2.24 (1.86 H, m, 2″-H, 2′-H), 2.10 (2.58 H, s, 4″-OAc), 2.07 (0.42 H, s, 4″-OAc), 1.66 (1 H, ddd, *J* 13.1, 11.6 and 4.0, 2″-H), 1.53 (0.86 H, dddd, *J* 13.3, 11.3, 3.6 and 2.6, 2′-H), 1.41 (0.14 H, dt, *J* 11.9 and 11.8, 2′-H), 1.34 (0.42 H, d, *J* 6.1, 5′-Me), 1.28 (2.58 H, d, *J* 6.3, 5′-Me) and 1.14 (3 H, d, *J* 6.3, 5″-Me); *m/z* (CI, NH_3) 366 (MNH_4^+), 3,48, 331, 299, 239, 204, 187, 172, 155, 130, 113, 95 and 85 (Found: MNH_4^+, 366.2128. $C_{16}H_{32}NO_8$ requires MNH_4, 366.2128).

O-(4-O-L-*Oleandrosyl*-L-*oleandrosyl*)*imidazole*-1-*thiocarboxylate* **69**.—The mono-protected disaccharide **68** (100 mg, 0.29 mmol) and thiocarbonyldiimidazole (350 mg, 1.96 mmol) were mixed under argon and THF (12 ml) added. After being stirred at room temperature for 44 h, the reaction mixture was concentrated under reduced pressure and the residue chromatographed on silica gel (diethyl ether). This gave the thiocarbamate **69** (49 mg, 57%), used immediately in the following coupling reaction, along with recovered sugar (32 mg).

5,4″-*Di*-O-*acetylavermectin B1a* **71**.—A solution of anhydrous silver perchlorate (7.5 mg, 0.036 mmol) in toluene (75 μl) was added dropwise to a mixture of the freshly prepared thiocarbamate **69** (17 mg, 0.038 mmol), 5-*O*-acetylavermectin B1a aglycone (10 mg, 0.016 mmol) and calcium carbonate (20 mg, 0.200 mmol) in THF (75 μl) under argon. After 10 min the reaction mixture was diluted with CH_2Cl_2 (800 μl) and loaded directly onto a silica gel column (gradient elution, 30–60% ethyl acetate–petroleum) to afford 5′,4″-di-*O*-acetylavermectin B1a **71** (7.2 mg, 64%) and 5′,4″-di-*O*-acetyl-1′-*epi*-avermectin B1a [1.8 mg, 16% based on recovered aglycone (2.7 mg)]. Less polar **71**, $[\alpha]_D^{20}$ +40.1 (*c* 1.27 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3472, 2962, 1741 and 1452; δ_H(500 MHz) 5.84 (1 H, m, 9-H), 5.76 (1 H, dd, *J* 9.8 and 2, 23-H), 5.74–5.69 (2 H, m, 10-H, 11-H), 5.55 (1 H, dd, *J* 9.8 and 2.6, 22-H), 5.55–5.53 (2 H, m, 19-H, 5-H), 5.41–5.37 (2 H, m, 3-H, 1″-H), 4.99 (1 H, m, 15-H), 4.77 (1 H, d, *J* 3.2, 1′-H), 4.67 (1 H, t, *J* 9.4, 4″-H), 4.66 (1 H, dd, *J* 14.5 and 2.3, 8-H), 4.58 (1 H, dd, *J* 14.5 and 2.3, 8-H), 4.01 (1 H, d, *J* 6.3, 6-H), 3.95 (1 H, s, 7-OH), 3.93 (1 H, br s, 13-H), 3.88–3.81 (3 H, m, 2-H, 5′-H, 5″-H), 3.65–3.58 (2 H, m, 3′-H, 3″-H), 3.48 (1 H, m, 25-H), 3.43 (3 H, s, 3-OMe), 3.37–3.34 (4 H, m, 3-OMe, 17-H), 3.23 (1 H, t, *J* 9.0, 4′-H), 2.52 (1 H, m, 12-H), 2.35–2.20 (5 H, m, 24-H, 16-H_2, 2′-H, 2″-H), 2.16 (3 H, s, OAc), 2.10 (3 H, s, OAc), 2.04 (1 H, m, 20-H), 1.80–1.78 (4 H, m, 4-Me, 18-H), 1.71–1.44 (9 H, m, 15-Me, 27-H_2, 26-H, 20-H, 2′-H, 2″-H), 1.25 (3 H, d, *J* 6.2, 5″-Me), 1.17 (3 H, d, *J* 7.0, 12-Me), 1.14 (3 H, d, *J* 6.3 Hz, 5′-Me) and 0.97–0.86 (10 H, m, 30-Me, 29-Me, 24-Me, 18-H); *m/z* 958 (M^+), 939, 924, 899, 879, 864, 835, 771, 736, 700, 679, 660, 627, 607, 591, 567, 549, 531, 494, 463, 439, 399, 381, 331, 305, 289, 267, 243 and 221 (Found: M^+, 957.5220. $C_{52}H_{76}O_{16}$ requires M, 957.5211) (Found: C, 65.05; H, 8.1. $C_{52}H_{76}O_{16}$ requires C, 65.25; H, 8.00%).

Avermectin B1a **1**.—A solution of 5,4″-di-*O*-acetylavermectin B1a **71** (49 mg, 0.051 mmol) in THF (1.0 ml) under argon was cooled to −78 °C and treated with $LiBEt_3H$ (1 mol dm^{-3} solution in THF; 500 μl, 0.50 mmol). After the mixture had been stirred for 2 h at −78 °C further $LiBEt_3H$ (1 mol dm^{-3} solution in THF; 500 μl, 0.50 mmol) was added. Stirring was continued at low temperature for 1 h, followed by warming to room temperature over 1 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2, and the resulting solution was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel (gradient elution, 80% ether–petroleum, 100% ether, 50% ether–ethyl acetate) gave *avermectin B1a* **1** (as a white foam (40 mg, 90%), $[\alpha]_D^{20}$ +63.7 (*c* 0.98 in $CHCl_3$) (lit.,[61] $[\alpha]_D^{27}$ +55.7, *c* 1.06 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3452, 2964, 2930, 1721, 1450, 1379, 1337, 1296, 1159, 1142, 1119, 1050, 985 and 756; δ_H(500 MHz) 5.86 (1 H, br d, *J* 10.5, 9-H), 5.78 (1 H, d, *J* 1.5, 23-H), 5.76–5.72 (2 H, m, 10-H, 11-H), 5.55 (1 H, dd, *J* 10.0 and 2.5, 22-H), 5.42 (1 H, br s, 3-H), 5.40 (1 H, d, *J* 4.0, 1″-H), 5.39 (1 H, m, 19-H), 4.99 (1 H, br d, *J* 7.0, 15-H), 4.77 (1 H, d, *J* 3.5, 1′-H), 4.71 (1 H, dd, *J* 14.5 and 2.5, 8′-H), 4.67 (1 H, dd, *J* 14.5 and 2.5, 8′-H), 4.30 (1 H, d, *J* 6.0, 5-H), 3.97 (1 H, d, *J* 6.5, 6-H), 3.94 (1 H, s, 13-H), 3.86 (1 H, m, 17-H), 3.83 (1 H, dq, *J* 9.5 and 6.0, 5′-H), 3.77 (1 H, dq, *J* 9.5 and 6.5, 5″-H), 3.62 (1 H, ddd, *J* 11.0, 8.5 and 4.5, 3′-H), 3.51–3.45 (2 H, m, 25-H, 3″-H), 3.44 (3 H, 3″-OMe), 3.42 (3 H, s, 3′-OMe), 3.30 (1 H, dd, *J* 4.5 and 2.0, 2-H), 3.24 (1 H, t, *J* 9.0, 4″-H), 3.17 (1 H, t, *J* 9.0, 4′-H), 2.53 (1 H, m, 12-H), 2.35–2.21 (5 H, m, 16-H_2, 24-H, 2′-H_{eq}), 2.01 (1 H, dd, *J* 12.0 and 3.0, 20-H_{eq}), 1.88 (3 H, s, 4-Me), 1.78 (1 H, dd, *J* 10.5 and 2.5, 18-H_{eq}), 1.68–1.43 (6 H, m, 20-H_{ax}, 26-H, 27-H_2, 2′-H_{ax}, 2″-H_{ax}), 1.49 (3 H, s, 14-Me), 1.28 (3 H, d, *J* 6.5, 5′-Me), 1.26 (3 H, d, *J* 6.5, 5″-Me), 1.17 (3 H, d, *J* 7.0, 12-Me), 0.94 (3 H, t, *J* 7.0, 27-Me), 0.92 (3 H, d, *J* 7.0, 24-Me), 0.92 (3 H, d, *J* 7.5, 26-Me), and 0.88 (1 H, dd, *J*, 12.5 and 6.5, 18-H_{ax}); *m/z* 566 (M^+ − Ole − Ole − H_2O), 305 [$C_{19}H_{29}O_3$, C(13)–C(28) fragment], 221 [$C_{14}H_{21}O_2$, C(1)–C(12) fragment], 169 ($C_{10}H_{17}O_2$), 145 ($C_7H_{13}O_3$, oleandrose fragment) and 113 ($C_6H_9O_2$) [Found (FAB, 3-nitrobenzyl alcohol): MH^+, 873.5000. $C_{48}H_{73}O_{14}$ requires MH, 873.5000] (Found: C, 65.85; H, 8.6. Calc. for $C_{48}H_{72}O_{14}$, C, 66.03; H, 8.31%).

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