A Directed Aldol Approach to (+)-Milbemycin β_3

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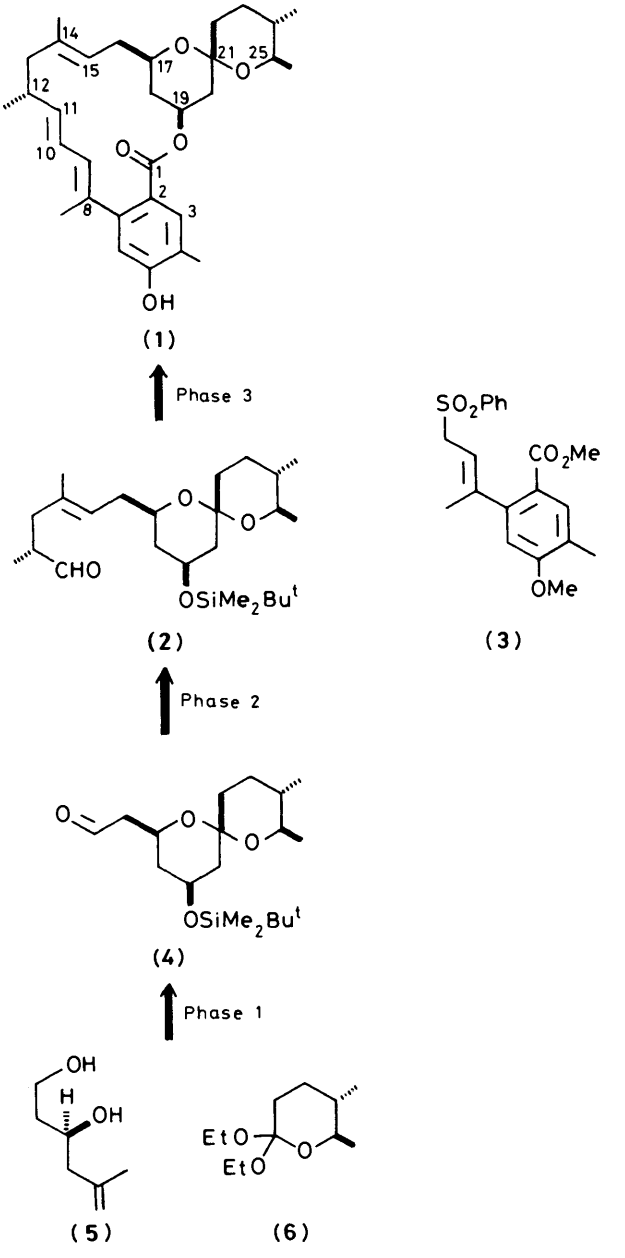
Key steps in a total synthesis of (+)-milbemycin β_3 are the construction of the 1,7-dioxaspiro[5.5]undecane (**10**) by a Lewis acid-catalysed intramolecular directed aldol reaction and the use of sulphone-based olefination reactions for the construction of the double bonds at C(10)–C(11) and C(14)–C(15) †

(+)-Milbemycin β_3 (**1**) is the simplest member of a family of over 20 metabolites isolated from *Streptomyces hygroscopicus* subspecies *aureolacrimosus* and a mutant strain.[1,2] Because of their potent pesticidal activity the milbemycins and their more complex relatives the avermectins have become popular synthetic targets.[3–7] We now give details[8] of the first of our syntheses[9] of (+)-milbemycin β_3 based on the use of an unprecedented Lewis acid-catalysed intramolecular directed aldol reaction as the pivotal step. The strategy outlined in Scheme 1 divides the synthesis into three phases.

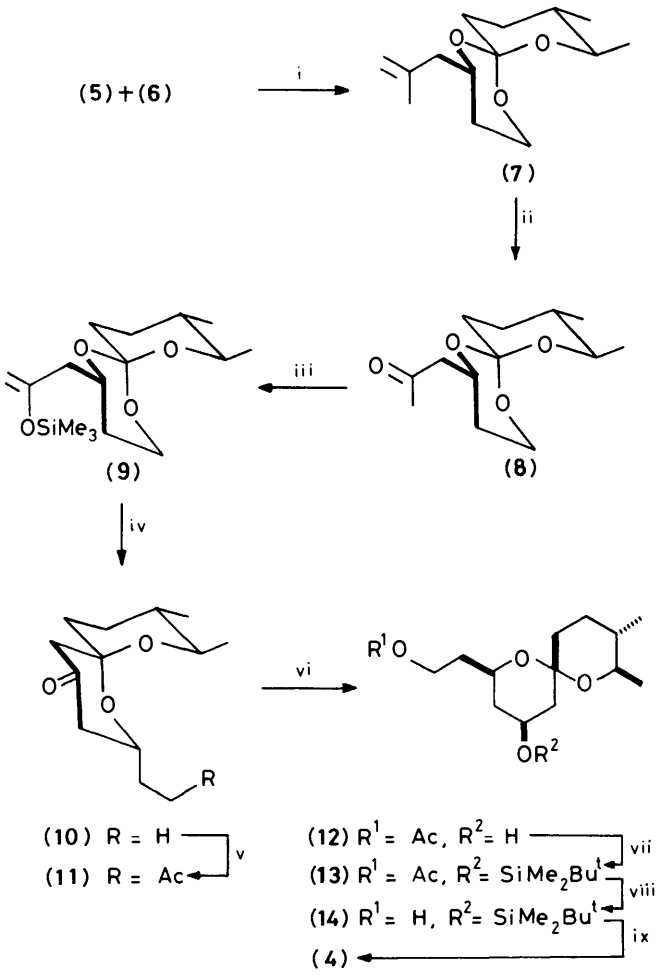
Phase 1: Synthesis of the Spiroacetal (**4**).—Condensation of the diol (**5**) and the *ortho*-lactone (**6**) (*vide infra*) generated a single diastereoisomeric spirocyclic *ortho* lactone (**7**) (Scheme 2) having the benefit of maximum anomeric stabilisation[10] and equatorial disposition of the pendant alkyl groups. The subsequent enol silane (**9**) underwent an intramolecular directed aldol reaction on treatment with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to give the spiro acetal (**10**) in 35% yield as a single diastereoisomer. The modest yield in the cyclisation reflects the instability of the spiroacetal to the reaction conditions but attempts to improve cyclisation efficiency by varying Lewis acid-catalyst were not fruitful: $BF_3{\cdot}Et_2O$ was clearly superior to $TiCl_4$, $ZnBr_2$, or $SnCl_4$ under a variety of conditions. Phase 1 was completed by conversion of (**10**) into the spiroacetal (**4**) having five of the six chiral centres of milbemycin β_3 as shown in Scheme 2. The main detraction to this route was the modest stereoselectivity observed in the reduction of the oxo group in compound (**10**)—3:1 in favour of the desired equatorial diastereoisomer.

The formation of a single diastereoisomeric spiro acetal from the enol silane (**9**) does not illuminate the mechanism of the cyclisation which is complicated by the fact that there are three dioxonium ion intermediates which can be derived from electrophilic cleavage of (**9**) depending on which of the three C–O bonds (a, b, or c) are broken. In accord with recent theories of Deslongchamps,[11] we assume a marked stereoelectronic preference for cleavage of bonds a and b because they are anti-periplanar two two non-bonded electron pairs, whereas bond c is anti-periplanar to only one electron pair. Cleavage of bond a (Scheme 3) generates a dioxonium ion (**15**) which can cyclise directly to (**16**) the precursor of (**10**). There was no evidence for the formation of the diastereoisomer (**19**). However, failure to observe formation of (**19**) is not conclusive evidence for stereoselective cyclisation *via* (**15**) since (**19**), if formed at all,

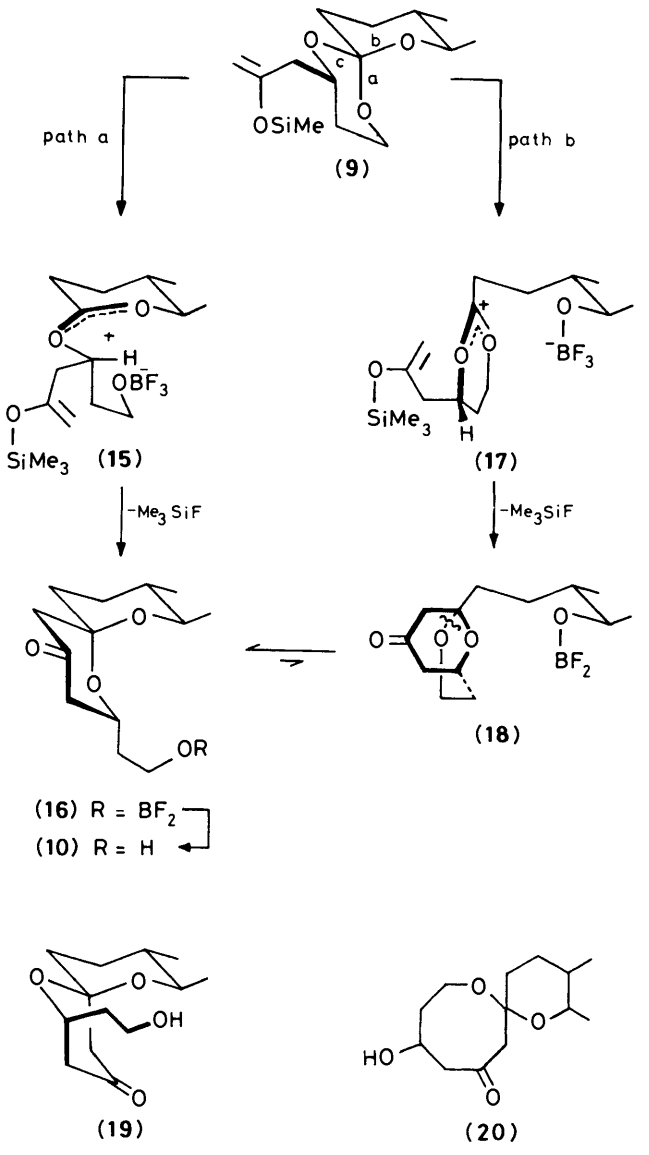
† Milbemycin numbering has been used in referring to the position of double bonds in various intermediates.



Scheme 1.



Scheme 2. *Reagents:* i, H^+–benzene (75%); ii, O_3–MeOH, −78 °C followed by excess of Me_2S (76%); iii, Pr^i_2NLi/THF, −78 °C followed by an excess of Me_3SiCl (*ca.* 96%); iv, $BF_3{\cdot}Et_2O/CH_2Cl_2$, −78 °C, (35%); v, AcCl pyridine, 0 °C (100%); vi, $NaBH_4$/dimethoxyethane, 0 °C (40% or 60% based on recovered starting material); vii, Bu^tMe_2SiCl/dimethylformamide–NEt_3; viii, $LiAlH_4$–Et_2O, 0 °C [90% overall from (**12**)]; ix, pyridinium chlorochromate/CH_2Cl_2 (89%)



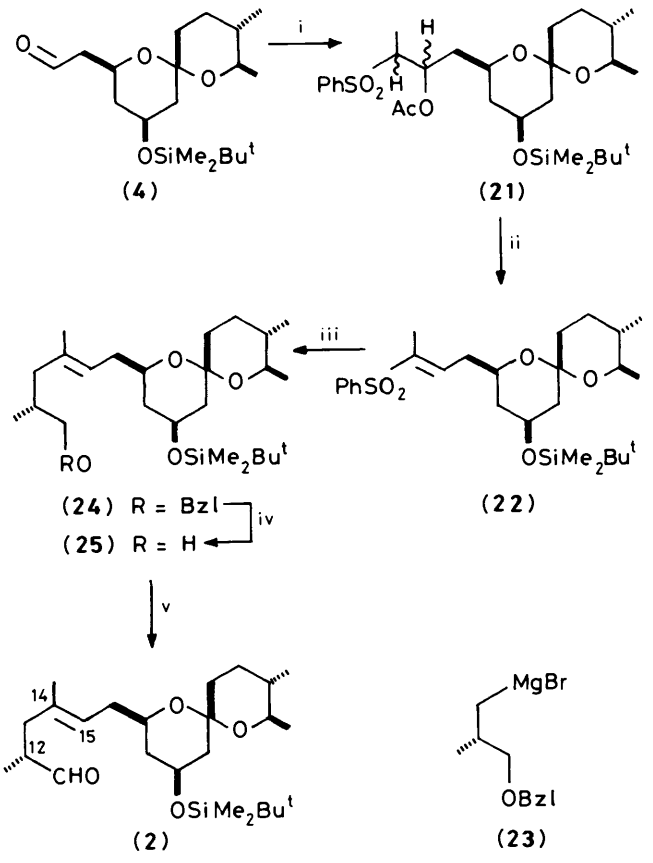
Scheme 3.

could have equilibrated under the reaction conditions to the more stable (**16**).

Formation of the observed spiro acetal (**10**) can also be explained by an indirect pathway involving cleavage of bond b in (**9**) to give the dioxonium ion (**17**) which can serve as a precursor to (**10**) as outlined in Scheme 3. Unfortunately, no conclusive evidence for cyclisation by path b was obtained since careful monitoring of the course of the cyclisation by t.l.c. failed to reveal the presence of any isolable intermediates on the pathway from (**9**) to (**10**). However, the dioxabicyclo-[3.2.1]octanone intermediate (**18**) would derive the thermodynamic advantage of two anomeric stabilisations by rearranging to (**16**) and would not have been observed if this transformation were rapid. Similarly, arguments can be invoked to explain the absence of the cyclisation product (**20**) derived from bond c cleavage even though there is ample precedent[12] for the formation of eight-membered rings by directed aldol reactions. Further efforts to elucidate the mechanism of the cyclisation were thwarted by low yields of identifiable products and instability of potential intermediates to the reaction conditions.

Phase 2: Synthesis of the Smith Intermediate (**2**).—The goal of phase 2 was elaboration of the aldehyde (**4**) to the aldehyde (**2**) which had previously been prepared in racemic form by Smith and co-workers[3] in their synthesis of (**1**). The stereoselective construction of the C(14)–C(15) trisubstituted double bond and simultaneous introduction of the remote chiral centre at C(12) was achieved in modest yield by a sequence developed by Julia and co-workers[13] (Scheme 4). Condensation of the aldehyde (**4**) with the lithio derivative of phenyl ethyl sulphone followed by acetylation gave a mixture of four diastereoisomeric β-acetoxy sulphones (**21**) which without purification were treated with NaOH in dioxane to effect stereoconvergent β-elimination to the (*E*)-vinyl sulphone (**22**). None of the corresponding (*Z*)-isomer could be detected by high field ^1H n.m.r. spectroscopy. The course of the elimination had to be carefully monitored by t.l.c. because prolonged exposure of (**22**) to the reaction conditions resulted in rearrangement to the allylic sulphone. Both the nature of the base and the solvent were critical to the success of the reaction[13] and best results were obtained by using freshly prepared finely powdered NaOH.

The last step in the sequence used to construct the

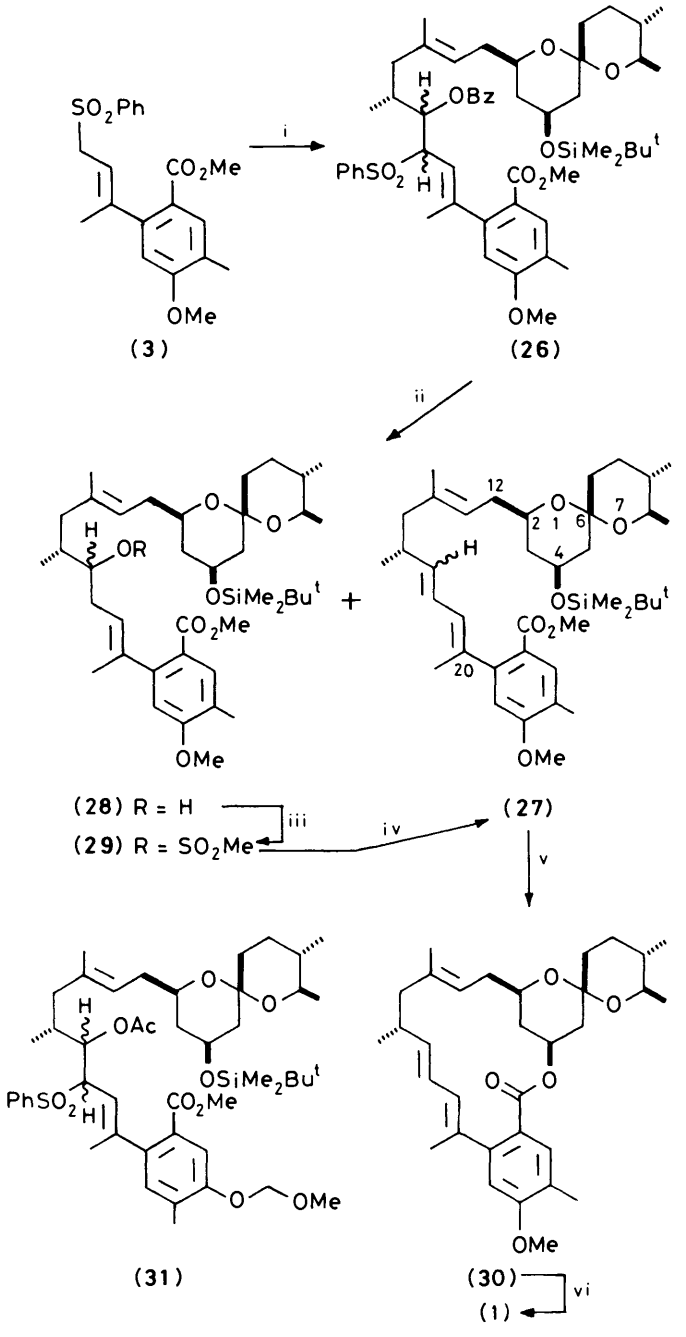


Scheme 4. *Reagents:* i, $PhSO_2CH(Li)Me/THF$, −78 °C followed by Ac_2O; ii, NaOH/dioxane, 20 °C [80% overall from (**4**)]; iii, (**23**)/THF, catalytic amount of $[Fe(acac)_3]$, 20 °C (32%); iv, $Na/NH_3(l)$ (98%); v, CrO_3·2pyridine/CH_2Cl_2 (94%)

C(14)–C(15) tri-substituted double bond involved an Fe^I-catalysed coupling of the Grignard reagent (**23**)[14] with the vinyl sulphone (**22**) to give compound (**24**) with >95% retention of double bond stereochemistry. Unfortunately, the Grignard reagent proved difficult to prepare with homocoupling being a major problem. Furthermore, the Fe^I-catalysed cross-coupling was also capricious and yields in the range 10—32% were obtained which could not be improved. The factors responsible for halting the progress of the coupling were never ascertained but there was some consolation in the ease with which unchanged vinyl sulphone could be recovered. The conversion of the compound (**24**) into the Smith aldehyde (**2**) was easy as shown in Scheme 4.

Phase 3: Conversion of the Aldehyde (**2**) *into* (+)-*Milbemycin* β_3.—The final phase of the synthesis was modelled very closely on the procedures reported by Smith and co-workers[3] with the exception that the C(10)–C(11) double bond was constructed *via* a Julia olefination[15] rather than a Horner-Wittig reaction. Our choice of this modification was motivated by the well-precedented *trans*-stereoselectivity[16] of the Julia olefination and our failure to prepare the requisite phosphine oxide by the published route.

Union of the aldehyde (**2**) and the lithio derivative of the sulphone (**3**) (*vide infra*) was efficient and gave a diastereoisomeric mixture of the β-benzoyloxy sulphones (**26**) as shown in Scheme 5. Much to our surprise the reductive elimination of (**26**) to the desired (*E,E*)-diene (**27**) was problematic for three reasons. First, the reaction was slow in comparison to many pre-



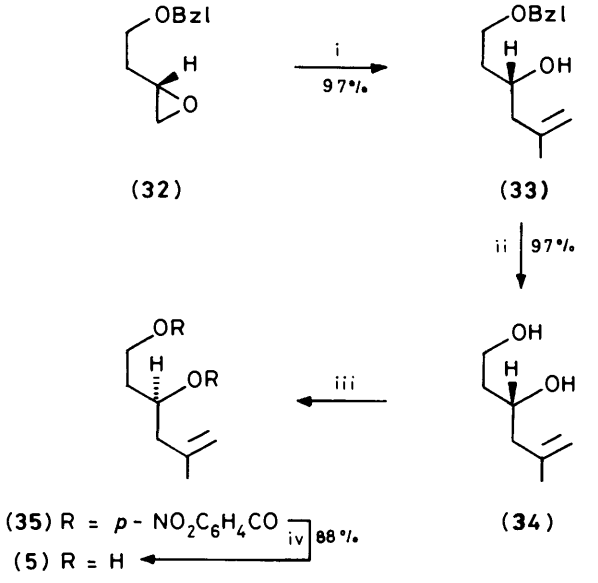
Scheme 5. *Reagents:* i, Pr^i_2NLi/THF, −78 °C followed by (**2**), followed by benzoyl chloride; ii, Na(Hg)/THF–MeOH, −20 °C [39% (**27**) as a 5:1 mixture of *E*:*Z* isomers and 51% (**28**)]; iii, $MeSO_2Cl$, NEt_3/CH_2Cl_2, −10 °C; iv, 1,5-diazabicyclo[4.3.0]non-5-ene(DBN)/Et_2O, reflux [72% (**27**) as a 3:2 mixture of *E*:*Z* isomers]; v, Bu_4NF/THF, 20 °C, followed by $(Me_3Si)_2NK/THF$, 20 °C (80%); vi, EtSNa/DMF, reflux (75%)

vious examples we have examined involving allylic sulphones[16] thus allowing time for base-catalysed side reactions such as ester methanolysis and retro-aldolisation to occur. Secondly, the diene (**27**) obtained was at best a 5:1 mixture of *trans*:*cis* at C(10)–C(11) double bond, whereas the proximate branching should have ensured much higher *trans*-stereoselectivity. Thirdly, the major product of the reaction was the mixture of diastereoisomeric alcohols (**28**), resulting from simple reductive desulphonylation and ester methanolysis, which could be

dehydrated to (**27**) but with virtually no stereoselectivity. The contrast between the anomalous behaviour of (**26**) and the analogue (**31**) was striking: reductive elimination of (**31**) to the diene was rapid, efficient, and highly (>90%) stereoselective. Similarly, by interchanging the position of the ester and phenylsulphonyl groups in (**26**)[5] reductive–elimination proceeded well.

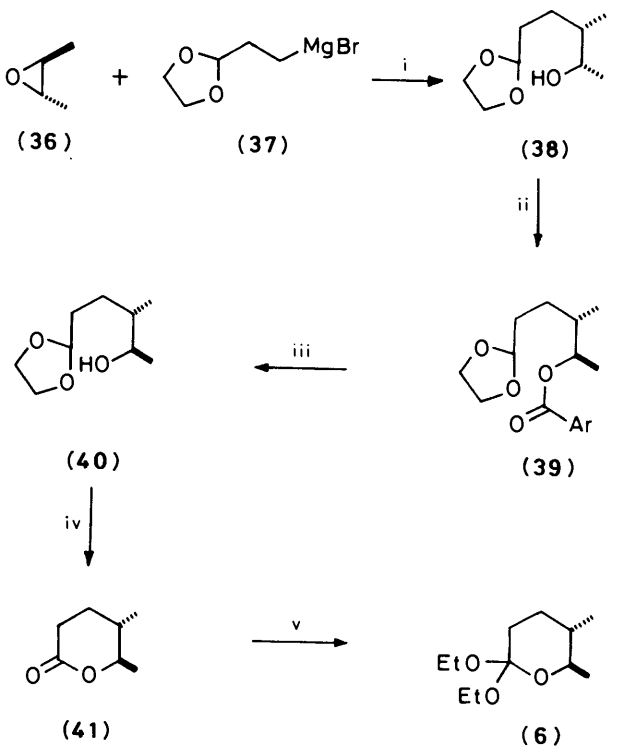
By a simple three-step sequence,[3] compound (**27**) was converted into (+)-milbemycin β_3 as shown in Scheme 5. Pure (+)-milbemycin β_3 crystallised as fine white needles from dilute cold hexane and gave high field ^1H and ^{13}C spectra identical with copies provided by Professor A. B. Smith. The optical rotation showed a strong solvent dependence. In MeOH (*c* 0.3), a value of +32.8° was recorded, whereas in *alcohol-free* $CHCl_3$, the value was +105° (*c* 0.1). Samples recovered from these various solvents gave identical ^1H n.m.r. spectra. (+)-Milbemycin β_3 is stable in the crystalline state at 0 °C for some time but decomposes slowly in solution at room temperature, presumably owing to aerial oxidation.

Preparation of Key Fragments (**3**), (**5**), *and* (**6**).—The starting diol (**5**) and the *ortho*-lactone (**6**) were prepared from the oxiranes (**32**)[17] and (**36**)[18,19] as shown in Schemes 6 and 7 respectively. These preparations were conducted on a substantial scale from cheap, readily available precursors—(*S*)-(−)-malic acid in the case of (**32**) and (2*R*,3*R*)-(+)-tartaric acid in the case of (**36**).



Scheme 6. *Reagents:* i, isopropenylmagnesium bromide, 10 mol % CuI/THF (97%); ii, $Na/NH_3(l)$ (97%); iii, *p*-$NO_2C_6H_4COOH$, $EtO_2CN{=}CO_2Et$, PPh_3/toluene (73%); iv, NaOH/MeOH (88%)

Synthesis of the sulphone (**3**) was not so easy. A direct approach to the carbon skeleton of (**3**) using a Diels–Alder reaction involving the enyne (**42**) and the diene (**47**)[20] (Scheme 8) took place preferentially at the tri-substituted double bond rather than the acetylene to give the cyclohexenone (**43**) in 45% yield after recrystallisation from ether–hexane (m.p. 82—84 °C). Only an 8% yield of the desired product (**44**) (oil) was obtained along with 9% of the regioisomer (**45**) (m.p. 172.5—175 °C from ether). However, regioselective cycloaddition to the acetylene (**46**) did take place to give the desired phthalide (**48**) after aqueous work-up. Unfortunately the phthalide (**48**) and its methyl ether (**49**) were inert to a wide range of nucleophiles in



Scheme 7. *Reagents:* i, 10 mol % CuI/THF (82%); ii, *p*-$NO_2C_6H_4CO_2H$, $EtO_2CN{=}NCO_2Et$, PPh_3/toluene (71%); iii, KOH/MeOH (88%); iv, H_3O^+/THF (90%) followed by Br_2, NaOAc/H_2O–HOAc (72%); v, $Et_3O{\cdot}BF_4/CH_2Cl_2$ followed by NaOEt/EtOH (71%)

both S_N1' and S_N2' reactions except under harsh conditions in which case decarboxylation and other side reactions supervened. Consequently, with rather more grace than gusto we were obliged to adopt the prolix route outlined in Scheme 8.

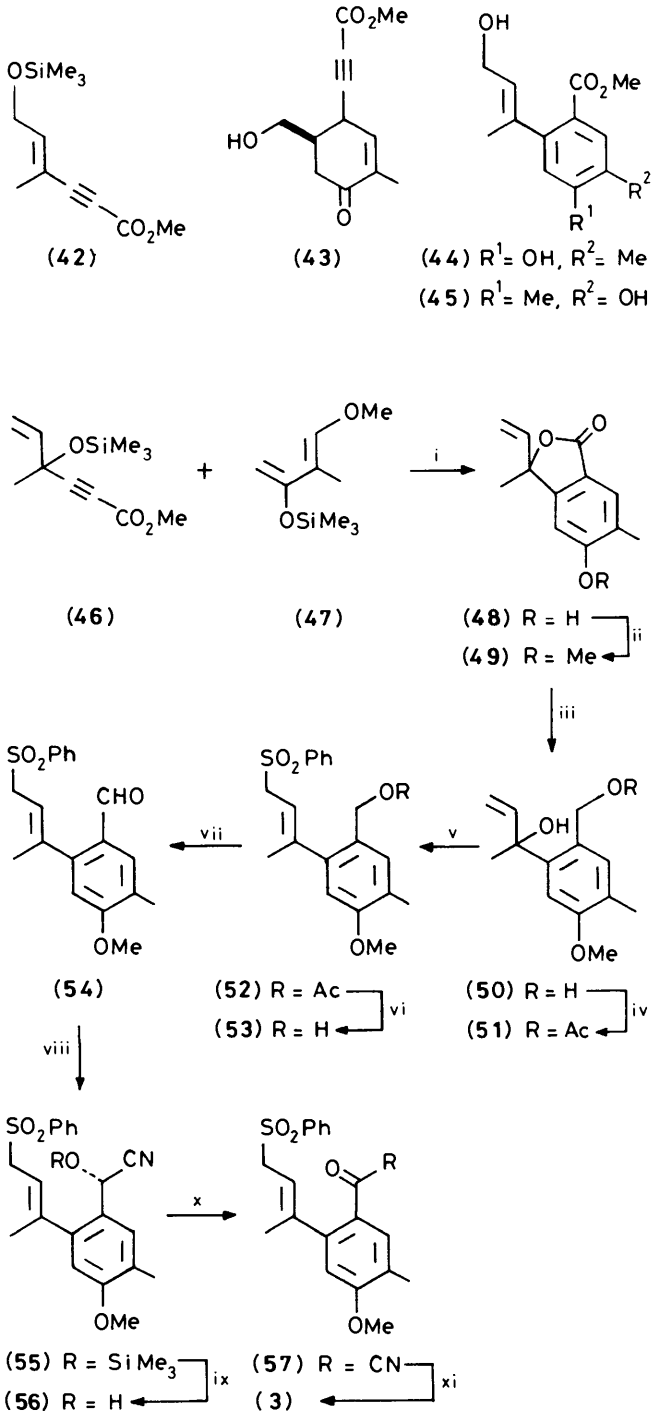
The directed aldol approach to (+)-milbemycin β_3 described herein was beset by problems of poor chemoselectivity in the synthesis of the spiroacetal[21] and the capricious nature of the Fe^I-catalysed cross-coupling reaction used to construct the C(14)–C(15) tri-substituted double bond. There was some compensation for the inefficiency of these key steps: they were highly stereoselective. Despite considerable experimentation we were unable to surmount these difficulties; consequently, a new, more practical approach was designed based on the use of metallated dihydropyran intermediates, full details[9] of which will be reported in due course.

Experimental

Column chromatography was carried out on Kieselgel 60 (0.04—0.063 mm) with eluant specified in parentheses. All reactions requiring anhydrous conditions were conducted in a flame-dried apparatus under a static atmosphere of dry nitrogen. Organic extracts were dried over $MgSO_4$ and evaporated at aspirator pressure using a rotary evaporator. Distillations in which the bath temperature is specified were performed with a Kugelrohr apparatus.

Diethyl ether (referred to as ether), tetrahydrofuran (THF), and dioxane were distilled from sodium wire; CH_2Cl_2 from P_2O_5; pyridine, triethylamine and di-isopropylamine from CaH_2; and MeOH from $Mg(OMe)_2$.

Chemical shifts are reported as δ values relative to Me_4Si as an internal standard. ^1H N.m.r. and ^{13}C n.m.r. spectra were recorded in $CDCl_3$ unless otherwise indicated on Jeol FX90Q



Scheme 8. *Reagents:* i, xylene, reflux followed by H_3O^+/THF, 20 °C (46%); ii, CH_2N_2/Et_2O (90%); iii, $LiAlH_4/Et_2O$ (97%); iv, Ac_2O/pyridine (100%); v, HBr/AcOH–Et_2O, 0 °C followed by $PhSO_2$-Na/DMF, 20 °C (67%); vi, K_2CO_3/MeOH, 20 °C (100%); vii, H_2CrO_4/acetone, 20 °C; viii, Me_3SiCN, $ZnBr_2/CH_2Cl_2$, reflux; ix, H_3O^+/THF, 20 °C; x, CrO_3·2pyridine/CH_2Cl_2, 20 °C; xi, H^+/MeOH–$CHCl_3$, reflux [82% overall from (**54**)]

or Bruker WH400 spectrometers. All coupling constants (J) are given in Hz. Inverted signals obtained with an INEPT pulse sequence are indicated by an asterisk. Peak intensities in the infrared (i.r.) spectra are specified as s (strong), m (medium), or w (weak). Accurate mass determinations were made on compounds estimated to be >95% pure by PMR or CMR and t.l.c.

Assignment of signals in the PMR and CMR spectra of intermediates (**10**)—(**27**) is consistently based on the assumption that these compounds are named as derivatives of 1,7-dioxaspiro[5.5]undecane [see *e.g.* (**27**), Scheme 5]. In the case of (**30**) and (**1**) milbemycin numbering has been used.

(2R,6R,8R,9S)-2-(2-*Methylallyl*)-8,9-*dimethyl*-1,5,7-*trioxaspiro*[5.5]*undecane* (**7**).—A solution of the lactone (**6**) (0.415 g, 2 mmol) in benzene (1 cm^3) was added to a solution of the diol (**5**) (0.25, 1.9 mmol) in benzene (1 cm^3) followed by a trace of HCl vapour. After 30 min solid K_2CO_3 was added and the reaction mixture stirred for a further 1 h before excess of base was filtered off and the product concentrated. Chromatography (2% Et_2O–hexane) and distillation [80 °C (bath)/0.05 mmHg] yielded the title compound (**7**) (0.345 g, 75%); $[\alpha]_D^{22}$ +38.8° (*c* 0.98 in $CHCl_3$); $\nu_{max.}$(film) 1 455m, 1 380s, 1 240s, 1 170s, 1 130s, 1 100m, 1 070s, 1 000s, 960m, and 900s cm^{-1}; δ_H (400 MHz) 4.75 (2 H, d, *J* 18.5, 14-H_2), 4.42 (1 H, dddd, *J* 11.5, 8, 5, 2.5, axial 2-H), 3.9 (1 H, ddd, *J* 13.8, 11.3, 2.9 axial 4-H), 3.68 (1 H, *J* 10.8, 4.9, >1, equatorial 4-H), 3.32 (1 H, dq, *J* 9.6, 6.3, axial 8-H), 2.35 (1 H, dd, *J* 13, 5, 12-H_A), 2.08 (1 H, dd, *J* 13, 8.7, 12-H_B), 1.83 (1 H, m, axial 11-H), 1.72 (3 H, s, 13-Me), 1.6 (3 H, m, 10-H_2, equatorial 11-H), 1.5 (1 H, m, equatorial 3-H), 1.44 (1 H, m, axial 3-H), 1.34 (1 H, m, axial 9-H), 1.2 (3 H, d, *J* 6, 8-Me), and 0.82 (3 H, d, *J* 6.5, 9-Me); δ_C (22.6 MHz) 141.5 (C-13), 113.1 (C-14), 109.8 (C-6), 74.3 (C-8), 67 (C-2), 58.3 (C-4), 44.4 (C-12), 36.4 (C-9), 34.7 (C-11), 30.1 (C-3), 29.6 (C-10), 23* (13-Me), 19.2 (8-Me), and 17.4 (9-Me); *m/z* 240 (M^+, 2%), 196 (20), 185 (15), 154 (45), 129 (56), 112 (23), 111 (53), 97 (100), 95 (38), 83 (27), 67 (21), and 56 (36) (Found: M^+, 240.172 65. $C_{14}H_{24}O_3$ requires *M*, 240.172 534).

(2R,6R,8R,9S)-8,9-*Dimethyl*-2-(2-*oxopropyl*)-1,5,7-*trioxaspiro*[5.5]*undecane* (**8**).—Ozonised oxygen was bubbled through a solution of compound (**7**) (0.85 g, 3.54 mmol) and pyridine (1 cm^3) in CH_2Cl_2 (55 cm^3) and MeOH (23 cm^3) at −70 °C until a blue colour was just apparent. The excess of ozone was blown away with nitrogen, dimethyl sulphide (4.72 cm^3, 62 mmol) added, and the reaction allowed to warm to room temperature. After 3 h the solvent was evaporated and the residue diluted with hexane, washed with water, dried, and concentrated before distillation [105 °C (bath)/0.01 mmHg] yielded the title compound (**8**) (0.65 g, 76%); $[\alpha]_D^{23}$ +64.8° (*c* 1.04 in $CHCl_3$); $\nu_{max.}$(film) 1 720s, 1 450m, 1 380s, 1 260m, 1 235s, 1 195m, 1 165s, 1 130s, 1 065s, 1 000s, 960m, 900m, and 735m cm^{-1}; δ_H (400 MHz) 4.75 (1 H, m, axial 2-H), 3.96 (1 H, ddd, *J* 13, 11, 2.5, axial 4-H), 3.67 (1 H, ddd, *J* 10.5, 4.3, 2.7, equatorial 4-H), 3.33 (1 H, dq, *J* 9.6, 6.6, axial 8-H), 2.72 (1 H, dd, *J* 16.4, 5.4, 12-H_A), 2.52 (1 H, dd, *J* 16.4, 7.7, 12-H_B), 2.16 (3 H, s, 14-H_3), 1.82 (1 H, m, axial 11-H), 1.7—1.55 (3 H, d, *J* 6.3, 8-Me), 0.83 (3 H, d, *J* 6.5, 9-Me); δ_C (22.6 MHz), 206.6 (C-13), 109.6 (C-6), 74.4 (C-8), 65.2 (C-2), 58 (C-4), 49.8 (C-12), 36.4* (C-9), 34.4 (C-11), 30.9* (C-14), 30.4 (C-3), 29.1 (C-10), 19.1* (8-Me), and 17.3* (9-Me); *m/z* 242 (M^+, 0.5%), 198 (3), 150 (3), 155 (28), 129 (20), 114 (15), 111 (10), 86 (13), 83 (10), 69 (14), 56 (36), 155 (28), 129 (20), 114 (15), 111 (10), 86 (13), 83 (10), 69 (14), 56 (36), 54 (10), and 43 (100) (Found: M^+, 242.152 10. $C_{13}H_{22}O_4$ requires *M*, 242.151 799).

(2R,6R,8R,9S)-2-(2-*Hydroxyethyl*)-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*one* (**10**).—A solution of compound (**8**) (0.888 g, 3.67 mmol) in THF (5 cm^3) was added to a solution of lithium di-isopropylamide (4.8 mmol) in THF at −70 °C. After 30 min trimethylsilyl chloride (2.18 g, 20 mmol) was added and the reaction allowed to warm to room temperature when it was concentrated, the residue taken up into hexane, and the solution

washed with cold water, dried, and concentrated to yield compound (**9**) (1.14 g, 96%); $\nu_{max.}$(film) 1 250s, 1 065s, 850s, and 760m cm^{-1}.

A solution of compound (**9**) (1.14 g, 3.5 mmol) in CH_2Cl_2 (10 cm^3) was added to a solution of $BF_3{\cdot}OEt_2$ (0.52 g, 3.67 mmol) in CH_2Cl_2 (7 cm^3) at −70 °C. After 30 min the reaction was quenched at −70 °C with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, and the extract washed with saturated $NaHCO_3$, dried, and concentrated. Chromatography (50% EtOAc–hexane) of the residue yielded the ketones (**8**) (0.36 mmol, 10%) and (**10**) (0.312 g, 35%); $[\alpha]_D^{20}$ +49.8° (*c* 1.2 in $CHCl_3$); $\nu_{max.}$(film) 3 440m, 2 960s, 2 930s, 2 880s, 1 725s, 1 450m, 1 380m, 1 315m, 1 250m, 1 230m, 1 180m, 1 100s, 1 080s, 1 055s, 990s, and 965s cm^{-1}; δ_H (400 MHz) 4.105 (1 H, dddd, *J* 11, 8.5, 3, 3, axial 2-H), 3.85 (2 H, t, *J* 5.75, 13-H_2), 3.28 (1 H, dq, *J* 9, 6.5, axial 8-H), 2.43 (1 H, A portion of AB system with further W coupling, J_{AB} 15, J_W 1.5, equatorial 5-H), 2.40 (1 H, B portion of AB system, J_{AB} 15, axial 5-H), 2.40 (1 H, s, OH), 2.38 (1 H, ddd, *J* 14.5, 3, 1.5, equatorial 3-H), 2.31 (1 H, dd, *J* 14.5, 11, axial 3-H), 1.96—1.82 (3 H, m, 12-H_2, 11-H_A), 1.65—1.42 (2 H, m, 11-H_B, 10-H_2), 1.28 (1 H, m, axial 9-H), 1.11 (3 H, d, *J* 6, 8-Me), 0.85 (3 H, d, *J* 6.5, 9-Me); δ_C (22.6 MHz), 205.4 (C-4), 99.3 (C-6), 72.3* (C-8), 68.2* (C-2), 60.5 (C-13), 51.8 (C-3 or C-5), 46.8 (C-3 or C-5), 38 (C-12), 35.8* (C-9), 35.0 (C-11), 27.9 (C-10), 19.2* (8-Me), and 17.2* (9-Me); *m/z* 242 (M^+, 6%), 224 (1), 198 (13), 180 (41), 126 (29), 111 (100), 99 (19), 84 (38), 60 (53), 55 (82), 43 (77), and 41 (72) (Found: M^+, 242.151 69. $C_{13}H_{22}O_4$ requires *M*, 242.151 799).

(2S,6S,8R,9S)-2-(2-*Acetoxyethyl*)-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*one* (**11**).—Acetyl chloride (33 mg, 0.43 mmol) was added to a solution of the lactone (**10**) (35 mg, 0.14 mmol) in pyridine (1 cm^3) at 0 °C. After 30 min at room temperature the reaction was diluted with ether, washed with dilute HCl, saturated aqueous $NaHCO_3$, and saturated brine, and then dried and concentrated to yield the title compound (**11**) (40 mg, 100%); $\nu_{max.}$(film) 1 740s, 1 240s, and 1 050m cm^{-1}; δ_H (90 MHz) 4.4—3.85 (3 H, m, 13-H_2, axial 2-H), 3.2 (1 H, m, axial 8-H), 2.4—2.15 (4 H, m, 3-H_2, 5-H_2), 2.04 (3 H, s, CH_3CO), 2.0—1.4 (7 H, m), 1.08 (3 H, d, *J* 6, 8-Me), and 0.82 (3 H, d, *J* 6, 9-Me).

(2R,4S,6R,8R,9S)-2-(2-*Acetoxyethyl*)-4-*hydroxy*-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**12**).—$NaBH_4$ (6 mg, 0.70 mmol) was added to a solution of the ketone (**11**) (40 mg, 0.14 mmol) in dimethoxyethane (4 cm^3) at 0 °C. After 3 h the reaction mixture was poured into saturated brine, the mixture extracted with ether, and the extract dried and concentrated. Chromatography (20% EtOAc–hexane) yielded unchanged ketone (**11**) (16 mg, 0.056 mmol, 40%), the (4*R*)-diastereoisomer (6 mg, 0.021 mmol, 15%), and (**12**) (16 mg, 0.056 mmol, 40%); 3 400m, 2 960s, 2 930s, 2 880s, 1 740s, 1 450m, 1 380s, 1 370s, 1 245s, 1 195m, 1 170m, 1 130m, 1 100m, 1 045s, 990s, and 950m cm^{-1}; δ_H (90 MHz) 4.4—3.95 (3 H, m, 13-H_2, axial 4-H), 3.75 (1 H, m, axial 2-H), 3.33 (1 H, m axial 8-H), 2.04 (3 H, s, CH_3CO), 2.1—1.25 (12 H, m), 1.1 (3 H, d, *J* 6, 8-Me), and 0.88 (3 H, d, *J* 5.5, 9-Me).

(2R,4S,6R,8R,9S)-4-(*Dimethyl-t-butylsiloxy*)-2-(2-*hydroxyethyl*)-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**14**).—A solution of compound (**12**) (16 mg, 0.052 mmol) and Bu^tMe_2SiCl (10 mg, 0.062 mmol) in DMF (0.2 cm^3) was stirred at room temperature for 2 h. It was then diluted with saturated aqueous $NaHCO_3$, extracted with ether, and the extract dried and concentrated to give crude compound (**13**) which was used in the next step without further purification.

$LiAlH_4$ (2 mg, 0.05 mmol) in ether was added to a solution of compound (**13**) (20 mg, 0.05 mmol) in ether (1 cm^3) at room temperature. After 10 min the reaction was quenched by the sequential addition of 1 drop of water, 1 drop of 15% aqueous NaOH, and 3 drops of water. After being stirred for a further 30 min the reaction mixture was filtered through Celite, and the filtrate concentrated. The residue upon chromatography (40% Et_2O–hexane) yielded the title compound (**14**) (18 mg, 90%); $\nu_{max.}$(film) 3 440m, 2 960s, 2 930s, 2 880s, 2 860s, 1 460m, 1 385m, 1 255m, 1 195m, 1 130m, 1 085s, 1 075s, 1 050s, 995s, 840s, and 780m cm^{-1}; δ_H (90 MHz) 4.11 (1 H, dddd, *J* 10.5, 5, 5, axial 4-H), 3.8 (2 H, t, *J* 5.7, 13-H_2), 3.8 (1 H, m, axial 2-H), 3.24 (1 H, dq, *J* 8.4, 6.4, axial 8-H), 2.75 (1 H, br s, OH), 2.0—1.25 (11 H, m), 1.12 (3 H, d, *J* 6.4, 8-Me), 0.87 (12 H, s, Bu^t, 9-Me), and 0.05 (6 H, s, Me_2Si).

(2S,4S,6R,8R,9S)-2-*Formylmethyl*-4-*dimethyl-t-butylsilyloxy*-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**4**).—Pyridinium chlorochromate (42 mg, 0.196 mmol) was added to a vigorously stirred solution of compound (**14**) (18 mg, 0.05 mmol) in CH_2Cl_2 (0.5 cm^3) with ground 3 Å molecular sieves (50 mg). After 15 min the reaction was diluted with ether and passed through Florisil to yield the title compound (**4**) (16 mg, 89%); $\nu_{max.}$(film) 1 730s, 1 460m, 1 385m, 1 255m, 1 195m, 1 135m, 1 085s, 995m, 840m, and 780m cm^{-1}; δ_H (400 MHz) 9.82 (1 H, dd, *J* 2.7, 1.85, 13-H), 4.12 (2 H, m, axial 2-H, axial 4-H), 3.23 (1 H, dq, *J* 9.8, 6.3, axial 8-H), 2.62 (1 H, ddd, *J* 16, 8.9, 2.7, 12-H_A), 2.46 (1 H, ddd, *J* 16, 4.1, 1.8), 1.87 (2 H, m, equatorial 3-H, equatorial 5-H), 1.625 (2 H, m, axial 3-H, axial 5-H), 1.55—1.2 (5 H, m, 10-H_2, 11-H_2, axial 9-H), 1.12 (3 H, d, *J* 6.3, 8-Me), 0.868 (9 H, s, Bu^t), 0.805 (3 H, d, *J* 6.6, 9-Me), 0.058 (6 H, s, Me_2Si); *m/z* 299 (18%), 281 (41), 255 (37), 213 (27), 181 (23), 173 (43), 171 (10), 169 (10), 103 (21), 155 (25), 145 (39), 143 (23), 131 (23), 129 (100), 111 (26), 101 (50), 95 (39), 75 (68), 69 (27), and 55 (22) (Found: M^+, 356.238 03. $C_{19}H_{26}O_4Si$ requires *M*, 356.238 273).

(2S,4S,6S,8R,9S)-4-(*Dimethyl-t-butylsiloxy*)-8,9-*dimethyl*-2-[(2E)-3-*phenylsulphonylbut*-2-*enyl*]-1,7-*dioxaspiro*[5.5]-*undecane* (**22**).—To a solution of ethyl phenyl sulphone (0.26 g, 1.54 mmol) in THF (3 cm^3) was added dropwise at −78 °C BuLi (2.5M in hexane; 0.6 cm^3, 1.5 mmol). After 15 min a solution of the aldehyde (**4**) (0.50 g, 1.4 mmol) in THF (3 cm^3) was added dropwise. The mixture was then stirred at −78 °C for 30 min after which acetic anhydride (0.3 cm^3, 2.8 mmol) was added dropwise to give a colourless solution. The cooling bath was removed and the mixture stirred at ambient temperature for 1 h after which ether (5 cm^3) and saturated aqueous NH_4Cl (5 cm^3) was added with rapid stirring. After the mixture had been stirred at room temperature for 4 h the layers were separated and the aqueous layer extracted with ether (2 × 10 cm^3). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give a mixture of the diastereoisomeric β-acetoxysulphones (**21**) (0.88 g) which was used in the next step without further purification.

To a stirred suspension of *finely powdered* sodium hydroxide (0.12 g, 2.8 mmol, prepared by careful addition of water to a rapidly stirred suspension of NaH in benzene) in dioxane (25 cm^3) was added in one portion a solution of the crude β-acetoxy sulphones (**21**) in dioxane (5 cm^3). The mixture was stirred at room temperature for 4 h after which it was diluted with ether (25 cm^3), washed with water (25 cm^3), dried, and evaporated. The residue was chromatographed (ether–hexane, 1:5) to give the vinyl sulphone (**22**) [0.57 g, 80% overall from (**4**)] as a colourless oil; $[\alpha]_D^{23}$ +34.5° (*c* 1.33 in $CHCl_3$); $\nu_{max.}$(film) 1 650m, 1 320s, 1 252s, 1 075s, 992s, 952s, 900s, and 690s cm^{-1}; δ_H (400 MHz) 7.84—7.87 (2 H, m), 7.6—7.49 (3 H, m), 7.03 (1 H, tq, *J* 1.3, 7.5, 13-H), 4.09 (1 H, dddd, *J* 5, 5, 11, 11, 4-H), 3.65 (1 H, m, 2-H), 3.22 (1 H, dq, *J* 6.3, 9.8, 8-H), 2.32—2.4 (2 H, m, 14-H_2), 1.88 (1 H, ddd, *J* 1.7, 4.9, 12.6, equatorial 5-H),

1.85 (3 H, d, *J* 1.2, 14-Me), 1.80 (1 H, dm, equatorial 3-H), 1.6—1.63 (1 H, m), 1.45—1.55 (3 H, m), 1.27 (1 H, dd, *J* 11, 12.6, axial 5-H), 1.18—1.28 (1 H, m, axial 9-H), 1.2 (1 H, ddd, *J* 7, 7, 11, axial 3-H), 1.12 (3 H, d, *J* 6.3, 8-Me), 0.88 (3 H, d, *J* 6, 9-Me), 0.87 (9 H, s), 0.05 (6 H, s); δ_C (22.6 MHz) 139.7, 138.5, 137.5, 133.0, 129.0, 97.6 (C-6), 71.3 (C-8), 66.6 (C-2), 65.1 (C-4), 45.0 (C-5), 41.3 (C-3), 36.62 (C-9), 35.78 (C-11), 34.7 (C-12), 27.8 (C-10), 25.9 (*Me*$_3$C), 19.4 (C-9 Me), 17.9 (Me$_3$*C*), 17.8 (C-8 Me), 11.7 (C-14 Me), and—4.4 (Me$_2$Si); *m/z* 453 (13%), 452 (31), 451 (100), 365 (25), 325 (11), 199 (15), 183 (11), 143 (19), 135 (24), 129 (17), 125 (22), 115 (11), 101 (24), 95 (14), 83 (21), 77 (18), 75 (49), and 73 (42) (Found: M^+, 508.267 07. $C_{27}H_{44}O_5SSi$ requires *M*, 508.267 857).

(2S,4S,6S,8R,9S)-2-[(5R,2E)-3,5-*Dimethyl*-6-*benzyloxyhex*-2-*enyl*]-4-(*dimethyl*-*t*-*butylsiloxy*)-8,9-*dimethyl*-1,7-*dioxaspiro*-[5.5]*undecane* (**24**).—1,2-Dibromoethane (50 μl) was added to magnesium powder (0.3 g, 12 g atom) in THF (5 cm^3) and the mixture refluxed for 5 min. It was then cooled to room temperature and a solution of (2*S*)-3-benzyloxy-2-methyl-1-bromopropane[14] (0.97 g, 4 mmol) in THF (2 cm^3) was added dropwise. The mixture was stirred vigorously at room temperature for 30 min, refluxed for 1 h, and cooled to room temperature to give a THF solution of the Grignard reagent (**23**).

The Grignard solution (0.5 cm^3) prepared above was added dropwise to a stirred solution of tris(acetonylacetonato)iron(III) (7 mg) in THF (2 cm^3) under argon. The colour changed from red to yellow to dark green–brown. After 5 min at room temperature a solution of the vinyl sulphone (**22**) (0.51 g, 1 mmol) in THF (3 cm^3) was added followed by a further portion of the Grignard reagent (1 cm^3). Thereafter, 1 cm^3 portions (1 cm^3) of Grignard reagent and catalyst (5 mg) were added at 1 h intervals for 3 h. The mixture was poured into saturated aqueous NH_4Cl and the product extracted into ether. The ether layer was washed with water, dried, and evaporated to give a yellow oil which was chromatographed on silica (ether–hexane, 1:5) to give unchanged compound (**22**) (0.305 g, 60%) and the coupled product (**24**) (169 mg, 32%) as a colourless oil: $[\alpha]_D^{21}$ + 27.1 (*c* 0.94 in $CHCl_3$); $\nu_{max.}$(film) 1 450m, 1 380m, 1 255m, 1 200m, 1 080s, 995s, 840m, 740m, and 700m cm^{-1}; δ_H (400 MHz) 7.34 (1 H, s, Ph), 7.33 (2 H, s, Ph), 7.28 (2 H, m, Ph), 5.20 (1 H, t, *J* 7, 13-H), 4.51 (1 H, A portion of AB, J_{AB} 12, PhCH$_A$), 4.49 (1 H, B portion of AB, J_{AB} 12, PhCH$_B$), 4.07 (1 H, dddd, *J* 12, 5, axial 4-H), 3.47 (1 H, m, axial 2-H), 3.33 (1 H, dd, *J* 9, 5.7, 17-H), 3.24 (1 H, dd, *J* 9, 6.7, 17-H), 3.25 (1 H, dq, *J* 9, 6, axial 8-H), 2.26—2.11 (3 H, m, 12-H$_2$, 15-H$_A$), 1.96 (1 H, m, 15-H$_B$) 1.86 (1 H, ddd, *J* 12.6, 4.9, 1.6, equatorial 3-H), 1.76 (1 H, dd, *J* 13.3, 8.7, equatorial 5-H), 1.60 (3 H, s, 14-Me), 1.65—1.43 (4 H, m, 11-H$_2$, 10-H$_2$), 1.28 (1 H, dd, *J* 12.5, 10.9, axial 5-H), 1.16 (1 H, dddd, *J* 11.5, axial 3-H), 1.13—1.12 (2 H, m, axial 9-H), 16-H), 1.09 (3 H, d, *J* 6.3, 8-Me), 0.89 (3 H, d, *J* 6.6, 16-Me), 0.87 (9 H, s, Bu^t), 0.81 (3 H, d, *J* 6.6, 9-Me), 0.051, 0.050 (2 × 3 H, 2 × s, SiMe$_2$); δ_C (22.6 MHz) 140, 135.1 (C-14), 128.3*, 127.4*, 122.3* (C-13), 97.5 (C-6), 75.9 (C-17), 73 (Ph-*C*H$_2$), 70.9* (C-8), 68* (C-2), 65.6* (C-4), 45.3 (C-5), 44.3 (C-15), 41.3 (C-3), 36.7* (C-9), 36 (C-11), 34.6 (C-12), 31.7* (C-16), 28 (C-10), 25.9* (Bu^t), 19.4* (8-Me), 18 (9-Me, *C*-Me$_3$), 17.2* (16-Me), 16.3* (14-Me), and—4.4* (SiMe$_2$); *m/z* 530 (M^+, 1.1%), 398 (10), 313 (36), 296 (24), 295 (1 100), 91 (97), and 73 (29) (Found: M^+, 530.378 78. $C_{32}H_{54}O_4Si$ requires *M*, 530.379 117.

(2S,4S,6S,8R,9S)-2-[(5R)-4-(*Dimethyl*-*t*-*butylsiloxy*)-2-[(5R,2E)-6-*hydroxy*-3,5-*dimethylhex*-2-*enyl*]-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**25**).—Sodium metal (0.1 g, 4.3 mol) was added to a solution of compound (**24**) (0.4 g, 0.75 mmol) in liquid ammonia (20 cm^3) at −70 °C until a deep blue colour persisted for 30 min. Solid NH_4Cl was added to disperse the blue colour and the ammonia was allowed to evaporate before the residue was extracted into ether, and the extract washed with water and saturated brine, dried, and concentrated. The residue was chromatographed (10% EtOAc–hexane) to yield the title compound (**25**) (0.325 g, 98%); $[\alpha]_D^{20}$ +52.4° (*c* 0.94 in $CHCl_3$); $\nu_{max.}$(film) 3 400br, 1 745m, 1 460m, 1 385m, 1 255m, 1 195m, 1 080s, 1 050s, 995s, 950m, 870m, 840s, and 780m; δ_H (400 MHz) 5.27 (1 H, t, *J* 7.1, 13-H), 4.073 (1 H, dddd, *J* 12, 5, axial 4-H), 3.5 (1 H, m, 2-H), 3.5 (1 H, m, 17-H$_A$), 3.42 (1 H, dd, *J* 10.5, 5, 17-H$_B$), 3.23 (1 H, dq, *J* 9.7, 6.25, axial 8-H), 2.20 (2 H, t, *J* 6.75, 12-H$_2$), 2.085 (1 H, dd, *J* 16.3, 9.9, 15-H$_A$), 1.9—1.78 (4 H, m, equatorial 3-H, equatorial 5-H, 15-H$_B$, 16-H), 1.636 (4 H, s, 14-Me, OH), 1.55—1.43 (4 H, m, 10-H$_2$, 11-H$_2$), 1.28 (1 H, dd, *J* 12.5, 10.9, axial 5-H), 1.22 (1 H, m, axial 9-H), 1.18 (1 H, ddd, *J* 11.5, axial 3-H), 1.09 (3 H, d, *J* 6.3, 8-Me), 0.87 (3 H, d, *J* 6.6, 16-Me), 0.868 (9 H, s, Bu^t), 0.810 (3 H, d, *J* 6.6, 9-Me), 0.054 (3 H, s, SiMe$_2$), and 0.050 (3 H, s, SiMe$_2$); *m/z* 422 (0.7%), 383 (14), 295 (100), 257 (25), 187 (35), 147 (49), 131 (28), 121 (29), 107 (36), 99 (40), 95 (43), 75 (81), 73 (75), 69 (49), and 55 (40) (Found: M^+, 440.332 54. $C_{25}H_{48}O_4Si$ requires *M*, 440.332 169).

(2S,4S,6S,8R,9S)-4-(*Dimethyl*-*t*-*butylsiloxy*)-2-[(5R,2E)-5-*formyl*-3-*methylhex*-2-*enyl*]-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]-*undecane* (**2**).—A solution of compound (**25**) (0.28 g, 0.64 mmol) in CH_2Cl_2 (2 cm^3) was added to a solution of CrO_3·2pyr (3.82 mmol) in CH_2Cl_2 (6 cm^3). After 20 min the reaction mixture was diluted with ether and washed with saturated $NaHCO_3$, dilute HCl, saturated $NaHCO_3$, saturated brine, dried, and concentrated. The residue was chromatographed (10% Et_2O–hexane) to yield compound (**2**) (0.26 g, 94%); $[\alpha]_D^{19}$ +49.1° (*c* 0.926 in $CHCl_3$); $\nu_{max.}$(film) 2 710w, 1 730s, 1 455m, 1 385s, 1 254s, 1 220m, 1 195s, 1 165m, 1 078s, 995s, 950m, 870s, 838s, and 775s; δ_H (400 MHz) 9.63 (1 H, d, *J* 2, CH=O), 5.28 (1 H, t, *J* 7, 13-H), 4.07 (1 H, dddd, *J* 11, 5, axial 4-H), 3.475 (1 H, dddd, *J* 11.5, 8, 6, 2, axial 2-H), 3.21 (1 H, dq, *J* 9.5, 6, axial 8-H), 2.575 (1 H, dddq, *J* 8, 6.5, 2, 7, 16-H), 2.455 (1 H, dd, *J* 13, 6.5, 15-H$_A$), 2.22 (1 H, dddd, *J* 14, 8, 7, 12-H$_A$), 2.17 (1 H, ddd, *J* 14, 6, 7, 12-H$_B$), 2.005 (1 H, dd, *J* 13, 8, 15-H$_B$), 1.86 [1 H, ddd, *J* 12.5, 5, 5, 1.5 (w), equatorial 5-H], 1.79 [1 H, dddd, *J* 11.5, 5, 2, 1.5 (w), equatorial 3-H], 1.62 (3 H, s, 14-Me, 1.62 and 1.5 (4 H, m, 10-H$_2$, 11-H$_2$), 1.275 (1 H, dd, *J* 12.5, 11, axial 5-H), 1.22 (1 H, m, axial 9-H), 1.16 (1 H, dddd, *J* 11.5, axial 3-H), 1.095 (3 H, d, *J* 6, 8-Me), 1.055 (3 H, d, *J* 7, 16-Me), 0.875 (9 H, s, Bu^t), 0.82 (3 Hm, d, *J* 6.5, 9-Me), and 0.05 (6 H, 2 × s, SiMe$_2$); *m/z* 363 (15%), 295 (44), 1 653 (65), 145 (56), 137 (55), 101 (45), 95 (56), 83 (32), 75 (100), 72 (86), 69 (66), 55 (64), 43 (55), and 41 (53) (Found: M^+, 438.317 19. $C_{25}H_{46}O_4Si$ requires *M*, 438.316 520).

(2S,4S,6S,8R,9S)-4-(*Dimethyl*-*t*-*butylsiloxy*)-2-[(5R,2E,6E/Z,8E)-9-(5-*methoxy*-2-*methoxycarbonyl*-p-*tolyl*)-3,5-*dimethyldeca*-2,6,8-*trienyl*]-8,9-*dimethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**27**).—To a rapidly stirred solution of lithium di-isopropylamide (0.30 mmol) in THF (1.5 cm^3) was added at −70 °C a solution of the sulphone (**3**) (0.113 g, 0.30 mmol) in THF (0.75 cm^3). After 10 min at −70 °C, a solution of the aldehyde (**2**) (0.127 g, 0.29 mmol) in THF (0.75 cm^3 was added dropwise. After a further 10 min at −70 °C, benzoyl chloride (0.5 cm^3, 4.1 mmol) was added in one portion and the reaction mixture allowed to warm to room temperature; after 1.5 h, 3-dimethylaminopropylamine (0.6 cm^3, 4.7 mmol) was added. The reaction was quenched with dilute HCl and extracted with ether, and the extract washed with saturated aqueous $NaHCO_3$ and saturated brine, dried, and concentrated. The residue was chromatographed (15% EtOAc–hexane) to yield compound (**26**) (0.210 g, 80%) which was used directly in the next step.

Sodium amalgam (5.65%; 0.234 g, 0.575 mmol) was added to a solution of compound (**26**) (0.110 g, 0.12 mmol) and Na_2HPO_4 (0.163 g, 1.15 mmol) in THF (2.0 cm^3) and MeOH

(0.5 cm^3) at −20 °C. After 2 h additional buffer (0.8 g, 0.575 mmol) and Na(Hg) (0.117 g, 0.287 mmol) were added and the reaction mixture stirred for a total of 5.5 h before being diluted with ether, quenched with saturated NH_4Cl, washed with saturated brine, dried, and concentrated. Chromatography (15% EtOAc–hexane) yielded (in order of elution) the title compound (**27**) (0.031 g, 39%); $\nu_{max.}(CCl_4)$, 1 725s, 1 608m, 1 550m, 1 500m, 1 460s, 1 435s, 1 380s, 1 328s, 1 255s, 1 195s, 1 160s, 1 080s, 945s, and 835s cm^{-1}; δ_H (400 MHz), 7.66 (1 H, s), 6.62 (1 H, s), 635 (ddd, *J* 15, 10.8, 1.1, 18-H), 6.2 [m, 18-H, 19-H (*Z,E* isomer)], 5.92 (d, *J* 11, 19-H), 5.67 (dd, *J* 15, 7.1, 17-H), 5.25 (m, 13′-H, 17-H), 4.07 (1 H, dddd, *J* 11, 11, 5, 5, axial 4-H), 3.866 (s, CO_2Me, *Z,E* isomer), 3.857 (s, OMe, *E,E* isomer), 3.805 (s, OMe, *E,E* isomer), 3.793 (s, OMe, *Z,E* isomer), 3.471 (1 H, m, axial 2-H), 3.24 (1 H, m, axial 8-H), 2.44 (1 H, m, 16-H), 2.20 (3 H, s, Ar-Me), 2.25—2.1 (3 H, m, 15-H_2, 12-H_A), 2.05 (3 H, s, 20-Me), 1.95—1.8 (3 H, m, 12-H_B, equatorial 3-H), 1.62 (3 H, s, 14-Me), 1.6—1.35 (4 H, m, 10-H_2, 11-H_2), 1.25—1.1 (3 H, m, axial 5-H, axial 3-H, axial 9-H), 1.09 (3 H, d, *J* 6.3, 8-Me), 0.99 (d, *J* 6.7, 16-Me, *E,E* isomer), 0.92 (d, *J* 6.6, 16-Me, *Z,E* isomer), 0.86 (9 H, s, Bu^t), 0.81 (3 H, d, *J* 6.5, 9-Me), and 0.04 (6 H, s, $SiMe_2$); *m/z* 654 (M^+, 1.8%), 522 (11), 295 (21), 273 (100), 241 (80), 219 (14), 213 (22), 181 (16), 129 (20), 113 (16), 101 (19), 85 (20), 75 (51), 73 (40), and 55 (21) (Found: M^+, 654.431 59. $C_{39}H_{62}O_6Si$ requires *M*, 654.431 543): followed by compound (**28**) (0.040 g, 51%); $\nu_{max.}(CCl_4)$ 3 525w, 2 960s, 2 930s, 2 880m, 2 860m, 1 710m, 1 635s, 1 440s, 1 380m, 1 340s, 1 260s, 1 160s, and 700m cm^{-1}; δ_H (400 MHz) 7.73 and 7.72 (1 H, 2 × s), 6.58 (1 H, s), 5.3—5.2 (2 H, m, 13-H, 19-H), 4.07 (1 H, dddd, *J* 11, 5, axial 4-H), 3.87 (3 H, s, CO_2Me), 3.812 and 3.810 (3 H, 2 × s, OMe), 3.58—3.45 (2 H, m, axial 2-H, 17-H), 3.25 (1 H, dq, *J* 9.7, 6.3, axial 8-H), 2.48—2.1 (6 H, m, 12-H_2, 15-H_2, 18-H_2), 2.21 (3 H, s, ArMe), 1.98 (3 H, s, 20-Me), 1.95—1.75 (3 H, m, OH, equatorial 3-H, equatorial 5-H), 1.65 (1 H, m, 11-H_B), 1.62 (3 H, s, 14-Me), 1.55—1.35 (3 H, m, 11-H_A, 10-H_2), 1.35—1.1 (4 H, m, axial 3-H, axial 5-H, axial 9-H, 16-H), 1.09 (3 H, d, *J* 6.3, 8-Me), 0.928 and 0.892 (3 H, 2 × d, *J* 6.5, 16-Me), 0.86 (9 H, s, Bu^t), 0.81 (3 H, d, *J* 6.5, 9-Me), and 0.04 (6 H, s, $SiMe_2$); *m/z* 672 (M^+, 0.8%), 307 (48), 295 (46), 235 (16), 234 (100), 219 (49), 203 (28), 159 (12), and 75 (19) (Found: M^+, 672.442 28. $C_{39}H_{64}O_7Si$ requires *M*, 672.442 093).

Methanesulphonyl chloride (0.009 cm^3, 0.116 mmol) was added to a solution of the alcohol (**28**) (0.07 g, 0.105 mmol) in Et_3N (0.029 cm^3) and CH_2Cl_2 (2 cm^3) at −10 °C. The reaction was slowly allowed to warm to room temperature where it was diluted with water and extracted with ether; the extract was washed with saturated brine, dried, and concentrated to yield the crude mesylate (**29**) which was used directly in the next step.

A solution of the mesylate in ether was refluxed in the presence of DBN (2 equiv.) for 6 h before being diluted with ether, washed with dilute HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried, and concentrated. Chromatography (10% EtOAc–hexane) of the residue yielded the diene (**27**) (0.049 g, 72%) as a 3:2 ratio of desired *E,E* to undesired *Z,E* isomers; all spectral data as above.

(+)-*Milbemycin* β_3 *Methyl Ether* (**30**).—A solution of compound (**27**) (0.092 g, 0.141 mmol) and $Bu_4NF{\cdot}3H_2O$ (0.5M in THF; 2 cm^3, 1 mmol) in THF (4 cm^3) was heated under reflux for 4 h before being quenched with saturated aqueous NH_4Cl. The product was extracted into ether, and the extract dried and concentrated. Chromatography (20% EtOAc–hexane) of the residue yielded the hydroxy ester (0.072 g, 93%); $\nu_{max.}(CCl_4)$ 3 620w, 3 530m, 1 720s, 1 255s, 1 160s, and 990s.

A solution of the above hydroxy ester (0.072 g, 0.133 mmol) in THF (7.5 cm^3) was added to a suspension of KH (0.2 g of 35% dispersion; 1.79 mmol) in THF (15 cm^3) at room temperature. After 30 min a solution of $KN(SiMe_3)_2$ (1M in THF; 0.25 cm^3, 0.25 mmol) was added and the reaction mixture stirred for an additional hour at room temperature before being carefully poured into cold water (20 cm^3). The product was extracted into ether, and the extract washed with saturated brine, dried and concentrated. Chromatography (2% EtOAc–hexane) of the residue yielded the title compound (**30**) (0.058 g, 80%); $[\alpha]_D^{21}$ + 99.1° (*c* 0.93 in $CHCl_3$); $\nu_{max.}(CCl_4)$ 1 715s, 1 620m, 1 505m, 1 450m, 1 380m, 1 335m, 1 315m, 1 270s, 1 260s, 1 165s, 1 000s, and 855 cm^{-1}; δ_H (400 MHz) 7.34 (1 H, s), 6.62 (1 H, s), 6.14 (1 H, dd, *J* 15, 10.9, 10-H), 5.72 (1 H, d, *J* 10.9, 9-H), 5.505 (1 H, dddd, *J* 11.6, 11.6, 4.7, 4.7, axial 19-H), 5.26 (1 H, dd, *J* 15, 9.4, 11-H), 4.89 (1 H, br d, *J* 10.6, 15-H), 3.82 (3 H, s, OMe), 3.6 (1 H, dddd, *J* 12, 10, 5, 2, axial 17-H), 3.29 (1 H, dq, *J* 9.8, 6.2, axial 25-H), 2.48 (1 H, m, 12-H), 2.30—2.1 (3 H, m, 16-H_2, 13-H_A), 2.185 (3 H, s, *Me*Ar), 2.11 (3 H, d, *J* 1.2, 8-Me), 2.06—1.91 (2 H, m, equatorial 18-H, equatorial 20-H), 1.852 (1 H, dd, *J* 12.4, 12.4, 13-H), 1.64 (3 H, s, 14-Me), 1.64—1.44 (4 H, m, 22-H_2, 23-H_2), 1.39 (1 H, dd, *J* 11.9, axial 20-H), 1.25 (1 H, m, axial 24-H), 1.14 (3 H, d, *J* 6.25, 25-Me), 1.03 (3 H, d, *J* 6.6, 12-Me), 0.83 (3 H, d, *J* 6.6, 24-Me), and 0.782 (1 H, dddd, *J* 12.1, axial 18-H); *m/z* 508 (M^+, 10%), 259 (42), 241 (20), 215 (16), 191 (16), 181 (68), 153 (100), 129 (22), 107 (15), 95 (29), 81 (21), and 69 (50) (Found: M^+, 508.320 43. $C_{32}H_{44}O_5$ requires *M*, 508.318 848).

(+)-*Milbemycin* β_3 (**1**).—Ethanethiol (0.021 g, 0.344 mmol) was added to NaH (0.008 g, 0.344 mmol) in DMF (2.2 cm^3) at room temperature. After 10 min a solution of compound (**30**) (0.055 g, 0.108 mmol) in DMF (0.75 cm^3) was added and the reaction mixture heated under reflux for 1.5 h; it was then cooled and acidified with dilute HCl. The product was extracted into ether, and the extract washed with saturated brine, dried, and concentrated. Chromatography (8% EtOAc–hexane) of the residue yielded the title compound (**1**) (0.0403 g, 75%), m.p. 175—177 °C; $[\alpha]_D^{20}$ + 32.5° (*c* 0.31 in MeOH) [lit. + 26.5° (*c* 0.20 in MeOH)]; $\nu_{max.}(CCl_4)$ 3 610shw, 2 965s, 2 930s, 2 875s, 1 710m, 1 615w, 1 505w, 1 450w, 1 380m, 1 310m, 1 278s, 1 240m, 1 230m, 1 195m, 1 170s, 1 148s, 1 120s, 1 100s, 1 055m, 1 000s, 965m, and 720w cm^{-1}; $\lambda_{max.}$(EtOH) 246 nm; δ_H (400 MHz) 7.33 (1 H, s, 3-H), 6.61 (1 H, s, 6-H), 6.12 (1 H, dd, *J* 14.9, 10.8, 10-H), 5.71 (1 H, br d, *J* 10.7, 9-H), 5.51 (1 H, dddd, *J* 11.6, 11.6, 4.7, 4.7, axial 19-H), 5.26 (1 H, dd, *J* 14.9, 9.5, 11-H), 4.98 (1 H, s, OH), 4.89 (1 H, br, d, *J* 10.8, 15-H), 3.68 (1 H, dddd, *J* ~11, ~11, ~6, ~2, axial 17-H), 3.29 (1 H, dq, *J* 9.7, 6.2, axial 25-H), 2.48 (1 H, m, 12-H), 2.32 (1 H, m, 16-H_A), 2.22 (3 H, s, 4-Me), 2.22—2.16 (2 H, m, 13-H_A, 16-H_B), 2.07 (3 H, d, *J* 1.107, 8-Me), 1.98 (1 H, m, equatorial 18-H), 1.93 (1 H, ddd, *J* 12, 5, 2, equatorial 20-H), 1.85 (1 H, dd, *J* 12.5, 12.5, 13-H_A), 1.63 (3 H, s, 14-Me), 1.67—1.45 (4 H, m, 22-H_2, 23-H_2), 1.40 (1 H, dd, *J* 12, axial 20-H), 1.26 (1 H, m, axial 24-H), 1.14 (3 H, d, *J* 6.2, 25-Me), 1.03 (3 H, d, *J* 6.6, 12-Me), 0.83 (3 H, d, *J* 6.6, 24-Me), and 0.77 (1 H, ddd, *J* 12, 12, 12, axial 18-H); δ_C (100.5 MHz) 169.23 (s, C-1), 155.24 (s, C-5), 144.0 (s, C-7), 140.25 (d, C-11), 135.78 (s, C-14), 133.87 (s, C-8), 131.79 (d, C-3), 128.73 (d, C-9), 125.32 (d, C-10), 124.15 (s, C-2), 122.18 (s, C-4), 121.35 (d, C-15), 114.03 (d, C-6), 47.67 (s, C-21), 71.16 (d, C-25), 68.0 (d, C-17), 67.6 (d, C-19), 48.7 (t), 41.17 (t), 36.56 (d, C-24), 36.53 (t), 36.25 (d, C-12), 35.76 (t), 33.88 (t), 27.74 (t), 21.6 (q, 12-Me), 19.4 (q, 25-Me), 18.01 (q, 8-Me), 17.88 (q, 24-Me), 16.11 (q, 14-Me), and 25.24 (q, 4-Me); *m/z* 494 (M^+, 11%), 245 (36), 244 (10), 227 (14), 181 (52), 177 (10), 154 (12), 153 (100), 129 (18), 122 (11), 107 (10), 95 (14), 93 (10), 83 (10), 81 (13), 60 (25), 55 (13), and 41 (14) (Found: M^+, 494.303 66. $C_{31}H_{42}O_5$ requires *M*, 494.303 206).

(3S)-1-*Benzyloxy*-3,4-*epoxybutane* (**29**).—(*S*)-(−)-Malic acid was converted in 5 steps[17] into the oxirane (**29**): b.p. 105 °C (bath)/0.05 mmHg; $[\alpha]_D^{19}$ −12.4° (*c* 2.39 in $CHCl_3$) [lit.,[17] −13.0° (*c* 2.5 in $CHCl_3$)]; $\nu_{max.}$(film) 1 450m, 1 360m, 1 100s, 1 030m, 910m, 830m, 740s, and 700s; δ_H (90 MHz) 7.3 (5 H, s),

4.51 (2 H, s), 3.65 (2 H, t, *J* 7), 3.1 (1 H, m), 2.8 (1 H, dd, *J* 7, 6), 2.55 (1 H, dd, *J* 7, 4), and 1.85 (2 H, m) (Found: M^+, 178.099 68. $C_{11}H_{14}O_2$ requires *M*, 178.099 373).

(3S)-1-*Benzyloxy*-5-*methylhex*-5-*en*-3-*ol* (**33**).—A solution of the Grignard reagent formed by the reaction of 2-bromopropene (13.6 g, 112.4 mmol) with magnesium turnings (2.73 g, 112.4 mmol) in THF (275 cm^3) was added to a suspension of CuI (1.07 g, 5.6 mol) in THF (140 cm^3) at −30 °C. After 10 min a solution of compound (**32**) (10 g, 56 mmol) in THF (95 cm^3) was added and the reaction kept at −30 °C for 1 h before being quenched with saturated aqueous NH_4Cl. The product was extracted into ether and the extract dried and concentrated before distillation [105 °C (bath)/0.01 mmHg] to yield the title compound (**33**) (12.04 g, 97%); $[\alpha]_D^{20}$ −3.75° (*c* 2.49 in $CHCl_3$); $\nu_{max.}$(film) 3 450m, 1 645w, 1 100s, 1 080m, 892m, 740s, and 700s; δ_H (90 MHz) 7.4 (5 H, s), 4.85 (2 H, m), 4.65 (2 H, s), 4.0 (1 H, m), 3.7 (2 H, m), 2.85 (1 H, s, OH), 2.25 (2 H, d, *J* 7), and 1.85 (5 H, m) (Found: M^+, 220.146 40. $C_{14}H_{20}O_2$ requires *M*, 220.146 321).

(3S)-5-*Methylhex*-5-*ene*-1,4-*diol* (**34**).—Sodium metal (2.53 g, 0.11 g atom) was added portionwise to a solution of compound (**33**) (12.1 g, 55 mmol) in liquid ammonia (500 cm^3) at −70 °C until a deep blue colour persisted for 30 min. Extra sodium (0.75 g, 0.032 mol) and Bu^{t}OH (1.5 cm^3) were added and the deep blue colour persisted for 2 h. Ethanol (100 cm^3) was added and the ammonia allowed to evaporate before the residue was quenched with saturated aqueous NH_4Cl. The product was extracted into CH_2Cl_2 and the extract dried and concentrated before distillation [80 °C (bath)/0.01 mmHg] to yield the title compound (**34**) (6.97 g, 97%); $[\alpha]_D^{23}$ −12.4° (*c* 1.61 in $CHCl_3$); $\nu_{max.}$(film) 3 340s, 1 645w, 1 060s, and 892s; δ_H (90 MHz) 4.85 (2 H, m), 4.15—3.75 (3 H, m), 2.70 (2 H, s, 2 × OH), 2.25 (2 H, d, *J* 7), and 1.75 (5 H, m) (Found: M^+, 130.099 03. $C_7H_{14}O_2$ requires *M*, 130.0993 73).

(3R)-5-*Methyl*-1,3-*bis*-p-*nitrobenzoyloxyhex*-5-*ene* (**35**).—A solution of compound (**34**) (0.85 g, 6.54 mmol) in toluene (10 cm^3) was added to a suspension of PPh_3(4.12 g, 15.1 mmol) and *p*-nitrobenzoic acid (2.62 g, 15.7 mmol) in toluene (40 cm^3) at −8 °C. After 5 min a solution of diethyl azodicarboxylate (2.73 g, 15.7 mmol) in benzene (8 cm^3) was added so as to maintain a temperature of −8 °C.[23] The reaction was allowed to warm to room temperature where it was maintained for 1 h before being quenched with saturated aqueous $NaHCO_3$. Chromatography (30% EtOAc–hexane) of the crude product yielded the title compound (**35**) (2.05 g, 73%); m.p. 97—99 °C (hexane); $[\alpha]_D^{22}$ +73.2° (*c* 1.08 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 725s, 1 608m, 1 530s, 1 285s, 1 270s, 1 120s, and 1 105s; δ_M (90 MHz) 8.2 (8 H, m), 5.55 (1 H, tt, *J* 6, 6), 4.82 (2 H, m), 4.50 (2 H, t, *J* 6), 2.6—2.1 (4 H, m), and 1.81 (3 H, s) (Found: M^+, 428.122 10. $C_{21}H_{20}N_2O_8$ requires *M*, 428.121 954).

(3R)-5-*Methylhex*-5-*ene*-1,3-*diol* (**5**).—Hydrolysis of diester (**35**) in methanolic NaOH in the usual way gave the diol (**5**) in 88% yield after distillation; b.p. 100 °C (bath)/0.3 mmHg; $[\alpha]_D^{22}$ 11.5° (*c* 1.74 in $CHCl_3$); the i.r., ^{1}H n.m.r., and mass spectra were identical with those described above for the (*S*)-(−)-isomer (**31**).

2-[(3S,4S)-4-*Hydroxy*-3-*methylpentyl*]-1,3-*dioxolane* (**38**).—A solution of the Grignard reagent formed by the reaction of 2-(2-bromoethyl)-1,3-dioxolane (37.7 g, 0.21 mol)[24] and magnesium turnings (10.2 g, 0.42 mol) in THF (100 cm^3) was added to a solution of CuBr·Me_2S[25] (7.14 g, 35 mmol) in Me_2S (100 cm^3) at −70 °C and the solution stirred for 40 min before compound (**36**) (10 g, 0.14 mol) in THF (20 cm^3) was added. The reaction was allowed to warm to 0 °C over 1.5 h before being quenched with saturated aqueous NH_4Cl–10% NH_4OH. The product was extracted into ether, and the extract dried and concentrated before distillation (b.p. 79—80 °C/0.1 mmHg) to yield the title compound (**38**) (19.7 g, 82%); $[\alpha]_D^{22}$ −15.3° (*c* 2.5 in $CHCl_3$); $\nu_{max.}$(film) 3 450s, 1 410m, 1 145m, 1 125m, 1 035m, 890m, and 775m; δ_H (90 MHz) 4.85 (1 H, t, *J* 4), 4.1—3.5 (5 H, m), 2.1 (1 H, s, OH), 1.9—1.25 (5 H, m), 1.15 (3 H, d, *J* 7), and 0.9 (3 H, d, *J* 6); δ_C (22.6 MHz) 104.0*, 70.7*, 64.8, 39.7*, 31.7, 26.7, 20.1*, and 14.3* (Found: M^+, 174.2240. $C_9H_{18}O_3$ requires *M*, 174.2256).

2-[(3S,4R)-3-*Methyl*-4-p-*nitrobenzoyloxypentyl*]-1,3-*dioxolane* (**39**).—A solution of compound (**38**) (19 g, 0.109 mol) in toluene (75 cm^3) was added to a mechanically stirred suspension of triphenylphosphine and *p*-nitrobenzoic acid (21.9 g, 0.13 mol) in toluene (250 cm^3) at −35 °C. After 5 min a solution of diethyl azodicarboxylate (22.82 g, 0.13 mol) in benzene (100 cm^3) was added dropwise so as to maintain an internal temperature of −35 °C. The reaction mixture was allowed to warm to room temperature where it was maintained for 1 h before being quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The extract was dried, concentrated, diluted with hexane, filtered, and chromatographed (10% Et_2O–hexane) to yield the title compound (**39**) (24.81 g, 71%); $[\alpha]_D^{22}$ −52.7° (*c* 0.67 in MeOH); $\nu_{max.}$(film) 1 720s, 1 610m, 1 530m, 1 280s, 1 105m, and 720m; δ_H (90 MHz) 8.2 (4 H, s), 5.13 (1 H, dq, *J* 7, 7), 4.85 (1 H, m), 3.9 (4 H, m), 2.1—1.45 (5 H, m), 1.35 (3 H, d, *J* 7), and 1.05 (3 H, d, *J* 7) (Found: M^+, 323.132 02. $C_{16}H_{21}NO_6$ requires *M*, 323.136 88).

2-[(3S,4R)-4-*Hydroxy*-3-*methylpentyl*]-1,3-*dioxolane* (**40**).—A solution of KOH (5.2 g, 92 mmol) in MeOH (100 cm^3) and water (100 cm^3) was added to a solution of compound (**39**) (24.8 g, 77 mmol) in MeOH (100 cm^3) and THF (100 cm^3) at room temperature. After 3.5 h the reaction mixture was concentrated, diluted with saturated brine, and extracted with CH_2Cl_2. The extract was dried, concentrated, and distilled, b.p. 83—85 °C/0.3 mm Hg), to yield the title compound (**40**) (11.71 g, 88%); $[\alpha]_D^{24}$ −16.0° (*c* 2.6 in $CHCl_3$); $\nu_{max.}$(film) 3 450s, 1 410m, 1 145m, 1 125m, 1 035m, 775m, and 890m; δ_H (90 MHz) 4.85 (1 H, t, *J* 4), 4.1—3.5 (5 H, m), 2.1 (1 H, s, OH), 1.9—1.25 (5 H, m), 1.15 (3 H, d, *J* 7), and 0.9 (3 H, d, *J* 6); δ_H (22.6 MHz) 104.9*, 71.3*, 64.8, 40*, 31.6, 24, 19.5, 147* (Found: M^+, 174.2240. $C_9H_{18}O_3$ requires *M*, 174.2256).

(5S,6R)-5,6-*Dimethylvalerolactone* (**41**).—A solution of compound (**40**) (11.7 g, 67.2 mmol) and toluene-*p*-sulphonic acid (150 mg) in THF (150 cm^3) and water (30 cm^3) was heated at 75 °C for 4 h before being quenched with saturated aqueous $NaHCO_3$. The product was extracted into ether and the extract dried, concentrated, and distilled [100 °C (bath)/15 mmHg] to yield the lactol (7.9 g, 90%); $\nu_{max.}$(film) 3 400s, 1 120s, 1 090s, and 1 005s; δ_H (90 MHz) 5.3 and 4.7 (1 H, 2 × m, 2-H), 4.45 (1 H, br s, OH), 3.75 and 3.25 (1 H, 2 × dq, *J* 7, 6), 2.1—1.2 (5 H, m), 1.2 (3 H, 2 × d, *J* 6), and 0.85 (3 H, 2 × d, *J* 6) (Found: M^+, 130.099 37. $C_7H_{14}O_2$ requires *M*, 130.099 373).

Bromine (0.42 cm^3) was added dropwise to a solution of the lactol (1.5 g, 11.5 mmol) and sodium acetate (11.4 g, 0.14 mol) in water (19 cm^3) and glacial acetic acid (13 cm^3) at room temperature. After 1.25 h the reaction mixture was diluted with water, extracted with ether, and the extract dried, concentrated, and distilled [70 °C (bath)/0.15 mmHg] to yield the title compound (**41**) (1.06 g, 72%); $[\alpha]_D^{21}$ +22.3 (*c* 4.66 in $CHCl_3$) [lit.,[4] +13.1° (*c* 4.86 in $CHCl_3$)]; $\nu_{max.}$(film) 1 740s, 1 250s, 1 225s, and 1 095s; δ_H (90 MHz) 4.05 (1 H, dq, *J* 9, 6), 2.9—2.3 (2 H, m), 2.2—1.4 (3 H, m), 1.35 (3 H, d, *J* 6), and 1.0 (3 H, d, *J* 6.5) (Found: M^+, 128.083 45. $C_7H_{12}O_2$ requires *M*, 128.083 72).

(5S,6R)-2,2-*Diethoxy*-5,6-*dimethyltetrahydropyran* (**6**).—Triethyloxonium tetrafluoroborate (1.15 g, 6.05 mmol) was

added to a solution of compound (**41**) (0.673 g, 5.25 mmol) in CH_2Cl_2 (10 cm^3) at room temperature. After 24 h the solution was added to NaOEt (15.7 mmol) in EtOH (19 cm^3) at −70 °C. After 45 min at −70 °C the reaction mixture was allowed to warm to room temperature where it was concentrated, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The extract was dried, concentrated, and distilled [70 °C (bath)/0.08 mmHg] to yield the title compound (**6**) (0.676 g, 71%); $[\alpha]_D^{20}$ +22.2° (*c* 1.03 in $CHCl_3$); $\nu_{max.}$(film) 2 980s, 1 450m, 1 380m, 1 245m, 1 225m, 1 170s, 1 135m, 1 075s, and 1 010s; δ_H (90 MHz) 3.8—3.3 (5 H, m), 2.2—1.1 (14 H, m), and 0.85 (3 H, d, *J* 6, 5-Me).

5-*Hydroxy*-2,6-*dimethyl*-2-*vinylphthalide* (**48**).—A mixture of the acetylene (**46**) (12.0 g, 53 mmol) and the diene[20] (**47**) 10.85 g, 58.3 mmol) in dry xylene (50 cm^3) was refluxed for 110 h. The bulk of the xylene was evaporated at *ca.* 1 mmHg and the residue dissolved in THF (100 cm^3) to which was added 1M H_2SO_4 (30 cm^3). The mixture was stirred at ambient temperature for 1 h after which it was neutralised by careful addition of solid $NaHCO_3$ until gas evolution ceased. Ether (200 cm^3) was added and the layers separated. The organic layer was washed with brine, dried, and evaporated to a crystalline mass from which the pure title compound (**48**) (4.15 g) was obtained from ether–hexane (1:1). Chromatography of the residues from the crystallisation gave a further crop (0.59 g) to give a total yield of 4.74 g (46%) of (**48**); m.p. 186—189 °C; δ_H [$CDCl_3$–$(CD_3)_2SO$, 90 MHz] 7.54 (1 H, s), 6.86 (1 H, s), 6.1 (1 H, dd, *J* 11,17), 5.05—5.55 (2 H, m), 2.6 (1 H, br, OH), 2.25 (3 H, s), and 1.68 (3 H, s); *m/z* 204 (M^+, 32%), 189 (100), 177 (38), 162 (19), 161 (35), 77 (12), and 43 (10) (Found: M^+, 204.078 76. $C_{12}H_{12}O_3$ requires *M*, 204.078 63).

Cycloaddition of the Enyne (**42**) *and the Diene* (**47**).—A mixture of the enyne (**42**) (1.10 g, 4.8 mmol) and the diene (**47**) (1.34 g, 7.2 mmol) was refluxed in xylene (3 cm^3) for 48 h. The xylene was removed under reduced pressure and the residue dissolved in THF (10 cm^3). To the solution was added 0.1M HCl (10 cm^3) and the mixture was then stirred at room temperature for 12 h. It was then diluted with ether and the organic phase separated; the aqueous phase was extracted with ether. The combined organic layers were washed in brine, dried, and concentrated. The residue was chromatographed (EtOAc–hexane, 2:3) to give in order of elution: compound (**43**) (0.36 g, 45%), m.p. 82—84 °C (ether–hexane); $\nu_{max.}$($CHCl_3$) 3 620m, 3 470m, 2 235s, 1 710s, 1 675s, 1 432s, 1 366s, 1 060s, and 1 018s cm^{-1}; δ_H (400 MHz) 6.51 (1 H, q, *J* 1.4), 3.90—3.97 (1 H, m), 3.78 (3 H, s), 3.64—3.72 (1 H, m), 2.73 (1 H, dd, *J* 4, 17), 2.49—2.58 (1 H, m), 2.36 (1 H, dd, *J* 12.4, 17), 1.79 (3 H, d, *J* 1.4), 1.57 (1 H, br, OH), and 1.4 (3 H, s); δ_C (22.6 MHz) 197.8, 154.0, 146.8, 134.5, 91.7, 73.8, 62.9, 52.8, 44.9, 36.7, 35.6, 20.6, and 15.5; *m/z* 236 (M^+, 59%), 205 (26), 179 (13), 177 (100), 163 (27), 162 (14), 161 (11), 135 (21), 121 (10), 107 (10), 93 (15), and 91 (24) (Found: C, 66.4; H, 6.55. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.82%); Compound (**45**) (0.079 g, 9%), m.p. 172.5—175 °C (ether); δ_H (90 MHz), 9.4 (1 H, br s, OH), 7.25 and 7.0 (1 H each, s), 5.4 (1 H, t with fine splitting, *J* 7), 4.28 (2 H, d, *J* 7), 3.8 (3 H, s), 2.22 (3 H, s), and 1.9 (3 H, s) (Found: C, 65.6; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83%); and finally complex (**44**) (0.070 g, 8%) as a viscous oil; δ_H (90 MHz) 8.0 (1 H, br s, OH), 7.75 and 6.65 (1 H each, s), 5.5 (1 H, t with fine splitting, *J* 7), 4.32 (2 H, d, *J* 7), 3.85 (3 H, s), 2.24 (3 H, s), and 1.93 (3 H, s).

5-*Methoxy*-2,6-*dimethyl*-2-*vinylphthalide* (**49**).—A solution of diazomethane (0.5M; 50 cm^3) was added to a stirred suspension of compound (**48**) (3.6 g, 17.6 mmol) in ether (25 cm^3) at room temperature. After 18 h, any excess of diazomethane was destroyed with HOAc and the reaction mixture was concentrated. The residue was filtered through silica (50% EtOAc–hexane) and concentrated to yield the title compound (**49**) (3.38 g, 90%); m.p. 137—138 °C (hexane); $\nu_{max.}$(CCl_4) 1 770s, 1 620m, 1 605m, 1 490m, 1 470m, 1 330m, 1 310s, 1 240m, 1 222s, 1 150m, 1 135m, 1 120m, 1 055m, 1 045s, and 930m; δ_H (90 MHz) 7.65 (1 H, s), 6.78 (1 H, s), 6.08 (1 H, dd, *J* 18, 11), 5.43 (1 H, d with fine coupling, *J* 18), 5.24 (1 H, d with fine coupling, *J* 11), 3.97 (3 H, s), and 2.29 (3 H, s); *m/z* 218 (M^+, 42%), 203 (100), 191 (38), 175 (49), 91 (13), and 77 (15) (Found: C, 71.45; H, 6.55. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%).

4-*Hydroxymethyl*-1-(2-*hydroxybut*-3-*en*-2-*yl*)-1-*methoxy*-2-*methylbenzene* (**50**).—A solution of compound (**49**) (3.2 g, 14.7 mmol) in THF (25 cm^3) was added to a suspension of $LiAlH_4$ (0.42 g, 11 mmol) in ether (30 cm^3) at room temperature. After 30 min the reaction mixture was quenched by the sequential addition of water (0.4 cm^3), 15% NaOH (0.4 cm^3), and water (1.2 cm^3). The mixture was stirred for 2 h after which the fine powder was filtered off and the filtrate concentrated to yield the title compound (**50**) (3.15 g, 97%); m.p. 93—95 °C (acetone–ether); $\nu_{max.}$(CCl_4) 3 600m, 3 430m, 1 615m, 1 570m, 1 505s, 1 465s, 1 260s, 1 095s, and 925s; δ_H (90 MHz) 7.11 (1 H, s), 6.91 (1 H, s), 6.23 (1 H, dd, *J* 18, 10), 5.25 (2 H, *m*), 4.86 (1 H, A portion of AB, J_{AB} 12.2), 4.55 (1 H, B portion of AB, J_{AB} 12.2), 3.87 (3 H, s), 3.45 (2 H, s, 2 × OH), 2.21 (3 H, s), and 1.74 (3 H, s); *m/z* 222 (M^+, 22%), 204 (31), 189 (100), 177 (33), 161 (50), 91 (22), and 77 (9) (Found: C, 70.05; H, 8.2. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%).

4-*Acetoxymethyl*-5-(2-*hydroxybut*-3-*en*-2-*yl*)-1-*methoxy*-2-*methylbenzene* (**51**).—Acetyl chloride (1.94 g, 24.8 mmol) was added to a solution of compound (**50**) (3.15 g, 14.2 mmol) in pyridine (30 cm^3) at 0 °C. After 40 min at room temperature the reaction mixture was diluted with ether and washed with dilute HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried, and concentrated to yield the title compound (**51**) (3.75 g, 100%); $\nu_{max.}$(film) 3 450m, 1 735s, 1 615m, 1 505s, 1 465m, 1 380m, 1 260s, 1 130m, 1 050m, 1 025m, 925m, and 885m; δ_H (90 MHz) 7.2 (1 H, s), 7.05 (1 H, s), 6.25 (1 H, dd, *J* 18, 10), 5.3 (4 H, m), 3.87 (3 H, s), 2.8 (1 H, s, OH), 2.21 (3 H, s), 2.08 (3 H, s), and 1.72 (3 H, s); *m/z* 264 (M^+, 22%), 204 (14), 189 (96), 186 (90), 161 (72), 92 (38), 77 (14), and 43 (100) (Found: M^+, 264.136 150. $C_{15}H_{20}O_4$ requires *M*, 264.136 82).

4-*Acetoxymethyl*-1-*methoxy*-2-*methyl*-5-(4-*phenylsulphonylbut*-2-*en*-2-*yl*)*benzene* (**52**).—A solution of HBr (45% in AcOH; 1.9 cm^3) in ether (10 cm^3) was added to a solution of compound (**51**) (2.45 g, 9.3 mmol) in ether at 0 °C. After 10 min the reaction was diluted with ether, washed with water, saturated aqueous $NaHCO_3$, and saturated brine, dried, and concentrated to give the primary allylic bromides (4:1 mixture of *E* and *Z* isomers). The crude product was dissolved in DMF (30 cm^3) and $NaSO_2Ph$ (3.4 g, 20.8 mmol) was added at room temperature. After 10 min the reaction was diluted with ether, washed with water and saturated brine, dried, and concentrated. Chromatography (10% EtOAc–hexane) of the residue yielded the title compound (**52**) (2.42 g, 67%); m.p. 79.5—80.5 °C (ether–hexane); $\nu_{max.}$(CCl_4) 1 742s, 1 615m, 1 505m, 1 465m, 1 450m, 1 380m, 1 362m, 1 325s, 1 230s, 1 150s, 1 125m, 1 050m, 855m, and 690m; δ_H (90 MHz) 8.0 (2 H, m), 7.7 (3 H, m), 7.2 (1 H, s), 6.5 (1 H, s), 5.41 (1 H, t, *J* 7), 4.91 (2 H, s), 4.05 (2 H, d, *J* 7), 3.85 (3 H, s), 2.22 (3 H, s), 2.08 (3 H, s), and 1.78 (3 H, s); *m/z* 388 (M^+, 3%), 188 (19), 187 (100), 175 (21), and 43 (30) (Found: C, 64.9; H, 6.1; S, 8.15. $C_{12}H_{24}SO_5$ requires C, 64.9; H, 6.2; S, 8.25%).

4-*Formyl*-1-*methoxy*-2-*methyl*-5-(4-*phenylsulphonylbut*-2-*en*-2-*yl*)*benzene* (**54**).—K_2CO_3 (2 g, 15 mmol) was added to a solution of compound (**52**) (2.42 g, 6.24 mmol) in MeOH (30

cm^3) at room temperature. After 20 min the reaction mixture was concentrated, diluted with ether, washed with water and saturated brine, dried, and concentrated to yield the benzyl alcohol (**53**) (2.16 g, 100%).

The crude product was dissolved in acetone (60 cm^3) and aqueous H_2CrO_4 (1.4M; 8 cm^3) was added at room temperature. The reaction was concentrated, diluted with ether, washed with water, 2M-NaOH, dilute HCl, and saturated brine, dried, and concentrated to yield the title compound (**54**) (1.9 g, 90%); m.p. 98—99 °C (ether–hexane); $\nu_{max.}(CCl_4)$ 1 685s, 1 605s, 1 560m, 1 500s, 1 465m, 1 447m, 1 325s, 1 280s, 1 235s, 1 150s, 1 120s, 1 050m, 855m, and 690m; δ_H (90 MHz) 9.85 (1 H, s), 8.05 (2 H, m), 7.25 (4 H, m), 6.57 (1 H, s), 5.45 (1 H, t, *J* 7), 4.11 (2 H, d, *J* 7), 3.93 (3 H, s), 2.24 (3 H, s), and 1.95 (3 H, s); *m/z* 344 (M^+, 0.3%), 203 (89), 175 (100), 160 (29), 115 (24), 77 (54), and 51 (19) (Found: C, 66.4; H, 5.7; S, 9.05. $C_{19}H_{20}SO_4$ requires C, 66.25; H, 5.85; S, 9.3%).

1-*Methoxy*-3-*methoxycarbonyl*-2-*methyl*-5-(4-*phenylsulphonylbut*-2-*en*-2-*yl*)*benzene* (**3**).—A solution of compound (**54**) (0.945 g, 2.75 mmol) and trimethylsilyl cyanide (0.36 g, 3.6 mmol) in CH_2Cl_2 (10 cm^3) was heated under reflux with a catalytic amount of $ZnBr_2$ for 2 h.[26] The reaction was concentrated to yield the *O*-trimethylsilyl cyanohydrin (**55**) [$\nu_{max.}$(film) 1 080s, 870s, and 840s] which was dissolved in THF (17 cm^3) and treated with 10% HCl (3.4 cm^3) at room temperature. After 1 h the reaction mixture was diluted with water, extracted with ether, and the extract washed with saturated aqueous $NaHCO_3$ and saturated brine, dried, and concentrated. Chromatography (20% EtOAc–hexane) of the residue yielded the cyanohydrin (**56**); δ_H (90 MHz) 8.0 (2 H, m), 7.65 (3 H, m), 7.48 (1 H, s), 6.48 (1 H, s), 5.45 (2 H, m), 4.05 (2 H, d, *J* 7), 3.82 (3 H, s), 2.24 (3 H, s), and 1.92 (3 H, s).

A solution of the cyanohydrin (**56**) (2.75 mmol) in CH_2Cl_2 (10 cm^3) was added to a solution of CrO_3·2pyr (18 mmol) in CH_2Cl_2 (27 cm^3) at room temperature. After 30 min the reaction was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$, 1M-HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried, and concentrated to yield the crude acyl cyanide (**57**).

The acyl cyanide (**5**) was refluxed in MeOH (30 cm^3) and $CHCl_3$ (10 cm^3) with 3 drops concentrated HCl for 16 h before being diluted with ether, washed with saturated $NaHCO_3$ and saturated brine, dried, and concentrated. Chromatography (30% EtOAc–hexane) of the residue yielded the methyl ester (**3**) (0.84 g, 82%); m.p. 97—99 °C (ether–hexane); $\nu_{max.}(CCl_4)$ 1 720s, 1 610m, 1 560m, 1 505m, 1 465m, 1 450m, 1 435m, 1 235s, 1 228s, 1 210s, 1 158s, 1 105m, 1 090m, 1 015m, and 690m; $\lambda_{max.}$(EtOH) 216 and 248 nm; δ_H (400 MHz) 7.96 (2 H, m, SO_2Ph), 7.69 (1 H, s), 7.66 (3 H, m), 6.41 (1 H, s), 5.24 (1 H, tq, *J* 7.9, 1.4), 4.01 (2 H, d, *J* 7.9), 3.875 and 3.791 (3 H each, s), 2.195 (3 H, s), and 1.78 (3 H, d, *J* 1.22); *m/z* 374 (M^+, 374.118 66. $C_{20}H_{22}SO_5$ requires *M*, 374.118 786) (Found: C, 64.1; H, 5.8; S, 8.25. $C_{20}H_{22}SO_5$ requires C, 64.15; H, 5.9; S, 8.25%).

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