Total Synthesis of (+)-Milbemycin β₃

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The total synthesis of (+)-milbemycin β_3 has been achieved in two ways beginning from the appropriate spiroacetal moiety. In the first, coupling of a vinyl-lithium derivative (**18**) with the spiroacetal aldehyde (**19**), available from Swern oxidation of the corresponding alcohol generated the C(11)–C(25) segment of milbemycin β_3. Removal of the allylic hydroxy group was achieved by tributyltin hydride reduction of the dithiocarbonate although a mixture of two double-bond isomers was obtained. In an alternative and superior approach the C(14)–C(15) trisubstituted double-bond of milbemycin β_3 was established by reaction of a Wittig reagent with the spiroacetal aldehyde (**19**). The product of this reaction, after conversion into the iodide and enantiospecific alkylation to generate the 12-methyl group, was further elaborated to the same C(11)–C(25) segment prepared previously. The aromatic portion of milbemycin was incorporated by the Lythgoe-Kocienski modification of the Julia reaction involving reaction of a sulphone anion and an α,β-unsaturated aldehyde followed by reductive elimination to generate the C(8)–C(10) diene system. Final macrocyclisation followed essentially established procedures.

In 1974 the structure of a new series of macrolide antibiotics with high pesticidal and insecticidal activity were described and named the milbemycins.[1] The stereochemistry of milbemycins β_1, β_2, and β_3 was later confirmed by X-ray analysis of a crystalline p-bromophenylurethane derivative of milbemycin β_1.[2] Milbemycins α_1 to α_{10} have, as a common structural feature, a hexahydrobenzofuran, three carbons of which form the southern part of the 16-membered macrolide ring. Milbemycins β_1 and β_2 are derived by a formal opening of the tetrahydrofuran ring; aromatisation of the tetrahydrobenzene ring affords milbemycin β_3. All the milbemycins contain a spiroacetal as a common structural feature within which all the other sources of variation reside. A related series of macrolides, the avermectins, have many features in common with the milbemycins; they also have additional oxygenation at C-13 bearing a disaccharide.[3] Milbemycin β_3 (**1**) is the simplest member of this group of macrocyclic natural products. Two total syntheses of milbemycin β_3 had been reported previous to our preliminary communication.[4] A route by Smith et al.[5] to yield racemic material began from racemic trans-4,5-dimethyl-valerolactone followed by two successive three-carbon additions which allowed the construction of a 15-aldehyde spiroacetal. Addition to the aldehyde and separation of the epimeric alcohols followed by a Claisen-Ireland reaction afforded the 'northern hemisphere'. Union to the aromatic portion was achieved via a Wittig-Horner reaction to generate the C(10)–C(11) double bond, cyclisation and deprotection then afforded the macrolide. An enantiospecific route was reported by Williams et al.[6] and utilised chiral trans-4,5-dimethyl-valerolactone derived from 1-citronellol. The second ring of the spiroacetal was added in one fragment via a sulphoxide anion addition to the lactone; subsequent manipulation afforded a 16-aldehyde spiroacetal. The C(9)–C(15) alkyl chain, again derived from 1-citronellol, was then added followed by reductive removal of the resulting allylic alchol which unfortunately resulted in loss of double-bond homogeneity. Incorporation of the aromatic portion afforded milbemycin β_3. Shortly after the communication[4] of our total synthesis, another synthesis by Kocienski et al. was reported.[7] This route again starts from trans-4,5-dimethyl-valerolactone which was converted into a spirocyclic ortholactone; subsequent intramolecular directed aldol and oxidation afforded the 15-aldehyde spiroacetal. Stereoselective formation of the C(14)–C(15) double bond and introduction of the remote chiral centre on C-12 yielded the

northern hemisphere. Construction of the C(10)–C(11) double bond via a Julia olefination gave poor stereocontrol, fortunately only the desired diene underwent macrolactonisation. Kocienski et al.[7] also report a second route to the northern hemisphere utilising nucleophilic opening of an epoxide with a metallated 3,4-dihydro-2H-pyran.

More recently a fifth route has been reported by Barrett et al.[8] which utilised the condensation of a diketone dianion with trans-4,5-dimethylvalerolactone to afford a spirodihydropyrone. Stereocontrolled hydrogenation and subsequent stereochemical correction afforded a 15-ester spiroacetal, homologation, and incorporation of the side-chain via a Julia reaction which proceeded with low stereocontrol. Addition of the aromatic portion using the protocol developed by Williams et al.[5] followed by cyclisation via a Mitsunobu reaction and de-O-methylation afforded (+)-milbemycin β_3. In addition to these total syntheses, numerous approaches to the spiroacetal portion of milbemycin β_3 have been reported.[5,6,9–11]

It was the objective of this work to develop a synthetic strategy which allowed the synthesis of milbemycin β_3 to take place in a building block (modular) manner by joining preformed sub-units. Not only is such an approach logistically attractive, but it also offers the opportunity for the ready incorporation of the appropriate sub-units required for the synthesis of each of the members of the milbemycin and avermectin families. In this and the preceding paper we demonstrate this strategy in a total synthesis of (+)-milbemycin β_3.

The retrosynthetic analysis is presented in Scheme 1. Our analysis divided milbemycin β_3 into three fragments, the spiroacetal moiety (**2**), the vinyl iodide (**3**) bearing the remote chiral centre at C-12, and the aromatic aldehyde (**4**). A structural feature common to both families of macrolides is the spiroacetal moiety, three carbons of which form part of the 16-membered macrocyclic ring. In the preceding paper we described the synthesis of the spiroacetal unit of milbemycin β_3 and β_1 (**2**) from the chiral lactone (**5**).[9] This lactone has proven to be an important building block in the synthesis of the spiroacetal portions of avermectins B_{1b}, B_{2b}, A_{1a}, and A_{2a}[10] and, in addition, it has also been used in the synthesis of the dioxygenated spiroacetal moieties of milbemycin α_7 and α_8.[11,12] With a versatile approach to the spiroacetal moiety in hand we turned our attention to the construction of the other two sub-units.
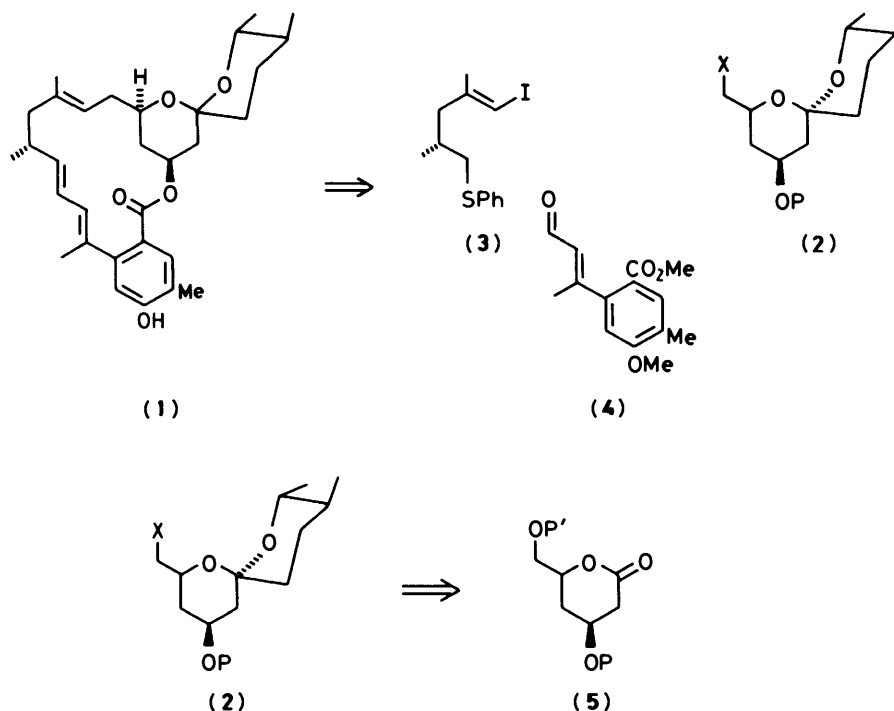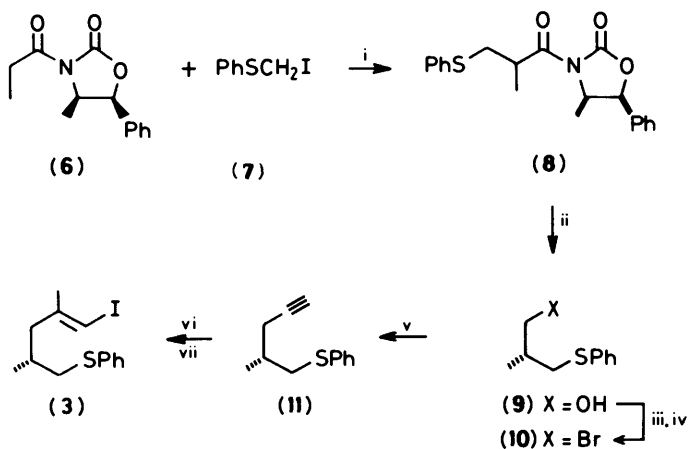
Scheme 1.

Alkyl Chain.—The seven-carbon fragment (3) containing the remote chiral centre at C-12 required to complete the synthesis of the northern hemisphere was generated *via* an enantiospecific alkylation of the oxazolidone (6)[13] with the very unstable iodide (7) (Scheme 2). This reaction proceeded with excellent stereocontrol (8) but very slowly and with only moderate chemical yield. The relatively poor nucleophilicity of the oxazolidone (6) was compounded by the instability of the iodide (7) above −20 °C. Reductive removal of the chiral auxiliary proceeded smoothly to furnish the alcohol (9) which was brominated in 75% yield (10); subsequent treatment with lithium acetylide gave the acetylene (11) in 60% yield together with a considerable amount of the eliminated product. Conversion of the bromide into the iodide failed to improve the yield of the acetylide displacement. Carboalumination[14] followed by treatment of the intermediate alane with iodine

Scheme 2. *Reagents:* i, LDA, THF, −20 °C, 5 days; ii, LiAlH₄, Et₂O; iii, *p*-TsCl, py; iv, LiBr, THF; v, LiC≡CH, NH₃, overnight; vi, Me₃Al, Zr(Cp)₂Cl₂, ClCH₂CH₂Cl, 12 h; vii, I₂, THF, −10 °C

gave the required vinyl iodide (3) with complete stereospecificity as determined by [13]C n.m.r. analysis.

An alternative alkylation of the oxazolidone (12)[13] with 1,3-di-iodo-2-methylpropene was also investigated but initial results suggested little advantage over the route previously described. In an alternative route and as a means of confirming the optical purity of the intermediate alcohol (9), the commercially available (*S*)-methyl 3-hydroxymethylpropionate (13) was protected as its tetrahydropyranyl (THP) ether (14) and the ester reduced to yield the alcohol (15). Preparation of the tosylate (16) and displacement by thiophenoxide afforded the thioether (17). Removal of the THP ether gave the alcohol (9), the specific rotation of which was in excellent agreement with that derived *via* the enantiospecific alkylation.
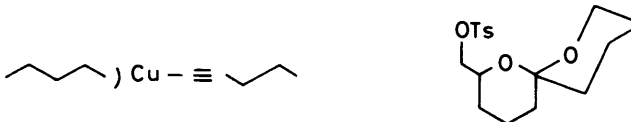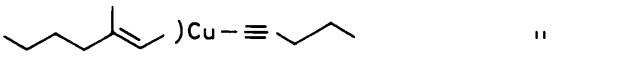
Synthesis of the Northern Hemisphere.—Our initial intention had been to complete the synthesis of the northern hemisphere by a vinyl cuprate displacement of a suitable electrophile derived from the spiroacetal (2). Initial model studies were promising (see Table), reaction of an alkyl cuprate with an unsubstituted spiroacetal tosylate (entry 1) giving the coupled product in 85% yield. However the less reactive vinyl cuprate gave none of the desired coupled product (entry 2). Subsequently a variety of cuprate species, reaction conditions, and electrophiles were investigated. It soon became obvious that increasing heteroatom substitution in both cuprate and spiroacetal fragments dramatically reduced the yield of the reaction. The spiroacetal oxygen substituent β to the leaving group exerts the greatest effect, confirming the well-documented β oxygen effect.[15] A further decrease in reactivity is noted in changing from tetrahydropyranyl iodide to the spiroacetal iodide (entries 4 and 5).

Coupling of fragments (3) and (2) was eventually achieved by reaction of the vinyl-lithium (18) with the spiroacetal aldehyde (19) (Scheme 3) available from Swern oxidation of the corresponding alcohol.[9] The aldehyde (19) easily forms a hydrate and thus was used without isolation.[16] Removal of the allylic alcohol (20) proved to be unexpectedly troublesome;

Table. Displacement reactions of model cuprates with tosylates and iodides

reaction with toluene-p-sulphonyl chloride (TsCl) or methane-sulphonyl chloride gave complex mixtures of eliminated products whilst attempts to brominate gave extensive decomposition. The acetate (21) could be prepared in good yield, but reduction with lithium in ethylamine gave the eliminated product (22). Palladium-catalysed reductions were also unsuccessful.[17] Removal of the allylic hydroxy group was ultimately achieved by the method of Williams et al.[6] by tributyltin hydride reduction of the dithiocarbonate (23), to afford the required product (24) as a mixture of double-bond isomers. Oxone oxidation then afforded the sulphone required for the incorporation of the aromatic portion.
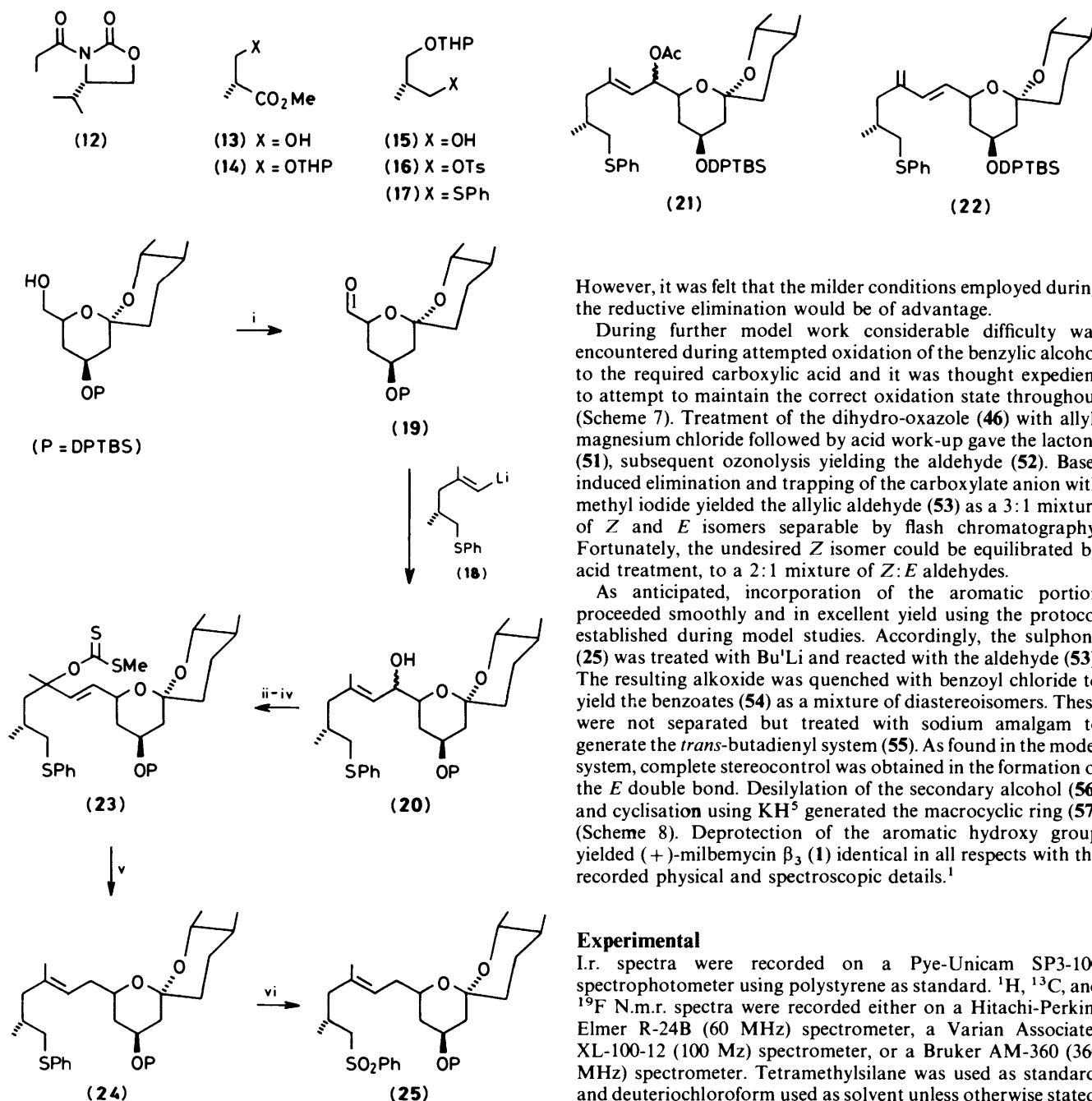
The difficulties involved in the reductive removal of the allylic hydroxy group led us to investigate an alternative route, which involved generating the required tri-substituted double bond via a Wittig reaction (Scheme 4). The spiroacetal diol (26) was treated with 1 equivalent of TsCl to prepare the primary tosylate (27), subsequent protection of the secondary alcohol (28) and displacement of the tosylate with cyanide afforded the nitrile (29). Dibal reduction gave the aldehyde (30) which was immediately treated with the Wittig reagent (31) to afford the α,β-unsaturated ester (32). This was shown to be a single component assigned as the E-isomer by ^{1}H and [13]C n.m.r.; a triplet at δ 6.7 assigned as the vinyl proton provided compelling evidence.

Dibal reduction afforded the corresponding allylic alcohol (33) which was converted into the unstable iodide (34). Since this was prone to double-bond isomerisation it was therefore used without purification.[18] Alkylation of the oxazolidone (12) served to generate the required chiral 13-methyl, after which subsequent reductive removal of the chiral auxiliary (36), tosylation (37), and treatment with thiophenoxide afforded

the northern hemisphere (24) identical with that prepared previously.

The aromatic portion. For the synthesis of the aromatic fragment two different approaches were investigated. Initial studies were centred around the construction of the aromatic ring via a Diels–Alder reaction between the diene (38) and the dienophile (39) to afford the adduct (40) (Scheme 5).[19] Acid hydrolysis of the silyl ethers led to ring aromatisation but also the undesired cyclisation to yield the phthalide (41). However ring aromatisation with concomitant oxidation of the side chain was achieved by treatment of the crude adduct with Jones reagent at 0 °C (42).[19] The stage was now set for the side-chain extension to the required aldehyde. Treatment with vinyl-magnesium bromide yielded an inseparable mixture of the phthalides (43) and (44). In an effort to suppress the formation of the phthalide (44) it was decided to protect the ester functionality as the dihydro-oxazole.

The required aromatic moiety could also be prepared from 4-methoxy-3-methylbenzoic acid (45) (Scheme 6) using the protocol developed by Smith et al.;[5] in our hands the use of freshly opened bottles of Bu^{s}Li increased the yield of the acylation from 45—50% to 90% (46). Treatment with vinylmagnesium bromide followed by acid hydrolysis yielded the phthalide in excellent yield, however all attempts on S_N2' displacement with nucleophiles such as halides, cyanide, and malonate were unsuccessful. Reduction of the phthalide yielded the diol (47) and the primary alcohol was selectively protected as the acetate (48). Oxidative rearrangement of the tertiary allylic alcohol with pyridinium chlorochromate (PCC) then gave the requires aldehyde (49) as a 1.5:1 mixture of E and Z isomers easily separable by flash chromatography. As an alternative, treatment of the allylic alcohol (48) with

(12)

(13) X = OH
(14) X = OTHP

(15) X = OH
(16) X = OTs
(17) X = SPh

(21)

(22)

(19)

(P = DPTBS)

(18)

(23)

(20)

(24)

(25)

Scheme 3. *Reagents:* i, Me$_2$SO, (COCl)$_2$, Et$_3$N; ii, NaH, THF; iii, CS$_2$, THF, reflux; iv, MeI; v, Bu$_3$SnH, AIBN, MePh; vi, KHSO$_5$, EtOH

phosphorus tribromide at 0 °C gave the allylic bromide (50) as a 3:1 ratio of *E* and *Z* isomers.

Formation of the macrocyclic ring. From this point two different methodologies for the construction of the *trans*-butadienyl system were investigated by model studies. In the first the anion of the sulphone derived from (3) was treated with the aldehyde (49) and the reaction quenched with benzoyl chloride. Reductive elimination using sodium amalgam at −20 °C generated the diene system.[20] The second approach involved the displacement of the allylic bromide (50) with the sulphone anion followed by elimination using Triton B in methanol at reflux.[21] Both methods proceeded in excellent yields and complete control of the double-bond stereochemistry.
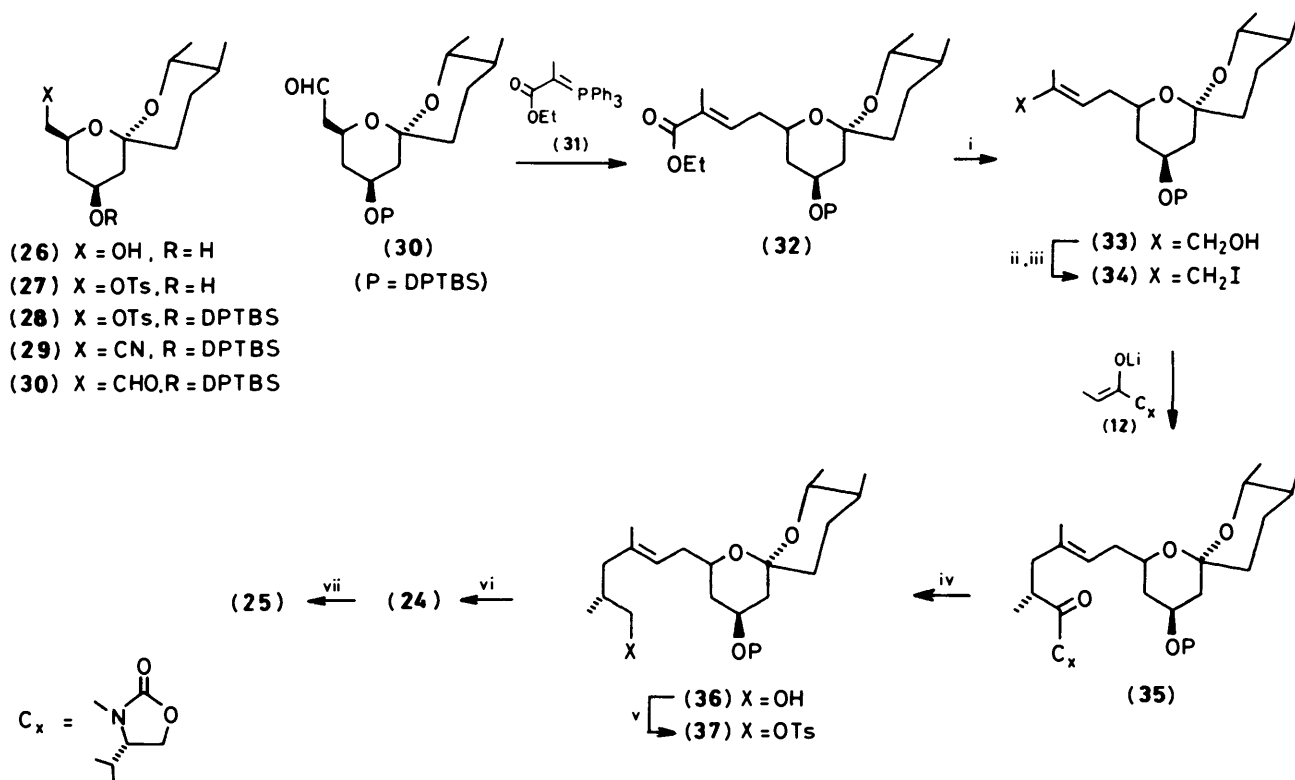
However, it was felt that the milder conditions employed during the reductive elimination would be of advantage.

During further model work considerable difficulty was encountered during attempted oxidation of the benzylic alcohol to the required carboxylic acid and it was thought expedient to attempt to maintain the correct oxidation state throughout (Scheme 7). Treatment of the dihydro-oxazole (46) with allyl-magnesium chloride followed by acid work-up gave the lactone (51), subsequent ozonolysis yielding the aldehyde (52). Base-induced elimination and trapping of the carboxylate anion with methyl iodide yielded the allylic aldehyde (53) as a 3:1 mixture of *Z* and *E* isomers separable by flash chromatography. Fortunately, the undesired *Z* isomer could be equilibrated by acid treatment, to a 2:1 mixture of *Z*:*E* aldehydes.
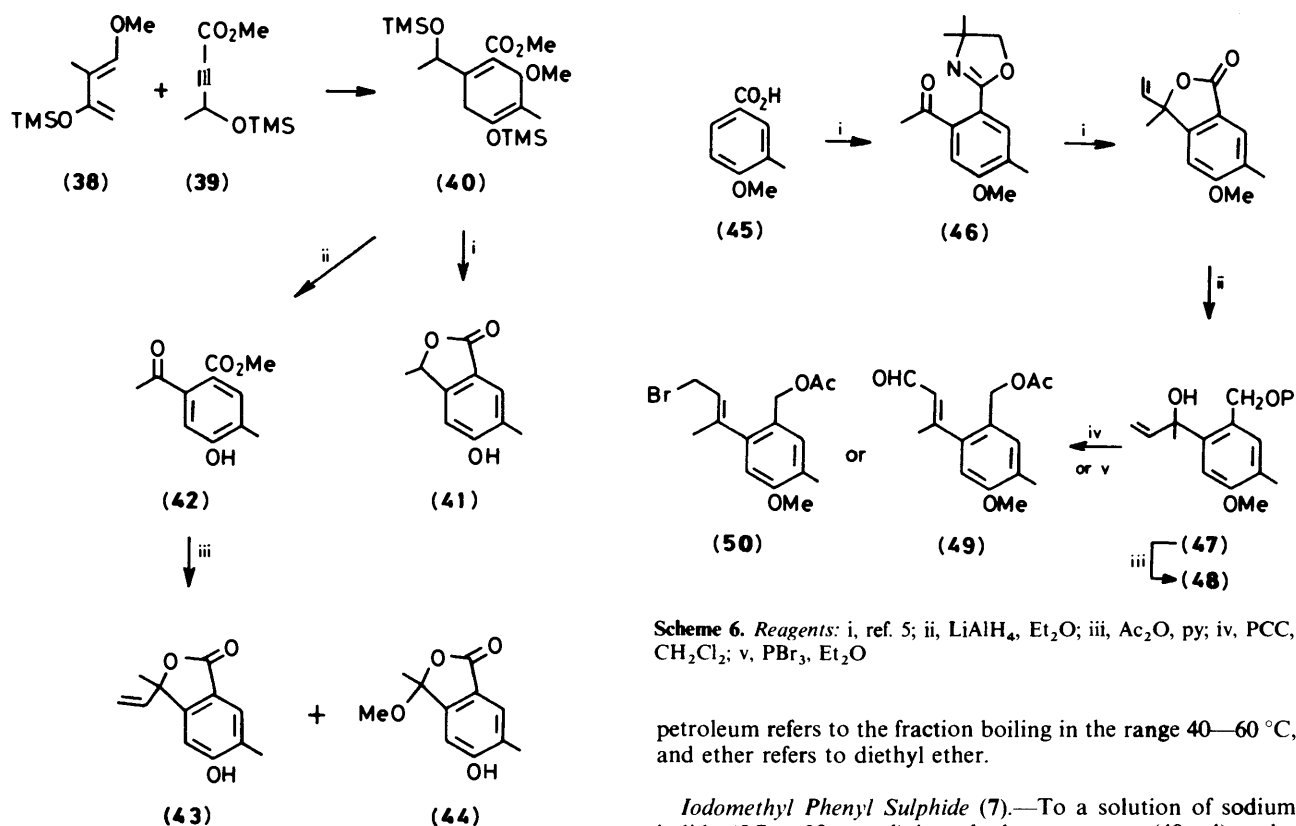
As anticipated, incorporation of the aromatic portion proceeded smoothly and in excellent yield using the protocol established during model studies. Accordingly, the sulphone (25) was treated with Bu^{t}Li and reacted with the aldehyde (53). The resulting alkoxide was quenched with benzoyl chloride to yield the benzoates (54) as a mixture of diastereoisomers. These were not separated but treated with sodium amalgam to generate the *trans*-butadienyl system (55). As found in the model system, complete stereocontrol was obtained in the formation of the *E* double bond. Desilylation of the secondary alcohol (56) and cyclisation using KH[5] generated the macrocyclic ring (57) (Scheme 8). Deprotection of the aromatic hydroxy group yielded (+)-milbemycin β$_3$ (1) identical in all respects with the recorded physical and spectroscopic details.[1]

Experimental

(26) X = OH, R = H
(27) X = OTs, R = H
(28) X = OTs, R = DPTBS
(29) X = CN, R = DPTBS
(30) X = CHO, R = DPTBS

(30)
(P = DPTBS)

(32)

(33) X = CH₂OH
(34) X = CH₂I

(36) X = OH
(37) X = OTs

(35)

(25) ← (24) ←

$$C_x = $$

Scheme 4. *Reagents:* i, Dibal, CH₂Cl₂; ii, MeSO₂Cl, py, DMAP; iii, NaI, THF; iv, LiAlH₄, Et₂O; v, *p*-TsCl, py; vi, PhS⁻, MeOH; vii, KHSO₅, EtOH

(38)   (39)   (40)

(42)   (41)

(43)   +   (44)

Scheme 5. *Reagents:* i, 0.1M HCl; ii, CrO₃, H₂SO₄, H₂O, acetone; iii, ⌀MgBr, THF

(45)   (46)

(50)   or   (49)

(47)
(48)

Scheme 6. *Reagents:* i, ref. 5; ii, LiAlH₄, Et₂O; iii, Ac₂O, py; iv, PCC, CH₂Cl₂; v, PBr₃, Et₂O

petroleum refers to the fraction boiling in the range 40—60 °C, and ether refers to diethyl ether.

Iodomethyl Phenyl Sulphide (**7**).—To a solution of sodium iodide (5.7 g, 33 mmol) in anhydrous acetone (40 ml) under nitrogen at room temperature was added chloromethyl phenyl sulphide (4 g, 25 mmol). The reaction was stirred overnight at
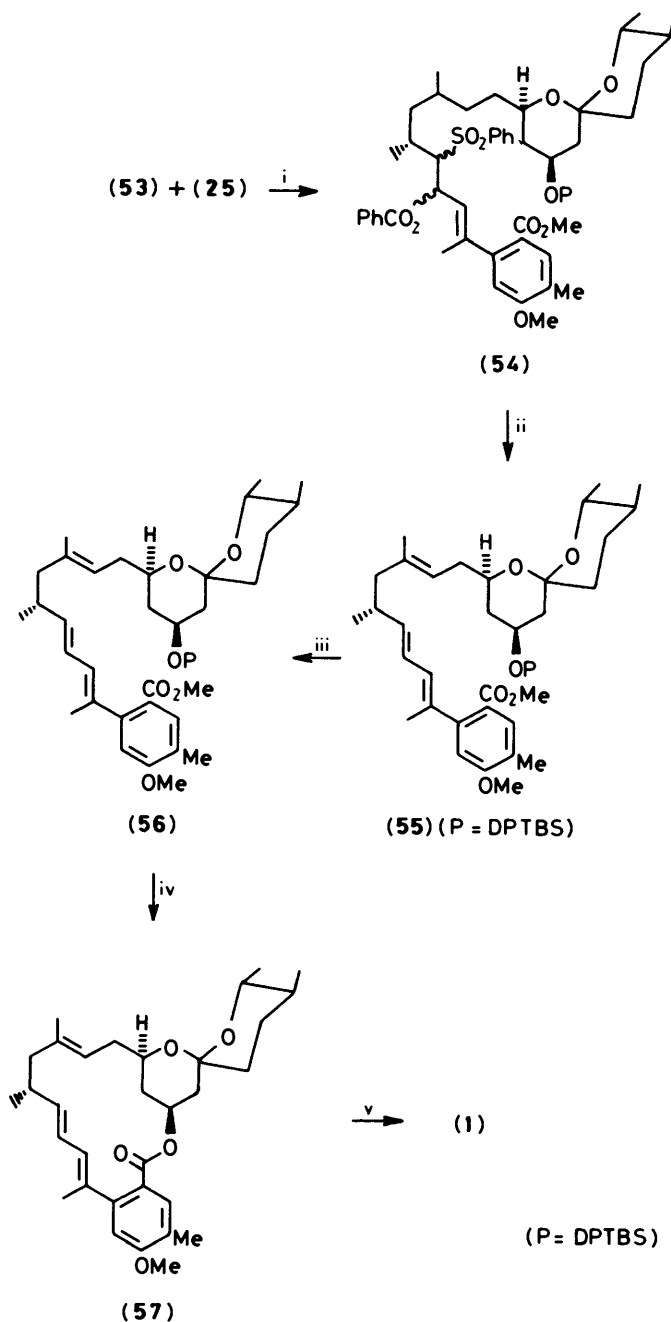
Scheme 7. *Reagents:* i, CH_2=$CHCH_2Br$, THF; ii, O_3; iii, Et_3N; iv, DBU, MeI

room temperature and then poured into water (100 ml) and extracted with pentane (2 × 100 ml). The combined organic extracts were washed with 10% aqueous $Na_2S_2O_5$ (50 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to yield iodomethyl phenyl sulphide (7) as a pale yellow oil which darkened rapidly. The crude material was dissolved in dry THF (10 ml) stored at −30 °C, and used without further purification.

(2S,4R,5S)-3-(3-*Phenylthiomethyl*-1-*oxopropyl*)-5-*phenyl-oxazolidin-2-one* (8).—Butyl-lithium (1.7M in hexane; 13 ml, 22 mmol) was added dropwise to a solution of di-isopropyl-amine (2.22 g, 22 mmol) in THF (50 ml) at −78 °C. The reaction mixture was then allowed to warm to 0 °C for 10 min after which it was cooled to −78 °C and a solution of the propionyloxazolidone (4.6 g, 20 mmol) in THF (20 ml) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h after which a solution of iodomethyl phenyl sulphide (*ca.* 5 g) in THF (10 ml) was added. The reaction mixture was then stored in a freezer (−20 °C) for 5 days. The reaction was quenched by the addition of saturated aqueous ammonium chloride (50 ml) and the mixture extracted with ether (3 × 50 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield an orange oil, purification of which by flash chromatography (light petroleum–ether, 1:1) afforded the title compound (8) as a colourless oil (2.1 g, 30%), contaminated with a small amount of the starting propionyloxazolidone; this was used without further purification.

(R)-(−)-2-*Methyl*-3-*phenylthiopropan*-1-*ol* (9).—A slurry of lithium aluminium hydride (1.2 g, 31.6 mmol) under argon in dry THF (20 ml) was cooled to 0 °C, and a solution of the oxazolidone (8) (3.74 g, 10.5 mmol) in THF (10 ml) was added dropwise. After 2 h at 0 °C the reaction mixture was warmed to room temperature and stirred overnight. Water (20 ml) was added cautiously and the residue extracted with ether (10 × 50 ml). The combined ether extracts were washed with brine (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to yield an oil which was purified by vacuum distillation to afford the title compound (9) (1.1 g, 58%), b.p. 120 °C at 0.5 mmHg (Found: C, 65.8; H, 7.5. $C_{10}H_{14}OS$ requires C, 65.9 H, 7.7%); $[\alpha]_D^{22}$ −17° (c 1.0 CH_2Cl_2); $\nu_{max.}$ 3 400(OH), 1 580, 1 480, 1 425, 1 025, 740, and 690 cm⁻¹; δ_H 1.0 (3 H, d, J 6, Me), 1.9 (1 H, m,

CH), 2.1 (1 H, br s, OH), 3.4 (2 H, m, CH_2S), 3.5 (2 H, d, J 6, CH_2O), and 7.3 (5 H, m, Ar); m/z 182.0748 (M^+, $C_{10}H_{14}OS$ requires M, 182.0755, 49%), 123(39), 110(100), 109(17), and 72(13)

(S)-2-*Methyl*-3-*tetrahydropyran*-2-*yloxypropyl Toluene*-p-*sulphonate* (16).—To a solution of (R)-(−)-2-methyl-3-(tetra-hydropyran-2-yloxy)propanol[20] (15) (5 g, 29 mmol) in anhydrous pyridine (30 ml) at 0 °C was added toluene-p-sulphonyl chloride (TsCl) (6 g, 31.6 mmol); the resulting solution was then stirred at 0 °C overnight. N,N-Dimethyl-aminopropylamine (5 ml) was then added to quench any excess of TsCl after which the reaction mixture was stirred at 0 °C for a further 15 min. The reaction mixture was then diluted with

Scheme 8. *Reagents:* i, Bu^iLi; ii, Na/Hg, MeOH, THF; iii, Bu_4NF, THF, 50 °C; iv, KH, room temp.; v, EtSNa, DMF

ether–light petroleum (1:1) (200 ml), washed with water (100 ml), 10% hydrochloric acid (until washings were neutral), and saturated aqueous sodium hydrogencarbonate (100 ml), and then dried (Na_2SO_4), and evaporated under reduced pressure to afford the title compound (16) as a colourless oil (8.3 g, 100%). This was used without further purification.

2-*Methyl-3-phenylthio*-1-(*tetrahydropyran-2-yloxy*)*propane* (17).—Thiophenol (7.64 g, 69.4 mmol) was added to a solution of sodium (1.66 g, 69.3 mmol) in methanol (150 ml), followed by a solution of the toluenesulphonate (16) (19 g) in methanol (50 ml). The resulting solution was stirred at room temperature overnight after which the solvent was removed at reduced pressure. The residue was dissolved in ether (100 ml) and the solution washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to afford the title compound (17) (15.4 g). This was used without further purification; δ_H (60 MHz) 1.05 (3 H, d, J 7, Me), 1.2—2.4 (7 H, m, 3 × CH_2, CH), 2.5—4.1 (6 H, m, 2 × CHO, CH_2S), 4.5 (1 H, s, OCHO), and 7.3 (5 H, m, Ar).

(R)-(−)-2-*Methyl-3-phenylthiopropan*-1-*ol* (9).—Camphorsulphonic acid (30 mg) was added to a solution of 2-methyl-3-phenylthio-1-(tetrahydropyran-2-yloxy)propane (17) (15.4 g) in methanol (100 ml) and the resulting solution stirred at room temperature overnight. Potassium carbonate (1 g) was then added and the solvent removed at reduced pressure to afford an oil which was purified by distillation at reduced pressure to yield the title compound (9) [10.51 g, 60% from (15)]; $[\alpha]_D^{22} - 18.9°$ (c 3.9 CH_2Cl_2), identical with that prepared previously.

(R)-2-*Methyl-3-phenylthiopropyl* Toluene-p-*sulphonate*.—Toluene-*p*-sulphonyl chloride (11 g, 57 mmol) was added to a cooled (0 °C) solution of the propanol (9) (9.5 g, 52 mmol) in pyridine (20 ml) and the resulting solution stirred at room temperature overnight. The reaction mixture was then diluted with ether (200 ml) and washed with 10% hydrochloric acid until the washings were acidic. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to afford a colourless oil (16.1 g) which was used without further purification; δ_H (60 MHz) 1.05 (3 H, d, J 6, Me), 2.1 (1 H, m, CH), 2.45 (3 H, s, Me), 2.9 (2 H, m, CH_2S), 4.05 (2 H, d, J 5, CH_2O), and 7.2—8.0 (9 H, m, ArH).

(S)-2-*Methyl-3-phenylthiopropyl* Bromide (10).—An intimate mixture of (R)-2-methyl-3-phenylthiopropyl toluene-*p*-sulphonate (16.1 g) and lithium bromide (16 g, 4 equiv.) was dried at 0.01 mmHg overnight. The mixture was then cooled (0 °C) and anhydrous THF (30 ml) added to it (exothermic reaction); the resulting suspension was stirred at room temperature overnight. The reaction mixture was then diluted with light petroleum–ether (10:1) (100 ml), washed with water (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to yield an oil that was purified by distillation to afford the title compound (10) [10.2 g, 80% from (9)], b.p. 75 °C at 0.2 mmHg; ν_{max} 1 585, 1 130, and 1 070 cm^{-1}; δ_H (100 MHz) 1.1 (3 H, d, J 7, Me) 2.0 (1 H, m, CH), 2.95 (2 H, m, CH_2S), 3.5 (2 H, m, CH_2Br), and 7.1 (5 H, m, Ar); m/z 245(1%), 165(20), and 77(100).

(R)-(+)-2-*Methyl-1-phenylthiopent-4-yne* (11).—Lithium (1 g, 0.14 mol) was added in small portions to a mechanically stirred solution of ferric nitrate (50 mg) in ammonia (500 ml). After formation of the grey suspension of lithamide a stream of dried acetylene was passed through the solution for 1 h. A solution of the bromide (10) (10.31 g, 0.04 mol) in THF (50 ml) was then added dropwise and the resulting mixture stirred overnight. Saturated aqueous ammonium chloride (200 ml) was then added dropwise and the ammonia allowed to evaporate.

Ether (100 ml) was then added and the phases separated. The aqueous phase was re-extracted with ether (100 ml) and the combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum–ether, 100:1) to afford 2-methyl-3-phenylthioprop-1-ene (2 g, 30%) followed by the *title compound* (11) (5.04 g, 64%), b.p. 67 °C at 0.3 mmHg (Found: C, 75.6; H, 7.45. $C_{12}H_{14}S$ requires C, 75.7; H, 7.4%); $[\alpha]_D^{22} + 33.6°$ (c 1.0, CH_2Cl_2); $\nu_{max.}$ 3 300 (≡CH), 2 100 (C≡C), 1 590, 1 480, and 1 430 cm^{-1}; δ_H (100 MHz) 1.1 (3 H, d, J 6, Me), 1.9 (1 H, m, CH), 2.0 (1 H, d, J 2, CH), 2.3 (2 H, m, CH_2), 3.0 (2 H, m, CH_2S), and 7.3 (5 H, m, ArH); m/z 190(90%), 77(100), and 65(15).

(4R)-(+)-2,4-*Dimethyl-1-iodo-5-phenylthiopent-1-ene* (3).—A solution of trimethylaluminium (25% solution in hexane; 10 ml, 2 equiv.) was added to a stirred solution of the pent-4-yne (11) (1.8 g, 9.5 mmol) and zirconocene dichloride (500 mg) in anhydrous dichloroethane (40 ml) under argon. The resulting solution was stirred overnight at room temperature and then quenched by the addition of a 10% solution of iodine in THF until the iodine colour persisted, followed by saturated aqueous sodium carbonate. The mixture was diluted with light petroleum (200 ml) and the organic phase separated, dried (Na_2SO_4), and the solvent evaporated under reduced pressure to afford a yellow oil (4 g). Purification by flash chromatography (light petroleum) afforded the title compound (3) (2.85 g, 91%), b.p. 82 °C at 0.2 mmHg; $[\alpha]_D^{22} + 10.8°$; $\nu_{max.}$ δ_H (360 MHz) 0.97 (3 H, d, J 6.7, Me), 1.74 (3 H, s, =CMe), 1.9 (1 H, m, CH), 2.07 (1 H, dd, J 8, 13, CHHC=), 2.39 (1 H, dd, J 6.8, 13, CHHC=), 2.70 (1 H, dd, J 7, 13, CHHS), 2.85 (1 H, dd, J 5.8, 13, CHHS), 5.86 (1 H, s, =CH), and 7.1—7.3 (5 H, m, ArH); δ_C (90 MHz) 19.2 (Me), 23.7 (Me), 31.2 (CH), 40.5 (CH_2), 46.2 (CH_2), 76.2 (=CH), 108 (C=), 125.6, 128.5, 128.6, and 145.8 (Ar); m/z 205(100%), 163(30), 135(18), 109(24), 95(30), and 77(27).

(1RS,5R,2′R,3′S,6′S,8′S,10′S)-(10′-*Diphenyl-t-butylsiloxy-2′,3′-dimethyl*-1′,7′-*dioxaspiro*[5.5]*undecan*-8′-*yl*]-3,5-*dimethyl-6-thiophenylhex*-2-*enol* (20).—A solution of dimethylsulphoxide (0.56 g, 7.24 mmol) in anhydrous THF (5 ml) was added dropwise to a stirred solution of oxalyl chloride (0.84 g, 6.6 mmol) in THF (15 ml) at −30 °C under argon. The reaction mixture was then stirred at −40 °C for 15 min, after which 4 ml of this solution was added to a solution of (2R,3S,6S,8S,10S)-(+)-10-dimethyl-t-butylsiloxy-8-hydroxy-2,3-dimethyl-1,7-dioxaspiro[5.5]undecane (2)[9] (0.56 g, 1.2 mmol) in THF (5 ml) at −80 °C. The reaction mixture was then allowed to warm to −40 °C for 5 min prior to the addition of triethylamine (0.6 g, 5.98 mmol); the resulting suspension was then stirred at 0 °C for 5 min after which it was re-cooled to −80 °C. To this mixture a solution of the vinyl-lithium (19), prepared by the addition of Bu^tLi (3.3 ml, 5.27 mmol) to (4R)-(+)-2,4-dimethyl-1-iodo-5-phenylthiopent-1-ene (3) (0.87 g, 2.6 mmol) in THF (20 ml) at −80 °C and stirring for 1 h, was added; the reaction mixture was stirred at −80 °C for 2 h. Ethanol (5 ml) was then added, and the mixture diluted with saturated aqueous ammonium chloride (20 ml) and allowed to warm to room temperature. The mixture was then extracted with ether (3 × 50 ml) and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was then purified by flash chromatography (ether–light petroleum 1:4) to afford the title compound (20) (315 mg, 60% based on recovered starting material); $\nu_{max.}$ 3 500 (OH), 1 605, 1 450, and 700 cm^{-1}; δ_H (60 MHz) 0.8 (3 H, d, J 6, Me), 0.9 (3 H, d, J 6, Me), 1.05 (9 H, s, Bu^t), 1.1—2.3 (18 H, m), 2.5—3.5 (4 H, m, CH_2S, 2 × CHO–), 4.0—4.5 (2 H, m, CHOS, CHOH), 5.1 (1 H, m, =CH), and 7.0—7.8 (15 H, m, ArH); m/z 654(1); followed by the spiroacetal alcohol (2) (190 mg, 34%).

(3RS,5R,2′R,3′S,6′S,8′S,10′R)-O-3-(10′-*Diphenyl-t-butyl-siloxy-2′,3′-dimethyl-1′,7′-dioxaspiro*[5.5]*undecan-8′-yl*)-3,5-*dimethyl-6-thiophenylhex-1-enyl* S-*Methyl* *Thiocarbonate* (**23**).—Sodium hydride (50% dispersion in oil; 100 mg) was washed with dry hexane (3 × 5 ml) and then suspended in anhydrous THF (5 ml). A solution of the hex-2-enol (**20**) (315 mg, 4.7 mmol) in THF (15 ml) was added and the resulting suspension stirred for 1 h at room temperature prior to the addition of carbon disulphide (0.5 ml, excess). The resulting mixture was stirred at room temperature for a further 3 h prior to the addition of iodomethane (0.5 ml, excess). The reaction mixture was then heated at reflux for 1 h, cooled to room temperature, diluted with ether (30 ml), and water (20 ml) was added; the organic phase was then separated, dried (MgSO$_4$), and evaporated under reduced pressure. The residue was passed through a small plug of silica with ether–light petroleum (1 : 10) as eluant to afford the thiocarbonate (**23**) (350 mg, 98%) which was not purified further; $v_{max.}$ 3 000, 1 680, 1 605, 1 505, 1 410, and 890 cm^{-1}.

(2R,3S,6S,10R)-(E)-(+)-10-*Diphenyl-t-butylsiloxy-8-[(5′R)-3′,5′-dimethyl-6′-thiophenylhex-2′-enyl*]-2,3-*dimethyl-1,7-dioxaspiro*[5.5]*undecane* (**24**).—A solution of the thiocarbonate (**23**) (400 mg, 0.53 mmol) tributyltin hydride (0.5 ml excess), and azoisobutyronitrile (10 mg) in benzene (20 ml) was heated at reflux under argon for 2 h. The solvent was then removed under reduced pressure and the residue purified by careful flash chromatography (ether–light petroleum, 1 : 24) to afford the title compound (**24**) (190 mg, 55%); $[\alpha]_D$ + 30° (*c* 0.1, CH$_2$Cl$_2$); $v_{max.}$ 2 970, 1 605, 1 100, and 700 cm^{-1}; δ_H (360 MHz) 0.76 (3 H, d, *J* 6, 3-Me), 0.96 (3 H, d, *J* 6, 2-Me), 1.05 (12 H, s, Bu^t, Me), 1.1—1.5 (8 H, m), 1.6 (3 H, s, =CMe), 1.6—2.2 (6 H, m), 2.68 (1 H, dd, *J* 13, 7, CH*H*S), 2.95 (1 H, dd, *J* 13, 5, C*H*HS), 3.1 (1 H, m, 2-H), 3.25 (1 H, m, 8-H), 4.17 (1 H, m, 10-H), 5.1 (1 H, t, *J* 7, =C*H*), and 7.2—7.8 (15, m, ArH); *m/z* 401(2), 240(20), 199(40), 91(100), and 77(15). Further elution yielded material (*ca.* 20%) presumed to be other double-bond isomers.

(2R,3S,6S,10R)-(E)-(+)-10-*Diphenyl-t-butylsiloxy-8-[(5′R)-3′,5′-dimethyl-6′-phenylsulphonylhex-2′-enyl*]-2,3-*dimethyl-1,7-dioxaspiro*[5.5]*undecane* (**25**).—A solution of oxone * (300 mg, 46 mmol) in water (1 ml) was added dropwise to a solution of the dioxaspiro[5.5]undecane (**24**) (150 mg, 0.23 mmol) in ethanol (20 ml) at 0 °C. After 5 h, the reaction mixture was diluted with water (20 ml) and extracted with chloroform (5 × 30 ml); the combined extracts were then dried (MgSO$_4$) and evaporated under reduced pressure and the residue purified by flash chromatography (ether–light petroleum, 1 : 4) to yield the title compound (**25**) (140 mg, 90%); $[\alpha]_D$ +31° (*c* 0.3, CH$_2$Cl$_2$); $v_{max.}$ 2 970, 1 450, 1 380, 1 300, 1 150, 1 110, and 700 cm^{-1}; δ_H (360 MHz) 0.74 (3 H, d, *J* 6.5, 3-Me), 0.94 (3 H, d, *J* 6, 2-Me), 1.0 (12 H, m, Bu^t, 5-Me), 1.15 (1 H, m, 3-H), 1.2 (1 H, ddd, *J* 12, 12, 12, 9 eq-H), 1.34 (3 H, s, =CMe), 1.35—1.7 (6 H, m), 1.8—2.2 (6 H, m), 2.83 (1 H, dd, *J* 8.4, 10, C*H*HS), 3.05 (1 H, m, 2-H), 3.1 (1 H, dd, *J* 3.6, 10, CH*H*S), 3.23 (1 H, m, 8-H), 4.16 (1 H, dddd, *J* 5, 5, 11, 11, 10-H), 5.04 (1 H, t, *J* 6.4, 2′-H), and 7.2—7.9 (15 H, m, Ar); *m/z* 401(1), 241(14), 207(10), 199(29), 181(11), 105(10), 91(100), and 77(14).

(2R,3S,6S,8S,10S)-(+)-2,3-*Dimethyl-10-hydroxy-8-(p-tolylsulphonyloxy)methyl-1,7-dioxaspiro*[5.5]*undecane* (**27**).—Toluene-*p*-sulphonyl chloride (0.78 g, 4.1 mmol) was added to a cooled (0 °C) solution of the dioxaspiro[5.5]undecane (**26**)[9] (0.94 g, 4.1 mmol) in pyridine (20 ml), and the resulting solution was stored at 0 °C overnight. The reaction mixture was diluted with ether (100 ml) and then washed with 10% hydrochloric acid (5 × 30 ml), 10% aqueous sodium hydrogencarbonate (30

ml), and brine (30 ml). The solvent was then removed under reduced pressure and the residue purified by flash chromatography (ether) to afford the title compound (**27**) (1.2 g, 80%) as a colourless oil; $[\alpha]_D^{22}$ + 32° (*c* 1.35, CH$_2$Cl$_2$); $v_{max.}$(liquid film) 3 400(OH), 2 950, 1 605, 1 500, 1 460, 1 175, 1 200, 1 005, 830, and 680 cm^{-1}; δ_H (360 MHz) 0.79 (3 H h, d, *J* 6.3, 3-Me), 1.06 (3 H, d, *J* 6.2, 2-Me), 1.17 (1 H, ddd, $J_{9ax.10} = J_{9ax.8} = J_{9ax.9eq} = 11.5$, 9ax-H), 1.2 (1 H, m, 3-H), 1.22 (1 H, dd, $J_{11ax.10}$, 12, $J_{11ax.eq}$, 11.5, 11ax-H), 1.35—1.45 (2 H, m, 4ax-H, 4eq-H), 1.5 (1 H, m, 5ax-H), 1.57 (1 H, ddd, $J_{5eq.5ax}$, 13, $J_{5eq.4eq} = J_{5eq.4ax} = 5.5$, 5eq-H), 1.7 (1 H, br s, OH), 1.88 (1 H, dddd, $J_{9eq.9ax}$ 11.5, $J_{9eq.10}$, 4.5, $J_{9eq.8} = J_{9eq.11} = 1.5$, 9eq-H), 1.95 (1 H, ddd, $J_{11eq.11ax}$, 12, $J_{11eq.10}$, 5, $J_{11eq.11ax}$, 1.5, 11eq-H), 3.18 (1 H, dq, $J_{2.3}$ 10.4, *J* 6.2, 2-H), 3.78 (1 H, m, 5-H), 4.05 (2 H, m, CH$_2$OTs), 4.12 (1 H, dddd, $J_{10.11eq} = J_{10.9eq}$ 4.5, $J_{10.11ax} = J_{10.9ax}$ 11.5, 10-H), 7.35 (2 H, d, *J* 7, ArH), and 7.8 (2 H, d, *J* 7, ArH); *m/z* 384.1606 (*M*$^+$, C$_{19}$H$_{28}$O$_6$S requires 384.1606, 2.6%), 340(7), 298(11), 199(11), 155(16), 129(24), 126(27), 108(36), 95(100), 91(48), 69(34), and 55(32).

(2R,3S,6S,8S,10S)-(+)-10-*Dimethyl-t-butylsilyloxy-2,3-dimethyl-8-(p-tolylsulphonyloxy)methyl-1,7-dioxaspiro*[5.5]*undecane* (**28**).—The dioxaspiro[5.5]undecane (**27**) (0.56 g, 1.47 mmol) was added to a solution of imidazole (0.4 g, 5.9 mmol) and diphenyl-t-butylsilyl chloride (0.4 g, 1.47 mmol) in dimethylformamide (DMF) (20 ml). The resulting solution was stirred at room temperature overnight and then diluted with water (50 ml), and extracted with light petroleum (3 × 50 ml). The combined extracts were dried (MgSO$_4$) and evaporated at reduced pressure and the residue purified by flash chromatography (light petroleum–ether, 4 : 1) to afford the title compound (**28**) (0.8 g, 88%); $[\alpha]_D^{22}$ +35° (*c* 1.9, CH$_2$Cl$_2$); $v_{max.}$ 2 950, 1 600, 1 590, 1 370, 1 200, 1 180, 1 120, 1 000, 710, and 670 cm^{-1}; δ_H (360 MHz) 0.73 (3 H, d, *J* 6.6, 3-Me), 0.91 (3 H, d, *J* 6.3, 2-Me), 1.02 (9 H, s, Bu^t), 1.11 (1 H, m, 3-H), 1.21 (1 H, ddd, $J_{9ax.9eq} = J_{9ax.8} = J_{9ax.10} = 11.6$, 9ax-H), 1.25—1.45 (3 H, m, 5ax-H, 4ax-H, 4eq-H), 1.45 (2 H, m, 9eq-H, 5eq-H), 1.86 (1 H, ddd, *J* 5, *J* 12, *J* 1.3 11eq-H), 2.43 (3 H, s, ArMe), 3.02 (1 H, dq, *J* 10, 6.3 2-H), 3.51 (1 H, m, 8-H), 3.93 (2 H, m, CH$_2$OTs), 4.14 (1 H, dddd, *J* 11.6, 12, 5, 5, 10-H), and 7.2—7.8 (14 H, m, Ar); *m/z* 622.2811 (*M*$^+$; C$_{35}$H$_{46}$O$_6$SSi requires 622.2784, 1%), 565(6), 451(2), 367(5), 353(17), 267(16), 197(100), 180(8), 155(6), 139(10), and 91(34).

(2R,3S,6S,8R,10R)-(+)-10-*Diphenyl-t-butylsilyoxy-8-cyano-methyl-2,3-dimethyl-1,7-dioxaspiro*[5.5]*undecane* (**29**).—A stirred solution of sodium cyanide (126 mg, 2.6 mmol) and the dioxaspiro[5.5]undecane (**28**) (0.8 g, 1.3 mmol) in anhydrous dimethylformamide (DMF) (30 ml) was heated to 70 °C under a nitrogen atmosphere for 12 h. The reaction mixture was then diluted with water (100 ml) and extracted with a mixture of light petroleum and ether (4 : 1; 5 × 100 ml). The organic extracts were then dried (MgSO$_4$) and evaporated under reduced pressure and the residue purified by flash chromatography (light petroleum–ether, 5 : 1) to afford as a colourless oil the title compound (**29**) (0.5 g, 80%); $[\alpha]_D^{22}$ + 39° (*c* 1.4, CH$_2$Cl$_2$); $v_{max.}$ 2 950, 2 260 (C≡N), 1 600, 1 460, 1 120, and 700 cm^{-1}; δ_H (360 MHz) 0.78 (3 H, d, *J* 6, 3-Me), 0.96 (3 H, d, *J* 6, 2-Me), 1.04 (9 H, s, Bu^t), 1.15 (1 H, m, 3-H), 1.32 (1 H, ddd, *J* 12, 9ax-H), 1.35—1.55 (4 H, m, 2 × 4-H, 5ax-H, 9ax-H), 1.64 (1 H, dd, *J* 10, 4, 5eq-H), 1.73 (1 H, dddd, *J* 12, 5, 5, 1.5, 9eq-H), 1.9 (1 H, ddd, *J* 12, 5, 1.5, 11eq-H), 2.4 (2 H, m, CH$_2$CN), 3.17 (1 H, dq, *J* 10, 6, 2-H), 3.57 (1 H, m, 8-H), 4.17 (1 H, dddd, *J* 5, 5, 12, 12, 10-H), and 7.2—7.8 (10 H, m, ArH); *m/z* 420.1997 (*M*$^+$ − Bu^t; requires 420.1995, 66%), 225(44), 199(60), 152(100), and 69(89).

(2′R,3′S,6′S,8′S,10′R)-(E)-(+)-*Ethyl* 4-(10′-*Diphenyl-t-butyl-siloxy-2′,3′-dimethyl-1′,7′-dioxaspiro*[5.5]*undecane-8′-yl*)-2-*methylbut-2-enoate* (**32**).—A solution of di-isobutylaluminium

hydride (1M solution in CH_2Cl_2; 0.3 ml, 0.3 mmol) was added dropwise to a solution of the dioxaspiro[5.5]undecane (**29**) (130 mg, 0.27 mmol) in CH_2Cl_2 (10 ml) at -78 °C. The resulting solution was allowed to warm to room temperature over 1 h and then stirred at room temperature for 5 h. First ethyl formate (0.1 ml) was added and then after 10 min cold 10% sulphuric acid (0.5 ml). The organic phase was separated and the aqueous phase re-extracted with CH_2Cl_2 (3 × 5 ml); the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude aldehyde (**30**) ($v_{max.}$ 2 900, 1 720, and 1 600 cm^{-1}), which was dissolved in CH_2Cl_2 (10 ml) and cooled to 0 °C; a solution of (ethoxycarbonylethylidene)triphenylphosphorane (**31**) (200 mg) in CH_2Cl_2 (10 ml) was then added. The resulting solution was stirred at room temperature overnight after which light petroleum (20 ml) was added and the precipitate filtered off; the filtrate was evaporated under reduced pressure and the residue purified by flash chromatography (light petroleum–ether, 95:5) to afford as a colourless oil the title compound (**32**) (130 mg); $[\alpha]_D^{22}$ + 39° (c 0.9, CH_2Cl_2); $v_{max.}$ 2 900, 1 715 (C=O), 1 650, 1 590, 1 450, 1 430, 1 380, 1 270, 1 110, 740, and 710 cm^{-1}; δ_H (360 MHz) 0.75 (3 H, d, J 7, 3'-Me), 0.95 (3 H, d, J 6, 2'-Me), 1.05 (9 H, s, Bu^t), 1.07 (1 H, m, 3'-H), 1.26 (3 H, t, J 7, CH_2CH_3), 1.27 (1 H, m, 9'-H), 1.4—1.5 (4 H, m, 2 × 4'-H), 5'ax-H, 11'ax-H) 1.6 (1 H, m, 5'eq-H), 1.65 (1 H, m, 9'eq-H), 1.79 (3 H, s, =CMe), 1.85 (1 H, ddd, J 12, 5, 1.5, 11eq-H), 2.2 (2 H, m, allylic H), 3.03 (1 H, dq, J 11, 6, 2-H), 3.3 (1 H, m, 8-H), 4.1 (2 H, q, J 7, CH_2Me), 4.14 (1 H, m, 10-H), 6.77 (1 H, t, J 2, =CH), 7.3 (6 H, m, ArH), and 7.6 (4 H, m, ArH); δ_C (90 MHz) 12.6, 14.3, 17.9, 19.1, 19.3, 26.9, 27.7, 34.9, 35.1, 36.4, 41.0, 44.8, 60.0, 60.3, 66.4, 66.7, 70.9, 97.4, 127.4, 129.0, 129.5, 134.4, 134.6, 135.7, 138.2, and 167.9; m/z 507.2587 (M^+ − Bu^t requires 507.2567, 100%), 381(11), 239(22), 225(26), 199(57), 183(24), and 135(20).

(2'R,3'S,6'S,8'R,10'R)-(E)-(+)-4-(10'-*Diphenyl-t-butylsiloxy-2',3'-dimethyl-1',7'-dioxaspiro[5.5]undecan-8'-yl)-2-methylbut-2-enol* (**33**).—A solution of di-isobutylaluminium hydride (1M solution in THF; 0.75 ml, 0.75 mmol) was added dropwise to a cooled solution of the ester (**32**) (140 mg, 0.25 mmol) in anhydrous ether (10 ml) at -78 °C under argon. The resulting solution was stirred at -78 °C for 1 h and then allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride (1 ml) was then added and the mixture stirred for 10 min. The organic phase was separated, the aqueous phase re-extracted with ether (3 × 5 ml), and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash chromatography (light petroleum–ether, 3:1) afforded as a colourless oil the title compound (**33**), (70 mg, 60%); $[\alpha]_D^{22}$ + 46° (c 0.9, CH_2Cl_2); $v_{max.}$ 3 300 (OH), 2 900, 1 600, 1 480, and 760 cm^{-1}; δ_H (100 MHz) 0.75 (3 H, d, J 7, 3-Me), 0.95 (3 H, d, J 6, 2-Me), 1.05 (9 H, s, Bu^t), 1.1—1.6 (9 H, m), 1.6 (3 H, s, =CMe), 1.9 (1 H, m, 11eq-H), 2.0—2.2 (2 H, m, allylic H), 3.1 (1 H, dq, J 10, 6, 2-H), 3.3 (1 H, m, 8-H), 3.95 (2 H, d, J 5, CH_2O), 4.17 (1 H, m, 10-H), 5.5 (1 H, t, J 7, =CH), and 7.3—7.8 (10 H, m, ArH); m/z 465.2440 (M^+ − Bu^t requires 465.2461, 3%), 447(17), 379(21), 255(16), 249(20), 225(25), 199(100), 183(27), 181(21), 135(22), 121(22), and 113(32).

(2R,3S,6S,8R,10R)-(E)-10-*Diphenyl-t-butylsiloxy-2,3-dimethyl-8-(4'-iodo-3'-methylbut-2'-enyl)-1,7-dioxaspiro[5.5]-undecane* (**34**).—Methanesulphonyl chloride (0.1 ml) was added to a solution of the but-2-enol (**33**) (230 mg, 0.44 mmol) in CH_2Cl_2 (10 ml), triethylamine (0.3 ml), and dimethylaminopyridine (5 mg) at 0 °C. The resulting solution was then stirred at 0 °C overnight and the reaction monitored by t.l.c. (light petroleum–ether, 1:1). After complete reaction, dimethylaminopropylamine (0.1 ml) was added and after 10 min the

solution was washed with 10% hydrochloric acid (10 ml) and brine (10 ml). The resulting solution was dried ($MgSO_4$), evaporated under reduced pressure, and the residue (200 mg) immediately dissolved in THF (5 ml) and added to sodium iodide (200 mg). The mixture was stirred for 12 h after which it was diluted with ether (25 ml), washed with water (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure at 0 °C to afford as a pale yellow oil the title compound (**34**). This was normally dissolved in anhydrous THF (5 ml) and used immediately or stored at -20 °C; δ_H (60 MHz) 0.8 (3 H, d, J 6, 3-Me), 0.9 (3 H, J 6, 2-Me), 1.1 (9 H, s, Bu^t), 1.1—2.1 (14 H, m), 2.8—3.4 (2 H, m, 2-H, 8-H), 3.8 (2 H, br s, CH_2I), 4.05 (1 H, m, 10-H), 5.5 (1 H, t, J 6, =CH), and 7.1—7.7 (10 H, m, ArH).

(2R,2'R,3'S,6'S,8'R,10'R)-2,4-*Dimethyl-6-(10'-diphenyl-t-butylsiloxy-2',3'-dimethyl-1',7'-dioxaspiro[5.5]undecan-8-yl)-hex-4-enoyl* 4S-(*propan-2-yl)oxazolidin-2-one* (**35**).—A solution of butyl-lithium (1.65M solution in hexane; 0.16 ml, 0.26 mmol) was added to a cooled (-60 °C) solution of di-isopropylamine (28 mg, 0.27 mmol) in anhydrous THF (5 ml) and the resulting solution was stirred at -20 °C for 1 h. The solution was then cooled to -78 °C prior to the addition of a solution of (4S)-(−)-3-propionyl-4-(propan-2-yl)oxazolidin-2-one (50 mg, 0.27 mmol) in THF (5 ml). The resulting solution was stirred at -40 °C for 1 h and then a solution of the dioxaspiro[5.5]-undecane (**34**) (155 mg, 0.25 mmol) in THF (5 ml) was added and the resulting solution stirred at -20 °C overnight. Water (20 ml) and ether (20 ml) were then added and the organic phase separated; the aqueous phase was then re-extracted with ether (2 × 20 ml) and the combined organic extracts were washed with cold 10% hydrochloric acid (10 ml) and 5% aqueous sodium hydrogencarbonate (10 ml), and then dried ($MgSO_4$). Purification by flash chromatography (light petroleum–ether, 10:1) afforded the title compound (**35**) (150 mg, 80%); $[\alpha]_D^{22}$ + 16° (c 0.1, CH_2Cl_2); $v_{max.}$ 2 900, 1 730, 1 600, 1 450, 1 380, 1 210, 1 000, and 700 cm^{-1}; δ_H (100 MHz) 0.76 (3 H, d, J 6.5, Me), 0.9—0.98 (9 H, m, 3 × Me), 1.03 (9 H, s, Bu^t), 1.06 (3 H, d, J 7, MeCHCO), 1.2—1.8 (8 H, m), 1.55 (3 H, s, =CMe), 1.8—2.2 (5 H, m), 2.4 (1 H, dd, J 11, 5-H), 2.5—2.7 (2 H, m, CHMe, CHMe$_2$), 3.1 (1 H, dq, J 10, 6, OCHMe), 3.25 (1 H, m, CH_2CHO–), 4.1—5.8 (3 H, m, CHN, CH_2O), 4.18 (1 H, m, CHOSi), 5.12 (1 H, t, J 6, =CH), and 7.2—7.7 (10 H, m, ArH); m/z 579(15%), 577(78), 194(100), 153(29), 135(37), 113(30), 107(49), 95(38), 78(67), and 77(20).

(2R,2'R,3'S,6'S,8'R,10'R)-(+)-6-(10'-*Diphenyl-t-butylsiloxy-2',3'-dimethyl-1',7'-dioxaspiro[5.5]undecan-8'-yl)-2,4-dimethyl-hex-4-enol* (**36**).—A solution of compound (**35**) (150 mg) in ether (2 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (10 mg) in ether (10 ml) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h prior to the addition of water (5 ml). The organic phase was separated, the aqueous phase re-extracted with ether (2 × 5 ml), and the combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash chromatography (light petroleum–ether, 2:1) afforded the title compound (**36**) (100 mg) as a colourless oil; $[\alpha]_D^{22}$ + 30° (c 0.1, CH_2Cl_2); $v_{max.}$ 3 300 (OH), 1 605, 1 450, and 700 cm^{-1}; δ_H (360 MHz) 0.77 (3 H, d, H, 6.6, 3'-Me), 0.84 (3 H, d, J 6.4, 2'-Me), 0.96 (3 H, d, J 6.3, 2-Me), 1.04 (9 H, s, Bu^t), 1.1—1.5 (8 H, m), 1.57 (3 H, s, =CMe), 1.6—2.2 (6 H, m), 3.1 (1 H, dq, J 10, 6.4, 2'-H), 3.3 (1 H, m, 8'-H), 3.45 (2 H, br m, CH_2OH), 4.17 (1 H, m, 10'-H), 5.15 (1 H, t, J 7, =CH), and 7.3—7.8 (10 H, m, ArH); m/z 194(100%), 135(40), 107(30), 78(67), and 77(30).

(2R,2'R,3'S,6'S,8'R,10'R)-(+)-6-(10'-*Diphenyl-t-butylsiloxy-2',3'-dimethyl-1',7'-dioxaspiro[5.5]undecan-8'-yl)-2,4-dimethyl-hex-4-enyl* Toluene-p-sulphonate (**37**) Toluene-p-sulphonyl

chloride (50 mg) was added to a stirred solution of the hex-4-enol (36) (100 mg) in pyridine (3 ml) at 0 °C, and the resulting solution was stirred at 0 °C overnight. Dimethylaminopropylamine (0.1 ml) was then added and the solution stirred for a further 10 min before dilution with ether (20 ml). The resulting solution was washed with water (10 ml), 10% hydrochloric acid (2 × 10 ml), and 5% aqueous sodium hydrogencarbonate (10 ml) and dried (MgSO₄). The solvent was evaporated at reduced pressure to yield the title compound (37) which was used without further purification; δ_H (60 MHz) 0.8 (3 H, d, Me), 0.9 (3 H, d, *J* 6, Me), 1.1 (9 H, s, Buᵗ), 1.1—1.2 (20 H, m), 2.4 (3 H, m, ArMe), 2.9—3.3 (2 H, m, 2 × HCO), 3.8 (2 H, m, CH₂O), 4.1 (1 H, m, CHOSi), 5.1 (1 H, t, *J* 6, =CH), and 7.1—7.9 (14 H, m, ArH).

(2R,3S,6S,8R,10R)-(E)-(+)-10-*Diphenyl-t-butylsiloxy*-8-[(5R)-3,5-*dimethyl*-6-*thiophenylhex*-2-*enyl*]-2,3-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecane* (24).—Sodium (100 mg, 0.43 mmol) was dissolved in anhydrous methanol (10 ml), and when dissolution was complete thiophenol (0.2 ml) was added; the reaction mixture was then stirred for a further 10 min. A solution of the toluene-*p*-sulphonate (37) (100 mg, 0.14 mmol) in methanol (1 ml) was then added to the reaction mixture and the resulting solution stirred at room temperature overnight. Ether (50 ml) was then added and the resulting solution washed with 10% aqueous sodium hydroxide (2 × 30 ml) and water (10 ml), dried (MgSO₄), and evaporated under reduced pressure; the residue was purified by flash chromatography to afford the title compound (24) (80 mg, 90%) identical with that prepared previously.

5-*Methoxy*-3,6-*dimethyl*-3-(*prop*-2'-*enyl*)*phthalide* (51).—A solution of allylmagnesium chloride (2M solution in THF; 10 ml, 20 mmol) was added dropwise to a stirred solution of the dihydro-oxazole (46) (5 g, 20 mmol) in THF (100 ml) at −60 °C under an atmosphere of nitrogen. The resulting solution was then heated under reflux for 1 h and then cooled to room temperature. 1.5M Sulphuric acid (50 ml) was then added and the resulting solution stirred overnight. Ether (100 ml) was added, the organic phase separated, and the aqueous phase re-extracted with ether (2 × 50 ml); the combined organic extracts were then dried (MgSO₄) and evaporated under reduced pressure. Purification by flash chromatography (light petroleum–ether, 1:1) afforded the title compound (51) as a pale yellow oil (3 g, 68%), b.p. 135—140 °C at 0.05 mmHg; $\nu_{max.}$ 3 000, 1 750, 1 605, and 800 cm⁻¹; δ_H (60 MHz) 1.5 (3 H, s, ArMe), 2.12 (3 H, s, Me), 2.55 (2 H, d, *J* 6, CH), 3.85 (3 H, s, OMe), 4.2—6.0 (3 H, m, vinylic H), 6.7 (1 H, s, 4-H), and 7.5 (1 H, s, 7-H); *m/z* 250(4), 191(100), 135(5), and 91(11).

5-*Methoxy*-3,6-*dimethyl*-3-*formylmethylphthalide* (52).—A stream of ozone was bubbled through a stirred solution of the phthalide (51) (3 g, 13 mmol) in dichloromethane (100 ml) at −60 °C.[2] After complete disappearance of starting material (t.l.c., light petroleum–ether, 1:1), a stream of dry nitrogen was bubbled through the solution for 10 min; triethylamine (4 ml) was then added and the solution allowed to warm to room temperature overnight. The resulting solution was then washed with 10% hydrochloric acid (100 ml) and brine (100 ml), dried (MgSO₄), and evaporated under reduced pressure. Purification by flash chromatography (ether) afforded a colourless oil which solidified with time and after recrystallisation from ether–cyclohexane yielded the *title compound* (52), m.p. 110—111 °C (Found: C, 66.8; H, 5.8. C₁₃H₁₄O₄ requires C, 66.66; H, 6.0%); $\nu_{max.}$ 3 000, 1 750, 1 625, 1 605, 1 500, 1 040, 800, and 740 cm⁻¹; δ_H 1.72 (3 H, s, ArMe), 2.25 (3 H, s, Me), 3.0 (2 H, d, *J* 3, CH₂), 3.95 (3 H, s, OMe), 6.9 (1 H, s, 4-H), 7.6 (1 H, s, 7-H), 9.6 (1 H, t, *J* 3, CHO); *m/z* 234.0891 (C₁₃H₁₄O₄ requires 234.0892, 13%), 192(15), 191(100), 135(5), 91(7), and 77(7).

Methyl 2-[(E)-1-*Formylprop*-2-*en*-2-*yl*]-4-*methoxy*-5-*methylbenzoate* (53).—A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.9 g, 12.5 mmol) in benzene (150 ml) was dried by heating under reflux with azeotropic removal of water for 1 h. The mixture was then cooled to room temperature and a solution of the phthalide (52) (2.8 g, 12 mmol) in anhydrous benzene (15 ml) was added. The mixture was stirred at room temperature for 15 min after which methyl iodide (2 g, excess) was added and the solution stirred for a further 15 min. The resulting solution was then washed with water (100 ml) and brine (100 ml), dried (MgSO₄), and evaporated under reduced pressure. Purification of the product by flash chromatography (light petroleum–ether, 2:1) afforded the *Z*-isomer of the title compound (1.8 g, 60%), m.p. 53 °C; $\lambda_{max.}$(EtOH) 242(9 600) and 223(8 800); $\nu_{max.}$(CH₂Cl₂) 1 715 (ester), 1 675 (CHO), 1 610, 1 425, 1 165, and 900 cm⁻¹; δ_H (60 MHz) 2.2 (6 H, s, 2 × Me), 3.8 (3 H, s, OMe), 3.85 (3 H, s, CO₂Me), 6.05 (1 H, d, *J* 7, =CH), 6.55 (1 H, s, 3-H), 7.7 (1 H, s, 6-H), and 9.2 (1 H, d, *J* 7, CHO); *m/z* 222(10), 219(100), 207(30), and 189(50); followed by the title compound (53) (0.6 g, 21%); $\lambda_{max.}$(EtOH) 247(32 000) and 217(23 000); $\nu_{max.}$(CH₂Cl₂) 3 050, 1 715 (ester), 1 670 (CHO), 1 610, 1 560, 1 425, 1 165, 1 080, and 900 cm⁻¹; δ_H (360 MHz) 2.2 (3 H, s, ArMe), 2.4 (3 H, d, *J* 1, Me), 3.75 (3 H, s, OMe), 3.8 (3 H, s, COMe), 5.8 (1 H, dd, *J* 7, 1, =CH), 6.5 (1 H, s, 3-H), 7.68 (1 H, s, 4-H), and 10.5 (1 H, d, *J* 7, CHO); *m/z* 222(5), 219(100), 207(22), 189(66), 176(20), and 77(11).

Methyl 2-[(6'R)-(10-*Diphenyl-t-butylsiloxy*-2,3-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecan*-8-*yl*)-6',8'-*dimethyldecan*-2',4',8'-*trien*-2'-*yl*]-4-*methoxy*-5-*methylbenzoate* (55).—t-Butyl-lithium (1.6M solution in hexane; 0.13 ml, 0.2 mmol) was added dropwise to a solution of the dioxaspiro[5.5]undecane (25) (140 mg, 2 mmol) in THF (5 ml) at −80 °C under argon and the reaction mixture was stirred at −50 °C for 1 h. A solution of the *E* ester (53) (103 mg, 4 mmol) in THF (5 ml) was then added and the reaction mixture stirred at −50 °C for a further hour; benzoyl chloride (0.5 ml) was then added. The reaction mixture was stirred at −50 °C for 10 min and at room temperature for 2 h. Dimethylaminopropylamine (0.5 ml) was added to the reaction mixture which was then diluted with ether (50 ml), washed with 10% hydrochloric acid (50 ml) and water (50 ml), dried (MgSO₄), and evaporated under reduced pressure. The residue was dissolved in methanol–THF (1:1; 6 ml) and cooled to −20 °C under argon. Sodium amalgam (5%, 0.75 g, 1.6 mmol) and sodium dihydrogen orthophosphate (0.3 g, 8 mmol) were added to the reaction mixture which was then stirred for 5 h at −20 °C; after this it was diluted with light petroleum (50 ml) and filtered. The filtrate was washed with water (50 ml), dried (MgSO₄), and evaporated under reduced pressure. The residue was purified by flash chromatography (ether–light petroleum 1:20) to yield the title compound (55) (120 mg, 76%), $\nu_{max.}$ 2 900, 1 715, 1 610, 1 560, 1 165, and 900 cm⁻¹; δ_H (360 MHz) 0.8 (3 H, d, *J* 6, Me), 0.97 (3 H, d, *J* 6, Me), 1.07 (12 H, br s, Buᵗ, Me), 1.1—1.3 (2 H, m), 1.32 (3 H, s, =CMe), 1.37 (3 H, s, =CMe), 1.4—1.8 (5 H, m), 1.9—2.3 (7 H, m), 3.1 (1 H, m, 2-H), 3.25 (1 H, m, 8-H), 3.85 (3 H, 8, OMe), 3.9 (3 H, s, OMe), 4.15 (1 H, m, CHOS), 4.75 (1 H, d, *J* 12, 5'-H), 5.1 (1 H, t, *J* 7, 9'-H), 5.95 (1 H, d, *J* 11, 3'-H), 6.35 (1 H, dd, *J* 11, 12, 4'-H), 6.61 (1 H, s, 3-ArH), and 7.3—7.8 (11 H, m); *m/z* 240(15), 207(10), 199(29), 91(100), and 77(14).

Methyl 2-[(6R)-10-(10-*Hydroxy*-2,3-*dimethyl*-1,7-*dioxaspiro*-[5.5]*undecan*-8-*yl*)-6,8-*dimethyldeca*-2,4,8-*trien*-2-*yl*]-4-*methoxy*-5-*methylbenzoate* (56).—A solution of the ester (55) (120 mg, 0.15 mmol) and tetrabutylammonium fluoride (1M solution in THF; 0.5 ml, 0.5 mmol) in THF (10 ml) was warmed to 50 °C for 10 min. The reaction mixture was then diluted with ether (50 ml), washed with water (10 ml), dried (MgSO₄), and evaporated under reduced pressure. The residue was purified by

flash chromatography to afford the title compound (**56**)[23] (78.5 mg, 95%).

O-*Methylmilbemycin* (57).—A solution of the ester (**56**) (59 mg, 0.11 mmol) in THF (2 ml) was added to a suspension of potassium hydride (6 mg, excess) in THF (3 ml) under argon and the resulting solution stirred at room temperature overnight. The reaction mixture was diluted with ether (10 ml), washed with water (5 ml), dried (MgSO₄), and evaporated under reduced pressure. The residue was purified by flash chromatography (ether–light petroleum 1:20) to afford the title compound (**57**)[23] (31 mg, 74% based on recovered starting material) $[\alpha]_D^{20}$ +90° (*c* 0.1, CHCl₃) followed by starting material (14 mg, 24%).

(+)-*Milbemycin* B₃ (1).—Sodium hydride (50% suspension in mineral oil; 10 mg) was washed with hexane (2 × 3 ml) and suspended in DMF (5 ml). Ethanethiol (0.2 ml) was then added. To the clear solution was added a solution of *O*-methylmilbemycin (31 mg, 0.06 mmol) in DMF (15 ml) and the reaction mixture was heated to reflux for 1 h. After cooling to room temperature the reaction mixture was diluted with ether (100 ml), washed with 10% hydrochloric acid (50 ml) and saturated brine (50 ml), dried (MgSO₄), and evaporated under reduced pressure. The residue was purified by flash chromatography (ether–light petroleum 3:7). The product was recrystallised from hexane to yield (+)-milbemycin β₃ (**1**) as white needles (26 mg, 85%), m.p. 185—187 °C (lit.,[23] 185—187 °C), $[\alpha]_D$ +105° (*c* 0.1, CHCl₃).

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