Milbemycin Synthesis: Synthesis of a Macrocyclic Analogue of Non-Aromatic β-Milbemycins

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Stereoselective base-catalysed addition of the keto ester **15** and 3-methylbut-3-en-2-one gave the hydroxycyclohexanone **16**. Reduction and methylation gave the monomethyl ether **23**, which was regioselectively converted into the butenolide **25** by oxidation using bromine in methanol and hydrolysis of the mixture of intermediate dimethoxydihydrofurans **24**. Bromination of the butenolide **25** followed by hydrolysis gave the hydroxybutenolide **40** which was condensed with the ylide generated from the phosphonium salt **62** to give the conjugated dienes **63** and **64**. Treatment with a trace of iodine induced (*Z*)- to (*E*)-isomerisation of the 10,11-double bond, and ester exchange under basic conditions with 2-(trimethylsilyl)ethanol followed by esterification with diazomethane gave the diesters **67** and **70**. Deprotection gave a mixture of the hydroxy acids **71** and **72**, and the hydroxy acid **71** was cyclised to give the macrolide **73**. Reduction of the methyl ester gave the alcohol **74**, a macrocyclic analogue of non-aromatic β-milbemycins.

The milbemycins and avermectins comprise an important group of macrocyclic natural products with pronounced biological activities.[1,2] Members of the group include the α-milbemycins which are characterised by the presence of a non-aromatic C(1)–C(9) fragment fused to a tetrahydrofuran ring, *e.g.* milbemycin α_1 **1**,[3] and the avermectins which are structurally similar except for a disaccharide attached at C(13), *e.g.* avermectin B_{2a} **2**.[4] In contrast, the β-milbemycins have a monocyclic C(1)–C(9) fragment and include both non-aromatic and aromatic compounds, *e.g.* milbemycin β_1 **3** and milbemycin β_3 **4**.[5]

The synthesis of milbemycins and avermectins has been of considerable interest because of their biological activities.[2] Several total syntheses of both the aromatic and non-aromatic β-milbemycins[6,7] and the more challenging α-milbemycins and avermectins have been described.[8] However, there remains a need for additional milbemycin syntheses which are convergent and which can be used to provide analogues for biological evaluation. We here report preliminary work which has helped to define a strategy for a milbemycin synthesis, together with a total synthesis of a macrocyclic analogue of the non-aromatic β-milbemycins.[9]

An approach to the synthesis of non-aromatic β-milbemycins, *e.g.* **3**, was envisaged in which a crucial step would be the formation of the C(10)–C(11) double bond by nucleophilic addition of the C(11)–C(25) fragment **5** to the aldehyde **6**. Deprotection and macrocyclisation of the coupled product would then complete a convergent synthesis of a non-aromatic β-milbemycin. The furan **7** was considered a suitable starting material for the stereospecific synthesis of the unsaturated protected γ-hydroxy aldehyde **6**.

In preliminary studies it was decided to leave out the C(3)–C(4) double bond in order to facilitate the development of the necessary methodology, and the cyclohexane derivative **8** was identified as our first synthetic target. The incorporation of compound **8** into a synthesis of a diene corresponding to the C(1)–C(12) fragment of a non-aromatic 3,4-dihydro-β-milbemycin would help to establish the viability of our strategy.[9]

The base-catalysed Robinson annelation of ethyl 3-oxo-3-phenylpropanoate (ethyl benzoylacetate) **9** with methyl vinyl ketone is known to give the hydroxycyclohexanone **10** stereoselectively.[10] This adduct, although racemic, has the same relative configuration at C(2) and C(7) as the target compound **8**. Moreover, reduction of the cyclohexanone **10** using sodium triacetoxyborohydride is highly stereoselective, giving the diol **11** which has the required stereochemistry at C(5). Indeed, prior to the onset of our work, this chemistry had been used to provide rapid access to simple milbemycin analogues.[10] It was decided to investigate the use of this Robinson annelation–reduction sequence to synthesize the target compound **8**.‡

Synthesis and Modification of the Ethyl Hydroxycyclohexanecarboxylate.—To gain familiarity with the Robinson reaction, 3-methylbut-3-en-2-one[11] was added to a solution of ethyl 3-oxo-3-phenylpropanoate and sodium hydroxide in ethanol. This gave the hydroxycyclohexanone **12**, which was reduced using sodium triacetoxyborohydride to give diol **13**[12] in excellent yield (Scheme 1). Attempts to monomethylate this diol at the 5-OH under basic conditions were unsuccessful, and mixtures of monomethylated and dimethylated products were obtained. However, trimethyloxonium tetrafluoroborate in the presence of anhydrous potassium carbonate was more effective, and gave the required methyl ether **14** in 68% yield together with a small amount of unchanged starting material.

Ethyl3-(2-furyl)-3-oxopropanoate[ethyl(3-furoyl)acetate]**15** was prepared by acylation of ethyl acetate using 3-furoyl chloride (Scheme 2). Lithium hexamethyldisilazide (LiHMDS) was used as the base in this reaction since lithium diisopropylamide (LDA) tended to react with the acid chloride. The addition of the keto ester **15** to 3-methylbut-3-en-2-one was found to be sensitive to the reaction conditions. The major product was identified as the required adduct **16**, which was isolated by recrystallisation of the crude mixture of products. However, chromatography of the reaction products gave the open-chain diketone **17** as a mixture of diastereoisomers in addition to the required product, and the use of an acidic work-up gave a third product identified as the cyclohexenone **18**. By avoiding the use of acidic conditions during isolation of the product, the required hydroxycyclohexanone **16** was isolated by crystallisation of the crude product mixture in yields of

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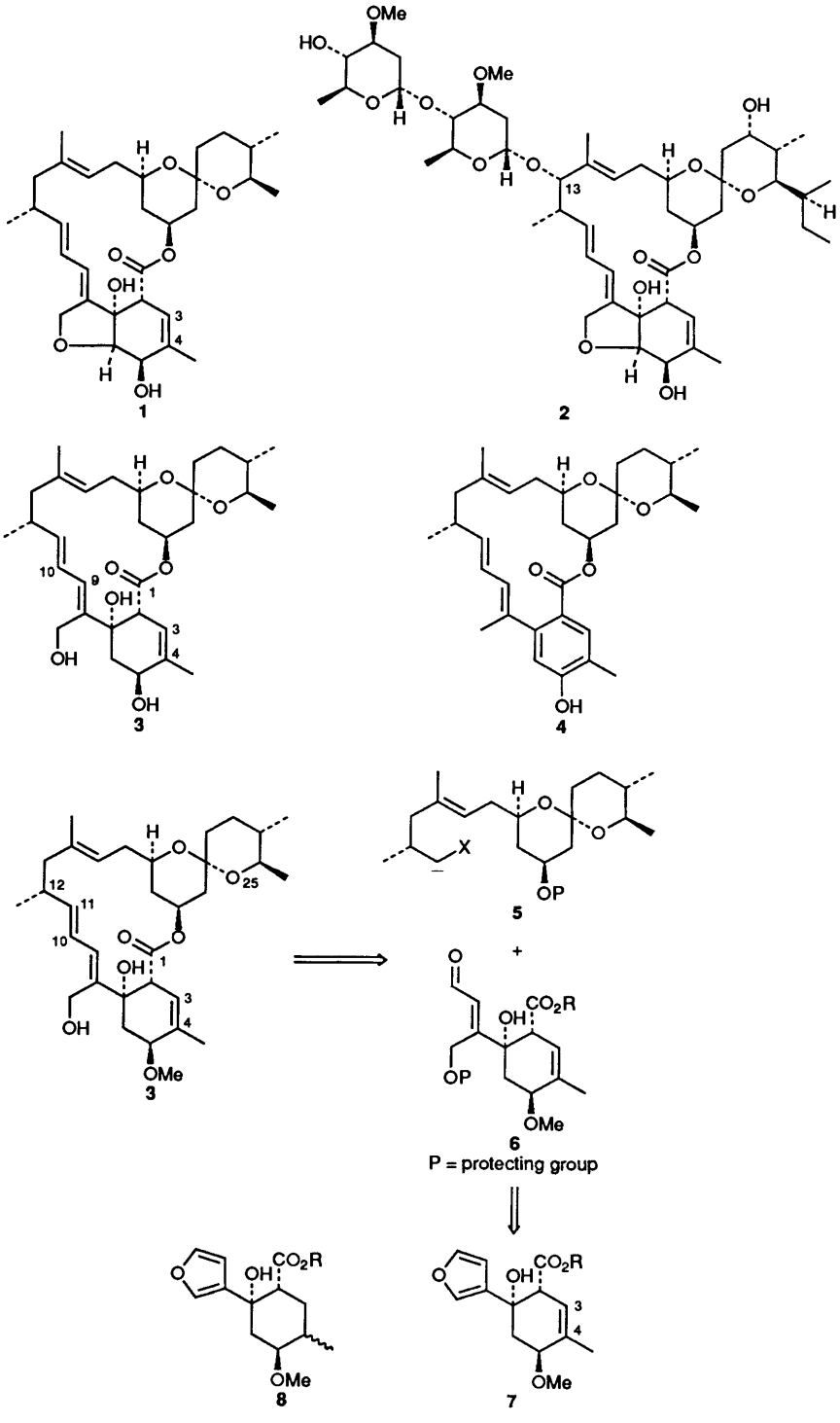
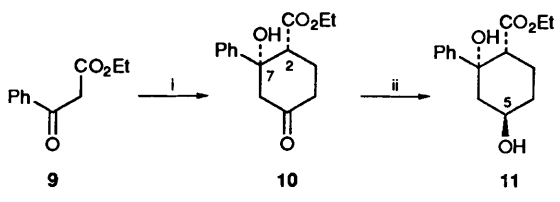
‡ The numbering system used in this discussion relates to that used for the milbemycins and avermectins. IUPAC numbering is used in the Experimental section.

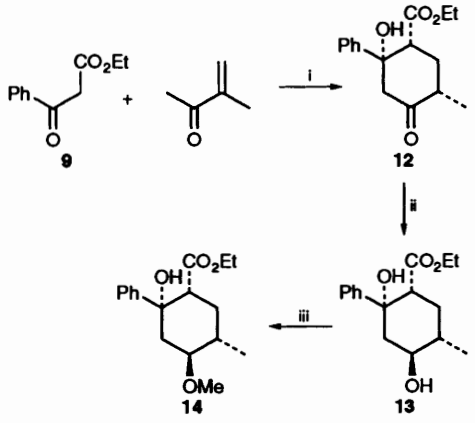




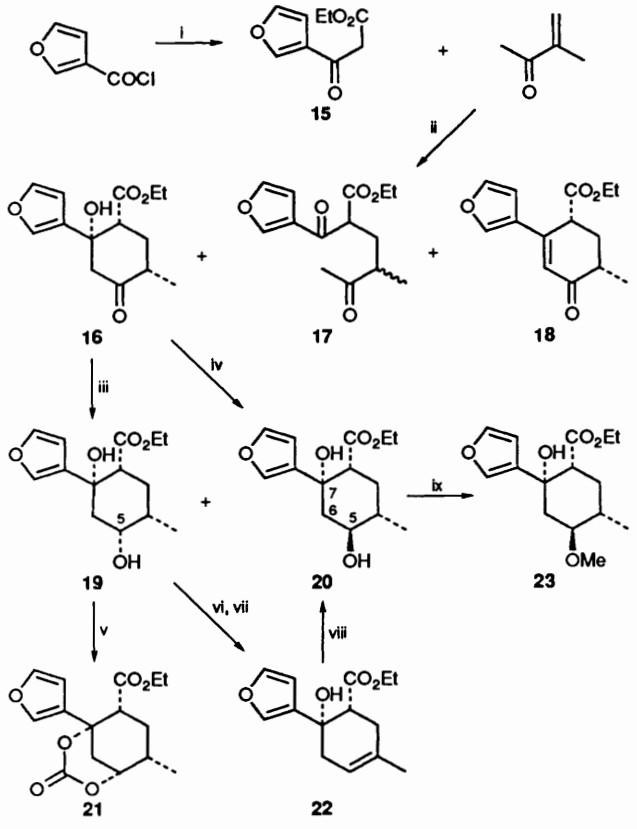
Reagents: i, but-3-en-2-one, NaOH; ii, $NaBH(OAc)_3$.

up to 70%. The structures of the adducts **12** and **16** were established by spectroscopic methods, and the stereochemistry of compound **16** was eventually confirmed by an X-ray study (see below).

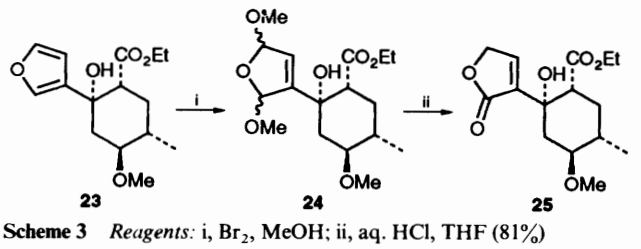
The reduction of the hydroxycyclohexanone **16** was studied using a range of reducing agents. With sodium borohydride in ethanol, two products were obtained in yields of 66 and 29%. The major product was identified as the diaxial diol **19** on the basis of extensive NMR studies and by conversion into the cyclic carbonate **21**, and the minor product was identified as the required 5β-isomer **20** by NMR spectroscopy. Of interest here was the presence of a four-bond W-coupling of 2.6 Hz between the 7-OH and 6-Hax. The diaxial diol **19** was the major product from reduction of the ketone **16** using sodium cyanoborohydride, lithium butylborohydride, or diisobutylaluminium hydride (DIBAL-H), and was the only product isolated using lithium tri-*sec*-butylborohydride (88%). The β-face of the ketone would appear to be the more accessible, with the α-face



Scheme 1 *Reagents:* i, NaOH, EtOH (62%); ii, $NaBH(OAc)_3$ (93%); iii, $Me_3O^+ BF_4^-$, K_2CO_3 (68%).

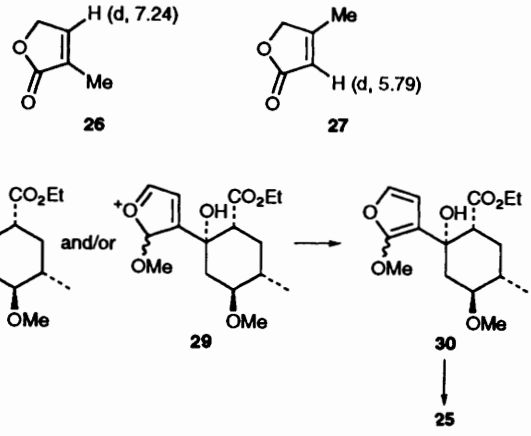


Scheme 2 *Reagents:* i, $LiN(SiMe_3)_2$, $MeCO_2Et$ (93%); ii, NaOH, EtOH (**16**, 56%); iii, $NaBH_4$, EtOH (**19**, 66%; **20**, 29%); $LiBHBu^s_3$ (**19**, 88%); iv, $NaBH(OAc)_3$ (**20**, 98%); v, $CO(imid)_2$ (68%); vi, methanesulfonyl chloride, pyridine (88%); vii, DBU (97%); viii, $BH_3{\cdot}Me_2S$; then H_2O_2, NaOH (43%); ix, $Me_3O^+ BF_4^-$ (72%).



Scheme 3 *Reagents:* i, Br_2, MeOH; ii, aq. HCl, THF (81%)

being shielded by the axial 7-OH. However as in the phenyl series, the stereoselectivity of reduction was reversed using intramolecular delivery[12] of sodium acetoxyborohydride by the 7-OH group giving the 5β-alcohol **20** (98%).



As an alternative route to the alcohol **20**, the diaxial diol **19** was converted into the alkene **22** by mesylation and elimination, and the alkene was hydroborated using borane–dimethyl sulfide complex. This gave the diol **20** (43%) together with a minor side-product which was not identified.

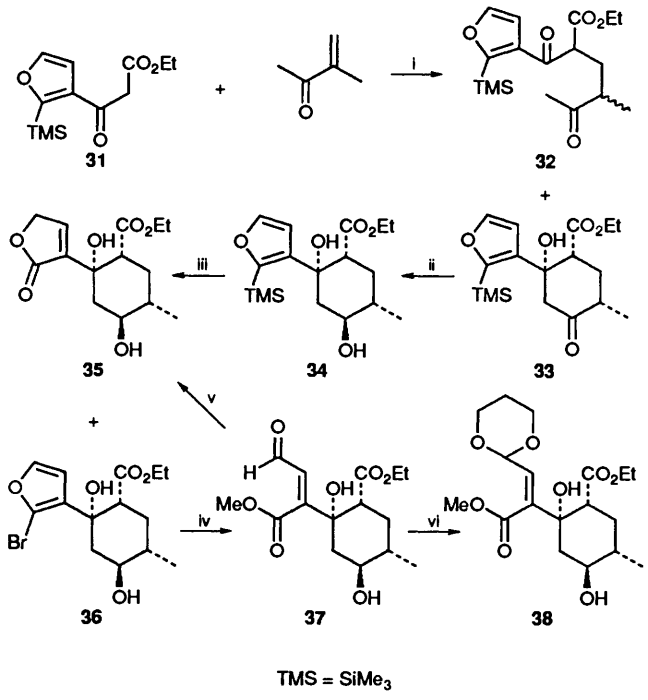
Selective monomethylation of the diol **20** was carried out using the trimethyloxonium tetrafluoroborate procedure to give the methyl ether **23** (72%). Methyl ether **23** corresponds to the primary synthetic target **8**, and so the synthesis of compound **23** completed the first phase of the proposed programme.

Modification of the Furan Ring.—The next phase of the synthesis involved the conversion of the furan **23** into a protected hydroxy aldehyde corresponding to 3,4-dihydro-**6**, and its incorporation into a synthesis of an analogue of the conjugated diene fragment of the milbemycins. A crucial aspect of this phase of the work was the discrimination between the 2- and 5-position of the furan.

Preliminary studies into the oxidation of the furan **23** with *m*-chloroperbenzoic acid (MCPBA), *tert*-butyl hydroperoxide in the presence of a vanadium catalyst,[13] or *N*-bromosuccinimide (NBS) in aqueous 1,4-dioxane, gave complex mixtures of products that were difficult to characterise. However, addition of bromine in methanol gave a mixture of the 2,5-dimethoxydihydrofurans **24**, which was hydrolysed using aqueous hydrochloric acid in tetrahydrofuran (THF) to give the butenolide **25** as a single regioisomer (Scheme 3).[14] The structure of the butenolide was established by comparison of the chemical shift of its vinyl proton (δ 7.5) with those of 3- and 4-methylfuran-2-(5*H*)-one **26** and **27** (δ 7.24 and 5.79, respectively).[15]

The excellent regioselectivity observed in this hydrolysis was somewhat unexpected and is consistent with the selective participation of the oxonium ion **29**. Loss of a proton from species **29** would give the 2-methoxyfuran **30**, which would hydrolyse rapidly to the butenolide **25**. It may be that the 7-OH displaces the methanol from the dimethoxydihydrofuran to give intermediate **29** *via* the epoxide **28**. Alternatively, perhaps the oxonium ion **29** is formed selectively because of stabilisation by the hydroxyalkyl substituent on the furan ring.

An alternative synthesis of the butenolide **25** was investigated which involved regioselective oxidation of a 2-(trimethylsilyl)-furan.[16] Ethyl 3-oxo-3-(2-trimethylsilyl-3-furyl)propanoate **31** was prepared by condensation of the acid chloride of 2-trimethylsilyl-3-furoic acid with ethyl acetate, and was treated with 3-methylbut-3-en-2-one and base to give the hydroxycyclohexanone **33** together with the open-chain diketone **32** (Scheme 4). These appeared to be in equilibrium, the yields of the hydroxycyclohexanone **33** being improved by repeated crystallisation of the crude product (60–70%). Reduction of the hydroxycyclohexanone using sodium triacetoxyborohydride

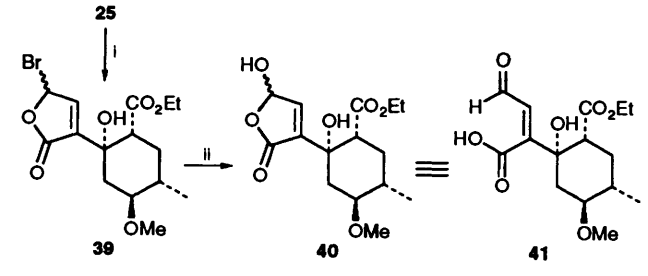


Scheme 4 *Reagents:* i, NaOH, EtOH (**33**, 66%); ii, $NaBH(OAc)_3$ (78%); iii, Br_2, MeOH; then aq. HCl, THF (**35**, 54%; **36**, 31%); iv, Br_2, MeOH; then TFA, acetone (68%); v, $NaBH_4$; vi, $HO[CH_2]_3OH$, $CuSO_4$ (50%).

gave the dihydroxycyclohexanecarboxylate **34** exclusively (78%).

Oxidation of the trimethylsilylfuran **34** using peracetic acid gave only modest yields of the butenolide **35**, and treatment of compound **34** with bromine in methanol gave a mixture of products which, on hydrolysis using aq. hydrochloric acid in THF, gave the butenolide **35** (54%) and the bromofuran **36** (30%). The latter product was useful in that it was converted into the aldehyde **37** by further oxidation using bromine in methanol followed by hydrolysis in aqueous acid. This procedure gave the aldehyde **37** in 68% yield based on the bromofuran **36**. Reaction of the aldehyde with sodium cyanoborohydride gave the butenolide **35** and treatment with propane-1,3-diol gave the acetal **38**. However, as a route to the butenolide **35**, this chemistry of the trimethylsilylfuran **34** didn't compare with the bromination and hydrolysis of the parent furan **23**.*

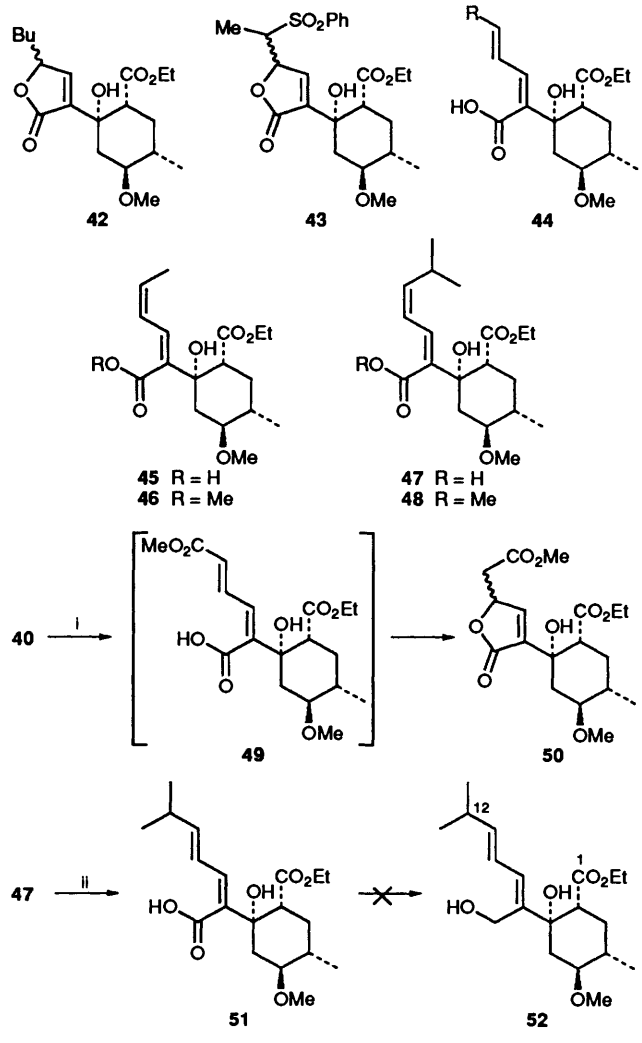
Bromination of the butenolide **25** using NBS gave the 5-bromobutenolide **39**, which gave an excellent yield of the 5-hydroxybutenolide **40** on mild acid hydrolysis (Scheme 5).[19]



Scheme 5 *Reagents:* i, *N*-bromosuccinimide; ii, aq. acetone (75% overall).

Under basic conditions, 5-hydroxybutenolides are known to equilibrate with ring-opened aldehyde-carboxylates. The hydroxybutenolide **40** is therefore synthetically equivalent to the aldehyde-carboxylic acid **41** and was expected to condense with *C*-nucleophiles to provide the conjugated diene fragment of the milbemycins.

Synthesis of Conjugated Dienes.—The next phase of the synthesis involved the conversion of the hydroxybutenolide into an analogue of the C(1)–C(12) fragment of a 3,4-dihydromilbemycin incorporating the (8*E*,10*E*)-diene unit. The addition of an excess of butyllithium or lithiated ethyl phenyl sulfone to the hydroxybutenolide **40** gave the 5-substituted butenolides **42** and **43** as mixtures of epimers,[20] but attempts to convert these into the dienyl acids **44** (R=Pr, Me) by base-induced or reductive elimination were unsuccessful. The hydroxybutenolide **40** was condensed with ethyl- and 2-methyl-propyl-triphenylphosphorane but gave predominantly the (*Z*,*Z*)-dienes **45** and **47**, which were characterised as their esters **46** and **48**, rather than the (*Z*,*E*)-isomers required as models for a milbemycin synthesis. Moreover, using methoxycarbonyl-methylenetriphenylphosphorane,[21] only the lactone **50** was isolated, formed perhaps by *in situ* cyclisation of the initially formed diene **49**.



Reagents: i, $Ph_3P{=}CHCO_2Me$; ii, I_2.

Attempts to reverse the (*Z*)-selectivity of the Wittig reactions by using the Schlosser modification were not promising.[22] However, it was found that clean isomerisation occurred on treatment of the Wittig products with a trace of iodine in benzene in sunlight. Thus the hydroxybutenolide **40** was

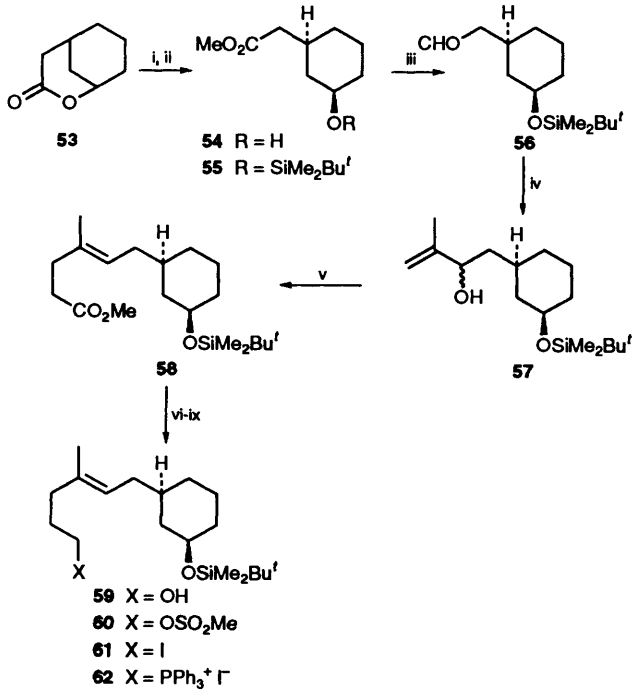
* The direct conversion of the silylfuran **34** into the hydroxybutenolide using singlet oxygen[17] was developed subsequently.[18]

condensed with 2-methylpropylidenetriphenylphosphorane and the product was isomerised using a trace of iodine to give the (*Z*,*E*)-dienyl acid **51** in > 70% overall yield.

To complete a synthesis of an analogue of the C(1)–C(12) fragment of a 3,4-dihydro-β-milbemycin, it remained to reduce the dienyl acid **51** to the primary alcohol **52**. However, all attempts to reduce the acid or a derivative of the acid, *e.g.* a mixed anhydride, were unsuccessful. Either unchanged starting material or complex mixtures of products were obtained.

Although disappointing, it was thought that this difficulty was due to a limitation of the model rather than the synthetic strategy. The primary alcohol group in compound **52** can easily approach the C(1) carboxy-group carbon to form a six-membered lactone. A stereoelectronically favoured *anti*-dehydration would then provide a conjugated trienyl lactone, which would be reduced further under the reaction conditions to give a complex mixture of products. As models showed that formation of a six-membered lactone is not possible for the milbemycins themselves due to conformational restrictions imposed by the macrocycle, it was decided to attempt to synthesize a *macrocyclic* milbemycin analogue to test the final steps of the synthetic strategy.

Synthesis of a Macrocyclic β-*Milbemycin Analogue.*—The phosphonium salt **62** was identified as a useful intermediate for the synthesis of a macrocyclic milbemycin analogue since it should lead to a 16-membered lactone with similar steric constraints to the milbemycins. Methanolysis of the bicyclic lactone **53**[23] gave the hydroxy ester **54**, protected as its silyl ether **55** (Scheme 6). The ester was reduced selectively to the



Scheme 6 *Reagents:* i, NaOMe, MeOH; ii, Bu^t-Me$_2$SiCl, imidazole (61% of **55** from **53**); iii, DIBAL-H (81%); iv, MeC(MgBr)=CH$_2$ (87%); v, MeC(OMe)$_3$, EtCO$_2$H, xylene, heat, 24 h; vi, LiAlH$_4$ (82% of **59** from **57**); vii, methanesulfonyl chloride, Et$_3$N; viii, NaI, acetone (87% from **59**); ix, Ph$_3$P, DMF.

aldehyde **56**, which gave a mixture of the epimeric alcohols **57** on addition of prop-2-en-2-ylmagnesium bromide. A Claisen rearrangement of these alcohols gave the unsaturated ester **58**, which was reduced to provide the primary alcohol **59**. This was converted into the phosphonium salt **62** *via* the mesylester **60** and the iodide **61**.

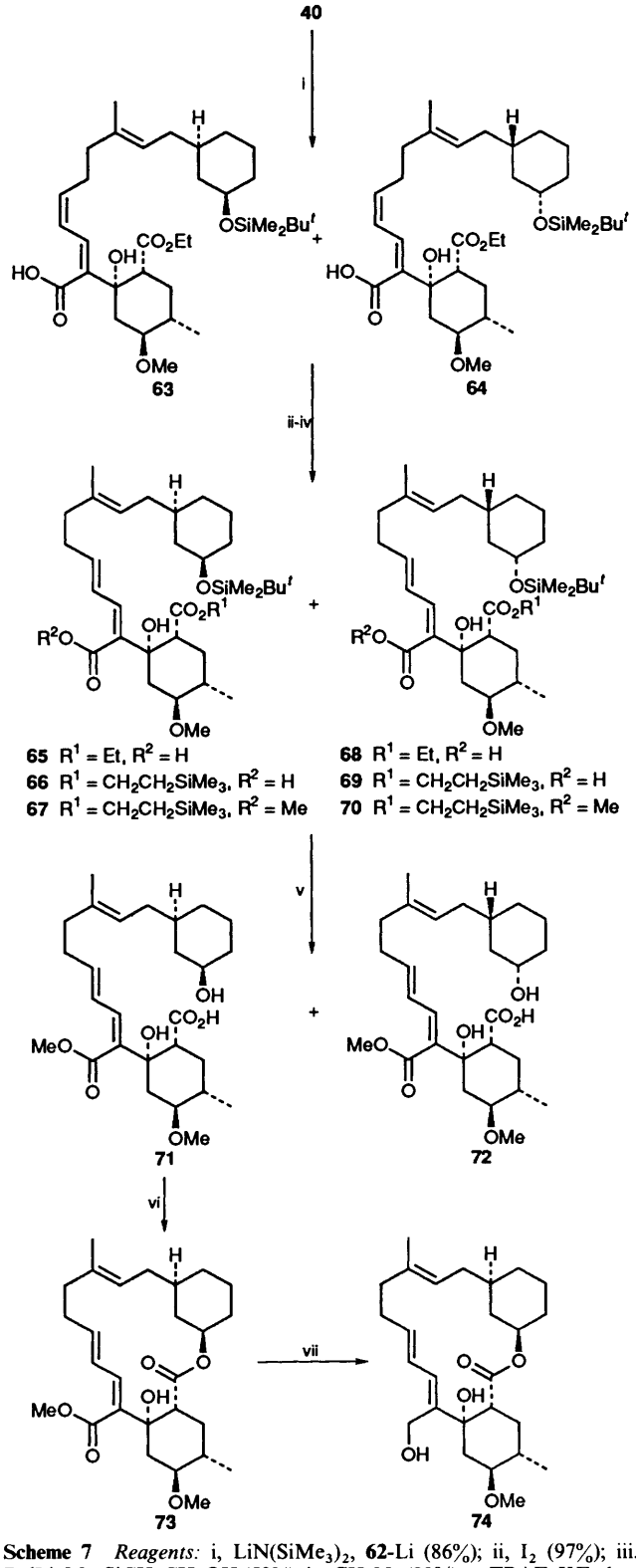
The Wittig condensation between the racemic phosphonium salt **62** and the racemic hydroxybutenolide **40** was carried out using LiHMDS as base. An excess of the phosphonium salt was treated with two mole equivalents of the base, and the solution of ylide so formed was added at −78 °C to a solution of the hydroxybutenolide which had previously been treated with two mole equivalents of LiHMDS. This procedure gave an 80% yield of a mixture of products identified as the diastereoisomeric dienyl acids **63**, **64**, **65** and **68**, mainly as their 10,11-(*Z*)-isomers **63** and **64** (Scheme 7). These diastereoisomers could not be separated, and were not distinguishable by ^{1}H NMR spectroscopy, but it was assumed that both were present since no discrimination was expected during the condensation of the racemic hydroxybutenolide with the racemic phosphorane. Treatment of the Wittig products **63** and **64** with a trace of iodine in benzene induced clean (*Z*)–(*E*)-isomerisation of their 10,11-double bonds, and gave the (*Z*,*E*)-acids **65** and **68**.

It was now necessary to reverse the functionality of the ester at C(1) and the acid at C(10′) before a macrolide analogous to a milbemycin could be formed. To this end, the mixture of acids **65** and **68** was treated with 2-(trimethylsilyl)ethanol under anhydrous, basic conditions to give the 2-trimethylsilyl esters **66** and **69** *via* ester exchange at C(1); the C(10′) acids were unchanged under these conditions. Esterification with diazomethane then gave the diesters **67** and **70**. These were deprotected using fluoride and acid to give the dihydroxy acids **71** and **72** which were distinguishable by ^{1}H NMR spectroscopy for the first time in the synthesis, perhaps because of long-range hydrogen bonding.

Treatment of the mixture of dihydroxy acids **71** and **72** with chloro-*N*-methylpyridinium iodide[24] and triethylamine under high-dilution conditions induced cyclisation of one of the diastereoisomers to give a single macrocyclic product. This was shown to be the required diastereoisomer **73** by X-ray crystallography,[9] and had been formed by selective cyclisation of the hydroxy acid **71**. No product from cyclisation of the 'unnatural' isomer **72** was isolated, and it would appear that compound **72** decomposed to baseline material under the cyclisation conditions. Models indicate that cyclisation of the dihydroxy acid **72** is impeded by the cyclohexane ring whereas for cyclisation of the 'natural' diastereoisomer **71** the cyclohexane ring facilitates macrocyclisation by restricting the conformations available to the cyclisation precursor.

Having prepared the macrocyclic methyl ester **73**, we examined the selective reduction of the ester. It was found that reduction using lithium bis-(2-methoxyethoxy)aluminium hydride (REDAL-H) was very effective, and gave the alcohol **74** in 85% yield so completing the synthesis of a macrocyclic analogue of milbemycin β_1 **3**.

Conclusions.—This synthesis of the macrocyclic alcohol **74** established the viability of our strategy for a convergent synthesis of β-milbemycins. It remained to develop a procedure for the regioselective introduction of the 3,4-double bond, and for the synthesis of the spiroacetal-containing fragment. Studies of these aspects,[18,25,26] and a synthesis of a non-aromatic β-milbemycin using this strategy,[7] will be outlined in future papers together with the application of this approach to the synthesis of α-milbemycins.[27,28] Of interest in the present work is the stereoselective formation and reduction of the hydroxycyclohexanones **16** and **33**, the regioselective hydrolysis of the dimethoxydihydrofuran **24**, the synthesis and isomerisation of the conjugated diene fragment of the milbemycins, the selective macrocyclisation of the hydroxy acid **71** which has the same relative configuration as the natural products, and the efficient reduction of the macrolide ester **73**.



Scheme 7 *Reagents:* i, $LiN(SiMe_3)_2$, **62**-Li (86%); ii, I_2 (97%); iii, Bu^{t}Li, $Me_3SiCH_2CH_2OH$ (53%); iv, CH_2N_2 (99%); v, TBAF, KF; then hydrochloric acid (93%); vi, 2-chloro-*N*-methylpyridinium iodide (44% based on **71**); vii, $LiAlH_2(OCH_2CH_2OMe)_2$ (85%).

Experimental

All non-aqueous reactions were performed under argon. ^1H NMR spectra were recorded on a Bruker WA 300 or a Bruker WH 500 spectrometer. *J*-Values are given in Hz. IR spectra were measured on a Perkin-Elmer 257 or on a Pye Unicam SP3-200 spectrometer as evaporated films unless otherwise stated. Mass spectra were recorded on a VG micromass ZAB 16F mass spectrometer using electron impact (EI) or chemical ionisation (CI) modes. M.p.s were determined on a Buchi 510 apparatus.

All solvents were dried and distilled before use. Light petroleum refers to the fraction which distils at 40–60 °C, and ether to diethyl ether. Chromatography refers to flash chromatography on Merck silica (40–63 mm^3; 230–400 mesh). 3-Furoyl chloride was prepared by heating of a solution of 3-furoic acid in thionyl dichloride under reflux for 1 h. Concentration under reduced pressure gave 3-furoyl chloride, which was used without further purification.

(1RS,2SR,5SR)-*Ethyl 2-Hydroxy-5-methyl-4-oxo-2-phenylcyclohexanecarboxylate* **12**.—3-Methylbut-3-en-2-one[11] (1 g, 12 mmol) was blown as a vapour in nitrogen over a period of 12 h into a solution of ethyl 3-oxo-3-phenylpropanoate[9] (1.2 cm^3, 6.9 mmol) and sodium hydroxide (0.1 g, 2.5 mmol) in ethanol (10 cm^3). The mixture was cooled to −22 °C, and the crude product was isolated by filtration. Recrystallisation from ethanol gave the *title compound* **12** (1.19 g, 62%) as plates, m.p. 90–92 °C (Found: C, 69.45; H, 7.05. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490, 1720, 1370, 1340, 1300 and 1180; δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 7, CH_2*Me*), 1.09 (3 H, d, *J* 6, CH*Me*), 2.1 (1 H, q, *J* 12.5, 6-H^{ax}), 2.2–2.3 (1 H, m, 6-H^{eq}), 2.4–2.55 (1 H, m, 5-H), 2.55 (2 H, s, 3-H_2), 3.47 (1 H, dd, *J* 12.5 and 4, 1-H), 3.8–3.99 (2 H, m, OCH_2Me), 4.16 (1 H, s, OH) and 7.1–7.3 (5 H, m, ArH); *m/z* (EI) 276 (M^+, 4%) and 77 (100).

(1RS,2SR,4SR,5SR)-*Ethyl 2,4-Dihydroxy-5-methyl-2-phenylcyclohexanecarboxylate* **13**.—Sodium borohydride (0.29 g, 8 mmol) was added to rapidly stirred acetic acid (20 cm^3) at such a rate that the temperature did not exceed 20 °C. After being stirred for 30 min, the solution was added to the ketone **12** (1.1 g, 4 mmol), and the reaction mixture was stirred for 30 min before being concentrated under reduced pressure, and the residue was dissolved in ether (100 cm^3). The ethereal solution was washed with aq. sodium hydroxide (1 mol dm^{-3}; 2 × 50 cm^3), dried over anhydrous potassium carbonate, and concentrated under reduced pressure to leave the *title compound* **13** (1.03 g, 93%), which was recrystallised from hexane–ether, m.p. 128 °C (Found: C, 69.05; H, 7.9. $C_{16}H_{22}O_4$ requires C, 69.05; H, 7.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3620, 3480, 3005, 1710, 1375, 1180, 1060 and 1030; δ_H(300 MHz; C_6D_6) 0.65 (3 H, t, *J* 7.5, CH_2*Me*), 1.09 (3 H, d, *J* 6, CH*Me*), 1.19 (1 H, br s, 4-OH), 1.32 (1 H, m, 5-H), 1.44 (1 H, ddd, *J* 12, 10 and 2, 3-H^{ax}), 1.68 (1 H, dt, *J* 12.5 and 3.5, 6-H^{eq}), 1.88 (1 H, q, *J* 12.5, 6-H^{ax}), 2.17 (1 H, dd, *J* 12 and 4.5, 3-H^{eq}), 2.92 (1 H, dd, *J* 12.5 and 3.5, 1-H), 3.66 (2 H, q, *J* 7.5, OCH_2Me), 3.78 (1 H, m, 4-H), 4.69 (1 H, d, *J* 2,2-OH) and 7.1–7.6 (5 H, m, ArH); *m/z* (EI) 278 (M^+, 9%) and 105 (100).

(1RS,2SR,4SR,5SR)-*Ethyl 2-Hydroxy-4-methoxy-5-methyl-2-phenylcyclohexanecarboxylate* **14**.—A solution of the diol **13** (190 mg, 0.68 mmol) in dichloromethane (5 cm^3) was added to a stirred suspension of trimethyloxonium tetrafluoroborate (950 mg, 0.64 mmol) and anhydrous potassium carbonate (430 mg) in dichloromethane (5 cm^3) at −22 °C. After being stirred for 18 h, the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (ether–light petroleum) gave unchanged starting material **13** (53 mg, 28% recovery) and the *title compound* **14** (135 mg, 68%) as needles, m.p. 56–58 °C (from hexane–ether) (Found: C, 69.7; H, 8.35. $C_{17}H_{24}O_4$ requires C, 69.85; H, 8.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480, 1710, 1375, 1180 and 1090; δ_H(300 MHz; C_6D_6) 0.63 (3 H, t, *J* 7, OCH_2*Me*), 1.11 (3 H, d, *J* 6.5, CH*Me*), 1.37 (1 H, ddd, *J* 13, 10.5 and 3, 3-H^{ax}), 1.42–1.67 (1 H, m, 5-H), 1.71 (1 H, dt, *J* 13 and 3.5, 6-H^{eq}), 1.93 (1 H, q, *J* 13, 6-H^{ax}), 2.41 (1 H, dd, *J* 13 and 4, 3-H^{eq}), 2.92 (1 H, dd, *J* 13 and 4, 1-H), 3.1 (3 H, s, OMe), 3.42 (1 H, td, *J* 10.5 and 4, 4-H), 3.6 (2 H,

q, *J* 7, OCH_2Me), 4.69 (1 H, d, *J* 3, OH) and 7.02–7.48 (5 H, m, ArH); *m/z* (EI) 292 (M^+, 2%) and 163 (100).

Ethyl 3-(3'-*Furyl*)-3-*oxopropanoate* **15**.—Butyllithium (68 cm^3; 1.6 mol dm^{-3} in hexane) was added to a solution of hexamethyldisilazane (22.2 cm^3, 105 mmol) in THF (130 cm^3) at 0 °C. After 30 min, the solution was cooled to −78 °C, ethyl acetate (5.2 cm^3, 53 mmol) was added over a 10 min period, and the mixture was stirred for 1.5 h. 3-Furoyl chloride [from 3-furoic acid (5.56 g, 49.6 mmol) in THF (50 cm^3)] was added slowly, and the mixture was stirred for 30 min. Saturated aq. ammonium chloride (50 cm^3) was added, and the mixture was allowed to warm to room temperature. Hydrochloric acid (80 cm^3; 3 mol dm^{-3}) was added, and the organic products were extracted into ether. Concentration of the extracts and distillation of the residue gave the *title compound* **15** (8.4 g, 93% from the acid), b.p. 98–105 °C (0.5 mmHg) (Found: C, 59.45; H, 5.55. $C_9H_{10}O_4$ requires C, 59.35; H, 5.55%); ν_{max}/cm^{-1} 3140, 1740, 1680, 1560 and 1510; δ_H(300 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7, OCH_2Me), 3.76 (2 H, s, 2-H_2), 4.20 (2 H, q, *J* 7, OCH_2Me), 6.79 (1 H, d, *J* 3, 4'-H), 7.46 (1 H, m, 5'-H) and 8.08 (1 H, dd, *J* 1.5 and 0.5, 2'-H); *m/z* (EI) 182 (M^+, 14%) and 95 (100). Traces of the enol tautomer (~5%) were apparent from the ^1H NMR spectrum; δ_H 5.35 (2-H).

(1RS,2SR,5SR)-*Ethyl* 2-(3'-*Furyl*)-2-*hydroxy*-5-*methyl*-4-*oxocyclohexanecarboxylate* **16**.—A solution of 3-methylbut-3-en-2-one[11] (3.1 g, 37 mmol) in ethanol (20 cm^3) was added over a period of 30 min to a solution of the ketoester **15** (6 g, 33 mmol) in anhydrous ethanol (80 cm^3) containing aq. sodium hydroxide (2.5 cm^3; 1 mol dm^{-3}), and the mixture was stirred for 17 h at ambient temperature before being concentrated under reduced pressure. The residue was taken up in ether (250 cm^3), and the ethereal solution washed with brine containing sodium hydroxide (2 × 100 cm^3, 0.05 mol dm^{-3} in sodium hydroxide). After drying (K_2CO_3), the organic phase was concentrated under reduced pressure. Recrystallisation of the residue from hexane–ether gave the *title compound* **16** (4.92 g, 56%) as plates, m.p. 60–62 °C (Found: C, 63.25; H, 6.7. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490, 1720, 1500, 1375, 1345, 1180 and 1030; δ_H(300 MHz; $CDCl_3$) 1.13 (3 H, d, *J* 6.5, CH*Me*), 1.17 (3 H, t, *J* 7.1, CH_2Me), 2.11 (1 H, q, *J* 13, 6-H^{ax}), 2.22 (1 H, ddd, *J* 13, 6 and 4.5, 6-H^{eq}), 2.46–2.55 (1 H, m, 5-H), 2.53 (1 H, dd, *J* 14.5 and 2.5, 3-H^{ax}), 2.69 (1 H, d, *J* 14.5, 3-H^{eq}), 3.24 (1 H, dd, *J* 13 and 4.5, 1-H), 4.05–4.14 (2 H, m, CH_2Me), 4.26 (1 H, d, *J* 2.5, OH), 6.36 (1 H, dd, *J* 1.5 and 1, 4'-H) and 7.35–7.39 (2 H, m, 2'- and 5'-H); *m/z* (EI) 266 (M^+, 13%), 249 (63) and 95 (100).

Concentration of the mother liquor and chromatography of the residue (ether–light petroleum) gave more of the cyclohexanone **16** (1.4 g, 16%) and a second product, identified as a mixture of diastereoisomers of the open-chain diketone **17** (1.1 g, 13%); δ_H(60 MHz; $CDCl_3$) 1.1–1.4 (6 H, m), 1.8–2.8 (6 H, m), 3.9 (1 H, m), 4.15 (2 H, q, *J* 7, CH_2Me), 6.8 (1 H, s), 7.4 (1 H, s), 8.1 (0.4 H, s) and 8.25 (0.6 H, s).

Reduction of the 4-*Oxocyclohexanecarboxylate* **16**.—*With sodium borohydride.* Sodium borohydride (150 mg, 4.2 mmol) was added to a solution of the ketone **16** (500 mg, 1.9 mmol) in ethanol (10 cm^3). After being stirred for 30 min, the reaction mixture was diluted with saturated aq. ammonium chloride (10 cm^3) and extracted into ether. The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (ether–light petroleum) gave two fractions. The major component was identified as (1RS,2SR,4RS,5SR)-*ethyl* 2-(3'-*furyl*)-2,4-*dihydroxy*-5-*methylcyclohexanecarboxylate* **19** (330 mg, 66%) as an oil (Found: M^+, 268.1312. $C_{14}H_{20}O_5$ requires M, 268.1311); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1710, 1500, 1180, 1095, 1030 and 1000; δ_H(300 MHz; $CDCl_3$) 1.01 (3 H, d, *J* 6.5, CH*Me*), 1.09 (3 H, t, *J* 7, CH_2Me), 1.5–1.7 (3 H, m), 1.90 (1 H, q, *J* 13.5, 6-H^{ax}), 2.23 (1 H, dd, *J* 15 and 3, 3-H^{eq}), 2.72 (1 H, dd, *J* 13.5 and 3, 1-H), 3.69 (1 H, narrow m, 4-H), 3.9–4.1 (2 H, m, CH_2Me), 4.09 (1 H, br d, *J* 8.7, 4-OH), 4.96 (1 H, d, *J* 2.5, 2-OH), 6.23 (1 H, dd, *J* 1.5 and 1, 4'-H) and 7.2–7.3 (2 H, m, ArH); *m/z* (EI) 268 (M^+, 12%) and 95 (100).

The minor component was identified as (1RS,2SR,4SR,5SR)-*ethyl* 2-(3'-*furyl*)-2,4-*dihydroxy*-5-*methylcyclohexanecarboxylate* **20** (146 mg, 29%) as a solid, recrystallised from hexane–ether as needles, m.p. 96–97 °C (Found: C, 62.65; H, 7.45. $C_{14}H_{20}O_5$ requires C, 62.65; H, 7.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3620, 3470, 1710, 1500, 1375, 1260, 1180 and 1030; δ_H(300 MHz; $CDCl_3$) 1.04 (3 H, d, *J* 6.5, CH*Me*), 1.08 (3 H, t, *J* 7, CH_2Me), 1.3–1.5 (2 H, m), 1.6–1.8 (3 H, m), 2.18 (1 H, dd, *J* 13 and 4.5, 3-H^{eq}), 2.68 (1 H, dd, *J* 12.5 and 5, 1-H), 3.65 (1 H, td, *J* 10.5 and 4.5, 4-H), 3.9–4.1 (2 H, m, CH_2Me), 4.36 (1 H, br s, 2-OH), 6.25 (1 H, t, *J* 1.5, 4'-H) and 7.26 (2 H, d, *J* 1.5, ArH); *m/z* (EI) 268 (M^+, 13%) and 95 (100).

*With lithium tri-*sec*-butylborohydride.* Lithium tri-*sec*-butylborohydride (0.27 cm^3; 1 mol dm^{-3} in THF) was added to a solution of the ketone **16** (73 mg, 0.27 mmol) in THF (5 cm^3) at −78 °C, and the mixture was stirred for 4.5 h. Aq. sodium hydroxide (3 mol dm^{-3}; 1 cm^3) was added, and the mixture was allowed to warm to room temperature. Aq. hydrogen peroxide (0.6 cm^3; 30%) was added and the mixture was stirred for 15 min before the addition of saturated ethanolic hydrogen chloride (1 cm^3). The mixture was diluted with ether and the organic phase was separated, washed with hydrochloric acid, and dried ($MgSO_4$). Concentration under reduced pressure gave the diol **19** (65 mg, 88%).

With sodium triacetoxyborohydride. Following the procedure outlined above, the ketone **16** (7.45 g, 28 mmol) gave the diol **20** (7.35 g, 98%), shown to be free of its epimer **19** by TLC and NMR spectroscopy.

(1RS,5SR,6RS,8SR)-*Ethyl* 5-(3'-*Furyl*)-8-*methyl*-3-*oxo*-2,4-*dioxabicyclo*[3.3.1]*nonane*-6-*carboxylate* **21**.—A solution of 1,1'-carbonyldiimidazole (50 mg, 0.31 mmol) in THF (1 cm^3) was added to a mixture of diol **19** (65.7 mg, 0.25 mmol) and a trace of sodium hydride in THF (2 cm^3), and the mixture was stirred for 15 min before being diluted with ether (30 cm^3), washed with dil. hydrochloric acid (30 cm^3; 1 mol dm^{-3}), and dried ($MgSO_4$). Concentration under reduced pressure gave a residue, which was chromatographed to give the *title compound* **21** (50 mg, 68%) as needles on recrystallisation from hexane–ether, m.p. 90 °C (Found: C, 61.2; H, 6.1. $C_{15}H_{18}O_6$ requires C, 61.5; H, 6.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1745, 1390, 1380, 1355, 1302, 1180, 1170, 1155, 1125, 1110, 1050 and 1035; δ_H(300 MHz; $CDCl_3$) 1.06 (3 H, t, *J* 7, CH_2Me), 1.19 (3 H, d, *J* 6, CH*Me*), 1.9–2.0 (3 H, m), 2.16 (1 H, dd, *J* 14.5 and 1.5, 9-H^{ax}), 2.38 (1 H, dd, *J* 14.5 and 4.5, 9-H^{eq}), 2.9 (1 H, m, 6-H), 3.9–4.1 (2 H, m, CH_2Me) 4.55 (1 H, m, 1-H), 6.36 (1 H, dd, *J* 2 and 1, 4'-H), 7.41 (1 H, t, *J* 1.8, ArH) and 7.48 (1 H, dd, *J* 2.1, ArH); *m/z* (EI) 294 (M^+, 8%) and 95 (100).

(1RS,6SR)-*Ethyl* 6-(3-*Furyl*)-6-*hydroxy*-3-*methylcyclohex*-3-*enecarboxylate* **22**.—Methanesulfonyl chloride (0.09 cm^3, 1.1 mmol) was added to a solution of diol **19** (276 mg, 1 mmol) in pyridine (10 cm^3) at 0 °C. After 16 h, the reaction mixture was poured into dil. hydrochloric acid (50 cm^3; 3 mol dm^{-3}). The aqueous mixture was extracted with ether (3 × 50 cm^3), and the extracts were dried ($MgSO_4$), and concentrated under reduced pressure to leave (1RS,2SR,4RS,5SR)-*ethyl* 2-(3-*furyl*)-2-*hydroxy*-5-*methyl*-4-(*methylsulfonyloxy*)*cyclohexanecarboxylate* (310 mg, 88%) as needles on recrystallisation from chloroform–hexane, m.p. 84–85 °C (Found: C, 52.0; H, 6.35; S, 9.1. $C_{15}H_{22}O_7S$ requires C, 52.0; H, 6.4; S, 9.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480, 1710, 1275, 1170, 1030, 975,

920, 900, 890 and 875; δ_H(300 MHz; C_6D_6) 0.76 (3 H, t, *J* 7, CH_2*Me*), 0.95 (3 H, d, *J* 6, CH*Me*), 0.9–1.2 (1 H, m, 5-H), 1.15 (1 H, dt, *J* 14 and 2.5), 1.28 (1 H, dt, *J* 12.5 and 3), 2.08 (1 H, q, *J* 12.5, 6-H^{ax}), 2.3–2.5 (2 H, m), 2.54 (3 H, s, OSO_2Me), 3.6–3.8 (2 H, m, CH_2Me), 4.5–4.6 (1 H, m, 4-H), 4.6 (1 H, d, *J* 2.5, 2-OH) and 6.08, 7.06 and 7.12 (each 1 H, m, ArH); *m/z* (EI) 346 (M^+, 1%) and 95 (100).

A solution of the methanesulfonate (246 mg, 0.71 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.5 cm^3) in THF (10 cm^3) was heated under reflux for 48 h. The reaction mixture was diluted with ether (50 cm^3), washed with dil. hydrochloric acid (50 cm^3; 1 mol dm^{-3}), dried ($MgSO_4$), and concentrated under reduced pressure to leave the *title compound* **22** (174 mg, 97%), recrystallised as fine needles from hexane–ether, m.p. 35 °C (Found: C, 67.25; H, 7.3. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 1710, 1500, 1295, 1180, 1160, 1030 and 900; δ_H(300 MHz; $CDCl_3$) 1.05 (3 H, t, *J* 7.5, CH_2*Me*), 1.67 (3 H, br s, 3-Me), 2.09 (1 H, dd, *J* 17 and 5.5, 2-H^{eq}), 2.26 (2 H, narrow m, 5-H_2), 2.4–2.5 (1 H, m, 2-H^{ax}), 2.88 (1 H, dd, *J* 11.5 and 6, 1-H), 3.9–4.1 (3 H, m), 5.3 (1 H, narrow m, 4-H), 6.24 (1 H, dd, *J* 1.5 and 1, ArH), 7.27 (1 H, t, *J* 2, ArH) and 7.31 (1 H, m, ArH); *m/z* (EI) 250 (M^+, 21%), 182 (88) and 95 (100).

Hydroboration of Alkene **22**.—Borane–dimethyl sulfide complex (0.2 cm^3; 2 mol dm^{-3} in THF) was added to a solution of the alkene **22** (31 mg, 0.125 mmol) in THF (5 cm^3) at 0 °C. After 20 min. aq. hydrogen peroxide (1 cm^3; 30%) was added followed, after a further 5 min, by aq. sodium hydroxide (1 cm^3; 2 mol dm^{-3}). The reaction mixture was diluted with ether (30 cm^3), washed with dil. hydrochloric acid (30 cm^3; 1 mol dm^{-3}), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed to give the diol **20** (14.5 mg, 43%) and a minor product (4 mg) which was not identified.

(1RS,2SR,4SR,5SR)-*Ethyl* 2-(3-*Furyl*)-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylate* **23**.—A mixture of diol **20** (4.5 g, 16.8 mmol), trimethyloxonium tetrafluoroborate (4.5 g, 31 mmol) and anhydrous potassium carbonate (13.5 g) in dichloromethane (100 cm^3) was stirred for 16 h. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was chromatographed to give unchanged diol **20** (0.89, 18% recovery) and the *title compound* **23** (3.4 g, 72%) as fine needles after recrystallisation from hexane–ether, m.p. 60 °C (Found: C, 63.6; H, 7.9. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480, 1710, 1500, 1378, 1180, 1100, 1030 and 870; δ_H(300 MHz; $CDCl_3$) 1.08 (3 H, d, *J* 6.5, CH*Me*), 1.15 (3 H, t, *J* 7, CH_2*Me*), 1.32 (1 H, ddd, *J* 13.5, 11 and 2.5, 3-H^{ax}), 1.4–1.6 (1 H, m, 5-H), 1.7–1.9 (2 H, m, 6-H_2), 2.41 (1 H, dd, *J* 13.5 and 4.5, 3-H^{eq}), 2.7–2.8 (1 H, m, 1-H), 3.23 (1 H, td, *J* 11 and 4.5, 4-H), 3.37 (3 H, s, OMe), 4.0–4.1 (2 H, m, CH_2Me), 4.42 (1 H, d, *J* 2.5, OH), 6.32 (1 H, t, *J* 1.4, ArH) and 7.34 (2 H, d, *J* 1, ArH); *m/z* (EI) 282 (M^+, 11%) and 153 (100).

(1RS,2SR,4SR,5SR)-*Ethyl* 2-(2′,5′-*Dihydro*-2′-*oxo*-3′-*furyl*)-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylate* **25**.—A solution of bromine (2.1 g, 13 mmol) in methanol (20 cm^3) was added to a solution of the furan **23** (3.4 g, 12.1 mmol) and sodium acetate (3 g, 37 mmol) in methanol at 0 °C over a period of 30 min. The mixture was concentrated under reduced pressure and the residue was dissolved in ether (250 cm^3). The ethereal solution was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to leave the dimethoxydihydrofurans **24** (4.75 g) as a mixture of diastereoisomers, used without further purification.

The dimethoxydihydrofuran mixture was dissolved in THF (100 cm^3) and hydrochloric acid (30 cm^3; 3 mol dm^{-3}) was added. After 30 min, sodium chloride (5 g) was added, and the mixture was extracted into ether. The extracts were dried ($MgSO_4$), and concentrated under reduced pressure, and the residue was chromatographed to give the *title compound* **25** (2.9 g, 81%) as needles after recrystallisation from hexane–ether, m.p. 92–94 °C (Found: C, 60.4; H, 7.5. $C_{15}H_{22}O_6$ requires C, 60.4; H, 7.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1755, 1700, 1190, 1100, 1060, 1030 and 1000; δ_H(300 MHz; $CDCl_3$) 1.08 (3 H, d, *J* 6.5, CH*Me*), 1.21 (3 H, t, *J* 7.5, CH_2*Me*), 1.55–1.7 (1 H, m, 5-H), 1.72 (1 H, q, *J* 11.5, 6-H^{ax}), 1.8 (1 H, t, *J* 12.5, 3-H^{ax}), 1.87 (1 H, dt, *J* 12, 4, 6-H^{eq}), 2.07 (1 H, dd, *J* 12.5 and 4, 3-H^{eq}), 3.2 (1 H, m, 4-H), 3.34 (3 H, s, OMe), 3.3–3.4 (1 H, m, 1-H), 4.0–4.17 (2 H, m, OCH_2Me), 4.54 (1 H, br s, OH), 4.75–4.8 (2 H, m, 5′-H_2) and 7.48–7.52 (1 H, m, 4′-H); *m/z* (EI) 299 (M^+ + 1, 100%).

Ethyl 3-*oxo*-3-(2′-*trimethylsilyl*-3′-*furyl*)*propanoate* **31**.—2-Trimethylsilyl-3-furoic acid (13.5 g, 73.4 mmol) was heated under reflux with thionyl dichloride (100 cm^3) for 40 min. The major part of the excess of thionyl dichloride was removed by distillation, and the remainder under reduced pressure, to leave 2-(trimethylsilyl)-3-furoyl chloride which was used without purification.

Butyllithium (96 cm^3; 1.6 mol dm^{-3} in hexane) was added to a solution of hexamethyldisilazane (32.5 cm^3, 154 mmol) in THF (200 cm^3) at 0 °C. After 30 min, the solution was cooled to −78 °C and ethyl acetate (7.2 cm^3, 73.7 mmol) was added over a period of 20 min. After 1.5 h, the crude 2-(trimethylsilyl)-3-furoyl chloride was added as a solution in THF (50 cm^3) over a period of 30 min. After a further 30 min, saturated aq. ammonium chloride was added, and the mixture was allowed to warm to room temperature. Hydrochloric acid (100 cm^3; 3 mol dm^{-3}) was added, and the organic products were extracted into ether. The extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was distilled to give the *title compound* **31** (18.6, 100%) as a liquid, b.p. 110 °C (0.5 mmHg) (Found: C, 57.3; H, 6.4. $C_{12}H_{18}O_4Si$ requires C, 57.1; H, 6.4%); ν_{max}/cm^{-1} 3120, 1740, 1680, 1630, 1545, 1280, 1250, 1210, 1145, 1040, 920, 850 and 770; δ_H(300 MHz;$CDCl_3$) (keto tautomer) 0.33 (9 H, s, $SiMe_3$), 1.26 (3 H, t, *J* 7, CH_2*Me*), 3.76 (2 H, s, 2-H_2), 4.21 (2 H, q, *J* 7, CH_2Me), 6.66 (1 H, d, *J* 2, 4′-H) and 7.60 (1 H, d, *J* 2, 5′-H); *m/z* (EI) 254 (M^+, 8%), 238 (92) and 167 (100). Minor peaks due to the enol tautomer (~ 10%) were observed in the ^1H NMR spectrum; δ_H 5.35 (1 H, s, 2-H).

(1RS,2SR,5SR)-*Ethyl* 2-*Hydroxy*-5-*methyl*-4-*oxo*-2-(2′-*trimethylsilyl*-3′-*furyl*)*cyclohexanecarboxylate* **33**.—A solution of 3-methylbut-3-en-2-one[11] (8 g, 95 mmol) in ethanol (50 cm^3) was added to a solution of the keto ester **31** (18.8 g, 74 mmol) in ethanol (150 cm^3) containing aq. sodium hydroxide (3 cm^3; 2 mol dm^{-3}) over a period of 1 h. After 24 h, the mixture was concentrated under reduced pressure, and the residue was partitioned between ether (400 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was recrystallised from hexane–ether to give the *title compound* **33** (8.6 g, 34%) as plates, m.p. 119–121 °C (Found: C, 60.55; H, 7.75. $C_{17}H_{26}O_5Si$ requires C, 60.35; H, 7.75%); δ_H(300 MHz; $CDCl_3$) 0.32 (9 H, s, $SiMe_3$), 1.11–1.16 (6 H, m), 2.11 (1 H, q, *J* 13, 6-H^{ax}), 2.16–2.25 (1 H, m), 2.45–2.54 (2 H, m), 2.64 (1 H, d, *J* 14.5, 3-H^{eq}), 3.32 (1 H, dd, *J* 12.5 and 4, 1-H), 4.01–4.12 (2 H, m, CH_2Me), 4.37 (1 H, d, *J* 2.5, OH), 6.26 (1 H, d, *J* 1.5, 4′-H) and 7.53 (1 H, d, *J* 1.5, 5′-H); *m/z* (EI) 338 (M^+, 6%), 323 (M^+ − 15, 60%) and 167 (100).

The mother liquors were concentrated under reduced pressure, and the residue was dissolved in ethanol (100 cm^3). Aq. sodium hydroxide (2 cm^3; 2 mol dm^{-3}) was added. After 8 h, the reaction mixture was worked up as outlined above to give a second crop of the cyclohexanecarboxylate **33** (3.6 g, 14%). The residue was chromatographed (ether–light petroleum) to give a third crop (4.2 g, 17%) (total yield of **33**; 16.4 g, 66%).

(1RS,2SR,4SR,5SR)-*Ethyl* 2,4-*Dihydroxy*-5-*methyl*-2-(2′-*trimethylsilyl*-3′-*furyl*)*cyclohexanecarboxylate* **34**.—Sodium borohydride (0.72 g, 20 mmol) was added to rapidly stirred acetic acid (20 cm^3) at such a rate that the temperature did not exceed 20 °C. After 30 min, the solution was added to the ketone **33** (3.4 g, 10 mmol), and the mixture was stirred for 3 h. The excess of acetic acid was removed under reduced pressure, and the residue was partitioned between ether (150 cm^3) and aq. sodium hydroxide (100 cm^3; 2 mol dm^{-3}). The organic phase was dried (K_2CO_3), and concentrated under reduced pressure, and the residue was recrystallised from hexane–ether to give the *title compound* **34** (2.7 g, 78%) as needles, m.p. 102–103 °C (Found: C, 60.15; H, 8.05. $C_{17}H_{28}O_5Si$ requires C, 59.95; H, 8.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3460, 1700, 1250, 1180, 1090 and 1030; δ_H(300 MHz; $CDCl_3$) 0.32 (9 H, s, $SiMe_3$), 1.10 (3 H, t, *J* 7, CH_2Me), 1.11 (3 H, d, *J* 6.5, CH*Me*), 1.4–1.6 (3 H, m), 1.6–1.8 (2 H, m), 2.18 (1 H, dd, *J* 13.5 and 4.5, 3-H^{eq}), 2.84 (1 H, m, 1-H), 3.71 (1 H, m, 4-H), 3.9–4.1 (2 H, m, CH_2Me), 4.43 (1 H, d, *J* 2.5, 2-OH), 6.18 (1 H, d, *J* 1.5, 4′-H) and 7.49 (1 H, d, *J* 1.5, 5′-H); *m/z* (EI) 340 (M^+, 11%) and 75 (100).

Oxidation of the 2-*Trimethylsilylfuran* **34**.—*With peracetic acid.* A solution of the 2-trimethylsilylfuran **34** (100 mg, 0.29 mmol), sodium acetate (100 mg) and peracetic acid (200 mm^3; 38% in acetic acid) in dichloromethane (5 cm^3) was heated under reflux for 16 h. The reaction mixture was diluted with dichloromethane (20 cm^3), washed with aq. sodium hydrogen carbonate (2 × 10 cm^3; 1 mol dm^{-3}), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (ether–ethyl acetate) gave unchanged furan **34** (53 mg, 53% recovery) and (1RS,2SR,4SR,5SR)-*ethyl* 2-(2′,5′-*dihydro*-2′-*oxo*-3′-*furyl*)-2,4-*dihydroxy*-5-*methylcyclohexanecarboxylate* **35** (14 mg, 14%) as needles on recrystallisation from ether, m.p. 132–133 °C (Found: C, 59.1; H, 6.9. $C_{14}H_{20}O_6$ requires C, 59.15; H, 7.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3620, 3480, 3020, 1750, 1700, 1190, 1090, 1060 and 1035; δ_H(300 MHz; $CDCl_3$) 1.1 (3 H, d, *J* 6, CH*Me*), 1.21 (3 H, t *J* 7, CH_2Me), 1.64–1.73 (3 H, m), 1.85–1.95 (3 H, m), 3.36 (1 H, dd, *J* 12.5 and 4, 1-H), 3.65 (1 H, br q, *J* 8, 4-H), 4.0–4.1 (2 H, m, CH_2Me), 4.55 (1 H, br s, 2-OH), 4.78 (2 H, m, 5′-H_2) and 7.49 (1 H, narrow m, 4′-H); *m/z* (CI) 302 (M^+ + 18, 37%) and 285 (M^+ + 1, 100).

With bromine in methanol. A solution of bromine (1.8 g, 11 mmol) in methanol (10 cm^3) was added to a solution of the furan **34** (3.4 g, 10 mmol) and sodium acetate (3 g, 37 mmol) in methanol (50 cm^3) at 0 °C over a period of 30 min. The reaction mixture was then concentrated under reduced pressure and partitioned between ether (150 cm^3) and saturated aq. sodium hydrogen carbonate (50 cm^3). The organic phase was dried (K_2CO_3), and concentrated under reduced pressure. The residue was dissolved in THF (100 cm^3), and hydrochloric acid (30 cm^3; 3 mol dm^{-3}) was added. After 30 min, sodium chloride (5 g) was added, and the mixture was extracted with ether. The extract was dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed to give the butenolide **35** (1.54 g, 54%) and (1RS,2SR,4SR,5SR)-*ethyl* 2-(2-*bromo*-3-*furyl*)-2,4-*dihydroxy*-5-*methylcyclohexanecarboxylate* **36** (1.07 g, 31%) as needles after recrystallisation from ether–hexane, m.p. 95–97 °C (Found: C, 48.3; H, 5.6. $C_{14}H_{19}BrO_5$ requires C, 48.45; H, 5.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3610, 3460, 1700, 1375, 1185, 1160 and 1030; δ_H(300 MHz; $CDCl_3$) 1.1–1.2 (6 H, m), 1.47–1.63 (1 H, m, 5-H), 1.67–1.92 (4 H, m), 2.19 (1 H, dd, *J* 13 and 5, 3-H^{eq}), 3.15 (1 H, dd, *J* 11 and 4, 1-H), 3.7 (1 H, td, *J* 10, 5, 4-H), 4.0–4.15 (2 H, m, CH_2Me), 4.51 (1 H, br s, OH), 6.45 (1 H, m, 4′-H) and 7.35 (1 H, m, 5′-H); *m/z* (EI) 331 (M^+ − 16, 25%) and 249 (100).

(1RS,2SR,4SR,5SR)-*Ethyl* 2-[(Z)-2′-*Formyl*-1′-(*methoxycarbonyl*)*ethenyl*]-2,4-*dihydroxy*-5-*methylcyclohexanecarboxylate* **37**.—A solution of bromine (180 mg, 1.1 mmol) in methanol (11 cm^3) was added to a solution of the bromofuran **36** (347 mg, 1 mmol) and sodium acetate (250 mg, 3 mmol) in methanol (15 cm^3) at 0 °C over a period of 15 min. The reaction mixture was then concentrated under reduced pressure, and partitioned between dichloromethane (40 cm^3) and brine (20 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure, and the residue was dissolved in aq. acetone (3.6 cm^3; 3:1 acetone–water). Trifluoroacetic acid (TFA) (10 mm^3) was added and, after 3 h, the solution was concentrated under reduced pressure. Chromatography of the residue (ether–light petroleum) gave the title compound **37** (212 mg, 68%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3680, 3610, 3460, 1730, 1690, 1190, 1115 and 1040; δ_H(300 MHz; $CDCl_3$) 1.08 (3 H, d, *J* 6.5, CH*Me*), 1.24 (3 H, t, *J* 7, OCH_2Me), 1.44–1.51 (1 H, m, 5-H), 1.61 (1 H, ddd, *J* 13.5, 11 and 1.5, 3-H^{ax}), 1.75 (1 H, q, *J* 12.5, 6-H^{ax}), 1.81 (1 H, br s, 4-OH), 1.89 (1 H, dt, *J* 13 and 4, 6-H^{eq}), 2.15 (1 H, dd, *J* 13.5 and 4.5, 3-H^{eq}), 2.82 (1 H, dd, *J* 12.5 and 4, 1-H), 3.66 (1 H, td, *J* 10.5 and 4.5, 4-H), 3.87 (3 H, s, OMe), 4.09–4.21 (2 H, m, CH_2Me), 4.57 (1 H, d, *J* 3, 2-OH), 6.42 (1 H, d, *J* 7.5, 2′-H) and 9.66 (1 H, d, *J* 7.5, CHO); *m/z* (CI) 298 (M^+ − 16, 100%).

(1RS,2SR,4SR,5SR)-*Ethyl* 2-[(Z)-2′-(1,3-*Dioxan*-2-*yl*)-1′-(*methoxycarbonyl*)*ethenyl*]-2,4-*dihydroxy*-5-*methylcyclohexanecarboxylate* **38**.—A mixture of the aldehyde **37** (450 mg, 1.4 mmol), propane-1,3-diol (0.4 cm^3), and copper sulfate (500 mg) was stirred in benzene (15 cm^3) for 16 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue gave the *title compound* **38** (265 mg, 50%) as needles after recrystallisation from hexane–ether, m.p. 136–138 °C (Found: C, 57.9; H, 7.6. $C_{18}H_{28}O_8$ requires C, 58.05; H, 7.6%); δ_H(300 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 6.5, CH*Me*), 1.24 (3 H, t, *J* 7, CH_2Me), 1.2–1.46 (1 H, m), 1.58–1.84 (4 H, m), 2.00–2.16 (2 H, m), 2.85 (1 H, dd, *J* 12 and 5, 1-H), 3.61 (1 H, td, *J* 10.5 and 4.5, 4-H), 3.75 (3 H, s, OMe), 3.71–3.81 (2 H, m), 4.04–4.2 (4 H, m), 4.34 (1 H, d, *J* 2.5, 2-OH), 5.16 (1 H, d, *J* 4.5, 1′-H) and 5.99 (1 H, d, *J* 4.5, 2′-H).

(1RS,2SR,4SR,5SR)-*Ethyl* 2-(2′,5′-*Dihydro*-5′-*hydroxy*-2′-*oxo*-3′-*furyl*)-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylate* **40**.—A mixture of the butenolide **25** (528 mg, 1.77 mmol) and NBS (410 mg, 2.3 mmol) in tetrachloromethane (15 cm^3) was heated under reflux for 4 h in the presence of light. The reaction mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure to leave the bromobutenolide **39** (692 mg) which was used without purification.

The bromobutenolide **39** (692 mg) was heated under reflux in aq. acetone (16 cm^3; 3:1 acetone–water) for 6 h. Brine (20 cm^3) and ether (40 cm^3) were added, and the organic phase was separated. The aqueous phase was extracted with ether (3 × 20 cm^3), and the combined ethereal phases were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ether–ethyl acetate) to give the *title compound* **40** (415 mg, 75%) as needles after recrystallisation from ether, m.p. 149–151 °C (Found: C, 57.25; H, 6.95. $C_{15}H_{22}O_7$ requires C, 57.3; H, 7.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3580, 3400br, 1770, 1700, 1185, 1100, 1015 and 925; δ_H(300 MHz; $CDCl_3$) 1.06 (3 H, d, *J* 6, CH*Me*), 1.21 (3 H, t, *J* 7, CH_2Me), 1.57–1.77 (3 H, m), 1.87 (1 H, dt, *J* 12.5, 4, 6-H^{eq}), 2.09 (1 H, dd, *J* 13 and 4, 3-H^{eq}), 3.19 (1 H, td, *J* 10.5 and 4.5, 4-H), 3.29 (1 H, dd, *J* 12 and 3.5, 1-H), 3.35 (3 H, s, OMe), 4.03–4.14 (2 H, m, CH_2Me), 4.4–4.5 (1 H, br s, OH), 4.8–5.0 (1 H, br s, OH), 6.06 (1 H, br s, 5′-H) and 7.18 (1 H, br s, 4′-H); *m/z* (EI) 296 (M^+ − 18, 9%) and 99 (100).

Reactions of Hydroxybutenolide **40** *with Nucleophiles.*—*With butyllithium.* Butyllithium (0.8 cm^3; 1.6 mol dm^{-3} in hexane) was added to a stirred solution of the hydroxybutenolide **40** (152 mg, 0.48 mmol) in THF (5 cm^3) at −78 °C. After 2 h, hydrochloric

acid (10 cm^3; 1 mol dm^{-3}) was added. Extraction (ether) followed by chromatography (ether–light petroleum) gave (1*RS*,2*SR*,4*SR*,5*SR*)-ethyl 2-(5'-butyl-2',5'-dihydro-2'-oxo-3'-furyl)-2-hydroxy-4-methoxy-5-methylcyclohexanecarboxylate **42** (107 mg, 63%) as two diastereoisomers, ratio 60:40; major diastereoisomer, $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1750, 1700, 1190, 1100 and 1030; δ_H(300 MHz; $CDCl_3$) 0.91 (3 H, m, CH_2CH_2Me), 106 (3 H, d, *J* CH*Me*), 1.20 (3 H, t, *J* 7, OCH_2Me), 1.23–1.45 (5 H, m), 1.58–1.89 (5 H, m), 2.04 (1 H, dd, *J* 13 and 4.5, 3-H^{eq}), 3.19 (1 H, td, *J* 10.5 and 4.5, 4-H), 3.33 (1 H, dd, *J* 12.5 and 4.1, 1-H), 3.35 (3 H, s, OMe), 4.01–4.12 (2 H, m, OCH_2Me), 4.54 (1 H, d, *J* 2.5, OH), 4.87 (1 H, ddd, *J* 7, 5.5 and 1.5, 5'-H) and 7.38 (1 H, d, *J* 1.5, 4'-H); *m/z* (EI) 336 (M^+ − 18, 10%) and 85 (100); minor diastereoisomer, $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 1750, 1690, 1335, 1100 and 1040; δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, m, CH_2CH_2Me), 1.05 (3 H, d, *J* 6, CH*Me*), 1.22 (3 H, t, *J* 7, OCH*Me*), 1.24–1.39 and 1.56–1.90 (each 5 H, m), 2.05 (1 H, dd, *J* 13 and 4.5, 3-H^{eq}), 3.19 (1 H, td, *J* 10.5 and 4.5, 4-H), 3.33 (1 H, dd, *J* 12.5 and 4, 1-H), 3.34 (3 H, s, OMe), 3.98–4.14 (2 H, m, OCH_2Me), 4.57 (1 H, d, *J* 2.5, OH), 4.93 (1 H, ddd, *J* 7, 5 and 1.5, 5'-H) and 7.35 (1 H, d, *J* 1.5, 4'-H); *m/z* (EI) 336 (M^+ − 18, 10%) and 85 (100).

With lithiated ethyl phenyl sulfone. Butyllithium (0.65 cm^3; 1.6 mol dm^{-3} in hexane) was added to a solution of ethyl phenyl sulfone (170 mg, 1 mmol) in THF (4 cm^3) at 0 °C. After 30 min, this solution was added to a solution of hydroxybutenolide **40** (100 mg, 0.32 mmol) in THF (5 cm^3) at −78 °C. After 45 min at −78 °C and 45 min at ambient temperature, the mixture was diluted with ether (30 cm^3), washed with dil. hydrochloric acid (20 cm^3; 1 mol dm^{-3}), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ether–light petroleum, 2:1) to give two fractions, each of which contained two diastereoisomers of the sulfonylethyl lactone **43** (combined yield 63 mg, 46%); major fraction $\nu_{max}(CHCl_3)/cm^{-1}$ 3480, 1760 and 1720; δ_H(300 MHz; $CDCl_3$) 5.5 (0.3 H, m, 5'-H), 5.5 (0.7 H, m, 5'-H), 7.4 (0.7 H, d, *J* 1.5, 4'-H), 7.5 (0.3 H, d, *J* 1.5, 4'-H) and 7.55–8.0 (5 H, m, ArH); minor fraction, $\nu_{max}(CHCl_3)/cm^{-1}$ 3480, 1760 and 1720; δ_H(300 MHz; $CDCl_3$) 5.42 (0.8 H, m, 5'-H), 5.44 (0.2 H, m, 5'-H) and 7.55–7.95 (6 H, m).

(1RS,2SR,4SR,5SR)-*Ethyl* 2-[(1'Z,3'EZ)-1'-*Carboxypenta-1',3'-dienyl*)]-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylate* **45**.—LDA (1.5 cm^3; 0.2 mol dm^{-3} in THF) was added to a solution of the hydroxybutenolide **40** (77 mg, 0.25 mmol) in THF (3 cm^3) at −78 °C, followed by triphenylphosphonium ethylide [from ethyltriphenylphosphonium iodide (139 mg, 0.33 mmol) and 200 μl of 1.6 mol dm^{-3} butyllithium (200 mm^3)] in THF (2 cm^3). The reaction mixture was allowed to warm to room temperature over a period of 1 h, and saturated aq. ammonium chloride (3 cm^3) was added. The mixture was extracted into ether, and the extracts were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (ether–light petroleum–acetic acid, 50:50:1) gave the title compound **45** (67 mg, 82%) as a 2:1 mixture of (3'*Z*) and (3'*E*) isomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 1695, 1370, 1185 and 1080; δ_H(300 MHz; $CDCl_3$) 1.02–1.07 (3 H, overlapping d, *J* 7, CH*Me*), 1.2 (3 H, overlapping t, *J* 7.5, CH_2Me), 1.48–2.00 (4 H, m), 1.82 (3 H, overlapping d, *J* 6, 5'-H_3), 2.23 (0.3 H, dd, *J* 13 and 5, 3-H^{eq}), 2.28 (0.7 H, dd, *J* 13 and 5, 3-H^{eq}), 3.13–3.3 (2 H, m), 3.5 (1 H, s, OMe), 3.51 (2 H, s, OMe), 4.05–4.25 (2 H, m, CH_2Me), 4.69 (0.3 H, br s, 2-OH), 4.75 (0.7 H, br s, 2-OH), 5.92 (0.7 H, dqd, *J* 10.5, 7 and 1, 4'-H), 6.07 (0.3 H, dq, *J* 14 and 7, 4'-H), 6.66 (0.7 H, tq, *J* 11.5 and 1.5, 3'-H), 6.75–6.9 (0.6 H, m) and 7.10 (0.7 H, dd, *J* 11.5 and 0.5, 2'-H); *m/z* (CI) 344 (M^+ + 18, 17%), 326 (M^+, 36) and 309 (M^+ − 17, 100).

Treatment of the crude acid **45** [prepared from the hydroxybutenolide **40** (100 mg, 0.32 mmol)] with an excess of diazomethane gave, after chromatography (ether–light petroleum), the methyl esters **46** (50 mg, 46%) as an inseparable (3:1) mixture of (3'*Z*) and (3'*E*) isomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1725, 1680, 1638, 1220 and 1115; δ_H(300 MHz; $CDCl_3$) major isomer, 5.77 (1 H, dqd, *J* 11, 6 and 1, 4'-H), 6.21 (1 H, ddq, 12, 11 and 1.5, 3'-H) and 6.99 (1 H, dd, *J* 12 and 1, 2'-H); minor isomer, 5.97 (1 H, dq, *J* 15 and 6.5, 4'-H), 6.36 (1 H, ddq, *J* 15, 11.5 and 1.5, 3'-H) and 6.68 (1 H, d, *J* 11, 2'-H); *m/z* (EI) 340 (M^+, 3.5%) and 211 (100).

(1RS,2SR,4SR,5SR)-*Ethyl* 2-[(1'Z,3'E)-1'-*Carboxy*-5'-*methylhexa*-1',3'-*dienyl*]-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylate* **51**.—Following the procedure outlined above, hydroxybutenolide **40** (77 mg, 0.25 mmol) and triphenylphosphonium 2-methylpropylide [from 2-methylpropyltriphenylphosphonium bromide (132 mg, 0.33 mmol)] gave a 4:1 mixture of the (3'*Z*) and (3'*E*) isomers of the dienyl acids **47** (67 mg, 75%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 2400–3600br, 1700, 1620, 1180, 1090, 1030 and 910; δ_H(300 MHz; $CDCl_3$) major isomer, 1.01 (6 H, d, *J* 6.5, $CHMe_2$), 1.06 (3 H, d, *J* 6, CH*Me*), 1.22 (3 H, t, *J* 7, CH_2Me), 1.5–1.8 (4 H, m), 2.26 (1 H, dd, *J* 13.5 and 4.5), 2.85–2.94 (1 H, m, 5'-H), 3.16–3.3 (2 H, m), 3.38 (3 H, s, OMe), 4.05–4.18 (2 H, m, CH_2Me), 5.0 (2 H, br s, OH), 5.61 (1 H, td, *J* 10.5 and 0.5, 4'-H), 6.48 (1 H, td, *J* 11.5 and 0.5, 3'-H) and 7.08 (1 H, dd, *J* 11.5 and 0.5, 2'-H); minor isomer, 6.03 (1 H, dd, *J* 14.5 and 7, 4'-H) and 6.75–6.84 (2 H, m, 2'- and 3'-H).

Treatment of a sample of the dienyl acids **47** with an excess of diazomethane gave the methyl esters **48** (56%), $\nu_{max}(CHCl_3)$ 3450, 1710, 1380, 1180 and 1090; δ_H(300 MHz; $CDCl_3$) major isomer, 5.49 (1 H, t, *J* 11, 4'-H), 6.07 (1 H, t, *J* 11, 3'-H) and 6.94 (1 H, d, *J* 11, 2'-H); minor isomer, 5.91 (1 H, dd, *J* 15 and 7, 4'-H), 6.31 (1 H, ddd, *J* 15, 11 and 1.5, 3'-H) and 6.68 (1 H, d, *J* 11, 2'-H); *m/z* (EI) 368 (M^+, 7%) and 239 (100).

Iodine (5 mol%) was added to a solution of the dienyl acids **47** in benzene. After 24 h the solution was diluted with more benzene, washed with saturated aq. sodium thiosulfate, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was recrystallised from dichloromethane–ether to give the *title compound* **51** as fine needles, m.p. 118–120 °C (Found: C, 64.35; H, 8.7. $C_{19}H_{30}O_6$ requires C, 64.4; H, 8.55%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1700, 1620, 1460, 1380, 1180, 1125 and 1010; δ_H(300 MHz; C_6D_6) 0.82 (6 H, overlapping d, *J* 7, $CHMe_2$), 0.90 (3 H, t, *J* 7, CH_2Me), 1.02 (3 H, d, *J* 6.5, CH*Me*), 1.45–1.65 (2 H, m), 1.82 (1 H, q, *J* 12.5, 6-H^{eq}), 2.09–2.17 (2 H, m), 2.39 (1 H, dd, *J* 13 and 4.5, 3-H^{eq}), 3.16 (3 H, s, OMe), 3.38 (1 H, td, *J* 10 and 4.5, 4-H), 3.53 (1 H, dd, *J* 12.5 and 4, 1-H), 3.75–3.95 (2 H, m, CH_2Me), 5.76 (1 H, dd, *J* 15 and 7, 4'-H), 7.04 (1 H, dd, *J* 15 and 11.5, 3'-H) and 7.23 (1 H, d, *J* 11.5, 2'-H); *m/z* (CI) 372 (M^+ + 18, 8%) and 296 (100).

(1RS,2SR,4SR,5SR)-*Ethyl* 2-(2',5'-*Dihydro*-5'-*methoxycarbonylmethyl*-2'-*oxo*-3'-*furyl*)-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylate* **50**.—A solution of the hydroxybutenolide **40** (100 mg, 0.32 mmol) and methoxycarbonylmethylenetriphenylphosphorane (330 mg, 1 mmol) in THF (10 cm^3) was heated under reflux for 3 h. The mixture was concentrated under reduced pressure, and the residue was chromatographed to give the title compound **50** (74 mg, 63%) as a 1:1 mixture of diastereoisomers; $\nu_{max}(CHCl_3)$ 3460, 1750, 1705, 1280, 1180, 1100 and 1040; δ_H(300 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 6, CH*Me*), 1.19 (1.5 H, t, *J* 7.5, CH_2Me), 1.22 (1.5 H, t, *J* 7, CH_2Me), 1.58–1.90 (4 H, m), 2.05 (1 H, dt, *J* 13 and 4.5, 6-H^{eq}), 2.53–2.85 (2 H, m), 3.18 (1 H, m, 4-H), 3.27–3.36 (1 H, m, 1-H), 3.33 (3 H, s, OMe), 3.72 and 3.73 (each 1.5 H, s, CO_2Me), 4.02–4.15 (2 H, m, CH_2Me), 4.52 and 4.54 (each 0.5 H, d, *J* 2.5, OH), 5.22–5.30 (1 H, m, 5'-H) and 7.47 and 7.49 (each 0.5 H, d, *J* 1.5, 4'-H); *m/z* (EI) 370 (M^+, 1%) and 169 (100).

(1'RS,3'SR)-2-[3-tert-*Butyldimethylsiloxy*)*cyclohexyl*]-*ethanal* **56**.—A solution of the bicyclic lactone **53**[23] (14 g, 100

mmol) and sodium methoxide (1 g, 19 mmol) in methanol (250 cm^3) was stirred for 2 h and then concentrated under reduced pressure. The residue was taken up in ether (500 cm^3), and the extracts were washed with brine (2 × 250 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure gave the methyl ester **54** (14.5 g) used without purification; ν_{max}/cm^{-1} 3480 and 1725; δ_H(300 MHz; $CDCl_3$) 0.77–1.03 (2 H, m), 1.06–1.39 (2 H, m), 1.58–2.13 (5 H, m), 2.2–2.3 (2 H, m), 2.55–2.78 (1 H, br s, OH), 3.52–3.64 (1 H, m, 3'-H), and 3.65 (3 H, s, OMe); *m/z* (CI) 173 (M^+ + 1, 2%) and 141 (100).

A solution of the crude methyl ester **54** (14.5 g), *tert*-butyldimethylsilyl chloride (16.4 g, 109 mmol), and imidazole (15 g, 221 mmol) in *N,N*-dimethylformamide (DMF) (40 cm^3) was stirred at ambient temperature for 48 h. The mixture was partitioned between light petroleum (500 cm^3) and water (500 cm^3), and the organic phase was dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ether–light petroleum) to give the silyl ester **55** (17.5 g, 61% from **53**) as an oil; ν_{max}/cm^{-1} 1740, 1255, 1170, 1100, 1053, 840 and 780; δ_H(300 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.88 (9 H, s, $SiCMe_3$), 1.01 (1 H, q, *J* 11.5, 2'-H), 1.1–1.3 (2 H, m), 1.56–1.95 (6 H, m), 2.23 (2 H, d, *J* 7, 2-H_2), 3.5–3.6 (1 H, m, 3'-H) and 3.67 (3 H, s, OMe); *m/z* (EI) 229 (M^+, 93%) and 75 (100).

DIBAL-H (9 cm^3; 1 mol dm^{-3} in toluene) was added to a solution of the methyl ester **55** (2.34 g, 9.2 mmol) in toluene (50 cm^3) at −78 °C. After 2 h, saturated aq. ammonium chloride (10 cm^3) was added, and the mixture was allowed to warm to room temperature. Hydrochloric acid (10 cm^3; 3 mol dm^{-3}) was added, and the organic phase was separated. The aqueous phase was extracted with ether (3 × 20 cm^3), and the combined organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (light petroleum–ether, 19:1) of the residue gave the *title compound* **56** (1.7 g, 81%), which was further purified by Kugelrohr distillation (oven temperature 140 °C; 0.5 mmHg) (Found: M − 57, 199.1150. $C_{10}H_{19}O_2Si$ requires *m/z*, 199.1154); ν_{max}/cm^{-1} 2710, 1725, 1255, 1105, 1060, 830 and 775; δ_H(300 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.88 (9 H, s, $SiCMe_3$), 1.09 (1 H, q, *J* 11, 2'-H^{ax}), 1.16–1.32 (2 H, m), 1.6–1.94 (6 H, m), 2.35 (2 H, m, 2-H_2), 3.55–3.68 (1 H, m, 3'-H) and 9.77 (1 H, t, *J* 2, 1-H); *m/z* (CI) 257 (M^+ + 1, 100%).

(1'RS,3'RS,4E)-6-[3'-(tert-*Butyldimethylsiloxy*)*cyclohexyl*]-4-*methylhex*-4-*en*-1-*ol* **59**.—A solution of the aldehyde **56** (8 g, 31 mmol) in THF (40 cm^3) was added dropwise to a solution of prop-2-en-2-ylmagnesium bromide in THF (40 cm^3; 1 mol dm^{-3}) at 0 °C. After 20 min, saturated aq. ammonium chloride (50 cm^3) was added, and the organic phase was separated. The aqueous phase was washed with ether (3 × 50 cm^3), and the combined organic phases dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ether–light petroleum) to give the alcohol **57** (8.2 g, 87%) as a mixture of diastereoisomers, which was further purified by Kugelrohr distillation, oven temperature 160 °C (0.5 mmHg); ν_{max}/cm^{-1} 3360, 1645, 1255, 1105, 1070, 835 and 775; δ_H(300 MHz; $CDCl_3$) 0.05 and 0.06 (each 3 H, s, SiMe), 0.89 (9 H, s, $SiCMe_3$), 1.73 (3 H, s, 3-Me), 0.8–2.0 (12 H, m), 3.45–3.64 (1 H, m, 3'-H), 4.17 (1 H, m, 2-H), and 4.83 and 4.95 (each 1 H, m, 4-H); *m/z* (CI) 299 (M^+ + 1, 26%) and 149 (100).

A solution of the alcohol **57** (8 g, 26.8 mmol), trimethyl orthoacetate (15 cm^3), and propanoic acid (0.3 cm^3) in commercial xylene (60 cm^3) was heated under reflux for 24 h. Concentration under reduced pressure gave the *ester* **58**, which was further purified by distillation using a Kugelrohr, oven temp. 200 °C (0.5 mmHg) (Found: C, 67.4; H, 11.05. $C_{20}H_{38}O_3Si$ requires C, 67.75; H, 10.8%); ν_{max}/cm^{-1} 1740, 1255, 1100, 835 and 775; δ_H(300 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.63–0.85 (1 H, m), 0.87 (9 H, s, $SiCMe_3$), 0.92 (1 H, q, *J* 12, 2'-H), 1.05–1.38 (3 H, m), 1.51–1.77 (2 H, m), 1.6 (3 H, s, 4-Me), 1.76–1.95 (2 H, m), 1.9 (2 H, t, *J* 7, 2-H_2), 2.26–2.49 (4 H, m), 3.43–3.57 (1 H, m, 3'-H), 3.63 (3 H, s, OMe) and 5.17 (1 H, t, *J* 7, 5-H); *m/z* (CI) 355 (M^+ + 1, 36%) and 223 (100).

The ester **58**, as a solution in ether (50 cm^3), was added slowly to a suspension of lithium aluminium hydride (1 g, 26 mmol) in ether (50 cm^3) at 0 °C. After 1 h, sodium sulfate decahydrate was added, the slurry was filtered and the residue was washed with ether. The combined filtrate and washings were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ether–light petroleum, 1:2) to give the *title compound* **59** (7.02 g, 82% from **57**) as a viscous oil, which was distilled using a Kugelrohr, oven temp. 220 °C (0.5 mmHg) (Found: C, 69.7; H, 12.1. $C_{19}H_{38}O_2Si$ required C, 69.9; H, 11.75%); ν_{max}/cm^{-1} 3330, 1255, 1095, 1055, 835 and 775; δ_H(300 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.74–0.85 (1 H, m), 0.89 (9 H, s, $SiCMe_3$), 0.95 (1 H, q, *J* 11.5, 2'-H^{ax}), 1.13–1.3 (3 H, m), 1.43 (1 H, br s, OH), 1.6 (3 H, s, 4-Me), 1.6–1.74 (4 H, m), 1.82–1.87 (2 H, m), 1.92 (2 H, t *J* 7, 3-H_2), 2.07 (2 H, t, *J* 7.5, 6-H_2), 3.48–3.54 (1 H, m, 3'-H), 3.64 (2 H, t, *J* 6.5, 2-H_2) and 5.18 (1 H, t, *J* 7.5, 5-H); *m/z* (CI) 327 (M^+ + 1, 7%) and 195 (100).

[(1'RS,3'RS,4E)-6-[3'-(tert-*Butyldimethylsiloxy*)*cyclohexyl*]-4-*methylhex*-4-*enyl*(*triphenyl*)*phosphonium Iodide* **62**.—Methanesulfonyl chloride (1.95 cm^3, 25 mmol) was added to a solution of alcohol **59** (6.66 g, 21 mmol) and triethylamine (3.7 cm^3, 34 mmol) in ether (100 cm^3). After 1 h, the mixture was filtered, and the filtrate was concentrated under reduced pressure to give the methanesulfonate **60** as an oil, used without further purification; ν_{max}/cm^{-1} 1250, 1180, 1090, 1055, 960, 930, 835 and 755; δ_H(300 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.74–0.88 (1 H, m), 0.89 (9 H, s, $SiCMe_3$), 0.96 (1 H, q, *J* 12, 2'-H^{ax}), 1.16–1.31 (3 H, m), 1.6 (3 H, d, *J* 1.5, 4-Me), 1.6–1.63 and 1.7 (each 1 H, m), 1.8–1.95 (4 H, m), 1.92 (2 H, t, *J* 7, 3-H_2), 2.11 (2 H, t, *J* 7.5, 6-H_2), 3.01 (3 H, s, OSO_2Me), 3.46–3.6 (1 H, m, 3'-H), 4.21 (2 H, t, *J* 6.5, 1-H_2) and 5.19 (1 H, td, *J* 7.5 and 1.2, 5-H); *m/z* (CI) 405 (M^+ + 1, 100%).

The methanesulphonate **60** was dissolved in a solution of sodium iodide in acetone (200 cm^3; 10% w/v). After 6 h, the mixture was diluted with light petroleum (600 cm^3), filtered through Celite, and concentrated under reduced pressure. The residue was chromatographed (ether–light petroleum, 1:99) to give the iodide **61** (7.85 g, 87% from **59**); ν_{max}/cm^{-1} 1250, 1100, 835 and 775; δ_H(300 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.64–0.88 (1 H, m), 0.89 (9 H, s, $SiCMe_3$), 0.96 (1 H, q, *J* 12, 2'-H^{ax}), 1.1–1.4 (3 H, m), 1.58 (3 H, s, 4-Me), 1.58–1.8 (2 H, m), 1.8–2.0 (4 H, m), 1.92 (2 H, t, *J* 7, 3-H_2), 2.1 (2 H, t, *J* 7, 6-H_2), 3.15 (2 H, t, *J* 7, 1-H_2), 3.47–3.58 (1 H, m, 3'-H) and 5.21 (1 H, br t, *J* 7.5, 5-H); *m/z* (CI) 437 (M^+ + 1, 100%).

A solution of the iodide **61** (970 mg, 2 mmol) and triphenylphosphine (600 mg, 2.3 mmol) in DMF (10 cm^3) was heated under reflux for 6 h. The mixture was concentrated under reduced pressure, and the residue was triturated with ether until solid. This solid was recrystallised from THF, washed with ether, and dried *in vacuo*, to give the title compound **62**, better used without purification.

(1RS,2SR,4SR,5SR)-*Ethyl* 2-{(1'Z,3'E,7'E)-9'-[3''-(tert-*Butyldimethylsiloxy*)*cyclohexyl*]-1'-*carboxy*-7'-*methylnona*-1',3',7'-*trienyl*}-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylates* **65** *and* **68**.—LiHMDS (2 cm^3; 0.5 mol dm^{-3} in THF–hexane) was added to a mixture of the phosphonium salt **62** [from **61** (436 mg, 1 mmol)] and THF (10 cm^3) at 0 °C. After 1 h, the solution was added to a solution of the hydroxybutenolide **40** (153 mg, 0.49 mmol) in THF (10 cm^3) at −78 °C which had previously been treated with LiHMDS (2 cm^3; 0.5 mol dm^{-3} in THF–hexane). The mixture was allowed to warm to ambient temperature, and saturated aq. ammonium chloride (20 cm^3)

was added. The organic phase was separated, and the aqueous phase was extracted with ether (3 × 20 cm^3). The combined organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed to give a mixture of the conjugated dienes **63**, **64**, **65**, and **68** (256 mg, 86%) as a 6:1 mixture of (3′*Z*)- and (3′*E*)-isomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 3475, 3400–2400, 1700, 1630, 1380, 1260, 1180 and 1095; δ_H(300 MHz; $CDCl_3$) (3′*Z*)-isomers **63** and **64**; 0.08 (6 H, s, $SiMe_2$), 0.85 (1 H, m), 0.9 (9 H, s, $SiCMe_3$), 0.97 (1 H, q, *J* 12.5, 2″-H^{ax}), 1.07 (3 H, d, *J* 6, CH*Me*), 1.0–1.4 (3 H, m), 1.21 (3 H, t *J* 7, CH_2*Me*), 1.59 (3 H, br s, 7′-Me), 1.5–2.0 (10 H, m), 2.1 (2 H, m), 2.25 (1 H, dd, *J* 13 and 4, 3-H^{eq}), 2.33–2.45 (2 H, m), 3.17–3.27 (2 H, m, 1- and 4-H), 3.38 (3 H, s, OMe), 3.47–3.6 (1 H, m, 3″-H), 4.05–4.2 (2 H, m, C*H*$_2$Me), 4.6 (1 H, br s, 2-OH), 5.18 (1 H, br t, *J* 6, 8′-H), 5.78 (1 H, dt, *J* 11 and 7, 4′-H), 6.58 (1 H, t, *J* 11.5, 3′-H) and 7.09 (1 H, d, *J* 12, 2′-H); *m/z* (CI, NH_3) 607 (M^+ + 1, 100%).

The mixture of conjugated dienes **63**, **64**, **65** and **68** was dissolved in benzene (10 cm^3) and iodine (100 mm^3; 0.2 mol dm^{-3} in benzene) was added. After 24 h, the benzene and the iodine were removed under reduced pressure to leave the title compounds **65** and **68** (250 mg), now a 9:1 mixture of the (3′*E*)- and (3′*Z*)-isomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 3475, 3600–2400, 1700, 1630, 1380, 1260, 1180 and 1095; δ_H(300 MHz; $CDCl_3$) (3′*E*) isomers **65** and **68**; 0.07 (6 H, s, $SiMe_2$), 0.75 (1 H, m), 0.92 (9 H, s, $SiCMe_3$), 0.99 (1 H, q, *J* 12, 2″-H^{ax}), 1.00–1.33 (3 H, m), 1.07 (3 H, d, *J* 6, CH*Me*), 1.23 (3 H, t, *J* 7, CH_2*Me*), 1.6 (3 H, br s, 7′-Me), 1.4–1.9 (10 H, m), 2.05 (2 H, m), 2.1–2.3 (3 H, m), 3.22 (1 H, td, *J* 10 and 4, 4-H), 3.27 (1 H, dd, *J* 13 and 4, 1-H), 3.39 (3 H, s, OMe), 3.49–3.64 (1 H, m, 3″-H), 4.02–4.26 (2 H, m, C*H*$_2$Me), 4.63 (1 H, br s, 2-OH), 5.17 (1 H, br t, *J* 7, 8′-H), 6.0 (1 H, dt, *J* 14 and 6, 4′-H) and 6.77–6.87 (2 H, m, 2′- and 3′-H); *m/z* (CI, NH_3) 607 (M^+ + 1, 72%), 589 (65) and 215 (100).

(1RS,2SR,4SR,5SR)-2-(*Trimethylsilyl*)*ethyl* 2-{(1′Z,3′E,7′-E)-9′-[3″-(tert-*Butyldimethylsiloxy*)*cyclohexyl*]-*1′-methoxycarbonyl-7′-methylnona*-1′,3′,7′-*trienyl*}-2-*hydroxy*-4-*methoxy*-5-*methylcyclohexanecarboxylates* **67** *and* **70**.—A solution of the ethyl esters **65** and **68** (1.05 g, 1.73 mmol) in THF (15 cm^3) was added to solution of 2-(trimethylsilyl)ethanol (3 cm^3, 21 mmol) in THF (25 cm^3) containing butyllithium (2 cm^3; 1.6 mol dm^{-3} in hexane), and the mixture was heated under reflux for 4 h. Saturated aq. ammonium chloride (30 cm^3) was added, the organic phase was separated, and the aqueous phase was extracted with ether (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ether–light petroleum, 1:1) of the residue gave the 2-trimethylsilylethyl esters **66** and **69** (620 mg, 53%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 3600–2400, 1700, 1630, 1260, 1180 and 1095; δ_H(300 MHz; $CDCl_3$) 0.03 (9 H, s, $SiMe_3$), 0.08 (6 H, s, $SiMe_2$), 0.89 (9 H, s, $SiCMe_3$), 0.67–1.38 (7 H, m), 1.06 (3 H, d, *J* 6, CH*Me*), 1.59 (3 H, s, 7′-Me), 1.45–1.98 (10 H, m), 2.05–2.35 (5 H, m), 3.2 (1 H, td, *J* 10 and 4, 4-H), 3.25 (1 H, dd, *J* 13 and 4, 1-H), 3.33 (3 H, s, OMe), 3.47–3.6 (1 H, m, 3″-H), 4.12–4.18 (2 H, m, OCH_2), 4.58 (1 H, br s, 2-OH), 5.16 (1 H, br t, *J* 7, 8′-H), 6.05 (1 H, dt, *J* 13 and 6, 4′-H) and 6.78–6.9 (2 H, m, 2′-and 3′-H).

This material was dissolved in ether (25 cm^3) and treated with an excess of diazomethane. After 1 h, acetic acid was added to destroy the excess of diazomethane, and the mixture was concentrated under reduced pressure to leave the title compounds **67** and **70** (625 mg, 52% from **65** and **68**); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1700, 1260, 1180 and 1095; δ_H(300 MHz; $CDCl_3$) 0.03 (9 H, s, $SiMe_3$), 0.08 (6 H, s, $SiMe_2$), 0.8 (9 H, s, $SiCMe_3$), 0.65–1.4 (7 H, m), 1.04 (3 H, d, *J* 6, CH*Me*), 1.59 (3 H, s, 7′-Me), 1.45–1.95 (10 H, m), 2.05–2.35 (5 H, m), 3.06 (1 H, dd, *J* 13 and 4, 1-H), 3.18 (1 H, td, *J* 10 and 4, 4-H), 3.35 (3 H, s, OMe), 3.45–3.6 (1 H, m, 3″-H), 3.8 (3 H, s, CO_2Me), 4.05–4.2 (2 H, m, OCH_2), 4.38 (1 H, d, *J* 2.5, 2-OH), 5.16 (1 H, br t, *J* 7, 8′-H), 5.97 (1 H, dt, *J* 15 and 7, 4′-H), 6.38 (1 H, dd, *J* 15 and 10, 3′-H) and 6.67 (1 H, d, *J* 11, 2′-H); *m/z* (CI, NH_3) 693 (M^+ + 1, 5%), 692 (M^+, 5%) and 615 (100).

(1RS,4RS,6SR,7SR,9SR,19RS,10Z,12E,16E)-*Methyl* 9-*Hydroxy*-7-*methoxy*-6,16-*dimethyl*-3-*oxo*-2-*oxatricyclo*-[17.3.1.0^{4,9}]*tricosa*-10,12,16-*triene*-10-*carboxylate* **73**.—Tetrabutylammonium fluoride (TBAF) (1.6 cm^3; 1 mol dm^{-3} in THF) was added to a mixture of esters **67** and **70** (450 mg, 0.65 mmol) and potassium fluoride (244 mg, 2.6 mmol) in THF (15 cm^3), and the mixture was stirred for 4 h. Hydrochloric acid (5 cm^3; 3 mol dm^{-3}) was added, and the mixture was stirred for 3 h. The organic phase was separated, and the aqueous phase was extracted with ether (3 × 10 cm^3). The combined organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (light petroleum–ether–acetic acid 40:60:2) gave the dihydroxy acids **71** and **72** (278 mg, 93%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1710, 1190 and 1090; δ_H(300 MHz; $CDCl_3$) 0.8–2.4 (20 H, complex m), 1.04 (3 H, d, *J* 6, CH*Me*), 1.55 (3 H, s, 7′-Me), 3.07 (1 H, td, *J* 10 and 4, 4-H), 3.1–3.23 (1 H, m, 1-H), 3.35 (3 H, s, OMe), 3.5–3.7 (1 H, m, 3″-H), 3.8 (3 H, s, CO_2Me), 4.8–5.3 (4 H, m, 8′-H and OH), 5.85–6.0 (1 H, m, 4′-H), 6.34 (1 H, m, 3′-H) and 6.6 and 6.62 (each 1 H, d, *J* 11, 2′-H).

A solution of the dihydroxy acids **71** and **72** (300 mg, 0.63 mmol) in dichloromethane (30 cm^3) and a solution of triethylamine (145 mm^3, 1 mmol) in dichloromethane (30 cm^3) were added simultaneously to a stirred suspension of 2-chloro-*N*-methyl-pyridinium iodide (670 mg, 2.8 mmol) in dichloromethane (200 cm^3) during 6 h. After a further 8 h, the mixture was concentrated under reduced pressure. Chromatography of the residue (ether–light petroleum–acetic acid 50:50:2) gave the *title compound* **73** (63 mg, 22%), recrystallized from hexane as prisms, m.p. 145–146 °C (Found: C, 70.4; H, 8.55. $C_{27}H_{40}O_6$ requires C, 70.40; 8.75%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1710, 1190, 1180 and 1090; δ_H(500 MHz; $CDCl_3$) 0.56 (1 H, td, *J* 13 and 11.5, 23-H^{ax}), 0.83–0.92 (1 H, m, 21-H^{ax}), 1.06 (3 H, d, *J* 6.5, CH*Me*), 1.26–1.36 (2 H, m, 20-H^{ax} and 21-H^{eq}), 1.38 (1 H, qq, *J* 11.5 and 3.5, 19-H), 1.47–1.55 (1 H, m, 6-H), 1.58 (1 H, td, *J* 10.5 and 3, 8-H), 1.58 (3 H, s, 16-Me), 1.64 (1 H, m, 20-H^{eq}), 1.73 (1 H, m, 23-H^{eq}), 1.74 (1 H, q, *J* 12.5, 5-H^{ax}), 1.77–1.88 (4 H, m, 5-H^{eq}, 18-H and 22-H_2), 2.03 (1 H, m, 18-H), 2.05–2.11 (1 H, m, 15-H), 2.21 (1 H, dd, *J* 13.5 and 4.5, 8-H^{eq}), 2.24–2.35 (3 H, m, 14-H_2 and 15-H), 3.20 (1 H, dd, *J* 13 and 4.5, 4-H), 3.21 (1 H, td, *J* 10.5 and 4.5, 7-H), 3.35 (3 H, s, 7-OMe), 3.79 (3 H, s, CO_2Me), 4.69 (1 H, d, *J* 3, OH), 4.77 (1 H, tt, *J* 11.5 and 4, 1-H), 4.9 (1 H, m, 17-H), 5.79 (1 H, ddd, *J* 15.5, 12 and 5.5, 13-H), 6.27 (1 H, ddd, *J* 15.5, 11.5 and 1, 12-H) and 6.55 (1 H, dd, *J* 11.5 and 1, 11-H); *m/z* (EI) 460 (M^+, 32%), 443 (100) and 411 (45).

(1RS,4RS,6SR,7SR,9SR,19RS,10E,12E,16E)-9-*Hydroxy*-10-*hydroxymethyl*-7-*methoxy*-6,16-*dimethyl*-2-*oxatricyclo*-[17.3.1.0^{4,9}]*tricosa*-10,12,16-*trien*-3-*one* **74**.—Lithium bis-(2-methoxyethoxy)aluminium hydride (REDAL-H) (1 cm^3; 0.1 mol dm^{-3} in toluene) was added to a solution of the ester **73** (15 mg, 0.033 mmol) in toluene (2 cm^3) at 0 °C. After 1 h, saturated aq. ammonium chloride was added, and the organic phase was separated. The aqueous phase was extracted with ether (5 × 5 cm^3), and the combined organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (ether–hexane, 1:3) of the residue gave the *title compound* **74** (12 mg, 85%) as a solid when recrystallised as prisms from hexane–ether, m.p. 154–156 °C (Found: C, 72.05; H, 9.3. $C_{26}H_{40}O_5$ requires C, 72.2; H, 9.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3610, 3480, 1710, 1460, 1400, 1200, 1180, 1100, 1020, 1010 and 985; δ_H(300 MHz; $CDCl_3$) 0.59 (1 H, q, *J* 11.5, 23-H^{ax}), 0.82–0.97 (1 H, m, 21-H^{ax}), 1.15–2.4 (19 H, complex m), 1.07 (3 H, d, *J* 6.5 CH*Me*), 1.6 (3 H, s, 16-Me), 2.75 (1 H, dd, *J* 9.5 and 7.5, 4-H), 3.21 (1 H, td, *J* 10.5

and 4.5, 7-H), 3.36 (3 H, s, OMe) 4.06 (1 H, d, *J* 2.5, OH), 4.2–4.28 (2 H, m, CH_2OH), 4.78–4.86 (1 H, m, 1-H), 4.93 (1 H, m, 17-H), 5.62–5.71 (1 H, m, 13-H) and 6.2–6.3 (2 H, m, 11- and 12-H); *m/z* (CI) 415 (100%).

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