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Total synthesis of milbemycins: a synthesis of (6*R*)-6-hydroxy-3,4-dihydromilbemycin E

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Following studies using benzyloxymethyl isopropenyl ketone **5** and ethyl 3-(3-furyl)-3-oxopropanoate **6**, Robinson reactions between aryloxymethyl isopropenyl ketones **19** and **5** and ethyl 3-(2-trimethylsilyl-3-furyl)-3-oxopropanoate **20** were found to be stereoselective giving cyclohexanones **21** and **41**, in which the 3-(arylmethoxy) substituents were *cis* to the 2-hydroxyl groups, as the major products. After reduction and protection of ketone **21**, selective PMB-deprotection, oxidation and stereoselective reduction inverted the configuration at C(3) to give the diol **30**. Protection of the secondary 3-hydroxyl group followed by modification of the protected 4-alcohol then gave the hydroxybutenolides **36** and **37** after oxidation of the silylated furan using singlet oxygen. The 3-benzyloxycyclohexanone **41** was also converted into the hydroxybutenolide **37** *via* the (2-trimethylsilylethoxy)methyl (SEM) ether **35**.
The Wittig reaction between the ylid generated from 2-methylpropyl(triphenyl)phosphonium salt and hydroxybutenolide **36** gave predominantly the (2*Z*,4*Z*)-dienyl acid **38** which was taken through to the butenolide **40**. Similarly, the racemic hydroxybutenolide **37** was condensed with the racemic ylid derived from phosphonium salt **53** to give, after SEM-deprotection and 5-membered lactone formation, a mixture of the (9*Z*,2′*Z*)-dienyl lactones **58** and **59** containing *ca.* 10% of the corresponding (9*Z*,2′*E*)-isomers **60** and **61**. (2′*Z*)/(2′*E*)-Isomerisation of the dienes **58** and **59** using iodine followed by deprotection gave a mixture of the seco-acids **62** and **63**. Selective macrocyclisation of the seco-acid **62** in which the relative configuration of the C(1)–C(7) and C(17)–C(19) fragments (milbemycin numbering) corresponded to that present in the natural milbemycins, gave the β-milbemycin analogue **65** after butenolide reduction. The hydroxybutenolide **37** was also condensed with the ylid derived from the phosphonium salt **1** and the product taken through to (6*R*)-6-hydroxy-3,4-dihydromilbemycin E **77**.
Preliminary attempts to convert the β-milbemycin analogues **65** and **77** into tetrahydrofurans corresponding to analogues of α-milbemycins by treatment with toluene *p*-sulfonyl chloride under basic conditions gave the primary allylic chlorides **78** and **79**.

Introduction

The milbemycins and avermectins are important natural products with potent and useful biological activities.[1] Their chemistry has been widely studied and several total syntheses have been reported.[2–4] One problem that was encountered in the early syntheses of avermectins was the regioselective introduction of the 3,4-double-bond since deconjugation of 2,3-unsaturated isomers was complicated by the formation of mixtures of epimers at C(2).[3,4] To avoid this problem, a synthesis of the non-aromatic β-milbemycins was developed in which the 3,4-double-bond was introduced regioselectively into the C(1)–C(10) fragment early in the synthesis and this approach was applied to complete a convergent total synthesis of milbemycin E **3** using the ylid derived from phosphonium salt **1** and the hydroxybutenolide **2**.[5]

It would be of interest to apply this strategy to complete a synthesis of the more common α-milbemycins, *e.g.* milbemycin G **4**,[6] which are characterised by the presence of an extra oxygen functionality at C(6) incorporated into a tetrahydrofuran ring. We now provide full details of a synthesis of (6*R*)-6-hydroxy-3,4-dihydromilbemycin E **77** as a prelude to a total synthesis of milbemycin G.[7]

Results and discussion

The hydroxybutenolide **2** had been prepared using a Robinson reaction of methyl isopropenyl ketone to assemble the six-membered ring, with the cyclohexenyl double-bond introduced *via* a selenoxide elimination and the hydroxybutenolide by singlet oxygen oxidation of a 2-trimethylsilylfuran.[5c] However, preliminary studies on the introduction of the additional oxygen functionality at C(3), the precursor of the ether at C(6) in the α-milbemycins, by oxidation of precursors of the hydroxybutenolide **2** were not encouraging. The Robinson annelation using alkoxymethyl isopropenyl ketones and ethyl 3-(3-furyl)-3-oxopropanoates was therefore investigated.

The Robinson reaction between benzyloxymethyl isopropenyl ketone **5** and the β-keto-ester **6**[5a] in aqueous ethanol was usefully stereoselective and gave the hydroxyketone **7**, in which the benzyloxymethyl group at C(3) was *cis* to the hydroxyl group at C(2), as the major product (70%), together with minor amounts of the epimers at C(1) and C(5), **8** (13%) and **9** (8%), which were isolated by chromatography, see Scheme 1. Structures were assigned to these compounds on the basis of ^{1}H NMR studies. For example, for the major product **7**, strong NOEs were observed between the three, *cis*-disposed, axial hydrogens, 1-H, 3-H and 5-H. For the minor product **8**, significant deshielding of the axial hydrogens 3-H and 5-H was observed consistent with the axial disposition of the ethoxycarbonyl group at C(1), and strong NOEs were still observed between 3-H and 5-H. For the third product **9**, no NOE was observed between 3-H and 5-H, instead irradiation of the 5-methyl group caused a large enhancement of the 3-H which in turn exhibited an NOE with 1-H. ^{1}H NMR coupling constants also supported these stereochemical assignments (see experimental).

The stereoselective formation of the adduct **7** as the major product was probably due to thermodynamic control and by its crystallization out of the reaction mixture. Indeed adducts **8** and **9** tended to isomerize to **7** on storage. In other solvents, *e.g.* in a mixture of ethanol and dichloromethane, the yields and stereoselectivities were lower and, in some cases, mixtures of diasteroisomeric open-chain Michael adducts were also isolated as minor products (*ca.* 7% in dichloromethane–ethanol).

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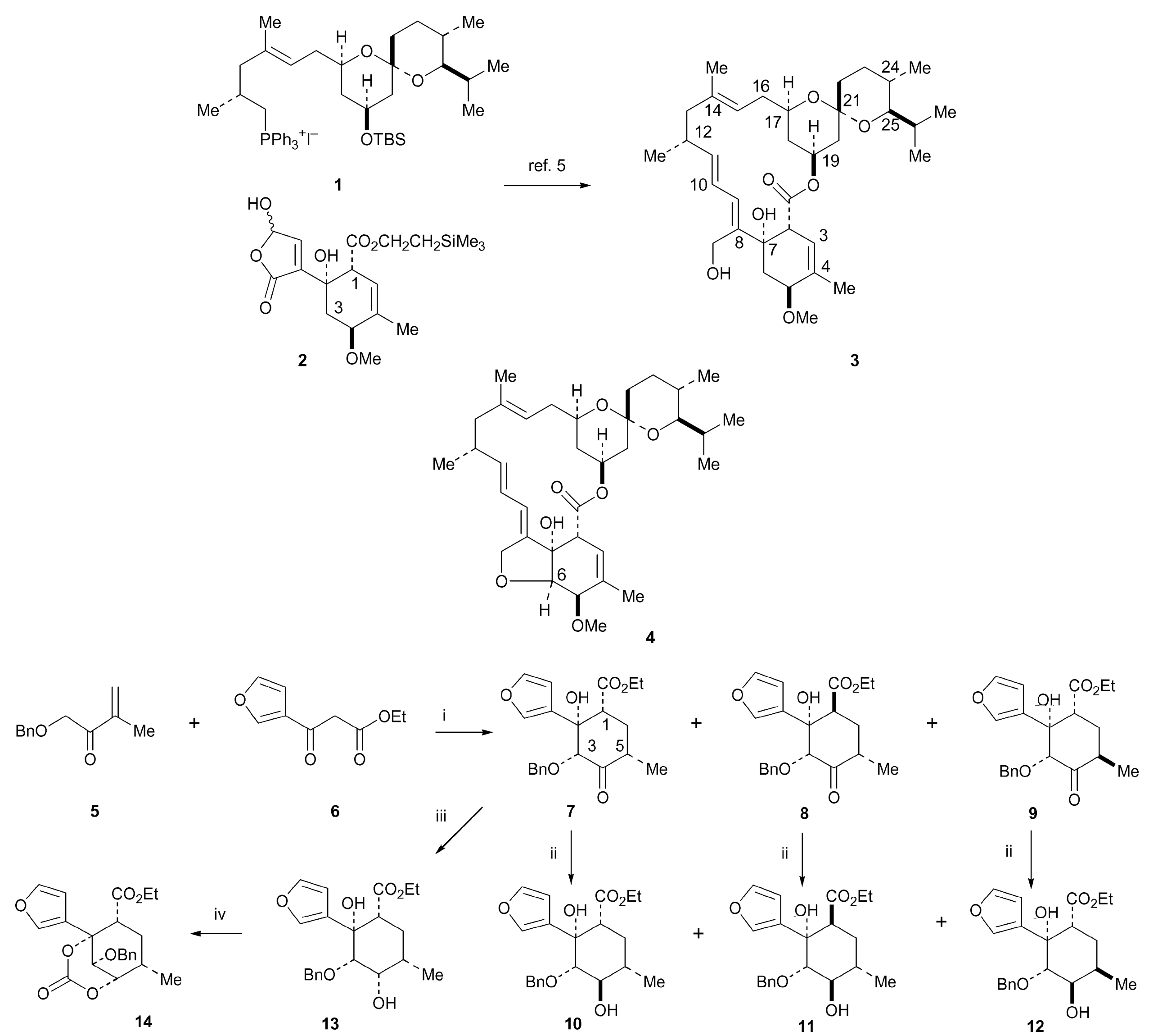


Scheme 1 *Reagents and conditions:* i, NaOH, EtOH, r.t., 24 h (**7**, 70%; **8**, 13%; **9**, 8%); ii, $NaBH_4$, AcOH, 30 min, r.t., then ketone added (**10**, 95%; **11**, 77%; **12**, 87%); iii, $NaBH_4$, EtOH, 3 h, r.t. (85%); iv, carbonyl diimidazole, benzene, NaH (trace), r.t., 6 h (67%).

Following earlier studies during the milbemycin E synthesis,[5c] reduction of the ketones **7**, **8** and **9** using sodium triacetoxyborohydride, was highly stereoselective and gave the *trans*-diols **10**, **11** and **12** by intramolecular delivery of hydride *via* intermediates in which the acetoxyborohydride was attached to the 2-hydroxyl group. In contrast, reduction of the hydroxyketone **7** by sodium borohydride proceeded *via* equatorial approach of the hydride to give the 1,3-*cis*-diol **13**.

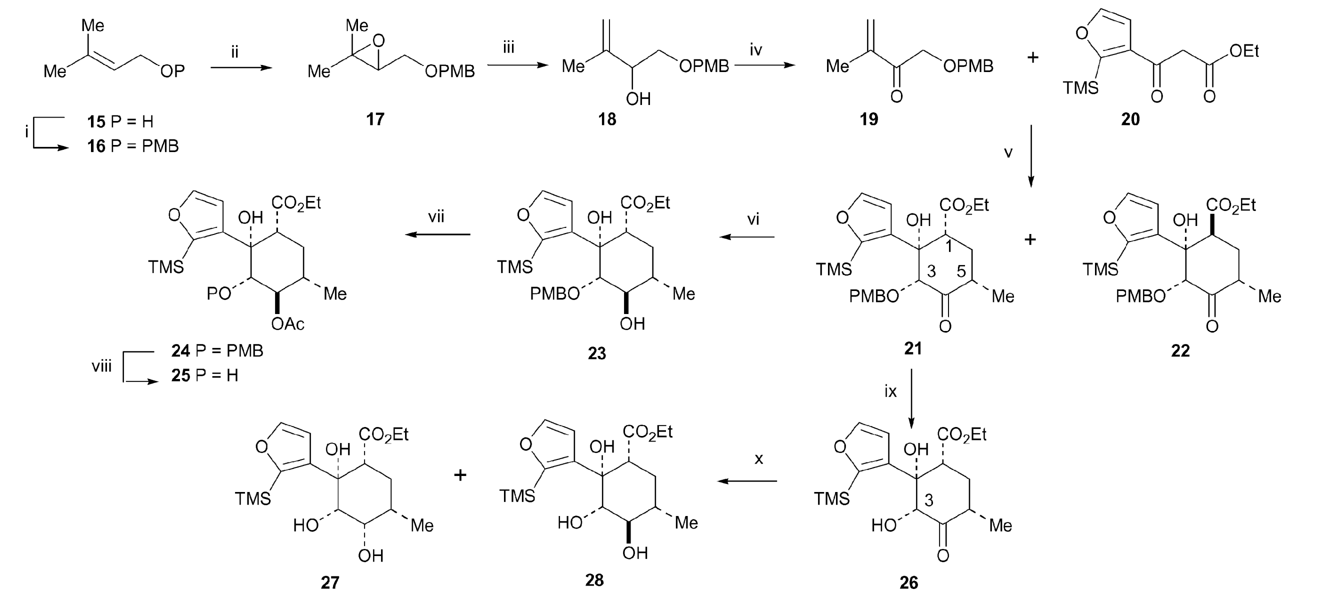
Structures were assigned to diols **10–13** by analogy with earlier work[5a] and were consistent with ^1H NMR studies including NOE data and vicinal coupling constants (see experimental). The configuration shown for the sodium borohydride reduction product was confirmed by formation of the cyclic carbonate **14** on reaction with carbonyl diimidazole.

These preliminary studies had shown that the incorporation of a benzyloxy substituent into the methyl group of isopropenyl methyl ketone was compatible with a stereoselective Robinson annelation, albeit giving rise to the unwanted configuration at C(3), at least as far as incorporation into an α-milbemycin synthesis was concerned. The next step was to check the compatibility of silylated furans, the preferred[5a] precursors of the hydroxybutenolides to be used in the crucial Wittig assembly step, with these reactions.

Isopropenyl *p*-methoxybenzyloxymethyl ketone **19** was prepared by conversion of 3-methylbut-2-en-1-ol **15** into its *p*-methoxybenzyl ether **16**, epoxidation, base induced rearrangement of the epoxide **17** so formed into the allylic alcohol **18** and a Swern oxidation,[8] see Scheme 2. The Robinson annelation between ketone **19** and ethyl 3-(2-trimethylsilyl-3-furyl)-3-oxopropanoate **20**[5a] was carried out using aqueous sodium hydroxide in ethanol and gave hydroxycyclohexanone **21** as the major product together with a small amount of its 1-epimer **22**. The configuration shown was assigned to the major, crystalline, adduct **21** by analogy with the earlier work, and on the basis of NOEs between the *cis*-configured axial hydrogens, 1-H, 3-H and 5-H. Its structure was subsequently confirmed by an X-ray analysis of a later intermediate, *vide infra*. The configuration of the minor adduct **22** was assigned on the basis of NMR data including the characteristic downfield shifts observed for the axial hydrogens 3-H and 5-H induced by the axial ethoxycarbonyl group.

The Robinson reaction of the alkoxymethyl ketone **19** had been usefully stereoselective, but again the major product had the opposite configuration at C(3) from that required for incorporation into a milbemycin synthesis. The configuration at this centre therefore had to be inverted.

Whereas the hydroxyketones **7**, **8** and **9** had been reduced stereoselectively by sodium triacetoxyborohydride prepared *in situ* from sodium borohydride and acetic acid, reduction of the hydroxyketone **21** under these conditions was very slow

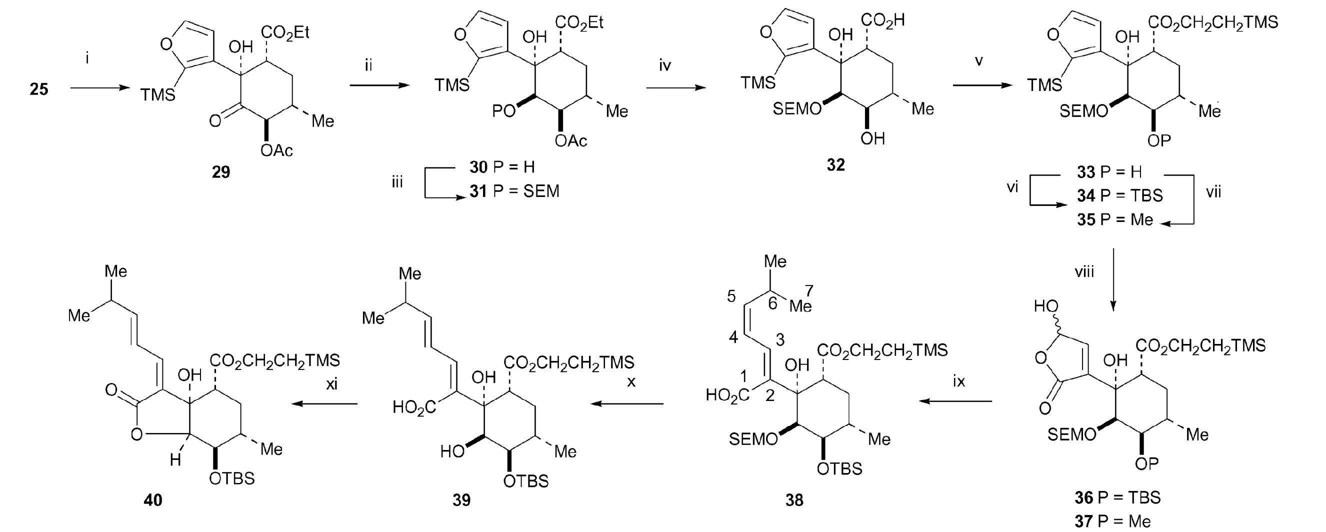


Scheme 2 *Reagents and conditions:* i, PMBCl, NaH, THF, TBAI, 16 h, r.t. (89%); ii, *m*CPBA, CH_2Cl_2, 0 °C, 2 h (85%); iii, $Al(O^iPr)_3$, xylene, reflux, 3 h (87%); iv, $(COCl)_2$, CH_2Cl_2, DMSO, −78 °C then Et_3N, r.t. (80%); v, NaOH, EtOH, 16 h, r.t. (**21**, 64%; **22**, 10%); vi, $Me_4NBH(OAc)_3$, AcOH, MeCN (1 : 1), 96 h, r.t. (89%); vii, Ac_2O, Et_3N, DMAP, CH_2Cl_2, 16 h, r.t. (93%); viii, DDQ, CH_2Cl_2, 3 h, r.t. (80%); ix, DDQ, H_2O, CH_2Cl_2, 3 h, r.t. (96%); x, $Me_4NBH(OAc)_3$, AcOH, MeCN (1 : 1), 1 h, r.t. (**27**, 51%; **28**, 16%).

and was often accompanied by unchanged starting material. Prolonged reaction with tetramethylammonium triacetoxyborohydride, 48 h, was required but did lead to a highly stereoselective reduction giving the alcohol **23** *via* intramolecular delivery of hydride from the acetoxyborohydride co-ordinated to the 2-hydroxyl group.[9] After acetylation of the 4-hydroxyl group, the *p*-methoxybenzyl group was removed oxidatively to give the alcohol **25**.

As the reduction of the hydroxyketone **21** had been slow, perhaps due to the additional steric hindrance of the trimethylsilyl group, reduction of the dihydroxyketone **26** prepared by oxidative removal of the *p*-methoxybenzyl group from the hydroxyketone **21** was briefly investigated. However, although reduction using tetramethylammonium triacetoxyborohydride was now complete in less than 1 h, two products were isolated in a 75 : 25 ratio and the major product was identified as the all-*cis*-triol **27** from ^{1}H NMR data (**27**, $J_{3,4} = J_{4,5} = 2.7$ Hz; **28**, $J_{3,4} = J_{4,5} = 9$ Hz). It would appear that delivery of hydride from the acetoxyborohydride when attached to the more accessible hydroxyl group at C(3) provides the preferred reaction pathway, and that this delivery can take place from the equatorial direction despite this being on the opposite face of the ring from the 3-hydroxyl group.

Swern oxidation of the alcohol **25** gave the ketone **29** which was reduced stereoselectively, again using tetramethylammonium triacetoxyborohydride, to give the alcohol **30** which now had the required configuration at C(3) for the proposed milbemycin synthesis, see Scheme 3. Following protection of the 3-hydroxyl group as its 2-trimethylsilylethoxymethyl (SEM) ether, simultaneous hydrolysis of the ethyl ester and the acetyl group gave the hydroxy acid **32**. The acid was converted into its 2-trimethylsilylethyl ester **33** and the 4-hydroxyl group protected as its *tert*-butyldimethylsilyl ether to give **34**. The analogous methyl ether **35** was also prepared, the latter conversion being best effected using lithium hexamethyldisilazide, cetyltrimethylammonium bromide (CTAB) and methyl iodide. Oxidation of the



Scheme 3 *Reagents and conditions:* i, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, r.t. (100%); ii, $Me_4NBH(OAc)_3$, AcOH, MeCN, 16 h, r.t. (85%); iii, $^iPr_2NEt$, SEMCl, CH_2Cl_2, 16 h, r.t. (90%); iv, NaOH, EtOH, THF, 72 h, r.t.; v, DCC, CH_2Cl_2, $Me_3SiCH_2CH_2OH$, 16 h, r.t. (87% from **31**); vi, 2,6-lutidine, TBSOTf, CH_2Cl_2, 3 h, r.t. (99%); vii, CTAB, MeI, THF, LHMDS in hexane, 0 °C, 15 min (93%); viii, tetraphenylporphine (TPP) (trace), CH_2Cl_2, MeOH, O_2, hν, 4 h, −78 °C, (**36**, 95%; **37**, 97%); ix, $^iPrCH_2PPh_3I$, LHMDS, −78 °C to −10 °C, 90 min. (89%); x, I_2, benzene, 3 h, hν (70%); xi, DCC, DMAP (cat.), CH_2Cl_2, 3 h, r.t. (90%).

trimethylsilylfurans **34** and **35** then gave the hydroxybutenolides **36** and **37** ready for incorporation into milbemycin syntheses, albeit racemic at this stage.

To check procedures for the Wittig reactions, the ylid prepared from 2-methylpropyl(triphenyl)phosphonium bromide was condensed with the hydroxybutenolide **36** to give the (2*Z*,4*Z*)-dienyl acid **38**. Very little of the analogous (2*Z*,4*E*)-isomer could be detected in the crude product mixture from the Wittig reaction, but treatment of the (2*Z*,4*Z*)-isomer **38** with a mole equivalent of iodine in benzene in the presence of a sun-lamp led to clean (4*Z*)/(4*E*)-isomerisation and simultaneous loss of the SEM group to give the (2*Z*,4*E*)-dihydroxy acid **39**. Lactonisation was then carried out using dicyclohexylcarbodiimide and 4-dimethylaminopyridine to give the butenolide **40**.

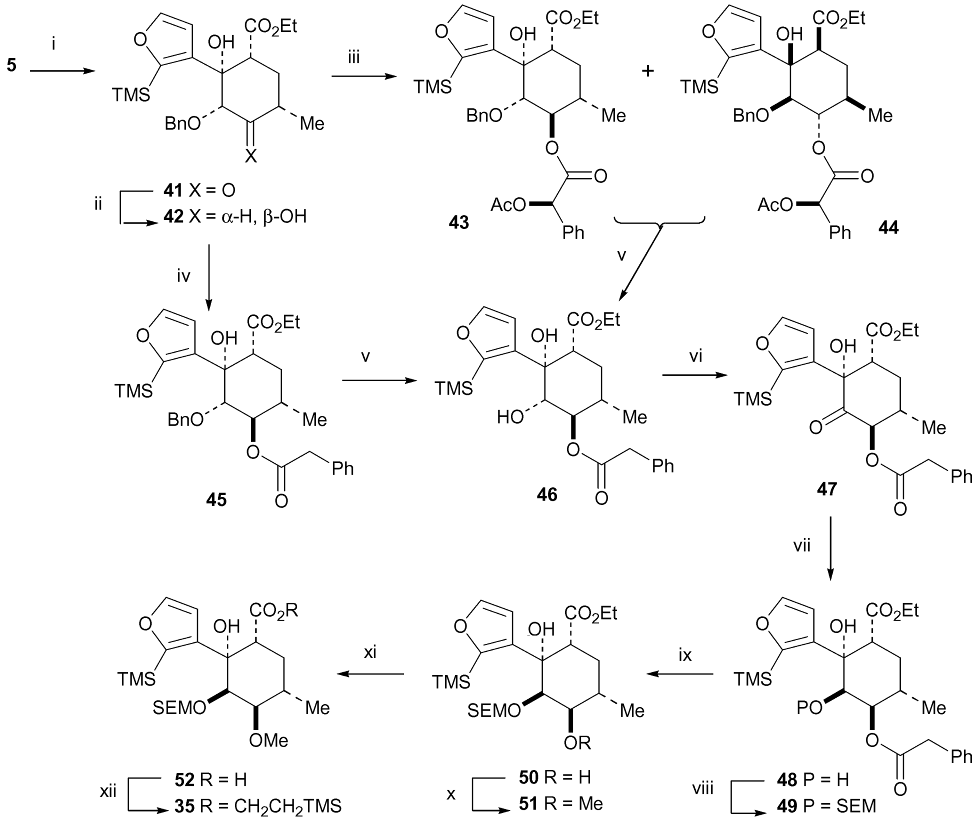
Before investigating the application of these procedures for the synthesis of macrocyclic analogues of milbemycins, a slightly modified synthesis of the hydroxybutenolide **37**, which provided for a resolution of the racemic material, was investigated, see Scheme 4. In this case, the Robinson reaction between the benzyloxymethyl isopropenyl ketone **5** and the β-keto ester **20** gave the hydroxycyclohexanone **41** which was reduced to the diol **42** using tetramethylammonium triacetoxyborohydride. Resolution of this diol was carried out by esterification with (*R*)-acetylmandelic acid[5d,10] to give a mixture of the crystalline diastereoisomeric esters **43** and **44**. These could be separated by chromatography but, more conveniently, the less polar isomer **44** could be isolated free of the more polar isomer **43** by selective crystallization from the mixture. Following this procedure, but using the (*S*)-acetyl mandelate, the enantiomer of **44**, which had incorporated the required enantiomer of diol **42**, was isolated in a 35% yield based on the racemic diol **42**.

Structures were assigned to esters **43** and **44** on the basis of the influence of the (*R*)-acetylmandelate group on the relative ^{1}H NMR chemical shifts of the six-membered ring hydrogens and substituents. For example, the 5-methyl substituent gave rise to a doublet at δ1.08 in the ^{1}H NMR spectrum of the more polar isomer **43** and at δ0.57 for the less polar isomer **44**.[11]

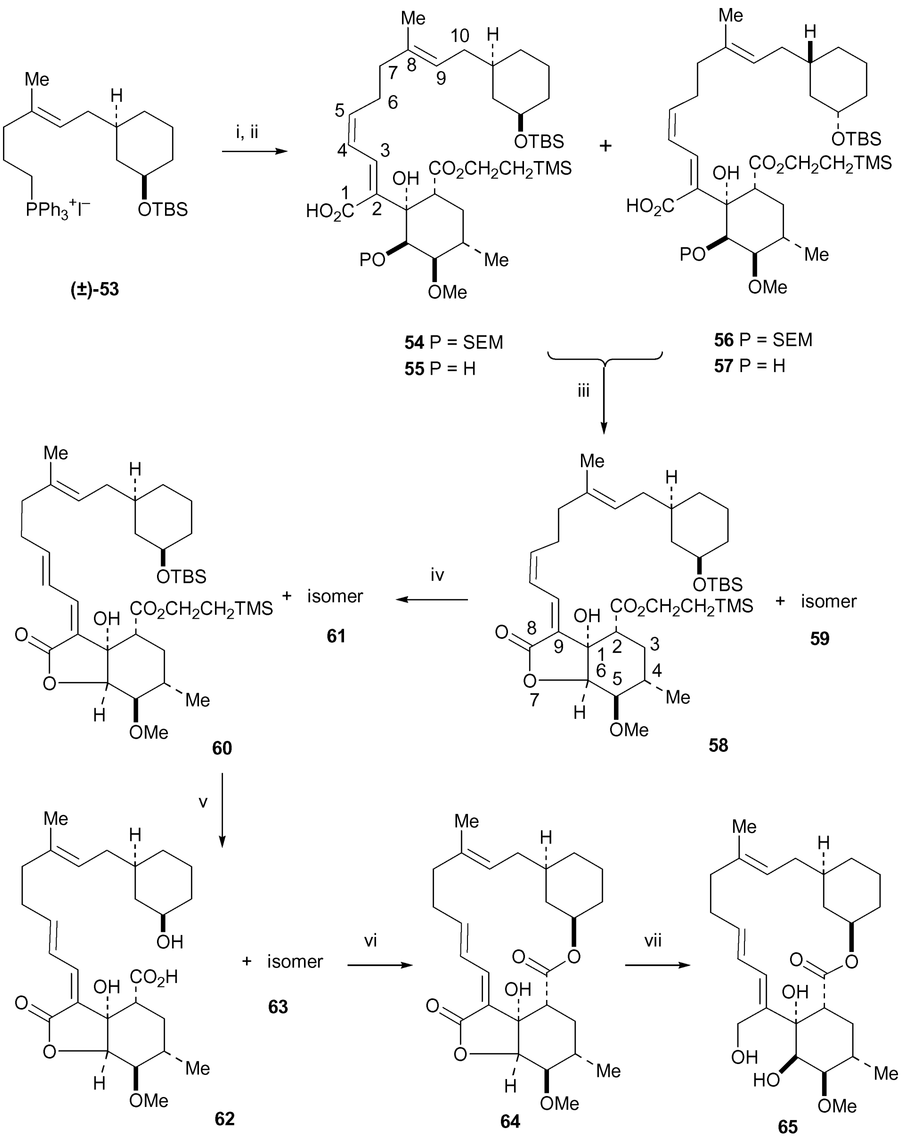
Although this resolution provided access to enantiomerically enriched intermediates, further preliminary work was carried out using racemic compounds. Thus hydrogenolysis of a mixture of the esters **43** and **44** gave the racemic phenylacetate **46** in which both the acetoxy substituent in the mandelate and the benzyl ether at C(3) had been cleaved. This racemic phenylacetate was also prepared by esterification of diol **42** using phenylacetic acid followed by hydrogenolysis of the benzyl ether **45**.

The relative configuration of the alcohol at C(3) in the racemic ester **46** was inverted by oxidation to the ketone **47** followed by triacetoxyborohydride reduction, and the product alcohol **48** protected as its SEM-ether **49**. Selective hydrolysis of the phenylacetate followed by *O*-methylation, in this case using silver oxide and methyl iodide, gave the methyl ether **51**, which was converted into the 2-trimethylsilyl ester **35**, an intermediate in the previous synthesis, by hydrolysis and esterification using 2-trimethylsilylethanol.

The Wittig reaction between the racemic hydroxybutenolide **37** and the racemic phosphonium salt **53**[5a] was carried out by adding an excess of lithium hexamethyldisilazide to a mixture of the hydroxybutenolide and phosphonium salt in tetrahydrofuran at −78 °C and gave a mixture of the (2*Z*,4*Z*)-dienes **54** and **56** together with *ca.* 10% of the corresponding (2*Z*,4*E*)-isomers. Apart from the presence of these minor (2*Z*,4*E*)-alkenes, the product appeared to be homogeneous, but as no kinetic resolution was to be expected in the Wittig process it was assumed that a 50 : 50 mixture of the racemic diastereoisomers **54** and **56** had been formed. No attempt was made to separate this mixture, since it was known from earlier work[5a] that only the seco-acid with the relative configuration corresponding to that in the natural products would cyclise, *vide infra*, Scheme 5.



Scheme 4 *Reagents and conditions:* i, **20**, NaOH, EtOH, 20 h, r.t. (50%); ii, $Me_4NBH(OAc)_3$, AcOH–MeCN (1 : 1), 96 h, r.t. (84%); iii, (*R*)-acetylmandelic acid, DMAP, DCC, CH_2Cl_2, 16 h, r.t. (**43** + **44**, 64%); iv, phenylacetic acid, DMAP, DCC, CH_2Cl_2 (85%); v, H_2, Pd/C, EtOH (73% from **43**/**44**; 91% from **45**); vi, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N (99%); vii, $Me_4NBH(OAc)_3$, AcOH–MeCN (99%); viii, $^iPr_2NEt$, SEMCl, CH_2Cl_2 (91%); ix, K_2CO_3, EtOH, 48 h, r.t. (70%); x, Ag_2O, MeI (62%); xi, NaOH, EtOH; xii, $Me_3SiCH_2CH_2OH$, DMAP, DCC, CH_2Cl_2 (80%).



Scheme 5 *Reagents and conditions:* i, (±)-**37**, LHMDS, −78 °C to −10 °C, 90 min (90%); ii, BuSH, $MgBr_2$, K_2CO_3, Et_2O, 10 min (88%); iii, DCC, DMAP, CH_2Cl_2, 3 h, r.t. (80%); iv, I_2, benzene, K_2CO_3, hν, 3 h, r.t. (75%); v, TBAF, THF, 16 h, r.t. (97%); vi, $Cl_3C_6H_2CO{\cdot}Cl$, Et_3N, xylene, 2 d then DMAP, xylene, 1 h (26% : 52% based on **62**); vii, DIBAL-H, toluene, −78 °C, 30 min (70%).

In this series, attempted simultaneous (4*Z*)/(4*E*)-isomerisation and removal of the SEM group from the acids **54** and **56** using iodine gave rise to mixtures of products with only partial SEM-deprotection. It was found to be more efficient to remove the SEM group first by treatment with magnesium(II) bromide and *n*-butanethiol[12] in the presence of potassium carbonate to prevent adventitious addition of hydrogen bromide to the 8,9-double-bond. Subsequent lactonization using dicyclohexylcarbodiimide and 4-dimethylaminopyridine gave the butenolides **58** and **59**, still as a *ca.* 90 : 10 mixture of the (2′*Z*)- and (2′*E*)-isomers. (2′*Z*)/(2′*E*)-Isomerisation was then achieved using a catalytic amount of iodine in benzene to give the (9*Z*,2′*E*)-dienes **60** and **61**. Conversion into the, now distinguishable, seco-acids **62** and **63** was carried out using tetrabutylammonium fluoride in tetrahydrofuran, and macrocyclisation was achieved using the modified Yamaguchi procedure.[13] As expected, only the seco-acid with the configuration corresponding to the natural products cyclised, and the required macrolide **64** was isolated as a single isomer in a 52% yield (based on seco-acid **62**). As this bis-lactone was crystalline, its structure was confirmed as shown by X-ray diffraction, see Fig. 1. Selective reduction of the 5-membered lactone over the macrolide was then achieved using diisobutylaluminium hydride in toluene and gave the β-milbemycin analogue **65**.

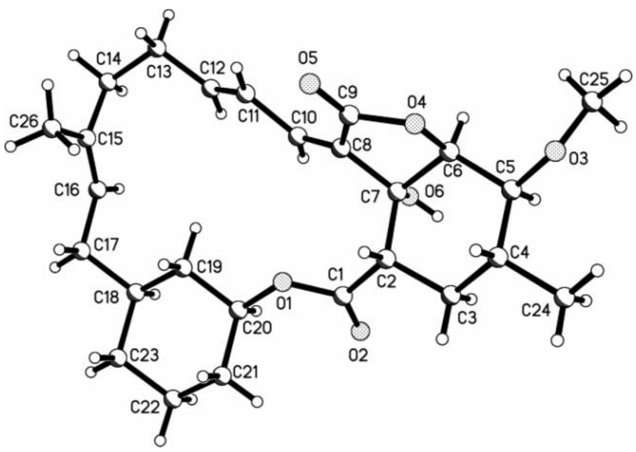
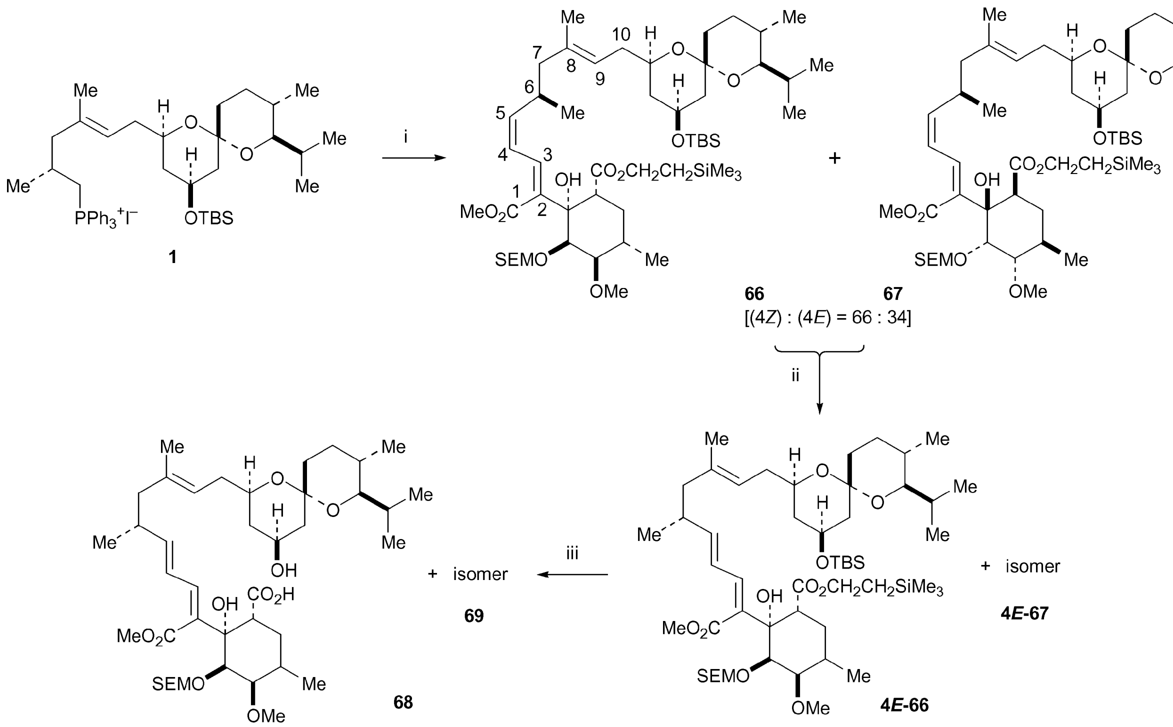


Fig. 1 Projection of the conformation of the macrolide **64** as determined by X-ray crystallography.

Having established a strategy for the assembly of macrolides in this series, the racemic hydroxybutenolide **37** was condensed with the enantiomerically enriched phosphonium salt **1** followed in this more complex case by esterification of the acid so formed



Scheme 6 *Reagents and conditions:* i, (±)-**37**, LHMDS, THF, −78 to −10 °C, 90 min then CH_2N_2, Et_2O, r.t. (66%); ii, I_2 (50 mol%), benzene, hν (90%); iii, TBAF, THF, 10 h (99%).

using diazomethane to give a *ca.* 2 : 1 mixture of the (4*Z*)- and (4*E*)-dienyl esters **66**, together with their diastereoisomers **67** which had incorporated the wrong enantiomer of the hydroxybutenolide. In this case an attempt was made to effect macrocyclisation of the seco-acids **68** and **69** formed by (4*Z*)- to (4*E*)-isomerisation of the dienes **66** and **67** using a sub-stoichiometric amount of iodine without removal of the SEM group, and desilylation with removal of the trimethylsilylethyl ester, but no large-ring product could be isolated, see Scheme 6. A stoichiometric amount of iodine was therefore used to carry out simultaneous (4*Z*)- to (4*E*)-diene isomerisation and SEM group removal from the Wittig products **66** and **67** to give the dihydroxydienes **70** and **71**, see Scheme 7. Treatment of this mixture of hydroxy methyl esters with silica gel in chloroform effected intramolecular transesterification to give the butenolides **72** and **73** and desilylation using tetrabutylammonium fluoride in tetrahydrofuran removed both the 2-trimethylsilyl ester and the *tert*-butyldimethylsilyl ether protecting groups to give a mixture of the distinguishable, but not separable, seco-acids **74** and **75**. As in the earlier series, macrocyclisation, in this case using dicyclohexylcarbodiimide, was successful only for the seco-acid which had the configuration of the natural milbemycins, and gave the required macrolide **76** (46% based on seco-acid **74**). Selective reduction of the 5-membered lactone then gave (6*R*)-6-hydroxy-3,4-dihydromilbemycin E **77**.

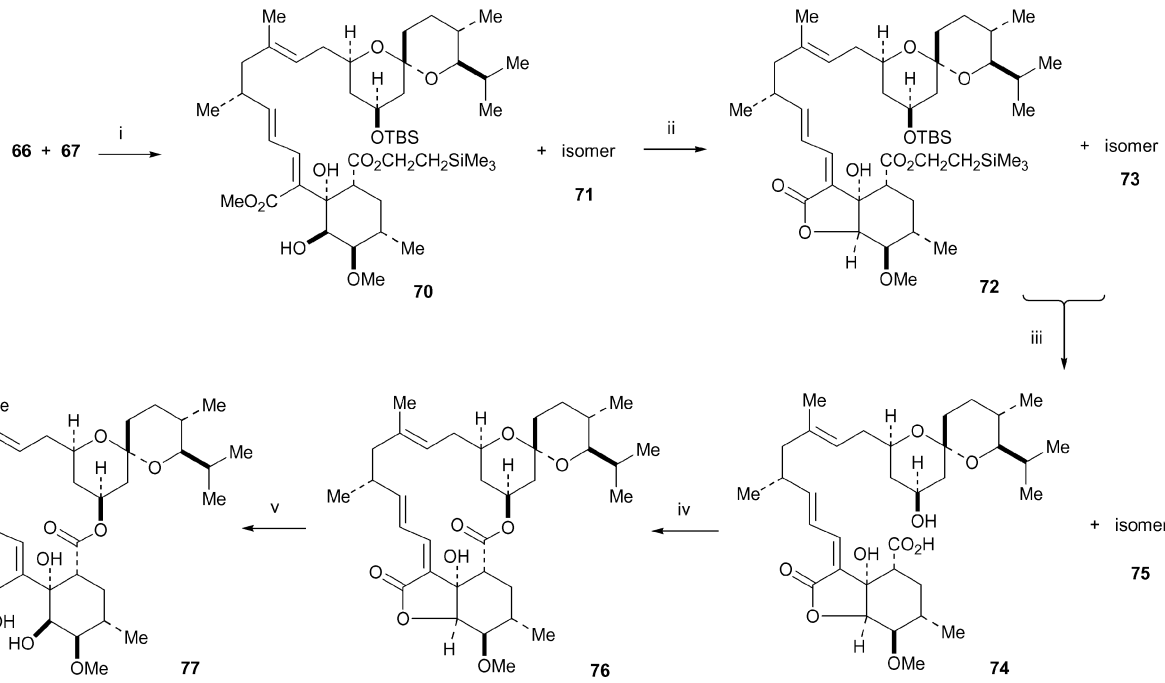
Since the ultimate objective of this work was to complete a synthesis of an α-milbemycin, preliminary attempts were made to convert the β-milbemycin analogues **65** and **77** into tetrahydrofurans corresponding to analogues of α-milbemycins. However, treatment of these triols with an excess of lithium diisopropylamide and one equivalent of toluene *p*-sulfonyl chloride gave rise to the formation of the primary allylic chlorides **78** and **79**, rather than the required tetrahydrofurans. Structures were assigned to these chlorides by comparison of their ^1H NMR data with those of milbemycin G **4** and its synthetic precursor, the chloride **80**.[14,15] In particular the peaks due to 9-H and 10-H in chloride **79** are at δ6.14 (d, *J* 11) and δ6.26 (dd, *J* 15, 11) with the corresponding peaks in chloride **80** being at δ6.38 (d, *J* 11) and at δ6.26 (dd, *J*, 15, 11). For comparison, in milbemycin G **4**, 9-H and 10-H overlap as a complex multiplet at δ5.69–5.77.[15]†

Summary and conclusions

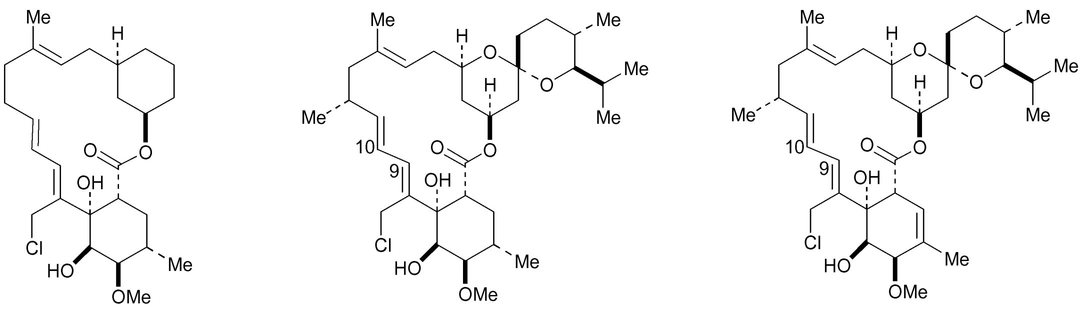
This work has shown that the approach used previously to prepare non-aromatic β-milbemycins as typified by a synthesis of milbemycin E **3**,[5] can be applied to synthesize milbemycins with a hydroxyl group at C(6) (milbemycin numbering). The Robinson reactions used to assemble the six-membered ring leading to the C(1)–C(10)-fragments were stereoselective but gave the unwanted configuration at C(6). Nevertheless, the configuration at this centre could be inverted by a redox process, and procedures were developed for the resolution of this fragment and for its incorporation into macrocyclic analogues of milbemycins culminating in a total synthesis of (6*R*)-6-hydroxy-3,4-dihydromilbemycin E **77**. During these studies it was observed that the macrocyclisation reactions were more efficient if carried out on intermediates in which a butenolide had been incorporated between the side-chain acid and the 6β-hydroxyl group, perhaps because of more limited degrees of freedom in this system.

The next stage in this programme was to show that the chemistry used to introduce the 6β-hydroxyl substituent was compatible with the 3,4-double-bond (milbemycin numbering) and to find procedures to effect the formation of the tetrahydrofuran ring found in the α-milbemycins. The results of this work and the completion of a total synthesis of milbemycin G **4** including the successful introduction of the tetrahydrofuran ring are described in the accompanying paper.[14,15]

† At the time of our preliminary communication on this work,[7b] it was thought that the triols **65** and **77** had been cyclised on treatment with lithium diisopropylamide and toluene *p*-sulfonyl chloride. It was only after the synthesis of milbemycin G was complete and the allylic chloride **80** identified[14,15] did it become apparent that the chlorides **78** and **79** had been formed in the present study.



Scheme 7 *Reagents and conditions:* i, I_2, benzene, hυ, 1.5 h (92%); ii, silica, $CHCl_3$ (98%); iii, TBAF, THF, 10 h (78%); iv, DCC, DMAP, CH_2Cl_2, 21 h (23% of **76**, 46% based on **74**); v, DIBAL-H, toluene, −78 °C, 1 h (74%).



78 **79** **80**

Experimental

Melting points were recorded on a Koffler heated stage microscope and are uncorrected. Proton NMR spectra were recorded in deuteriated chloroform unless otherwise indicated on Bruker AC300, Varian XXL300 and Varian Unity 500 spectrometers; coupling constants are given in Hz and chemical shifts relative to Me_4Si. IR spectra were recorded on a Perkin Elmer 1710FT spectrometer and were run as liquid films, KBr discs or as solutions in chloroform. Mass spectra were measured on a Kratos MS25 spectrometer coupled to a DS55 data system. Optical rotations were measured on an Optical Activity AA100 polarimeter at ambient temperature, typically 20 °C.

Chromatography refers to flash chromatography[16] using Merck silica gel 60H (40–63 mm^3, 230–300 mesh). Light petroleum refers to the fraction boiling at 40–60 °C and ether to diethyl ether. All solvents and reagents were purified before use by standard techniques.[17] All non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen.

Ethyl (1*RS*,2*SR*,3*RS*,5*SR*)-2-(3-furyl)-2-hydroxy-5-methyl-3-phenylmethoxy-4-oxocyclohexane-1-carboxylate 7, (1*SR*,2*SR*,3*RS*,5*SR*)-2-(3-furyl)-2-hydroxy-5-methyl-3-phenylmethoxy-4-oxocyclohexane-1-carboxylate 8 and (1*RS*,2*SR*,3*RS*,5*RS*)-2-(3-furyl)-2-hydroxy-5-methyl-3-phenylmethoxy-4-oxocyclohexane-1-carboxylate 9

The benzyloxymethyl ketone **5** (6.8 g, 38 mmol) in ethanol (19 cm^3) was added to a mixture of the keto ester **6**[5a] (5.77 g, 32 mmol) in ethanol (70 cm^3) and aqueous sodium hydroxide (10%; 2.2 cm^3) and the mixture stirred at ambient temperature for 24 h. The solid which had separated out was filtered off and recrystallized from ether–hexane to give the *title compound* **7** (70%), mp 94–95 °C. (Found: C, 67.5; H, 6.4%. $C_{21}H_{24}O_6$ requires C, 67.75; H, 6.50%), ν_{max} ($CHCl_3$) 3478, 1723, 1053 and 1030 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.12 (3 H, t, *J* 7, CH_2CH_3), 1.15 (3 H, d, *J* 6, 5-CH_3), 2.12 (2 H, m, 6-H_2), 2.5 (1 H, m, 5-H), 3.2 (1 H, dd, *J* 7.5, 8, 1-H), 3.8 (1 H, s, 3-H), 3.9 (1 H, s, OH), 4.05 (2 H, m, CH_2CH_3), 4.3 and 4.8 (each 1 H, d, *J* 12.5, O*H*CHPh), 6.3 (1 H, s, 4′-H), 7.0 (2 H, m, ArH, 7.2 (3 H, m, ArH) and 7.4 (2 H, m, 2′-H and 5′-H); *m*/*z* (EI) 372 (M^+, 1%), 263 (4) and 95 (100). The filtrate was concentrated under reduced pressure and the residue taken up in ether (30 cm^3). The ether solution was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave first the *title compound* **8** (13%), mp 78–80 °C. (Found: C, 67.65; H, 6.5%. $C_{21}H_{24}O_6$ requires C, 67.75; H, 6.50%), ν_{max} (KBr) 3474, 1713, 1455, 1373 and 1195 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.88 (3 H, t, *J* 7.5, CH_2CH_3), 1.1 (3 H, d, *J* 7.5, 5-CH_3), 1.8 (1 H, ddd, *J* 13, 7, 1, 6-H), 2.25 (1 H, dt, *J* 6, 13, 6-H′), 3.1 (2 H, m, 5-H, OH), 3.2 (1 H, dd, *J* 6, 1.5, 1-H), 3.85 (2 H, m, CH_2CH_3), 4.3 and 5.0 (each 1 H, d, *J* 11, O*H*CHPh), 5.15 (1 H, s, 3-H), 6.3 (1 H, s, 4′-H) and 7.2 (7 H, m, ArH, 2′-H, 5′-H); *m*/*z* (EI) 372 (M^+, 5%) and 95 (100). Further elution gave the *title compound* **9** (8%), mp 85 °C. (Found: C, 68.0; H, 6.5%. $C_{21}H_{24}O_6$ requires C, 67.75; H, 6.50%), ν_{max} (KBr) 3416, 1710, 1187, 1164, 1026 and

965 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.08 (3 H, t, *J* 7.5, CH_2CH_3), 1.15 (3 H, d, *J* 7.5, 5-CH_3), 1.52 and 2.47 (each 1 H, m, 6-H), 3.0 (1 H, m, 5-H), 3.1 (1 H, dd, *J* 8, 3, 1-H), 3.98 (2 H, m, CH_2CH_3), 4.02 (1 H, s, 3-H), 4.42 and 4.6 (each 1 H, d, *J* 12, O*H*CHPh), 4.78 (1 H, br. s, OH), 6.3 (1 H, s, 4′-H) and 7.05–7.4 (7 H, m, ArH, 2′-H, 5′-H); *m/z* (CI) 390 (M^+ + 18, 66%), 355 (98), 265 (57), 208 (79) and 95 (100). Finally a further small amount of the major product **7** (*ca.* 5%) was eluted from the column.

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-3-benzyloxy-2,4-dihydroxy-2-(3-furyl)-5-methylcyclohexane-1-carboxylate 10

Sodium borohydride (23 mg, 0.62 mmol) was added to acetic acid (1.7 cm^3) portionwise over 20 min maintaining a temperature of 15–18 °C and the mixture stirred at ambient temperature for 30 min then added to the hydroxycyclohexanone **7** (57 mg, 0.154 mmol). The mixture was stirred for 3 h then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 cm^3) and the solution washed with aqueous sodium hydroxide (3 M, 3 × 5 cm^3). The aqueous phase was re-extracted and the combined organic extracts washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from ether–hexane to give the *title compound* **10** (100%), mp 98–99 °C. (Found: C, 67.0; H, 6.9%. $C_{21}H_{26}O_6$ requires C, 67.35; H, 7.0%); ν_{max} (KBr) 3430, 1712 and 1187 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.1 (3 H, t, *J* 7, CH_2CH_3), 1.12 (3 H, d, *J* 7.5, 5-CH_3), 1.6 (1 H, m, 5-H), 1.8 (2 H, m, 6-H_2), 2.15 (1 H, br. s, OH), 2.82 (1 H, dd, *J* 12, 1.5, 1-H), 3.2 (1 H, d, *J* 9, 3-H), 3.65 (1 H, t, *J* 9, 4-H), 4.0 (3 H, m, OH, CH_2CH_3), 4.15 and 4.32 (each 1 H, d, *J* 11, O*H*CHPh), 6.45 (1 H, s, 4′-H), 7.1–7.3 (5 H, m, ArH), 7.44 (1 H, m, 5′-H) and 7.5 (1 H, m, 2′-H); *m/z* (EI) 374 (M^+, 1.6%), 250 (60), 174 (51) and 91 (100).

Ethyl (1*SR*,2*SR*,3*SR*,4*RS*,5*SR*)-3-benzyloxy-2,4-dihydroxy-2-(3-furyl)-5-methylcyclohexane-1-carboxylate 11

Following the procedure outlined above for the preparation of diol **10**, the hydroxyketone **8** (105 mg, 0.28 mmol) gave the *title compound* **11** (81 mg, 77%), as an oil. [Found (EI): M^+, 374.1729. $C_{21}H_{26}O_6$ requires M, 374.1729]; ν_{max} ($CHCl_3$) 3495, 1726 and 1188 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.05 (3 H, d, *J* 7.5, 5-CH_3), 1.15 (3 H, t, *J* 7, CH_2CH_3), 1.17 (1 H, m, 6-H_{eq}), 1.95 (1 H, dt, *J* 5.5, 14, 6-H_{ax}), 2.1 (1 H, m, 5-H), 2.9 (1 H, dd, *J* 5.5, 1.5, 1-H), 3.05 (1 H, br. s, OH), 3.5 (1 H, dd, *J* 7.5, 8.5, 4-H), 4.05 (2 H, q, *J* 7, CH_2CH_3), 4.3 (1 H, d, *J* 8.5, 3-H), 4.45 and 4.65 (each 1 H, d, *J* 10, O*H*CHPh), 6.45 (1 H, s, 4′-H), 7.1–7.3 (5 H, m, ArH), 7.35 (1 H, m, 5′-H) and 7.5 (1 H, m, 2′-H); *m/z* (EI) 374 (M^+, 2%), 357 (30), 339 (39), 250 (47) and 91 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*RS*)-3-benzyloxy-2,4-dihydroxy-2-(3-furyl)-5-methylcyclohexane-1-carboxylate 12

Following the procedure outlined above for the preparation of diol **10**, the hydroxyketone **9** (50 mg, 0.13 mmol) gave the *title compound* **12** (42 mg, 87%), as a white solid, mp 130–132 °C. (Found: C, 67.0; H, 7.0%. $C_{21}H_{26}O_6$ requires C, 67.35; H, 7.0%); ν_{max} (KBr) 3489, 1710, 1500, 1188, 1109, 1079, 1030 and 1002 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.8 (3 H, t, *J* 7, CH_2CH_3), 1.12 (3 H, d, *J* 7.5, 5-CH_3), 1.52 (1 H, dt, *J* 13.5, 3, 6-H_{eq}), 2.25 (2 H, m, 5-H, OH), 2.42 (1 H, dt, *J* 4, 13.5, 6-H_{ax}), 3.0 (1 H, dd, *J* 13.5, 4, 1-H), 3.37 (1 H, d, *J* 10, 3-H), 3.79 (2 H, m, CH_2CH_3), 4.24 and 4.34 (each 1 H, d, *J* 11, O*H*CHPh), 4.35 (1 H, m, OH), 4.42 (1 H, dd, *J* 10, 5.5, 4-H), 6.28 (1 H, s, 4′-H), 7.1–7.3 (6 H, m, ArH, 5′-H) and 7.45 (1 H, m, 2′-H); *m/z* (EI) 374 (M^+, 4%) and 250 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*SR*,5*SR*)-3-benzyloxy-2,4-dihydroxy-2-(3-furyl)-5-methylcyclohexane-1-carboxylate 13

Sodium borohydride (133 mg, 3.5 mmol) was added portionwise to the hydroxyketone **7** (131 mg, 0.352 mmol) in ethanol (1 cm^3) and the mixture stirred for 3 h. Ether (5 cm^3) was added and the mixture washed with water (3 × 5 cm^3). After re-extraction of the aqueous phase, the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the *title compound* **13** (112 mg, 85%), as a white solid, mp 113–114 °C. (Found: C, 67.3; H, 7.0%. $C_{21}H_{26}O_6$ requires C, 67.35; H, 7.0%); ν_{max} ($CHCl_3$) 3419, 3064, 1707 and 1191 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.68 (3 H, t *J* 6.5, CH_2CH_3), 1.05 (4 H, m, 5-CH_3, 5-H), 1.22 (1 H, m, 6-H), 1.97 (1 H, q, *J* 12, 6-H′), 2.35 (1 H, dd, *J* 12, 4, 1-H), 2.78 (1 H, d, *J* 3, 3-H), 3.61 (2 H, m, CH_2CH_3), 3.85 (1 H, br. d, *J* 9, OH), 4.05 (1 H, d, *J* 3, 4-H), 4.1 and 4.45 (each 1 H, d, *J* 11, O*H*CHPh), 4.92 (1 H, s, OH), 6.19 (1 H, s, 4′-H), 6.9–7.1 (6 H, m, ArH, 5′-H) and 7.5 (1 H, m, 2′-H); *m/z* (EI) 374 (M^+, 1%) and 91 (100).

Carbonyl diimidazole (153 mg, 0.94 mmol) was added to the *cis*-diol **13** (88 mg, 0.235 mmol) in anhydrous benzene (2 cm^3) containing a trace of sodium hydride and the mixture stirred for 36 h at ambient temperature. Ethyl acetate (5 cm^3) was added and the mixture washed with water (3 × 3 cm^3). After re-extraction of the aqueous phase, the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the cyclic carbonate **14** (63 mg, 67%) as a white solid, mp 184–185 °C; ν_{max} ($CHCl_3$) 3020, 1748, 1630, 1602 and 1154 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.13 (3 H, t *J* 7.5, CH_2CH_3), 1.2 (3 H, d, *J* 6, 5-CH_3), 1.9 (3 H, m, 5-H, 6-H_2), 2.9 (1 H, m, 1-H), 3.46 (1 H, d, *J* 2, 3-H), 3.98 (2 H, m, CH_2CH_3), 4.4 and 4.5 (each 1 H, d, *J* 12.5, O*H*CHPh), 4.53 (1 H, m, 4-H), 6.3 (1 H, s, 4′-H), 7.1–7.3 (5 H, m, ArH), 7.42 (1 H, m, 5′-H) and 7.5 (1 H, m, 2′-H); *m/z* (CI) 418 (M^+ + 18, 100%).

1-*p*-Methoxybenzyloxy-3-methylbut-2-ene 16

Sodium hydride (3 g, 128 mmol) was washed with THF (3 × 20 cm^3), suspended in THF (50 cm^3) and a solution of 3-methylbut-2-en-1-o1 **15** (10 g, 116 mmol) in THF (50 cm^3) was added slowly. The mixture was stirred for 30 min before cooling to 0 °C and tetra-*n*-butylammonium iodide (4.28 g, 11.6 mmol) and *p*-methoxybenzyl chloride (19.9 g, 128 mmol) were added. The reaction was stirred for 16 h at room temperature, cooled to 0 °C, then water (20 cm^3) was added. The mixture was diluted with ether (100 cm^3), washed with water (2 × 20 cm^3) and the aqueous phase was re-extracted. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the ether **16** (21.3 g, 89%) as a yellow oil. Chromatography of a sample using light petroleum–ether (9 : 1) as eluant gave the *title compound* **16**. [Found (EI): M^+, 206.1296. $C_{13}H_{18}O_2$ requires M, 206.1307]; ν_{max} ($CHCl_3$) 1613, 1514, 1448, 1379, 1176 and 1074 cm^{-1}; δ_H (300 MH; $CDC1_3$) 1.65 and 1.79 (each 3 H, s, CH_3), 3.8 (3 H, s, OCH_3), 3.98 (2 H, d, *J* 7, 1-H_2), 4.45 (2 H, s, CH_2Ar), 5.4 (1 H, m, 2-H), 6.9 (2 H, m, ArH) and 7.3 (2 H, m, ArH); *m/z* (EI) 206 (M^+, 32%), 156 (21) and 121 (100).

1-*p*-Methoxybenzyloxy-3-methylbut-2-ene epoxide 17

A solution of olefin **16** (21.3 g, 103 mmol) in dichloromethane (100 cm^3) was added to a suspension of *m*-chloroperbenzoic acid (43.6 g, 140 mmol) in dichloromethane (250 cm^3) at 0 °C. The mixture was stirred at this temperature for 2 h before filtering through celite, washing with aqueous sodium bicarbonate (3 × 50 cm^3) and re-extracting the aqueous phase. The combined organic phases were dried ($MgSO_4$) and concentrated to give the epoxide **17** (19.4 g, 85%) as a yellow oil. Chromatography of a sample using light petroleum–ether (9 : 1) as eluant gave the *title compound* **17**. [Found (EI): M^+, 222.1259. $C_{13}H_{18}O_3$ requires M, 222.1256]; ν_{max} ($CHCl_3$) 1727, 1613, 1587, 1514, 1463, 1380, 1303, 1175, 1083, 1036 and 907 cm^{-1}; δ_H (200 MHz, $CDC1_3$) 1.26 and 1.35 (each 3 H, s, CH_3), 3.0 (1 H, t, *J* 5, 2-H), 3.55 (1 H, dd, *J* 11, 5 Hz, 1-H), 3.65 (1 H, dd, *J* 11, 5 Hz, 1-H), 3.82 (3 H, s,

OCH_3), 4.48 and 4.6 (each l H, d, *J* 12, HC*H*Ar) and 6.9 and 7.3 (each 2 H, m, ArH); *m/z* (EI) 222 (M^+, 0.5%), 156 (7), 137 (59) and 121 (100).

1-*p*-Methoxybenzyloxy-3-methylbut-3-en-2-ol 18

Epoxide **17** (19.4 g, 87.4 mmol) and aluminium isopropoxide (25 g, 122 mmol) were heated under reflux in xylene (100 cm^3) for 3 h. The mixture was cooled and washed with aqueous hydrogen chloride (3 M; 2 × 20 cm^3). The aqueous phase was re-extracted and the combined organic phases dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave the *title compound* **18** (16.53 g, 87%) as a clear oil. [Found (EI): M^+, 222.1257. $C_{13}H_{18}O_3$ requires M, 222.1256]; ν_{max} ($CHCl_3$) 3400, 3075, 1653, 1613, 1587, 1514, 1463, 1363, 1175, 1035 and 902 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.75 (3 H, s, 3-CH_3), 2.5 (1 H, br. s, OH), 3.4 (1 H, dd, *J* 9.5, 8, 1-H), 3.55 (1 H, dd, *J* 9.5, 3, 1-H), 3.82 (3 H, s, OCH_3), 4.28 (1 H, dd, *J* 8, 3, 2-H), 4.52 (2 H, s, CH_2Ar), 4.95 (1 H, s, 4-H), 5.08 (1 H, s, 4-H) and 6.88 and 7.3 (each 2 H, m, ArH); *m/z* (EI) 222 (M^+, 5%), 152 (5), 137 (25) and 121 (100).

1-*p*-Methoxybenzyloxy-3-methylbut-3-en-2-one 19

Dimethyl sulfoxide (1.07 g, 13.6 mmol) in dichloromethane (6 cm^3) was added to oxalyl chloride (0.95 g, 7.5 mmol) in dichloromethane (10 cm^3) at −78 °C followed by the alcohol **18** (1.5 g, 6.8 mmol) in dichloromethane (6 cm^3). The mixture was stirred for 15 min before triethylamine (4.75 cm^3, 34 mmol) was added and the mixture warmed to room temperature. The solution was diluted with ether (100 cm^3), washed with saturated aqueous ammonium chloride (30 cm^3) and the organic phase dried ($MgSO_4$). After concentration under reduced pressure, the residue was chromatographed using light petroleum–ether (4 : 1) as eluant to give the *title compound* **19** (1.19 g, 80%) as a clear oil. [Found (EI): M^+ − H, 219.1028. $C_{13}H_{15}O_3$ requires M, 219.1021]; ν_{max} ($CHCl_3$) 1690, 1613, 1586, 1513, 1461, 1374, 1301, 1175, 1060, 1034 and 943 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.9 (3 H, s, 3-CH_3), 3.8 (3 H, s, OCH_3), 4.45 (2 H, s, CH_2Ar), 4.55 (2 H, s, 1-H_2), 5.75 (1 H, s, 4-H), 5.9 (1 H, s, 4-H) and 6.9 and 7.3 (each 2 H, m, ArH); *m/z* (CI) 220 (M^+, 5%), 219 (33), 138 (28) and 121(100).

Ethyl (1*RS*,2*SR*,3*RS*,5*SR*)-3-*p*-methoxybenzyloxy-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 21 and ethyl (1*SR*,2*SR*,3*RS*,5*SR*)-3-*p*-methoxybenzyloxy-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 22

A solution of ketone **19** (0.85 g, 3.89 mmol), keto-ester **20** (0.99 g, 3.89 mmol) and aqueous sodium hydroxide (3 M; 0.26 cm^3) was stirred in ethanol (6 cm^3) for 16 h at room temperature then allowed to stand for a further 16 h at −30 °C. Crystals of the cyclohexanone **21** were filtered off and washed with ice-cold ethanol. The washings were diluted with ether (50 cm^3) and washed with brine (10 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure gave more of the *title compound* **21** (1.17 g, 64% in total) as a crystalline solid, mp 127–128 °C; ν_{max} ($CHCl_3$) 3553, 3469, 3418, 1722, 1638, 1588, 1515, 1467, 1399, 1380, 1349, 1302, 1274, 1148, 1099, 1036 and 914 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.22 [9 H, s, $Si(CH_3)_3$], 1.02 (3 H, t, *J* 7, CO_2CH_3),1.13 (1 H, d, *J* 6.5, 5-CH_3), 2.03–2.19 (2 H, m, 6-H_2), 2.48 (1 H, m, 5-H), 3.19 (1 H, m, 1-H), 3.75 (3 H, s, OCH_3), 3.82 (1 H, s, 3-H), 3.86 (1 H, s, 2-OH), 3.88–4.07 (2 H, m, CO_2CH_2), 4.18 and 4.54 (each 1 H, d, *J* 12, HC*H*Ar), 6.17 (1 H, s, 4′-H), 6.7 and 6.85 (each 2 H, d, *J* 8, ArH) and 7.53 (1 H, d, *J* 2, 5′-H); *m/z* (CI) 492 (M^+ + 18, 48), 475 (M^+ + 1, 20%), 457 (19), 429 (18), 385 (16) and 337 (30). After concentration of the filtrate, chromatography of the residue using light petroleum–ether (2 : 1) as eluant gave the *title compound* **22** (0.19 g, 10%) as a solid, mp 104 °C. [Found (EI): M^+ + H, 475.2167. $C_{25}H_{35}O_7Si$ requires M, 475.2152]; ν_{max} ($CHCl_3$) 3398, 1727, 1613, 1515, 1460, 1377, 1094 and 946 cm^{-1}; δ_H (300 MHz; $CDCl_3$), 0.32 [9 H, s, $Si(CH_3)_3$], 1.16 (3 H, d, *J* 6.5, 5-CH_3), 1.18 (3 H, t, *J* 7, $CO_2CH_2CH_3$), 2.02 (1 H, ddd *J* 13.5, 6, 1.7 Hz, 6-H), 2.2 (1 H, td, *J* 13.5, 5.5 Hz, 6-H), 3.07 (1 H, s, 3-H), 3.12 (2 H, m, 1-H, 5-H), 3.82 (3 H, s, OCH_3), 4.05 (2 H, m, CO_2CH_2), 4.45 and 4.82 (each 1 H, d, *J* 11, HC*H*Ar), 5.02 (1 H, s, 2-OH), 6.03 (1 H, d, *J* 1.8, 4′-H), 6.84 and 7.12 (each 2 H, d, *J* 7, ArH) and 7.48 (1 H, d, *J* 1.8, 5′-H); *m/z* (CI) 492 (M^+ + 18, 40), 475 (M^+ + 1, 85), 429 (57) and 385 (21). Further elution of the column gave a further small amount (*ca.* 5%) of the major product **21**.

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-3-*p*-methoxybenzyloxy-2,4-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 23

The ketone **21** (4 g, 8.44 mmol) was dissolved in acetonitrile and acetic acid (1 : 1; 60 cm^3), tetramethylammonium triacetoxyborohydride (17.71 g, 67.64 mmol) was added and the mixture stirred for 96 h. After concentration under reduced pressure, the residue was dissolved in ether (100 cm^3) and the solution washed with aqueous sodium hydroxide (1 M; 20 cm^3). The aqueous phase was re-extracted and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (4 : 1) as eluant gave the *title compound* **23** (3.57 g, 89%) as a white solid, mp 128–129 °C. (Found: C, 62.8; H, 7.7. $C_{25}H_{36}O_7Si$ requires C, 63.0; H, 7.6%); ν_{max} ($CHCl_3$) 3455, 1780, 1710, 1613, 1514, 1463, 1377, 1098, 1057, 1034 and 918 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 0.03 [9 H, s, $Si(CH_3)_3$], 1.02 (3 H, t, *J* 7, OCH_2CH_3), 1.07 (3 H, d, *J* 6.5, 5-CH_3), 1.59 (1 H, m, 5-H), 1.7 (1 H, m, 6-H), 1.8 (1 H, q, *J* 12, 6-H), 2.19 (1 H, d, *J* 1.5, 4-OH), 2.8 (1 H, dd, *J* 7 and 2 Hz, 1-H), 3.19 (1 H, d, *J* 9, 3-H), 3.55 (1 H, td, *J* 9, 1.5 Hz, 4-H), 3.75 (3 H, s, OCH_3), 3.85–4.12 (5 H, m, CH_2Ar, OCH_2CH_3, 2-OH), 6.3 (1 H, d, *J* 2, 4′-H), 6.78 and 6.98 (each 2 H, m, ArH) and 7.6 (1 H, d, *J* 2, 5′-H); *m/z* (CI) 477 (M^+ + 1, 12.5%), 459 (27), 387 (22), 337 (13) and 121 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-4-acetoxy-2-hydroxy-3-*p*-methoxybenzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 24

Triethylamine (352 mg, 3.45 mmol), DMAP (a trace) and acetic anhydride (266 mg, 2.66 mmol) were added to a solution of diol **23** (0.86 g, 1.8 mmol) and the mixture stirred for 16 h. The mixture was diluted with ether (150 cm^3), washed with brine (45 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave the *title compound* **24** (0.87 g, 93%) as a white solid, mp 154–156 °C. (Found: C, 62.7; H, 7.6. $C_{27}H_{38}O_8Si$ requires C, 62.55; H, 7.4%); ν_{max} ($CHCl_3$) 3469, 1736, 1613, 1514, 1433, 1373, 1072, 1036 and 905 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.25 [9 H, s, $Si(CH_3)_3$], 1.02 (3 H, d, *J* 6, 5-CH_3), 1.07 (3 H, t, *J* 7, OCH_2CH_3), 1.8 (2 H, m, 5-H, 6-H), 2.0 [3 H, s, $OC(O)CH_3$], 2.02 (1 H, q, *J* 13, 6-H), 2.84 (1 H, dd, *J* 12.7, 3.7 Hz, 1-H), 3.43 (1 H, d, *J* 9.7, 3-H), 3.81 (3 H, OCH_3), 3.83 (1 H, s, 2-OH), 3.9–4.18 (4 H, m, CH_2Ar, OCH_2CH_3), 5.18 (1 H, t, *J* 9.7, 4-H), 6.34 (1 H, d, *J* 1.7, 4′-H), 6.81 and 6.92 (each 2 H, m, ArH) and 7.65 (1 H, d, *J* 1.7, 5′-H); *m/z* (CI) 519 (M^+ + 1, 5%), 501 (13), 441 (20), 429 (9) and 121 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-4-acetoxy-2,3-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 25

The *p*-methoxybenzyl ether **24** (40 mg, 0.07 mmol) was deprotected following the procedure outlined for ketone **21** to give the *title compound* **25** (24 mg, 80%) as a white solid, mp 103–104 °C. (Found: C, 57.4; H, 7.7. $C_{19}H_{30}O_7Si$ requires C, 57.25; H, 7.6%); ν_{max} ($CHCl_3$) 3466, 1735, 1604, 1566, 1512, 1461, 1373, 1111, 1067, 943 and 881 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.03 [9 H, s, $Si(CH_3)_3$], 1.0 (3 H, d, *J* 6, 5-CH_3), 1.08 (3 H, t, *J* 7.5,

OCH_2CH_3), 1.75–1.9 (4 H, m, 6-H_2, 5-H, 3-OH), 2.1 [3 H, s, OC(O)CH_3], 2.85 (1 H, dd, *J* 12, 6 Hz, 1-H), 3.38 (1 H, t, *J* 9.5, 3-H), 3.9–4.1 (2 H, m, OCH_2CH_3), 4.5 (1 H, s, 2-OH), 5.02 (1 H, t, *J* 9.5, 4-H), 6.2 (1 H, d, *J* 1.5, 4′-H), 7.55 (1 H, d, *J* 1.5, 5′-H); *m*/*z* (CI) 416 (M^+ + 18, 6%), 397 (1), 381 (15), 321 (14) and 309 (50).

Ethyl (1*RS*,2*SR*,3*RS*,5*SR*)-2,3-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 26

Dichlorodicyanoquinone (72 mg, 0.32 mmol) was added to the ketone **21** (100 mg, 0.21 mmol) in dichloromethane (1 cm^3) and water (0.2 cm^3) and the mixture was stirred for 3 h. Aqueous sodium bicarbonate (0.5 cm^3) was added and the mixture was diluted with ether (20 cm^3) and washed with brine (2 cm^3). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave the *title compound* **26** (75 mg, 96%) as a white solid, mp 84–86 °C. (Found: C, 58.0, H, 7.5. $C_{17}H_{26}O_6Si$ requires C, 57.6; H, 7.4%); ν_{max} ($CHCl_3$) 3300, 1781, 1722, 1658, 1461, 1378, 109 and 915 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.3 [9 H, s, Si(CH_3)$_3$], 1.05 (3 H, t, *J* 7, CO_2CH_3), 1.2 (3 H, d, *J* 6, 5-CH_3), 2.1 (1 H, q, *J* 12.5, 6-H), 2.25 (1 H, m, 6-H′), 2.65 (1 H, m, 5-H), 3.32 (1 H, dd, *J* 12.5, 4, 1-H), 3.52 (1 H, d, *J* 6, 3-OH), 3.9–4.1 (3 H, m, CO_2CH_2, 2-OH), 4.15 (1 H, d, *J* 6, 3-H), 6.31 (1 H, d, *J* 1.7, 4′-H) and 7.58 (1 H, d, *J* 1.7, 5′-H); *m*/*z* (CI) 372 (M^+ + 18, 11), 355 (M^+ + 1, 29%) and 337 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*SR*,5*SR*)-5-methyl-2,3,4-trihydroxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 27 and ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-5-methyl-2,3,4-trihydroxy-2-(2-trimethylsilyl-3-furyl)-cyclohexane-1-carboxylate 28

Tetramethylammonium triacetoxyborohydride (170 mg, 0.65 mmol) was added to a solution of hydroxy ketone **26** (120 mg, 0.32 mmol) in acetonitrile (1 cm^3) and acetic acid (1 cm^3) and the mixture was stirred for 1 h. The solvents were removed under reduced pressure and chromatography of the residue, using light petroleum–ether (1 : 1) as eluant, gave the *title compound* **27** (62 mg, 51%), as a white solid, mp 124–125 °C. (Found: C, 57.3; H, 8.0. $C_{17}H_{28}O_6Si$ requires C, 57.3; H, 7.92%); ν_{max} ($CHCl_3$) 3402, 1710, 1462, 1377, 1150, 1116 and 1064 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 0.3 [9 H, s, Si(CH_3)$_3$], 1.05 (3 H, t, *J* 7.5, OCH_2CH_3), 1.15 (3 H, d, *J* 6, 5-CH_3), 1.65 (1 H, m, 6-H), 1.8 (1 H, m, 5-H), 1.95 (1 H, q, *J* 12.5, 6-H′), 2.5 (1 H, d, *J* 7.5, 3-OH), 2.82 (1 H, dd, *J* 12.5, 4.5, 1-H), 3.4 (1 H, dd, *J* 7.5, 2.7 Hz, 3-H), 3.57 (1 H, d, *J* 9.5, 4-OH), 3.9 (1 H, dt, *J* 9.5, 2.7 Hz, 4-H), 4.0 (2 H, m, CO_2CH_2), 5.08 (1 H, s, 2-OH), 6.15 (1 H, d, *J* 1.5, 4′-H) and 7.58 (1 H, d, *J* 1.5, 5′-H); *m*/*z* (EI) 356 (M^+, 7%), 323 (10), 267 (22) and 255 (100). On further elution, the *title compound* **28** (18 mg, 16%) was isolated as an oil. [Found (EI): M^+, 356.1669. $C_{17}H_{28}O_6Si$ requires M, 356.1655]; ν_{max} ($CHCl_3$) 3400, 1711, 1461, 1377, 1278, 1150, 1104, 1056 and 896 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.35 (9 H, s, TMS), 1.03 (3 H, t, *J* 7.2, OCH_2CH_3), 1.15 (3 H, d, *J* 6.5, 5-CH_3), 1.6–1.85 (4 H, m, 6-H_2, 5-H, 3-OH), 2.5 (1 H, s, 4-OH), 2.85 (1 H, m, 1-H), 3.25 (1 H, t, *J* 9, 4-H), 3.55 (1 H, t, *J* 9, 3-H), 4.0 (2 H, m, OCH_2CH_3), 4.5 (1 H, s, 2-OH), 6.32 (1 H, d, *J* 1.5, 4′-H) and 7.49 (1 H, d, *J* 1.5, 5′-H); *m*/*z* (EI) 357 (M^+ + 1, 58%), 343 (24), 255 (14) and 245 (32).

Ethyl (1*RS*,2*SR*,4*RS*,5*SR*)-4-acetoxy-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-3-oxocyclohexane-1-carboxylate 29

Dimethyl sulfoxide (0.19 g, 2.39 mmol) in dichloromethane (1 cm^3) followed by alcohol **25** (0.5 g, 1.25 mmol) in dichloromethane (1 cm^3) were added to oxalyl chloride (0.18 g, 1.25 mmol) in dichloromethane (3 cm^3) at −78 °C. The mixture was stirred for 15 min, triethylamine (0.63 g, 6.3 mmol) was added and the mixture allowed to warm to room temperature. The mixture was diluted with ether (50 cm^3) and washed with saturated aqueous ammonium chloride (10 cm^3). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave the *title compound* **29** (0.49 g) as a white solid, mp 113–114 °C. (Found: C, 57.5; H, 7.2. $C_{19}H_{28}O_7Si$ requires C, 57.55; H, 7.1%); ν_{max} ($CHCl_3$) 3447, 1742, 1708, 1565, 1462, 1373, 1342, 1287, 1136, 1071, 1060 and 985 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.3 [9 H, s, Si(CH_3)$_3$], 1.18 (3 H, t, *J* 7, OCH_2CH_3), 1.13 (3 H, d, *J* 7, 5-CH_3), 2.05 (2 H, m, 6-H, 5-H), 2.18 [3 H, s, OC(O)CH_3], 2.35 (1 H, q, *J* 12.5, 6-H′), 3.03 (1 H, dd, *J* 13, 4, 1-H), 4.1 (2 H, m, OCH_2CH_3), 4.9 (1 H, s, 2-OH), 5.71 (1 H, d, *J* 11, 4-H), 6.22 (1 H, d, *J* 1.7, 4′-H), 7.6 (1 H, d, *J* 1.7, 5′-H); *m*/*z* (CI) 414 (M^+ + 18, 9), 397 (M^+ + 1, 11%), 379 (16), 337 (71), 324 (43) and 247 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-4-acetoxy-2,3-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 30

Tetramethylammonium triacetoxyborohydride (1.38 g, 5.2 mmol) was added to a solution of the ketone **29** (0.41 g, 1.05 mmol) in acetic acid (4 cm^3) and acetonitrile (4 cm^3) and the mixture was stirred for 16 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (2 : 1) as eluant gave the *title compound* **30** (0.35 g, 85%) as a white solid, mp 175–177 °C. (Found: C, 57.3; H, 7.5. $C_{19}H_{30}O_7Si$ requires C, 57.25; H, 7.6%); ν_{max} ($CHCl_3$) 3454, 1708, 1465, 1374, 1345, 1283, 1263, 1100, 1045, 914 and 879 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 0.35 [9 H, s, Si(CH_3)$_3$], 1.2 (3 H, d, *J* 6.5, 5-CH_3), 1.18 (3 H, t, *J* 7.25, OCH_2CH_3), 1.8 (1 H, d, *J* 3, 3-OH), 1.85 (2 H, m, 6-H_2), 2.12 [3 H, s, OC(O)CH_3], 2.2 (1 H, m, 5-H), 3.34 (1 H, dd, *J* 12, 5, 1-H), 3.88 (1 H, t, *J* 3, 3-H), 4.08 (2 H, qd, *J* 7.25, 1.5, OCH_2CH_3), 4.52 (1 H, s, 2-OH), 5.22 (1 H, dd, *J* 11, 3, 4-H), 6.38 (1 H, d, *J* 1.5, 4′-H) and 7.75 (1 H, d, *J* 1.5, 5′-H); *m*/*z* (EI) 398 (M^+, 7%), 383 (38), 323 (14), 321 (11), 305 (22) and 91 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-4-acetoxy-2-hydroxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 31

Hunig's base (2.67 g, 20.7 mmol) and SEM chloride (2.06 g, 12.37 mmol) were added to diol **30** (3.05 g, 7.66 mmol) in dichloromethane (7.5 cm^3) at 0 °C and the reaction was stirred for 16 h. Water (5 cm^3) and ether (100 cm^3) were added and the aqueous phase extracted with more ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (2 : 1) as eluant gave the *title compound* **31** (3.61 g, 90%) as a solid, mp 71–74 °C. [Found (EI): M^+, 528.2591. $C_{25}H_{44}O_8Si_2$ requires M, 528.2575]; ν_{max} ($CHCl_3$) 3468, 1739, 1710, 1463, 1371, 1337, 1292, 1100, 1052 and 1026 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.0 and 0.3 [each 9 H, s, Si(CH_3)$_3$], 0.8 (2 H, m, CH_2Si), 0.97 (3 H, d, *J* 6.5, 5-CH_3), 1.13 (3 H, t, *J* 7, OCH_2CH_3), 1.75 (1 H, q, *J* 12, 6-H), 1.85 (1 H, m, 6-H), 2.05 [3 H, s, OC(O)CH_3], 2.15 (1 H, m, 5-H), 3.22 (2 H, m, 1″-H, 1-H), 3.48 (1 H, m, 1″-H′), 3.8 (1 H, d, *J* 2.5, 3-H), 4.2 (2 H, m, OCH_2CH_3), 4.42 (1 H, d, *J* 6.25, O*H*CHO), 4.41 (1 H, s, 2-OH), 4.46 (1 H, d, *J* 6.25, OHC*H*O), 5.17 (1 H, dd, *J* 11, 2.5, 4-H), 6.28 (1 H, d, *J* 1.5, 4′-H) and 7.45 (1 H, d, *J* 1.5, 5′-H); *m*/*z* (FAB) 529 (M^+ + 1, 1%), 513 (0.5), 483 (0.5) and 453 (0.5).

(1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2,4-Dihydroxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylic acid 32

Sodium hydroxide (15 M, 0.75 cm^3) was added to a solution of ester **31** (0.5 g, 0.95 mmol) in ethanol (2 cm^3) and THF (1 cm^3) and the mixture was stirred for 72 h. The solution was acidified to pH 2 by the addition of aqueous hydrogen chloride (3 M). The mixture was extracted with ether (5 × 25 cm^3), dried ($MgSO_4$) and concentrated to give *title compound* **32** as a clear oil.

[Found (EI): M^+, 458.2178. $C_{21}H_{38}O_7Si_2$ requires M, 458.2156]; ν_{max} ($CHCl_3$) 3435, 1708, 1382, 1155, 1058 and 1019 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.0 and 0.3 [9 H, s, $Si(CH_3)_3$], 0.92 (2 H, m, CH_2Si), 1.1 (3 H, d, *J* 6, 5-CH_3), 1.6–1.9 (3 H, m, 6-H_2, 5-H), 3.2 (1 H, dd, *J* 12, 2.5 Hz, 1-H), 3.45 (1 H, m, 1″-H), 3.5 (1 H, d, *J* 2.5, 3-H), 3.7 (2 H, m, 4-H, 1″-H), 4.03 (1 H, d, *J* 6, O*H*CHO), 4.22 (1 H, s, 2-OH), 4.58 (1 H, d, *J* 6, OHC*H*O), 6.28 (1 H, d, *J* 1.5, 4′-H) and 7.5 (1 H, d, *J* 1.7, 5′-H); *m/z* (CI) 459 (M^+ + 1, 4%), 413 (3), 411 (2), 383 (6), 341 (10) and 90 (100).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2,4-dihydroxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 33

Dicyclohexylcarbodiimide (244 mg, 1.14 mmol) in dichloromethane (2 cm^3) was added to a solution of acid **32** (0.95 mmol), 2-trimethylsilylethanol (0.68 cm^3, 4.75 mmol) and DMAP (trace) in dichloromethane (3 cm^3) and the mixture stirred for 16 h. The mixture was diluted with ether (30 cm^3), washed with saturated aqueous citric acid (10 cm^3) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave the *title compound* **33** (0.455 g, 87% based on **31**), as a clear oil, ν_{max} ($CHCl_3$) 3449, 1708, 1460, 1384, 1337, 1173, 1099, 1062 and 1021 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.0 [18 H, s, 2 × $Si(CH_3)_3$], 0.3 [9 H, s, $Si(CH_3)_3$], 0.9 (4 H, m, 2 × CH_2Si), 1.1 (3 H, d, *J* 6, 5-CH_3), 1.72 (3 H, m, 6-H_2, 5-H), 3.12 (1 H, dd, *J* 12, 4, 1-H), 3.3 (1 H, d, *J* 9, 4-OH), 3.45 (1 H, m, 1″-H), 3.51 (1 H, d, *J* 3, 3-H), 3.7 (2 H, m, 4-H, 1″-H), 4.03 (3 H, m, O*H*CHO, OC*H*$_2$CH$_2$), 4.53 (1 H, s, 2-OH), 4.55 (1 H, d, *J* 6.5, OHC*HO*), 6.25 (1 H, d, *J* 1.5, 4′-H), 7.48 (1 H, d, *J* 1.5, 5′-H); *m/z* (FAB) 559 (M^+ + 1, 0.2%) and 442 (10).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 34

2,6-Lutidine (0.15 cm^3, 1.33 mmol) was added dropwise to solution of the alcohol **33** (212 mg, 0.38 mmol) in dichloromethane (4 cm^3) at 0 °C, followed by *tert*-butyldimethylsilyl triflate (0.18 cm^3, 0.76 mmol). The mixture was stirred at room temperature for 3 h before diluting with ether (25 cm^3) and washing with brine (5 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (10 : 1) as eluant gave the *title compound* **34** (0.254 g, 99%) as a clear oil. [Found (CI): M^+ + H, 673.3835. $C_{32}H_{65}O_7Si_4$ requires M, 673.3808]; ν_{max} ($CHCl_3$) 3458, 1709, 1463, 1386, 1338, 1173, 1085 and 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.03 [18 H, s, 2 × $Si(CH_3)_3$], 0.15 [6 H, s, $Si(CH_3)_2$], 0.32 [9 H, s, $Si(CH_3)_3$], 0.75 (4 H, m, 2 × CH_2Si), 0.92 [9 H, s, $SiC(CH_3)_3$]), 1.0 (3 H, d, *J* 6.5, 5-CH_3), 1.62 (1 H, q, *J* 12, 6-H), 1.75 (1 H, dt, *J* 12, 3, 6-H), 2.05 (1 H, m, 5-H), 3.2 (3 H, m, OC*H*$_2$CH$_2$, 1-H), 3.62 (1 H, d, *J* 2.25, 3-H), 3.95 (1 H, dd, *J* 11.25, 2.25, 4-H), 4.05 (2 H, m, OC*H*$_2$CH$_2$), 4.5 (1 H, s, 2-OH), 4.58 and 4.27 (each 1 H, d, *J* 6, O*H*CHO), 6.32 (1 H, d, *J* 1.5, 4′-H) and 7.45 (1 H, d, *J* 1.5, 5′-H); *m/z* (FAB) 673 (M^+ + 1, 0.1%), 569 (0.5), 555 (0.75) and 511 (0.5).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 35

Cetyltrimethylammonium bromide (CTAB) (0.595 g, 1.61 mmol) and methyl iodide (1.66 cm^3) were added to a solution of the alcohol **33** (0.818 g, 1.47 mmol) in THF (7 cm^3) and the mixture was cooled to 0 °C. LHMDS (1 M in hexanes, 3 cm^3, 3 mmol) was added and the reaction mixture was stirred for 15 min. Water (2 cm^3) was added, the mixture extracted with ether (3 × 25 cm^3), and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (9 : 1) as eluant gave the *title compound* **35** (0.782 g, 93%) as a viscous oil, ν_{max} ($CHCl_3$) 3459, 1738, 1709, 1454, 1381, 1335, 1171, 1102 and 1047 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.8, 0.05 and 0.32 [each 9 H, s, $Si(CH_3)_3$], 0.78 and 0.89 (each 2 H, m, CH_2Si), 1.03 (3 H, d, *J* 7, 5-CH_3), 1.68 (1 H, q, *J* 13.5, 6-H), 1.78 (1 H, dt, *J* 13.5, 4.5, 6-H′), 2.0 (1 H, m, 5-H), 3.12 (1 H, m, 1″-H), 3.21 (1 H, dd, *J* 13, 4, 1-H), 3.38 (3 H, s, OCH_3), 3.33–3.48 (2 H, m, 1″-H, 4-H), 3.94 (1 H, d, *J* 2.5, 3-H), 4.05 (2 H, m, OC*H*$_2$CH$_2$), 4.22 (1 H, d, *J* 6.5, O*H*CHO), 4.47 (1 H, s, 2-OH), 4.61 (1 H, d, *J* 6.5, OHC*H*O), 6.28 (1 H, d, *J* 1.5, 4′-H) and 7.46 (1 H, d, *J* 1.5, 5′-H). All other data were identical to those of a sample prepared *via* the acid **52**, *vide infra*.

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-4-(1-*tert*-butyldimethylsilyloxy)-2-hydroxy-2-[5(*RS*,*SR*)-5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl]-5-methyl-3-(2-trimethylsilylethoxy)-methoxycyclohexane-1-carboxylate 36

A trace of tetraphenylporphine was added to a solution of furan **34** (0.368 g, 0.55 mmol) in dichloromethane (12.5 cm^3) and methanol (12.5 cm^3) and the mixture was cooled to −78 °C. A stream of O_2 was bubbled through in the presence of a sun-lamp for 4 h, then the mixture was allowed to warm to ambient temperature. After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (2 : 1) as eluant gave the *title compound* **36** (0.33 g, 95%) as a foamy solid, ν_{max} ($CHCl_3$) 3442, 1771, 1707, 1463, 1412, 1343, 1286, 1172, 1158, 1089 and 1023 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.9 [9 H, s, $Si(CH_3)_3$], 0.02 and 0.03 (each 4.5 H, s, 2 × TMS), 0.09 [6 H, s, $Si(CH_3)_2$], 0.88 [9 H, s, $SiC(CH_3)_3$], 0.85–1.0 (7 H, m, 5-CH_3, 2 × CH_2Si), 1.5–1.9 (3 H, m, 6-H_2, 5-H), 3.08 (0.5 H, dd, *J* 12, 4, 1-H), 3.3–3.85 (4.5 H, m, 1″-H, 5′-OH, 3-H, 4-H, 1-H), 4.14 (2 H, m, OC*H*$_2$CH$_2$), 4.31 (0.5 H, s, 2-OH), 4.55 (2.5 H, m, 1″-H, O*H*CHO, 2-OH), 4.85 (1 H, m, OHC*H*O), 5.95 (1 H, m, 5′-H), 7.0 (0.5 H, s, 4′-H) and 7.28 (0.5 H, s, 4′-H).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2-hydroxy-2-[5(*RS*,*SR*)-5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl]-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy)methoxycyclohexane-1-carboxylate 37

Following the procedure outlined for the preparation of hydroxybutenolide **36**, the 2-trimethylsilylfuran **35** (110 mg, 0.19 mmol) gave the *title compound* **37** (99 mg, 97%) as a mixture of epimers, ν_{max} ($CHCl_3$) 3431, 1771, 1704, 1456, 1387, 1338, 1288, 1109, 1059, 1019, 975 and 862 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.0 and 0.03 [each 9 H, s, $Si(CH_3)_3$], 0.8–1.05 (4 H, m, 2 × CH_2Si), 1.03 (3 H, d, *J* 6, 5-CH_3), 1.5–2.0 (3 H, m, 6-H_2, 5-H), 3.2 (1.5 H, m, 1-H, 4-H), 3.38 (0.5 H, m, 4-H), 3.4 (3 H, s, OCH_3), 3.5 (1 H, m, 1″-H), 3.62–3.92 (2 H, m, 3-H, 1″-H), 4.15 (2 H, m, OC*H*$_2$CH$_2$), 4.38–4.62 (2 H, m, 2-OH, O*H*CHO), 4.83 (1 H, m, OHC*H*O), 6.0 (1 H, d, *J* 13, 5′-H), 7.03 (0.5 H, d, *J* 1.5, 4′-H) and 7.32 (0.5 H, d, *J* 1.5, 4′- H); *m/z* (FAB) 555 (M^+ + 23, 2%), 475 (8), 459 (2), 447 (10) and 429 (15).

(2*Z*,4*Z*)-2-[(1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-4-*tert*-Butyldimethylsilyloxy-2-hydroxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-1-(2-trimethylsilylethoxy-carbonyl)cyclohexan-2-yl]-6-methylhepta-2,4-dienoic acid 38

A solution of lithium hexamethyldisilazide (1 M in hexanes, 0.31 cm^3, 0.31 mmol) in THF (1 cm^3) was cooled to −78 °C and added *via* a cannula to a solution of the hydroxybutenolide **36** (64 mg, 0.1 mmol) and 2-methylpropyl(triphenyl)phosphonium iodide (49 mg, 0.12 mmol) in THF (2.5 cm^3) at −78 °C. Over 1 h, the mixture was slowly warmed to −10 °C and stirred at this temperature for 30 minutes. Saturated aqueous ammonium chloride (1 cm^3) was added and the mixture diluted with ether (10 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (1 : 1) with 1% acetic acid as eluant gave the *title compound* **38** (62 mg, 89%) as a viscous oil. [Found (EI): $M^+ - H$, 671.3836. $C_{33}H_{63}O_8Si_3$ requires M, 671.3831]; ν_{max} ($CHCl_3$) 3856–2400, 2363, 1708, 1640, 1511, 1463, 1388, 1173, 1087, 1029 and 861 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.4 and 0.01 [9 H, s, $Si(CH_3)_3$], 0.09 and 0.091 (each 3 H, s, 2 × $SiCH_3$), 0.8–1.0 [22 H, m, $SiC(CH_3)_3$, 6-CH_3, 7-H_3, 2 × CH_2Si, 5′-CH_3), 1.55 (1 H, q, *J* 12.5, 6′-H), 1.8 (1 H, dt, *J* 12.5, 4 Hz, 6′-H′), 1.9 (1 H, m, 5′-H), 2.82 (1 H, m, 6-H), 3.0 (1 H, dd, *J* 12.5, 4 Hz, 1′-H), 3.5 (2 H, m, 1″-H_2), 3.58 (1 H, d, *J* 2.5, 3′-H), 3.79 (1 H, dd, *J* 10, 2.5 Hz, 4′-H), 4.15 (2 H, m, OCH_2), 4.81 and 4.83 (each 1 H, d, *J* 11, HC*H*O), 4.9 (1 H, s, 2′-OH), 5.51 (1 H, t, *J* 11.5, 5-H), 6.22 (1 H, t, *J* 11.5, 4-H) and 6.81 (1 H, d, *J* 11.5, 3-H); *m/z* (FAB) 671 ($M^+ - 1$, 100%) and 631 (25).

(2*Z*,4*E*)-2-[(1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-4-*tert*-Butyldimethylsilyloxy-2,3-dihydroxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)cyclohexan-2-yl]-6-methylhepta-2,4-dienoic acid 39

Iodine (17 mg, 0.07 mmol) in benzene (0.5 cm^3) was added to a solution of the diene **38** (41 mg, 0.06 mmol) in benzene (1.2 cm^3) and the mixture was stirred for 3 h in the presence of a sun-lamp. The mixture was then diluted with ether (10 cm^3), washed with saturated aqueous sodium thiosulfate (1 cm^3) and the aqueous phase re-extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (1 : 1) with 1% acetic acid as eluant gave the *title compound* **39** (23 mg, 70%) as a viscous oil. [Found (EI): $M^+ - H$, 541.3028. $C_{27}H_{49}O_7Si_2$ requires M, 541.3017]; ν_{max} ($CHCl_3$) 3905–2400, 1708, 1639, 1562, 1462, 1342, 1176, 1135, 1069 and 978 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.05 [9 H, s, $Si(CH_3)_3$], 0.15 [6 H, s, $Si(CH_3)_2$], 0.9 [9 H, s, $Si(CH_3)_3$], 1.05 (11 H, m, 6-CH_3, 7-H_3, 5′-CH_3, CH_2Si), 1.75 (3 H, m, 5′-H, 6′-H_2), 2.4 (1 H, m, 6-H), 3.1 (1 H, dd, *J* 11.5, 4, 1′-H), 3.6 (1 H, d, *J* 3, 3′-H), 3.74 (1 H, dd, *J* 10, 3, 4′-H), 4.18 (2 H, m, $O_2CH_2CH_2$), 4.7 (1 H, s, 2′-OH), 5.97 (1 H, dd, *J* 15, 7, 5-H), 6.54 (1 H, ddd, *J* 15, 11, 1, 4-H) and 6.74 (1 H, d, *J* 11, 3-H); *m/z* (FAB) 541 ($M^+ - 1$, 100%) and 153 (40).

2-Trimethylsilylethyl (1*SR*,2*RS*,4*SR*,5*RS*,6*RS*,9*Z*)-5-*tert*-butyldimethylsilyloxy-1-hydroxy-4-methyl-9-[(2*E*)-4-methylpent-2-enylidene]-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylate 40

4-Dimethylaminopyridine (a trace) and dicyclohexylcarbodiimide (25 mg, 0.12 mmol) in dichloromethane (1 cm^3) were added to a solution of the hydroxy acid **39** (22 mg, 0.04 mmol) in dichloromethane (4 cm^3) and the mixture was stirred for 3 h. The reaction mixture was then diluted with ether (10 cm^3) and washed with aqueous saturated citric acid (1 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave the *title compound* **40** (19 mg, 90%) as a clear oil. [Found (CI): $M^+ + H$, 525.3078. $C_{27}H_{49}O_6Si_2$ requires M, 525.3068]; ν_{max} ($CHCl_3$) 3400, 1762, 1704, 1653, 1546, 1463, 1361, 1178, 1140, 1113, 1057 and 987 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.05 [9 H, s, $Si(CH_3)_3$], 0.1 [6 H, s, $Si(CH_3)_2$], 0.9 [9 H, s, $SiC(CH_3)_3$], 1.0 (2 H, m, CH_2Si), 1.12 (9 H, m, 4′-CH_3, 5′-H_3, 4-CH_3), 1.3 (1 H, m, 4-H), 1.55 (1 H, m, 3-H), 1.9 (1 H, m, 3-H′), 2.47 (1 H, m, 4′-H), 2.65 (1 H, dd, *J* 13, 3, 2-H), 3.64 (1 H, dd, *J* 9, 4, 5-H), 4.13 (1 H, d, *J* 4, 6-H), 4.19 (2 H, m, OCH_2CH_2), 5.35 (1 H, s, 1-OH), 6.06 (1 H, dd, *J* 15, 7 Hz, 3′-H), 6.53 (1 H, d, *J* 11, 1′-H), 7.2 (1 H, dd, *J* 15, 11 Hz, 2′-H); *m/z* (FAB) 525 ($M^+ + 1$, 50%), 507 (75) and 479 (100).

Ethyl (1*RS*,2*SR*,3*RS*,5*SR*)-3-benzyloxy-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 41

The β-ketoester **20** (8.1 g, 31.9 mmol) was dissolved in ethanol (63 cm^3) and aqueous sodium hydroxide (2 M, 2 cm^3) was added. The benzyloxymethyl ketone **5** (6.05 g, 31.9 mmol) in ethanol (15.4 cm^3) was added and stirring was continued for 20 h. The solvent was removed under reduced pressure and the residue partitioned between ether (200 cm^3) and brine (75 cm^3). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and the residue purified by flash chromatography, using light petroleum–ether (4 : 1) as eluant, to yield the *title compound* **41** (7 g, 50%) as a white powder, mp 107–109 °C. [Found (EI): M^+, 444.1968. $C_{24}H_{32}O_5Si$ requires M, 444.1965]; ν_{max} (film) 3463, 1726, 1497, 1454, 1397, 1378, 1346, 1303, 1274, 1149, 1099 and 1050 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.25 [9 H, s, $Si(CH_3)_3$], 1.04 (3 H, t, *J* 7.5, CH_2CH_3), 1.16 (3 H, d, *J* 7, 5-CH_3), 2.05–2.19 (2 H, m, 6-H_2), 2.51 (1 H, m, 5-H), 3.22 (1 H, m, 1-H), 3.86 (1 H, s, 2-OH), 3.12 (1 H, s, 3-H), 3.99 (2 H, m, CH_2CH_3), 4.25 and 4.67 (each 1 H, d, *J* 13, Ph*H*CHO), 6.18 (1 H, s, 4′-H), 6.92 (2 H, m, ArH), 7.20 (3 H, m, ArH) and 7.56 (1 H, d, *J* 2 Hz, 5′-H); *m/z* (EI) 444 (M^+, 2%), 190 (23), 167 (88) and 91 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-3-benzyloxy-2,4-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 42

The hydroxycyclohexanone **41** (3 g, 6.76 mmol) was dissolved in acetonitrile (24 cm^3) and acetic acid (24 cm^3) at ambient temperature and tetramethylammonium triacetoxyborohydride (14 g, 53.2 mmol) was added. The mixture was stirred for 96 h and the solvent removed under reduced pressure. The residue was dissolved in ether (100 cm^3), washed with saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3) and the aqueous phase extracted with ether (3 × 50 cm^3). The combined organic phases were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated to give the *title compound* **42** (2.52 g, 84%) as a viscous oil. [Found (EI): M^+, 446.2131. $C_{24}H_{34}O_6Si$ requires M, 446.2125]; ν_{max} (film) 3471, 1710, 1455, 1377, 1346, 1249, 1187, 1149, 1100, 1074 and 843 cm^{-1}; δ_H (300 Mz; $CDCl_3$) 0.3 [9 H, s, $Si(CH_3)_3$], 1.03 (3 H, t, *J* 7, CH_2CH_3), 1.1 (3 H, d, *J* 7, 5-CH_3), 1.58–1.91 (3 H, m, 5-H and 6-H_2), 2.21 (1 H, d, *J* 1.5, 4-OH), 2.32 (1 H, dd, *J* 13, 4.5, 1-H), 3.23 (1 H, d, *J* 9, 3-H), 3.61 (1 H, t, *J* 9, 4-H), 3.87–4.07 (4 H, m, 2-OH, CH_2CH_3, Ph*H*CHO), 4.18 (1 H, d, *J* 11, PhHC*H*O), 6.32 (1 H, s, 4′-H), 7.10 (2 H, m, ArH), 7.29 (3 H, m, ArH) and 7.62 (1 H, s, 5′-H); *m/z* (EI) 446 (M^+, 0.7%), 250 (32), 174 (53), 167 (28) and 91(100).

Ethyl (1*R*,2*S*,3*S*,4*R*,5*S*)-3-benzyloxy-4-[(2*R*)-2-ethanoyloxy-2-phenylethanoyloxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 43 and ethyl (1*S*,2*R*,3*R*,4*S*,5*R*)-3-benzyloxy-4-[(2*R*)-2-ethanoyloxy-2-phenylethanoyloxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 44

The diol **42** (120 mg, 0.27 mmol), (*R*)-acetylmandelic acid (78 mg, 0.41 mmol) and DMAP (1.7 mg, 0.014 mmol) were dissolved in dichloromethane (1 cm^3) at 0 °C, and dicyclohexylcarbodiimide (83 mg, 0.41 mmol) in dichloromethane (0.5 cm^3) was added. The reaction mixture was stirred at ambient temperature for 16 h, diluted with ether (5 cm^3) and filtered through celite. The solvent was removed under reduced pressure and the residue chromatographed using light petroleum–ether (4 : 1) as eluant to yield the *title compounds* **43** and **44** (107 mg, 64%). Recrystallization of the mixture from hot hexane gave the less polar isomer **44** (44.8 mg, 42% of the mixture) as white needles, mp 131–133 °C (82–85 °C phase change). (Found C, 65.8; H, 7.1. $C_{34}H_{42}O_9Si$ requires C, 65.6; H, 6.8%); $[\alpha]_D$ +8.4 (*c* 0.57 in $CHCl_3$); ν_{max} (film) 3472, 1744, 1706, 1374, 1234, 1209, 1183, 1048 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.12 [9 H, s,

$Si(CH_3)_3$], 0.53 (3 H, d, *J* 7, 5-CH_3), 1.0 (3 H, t, *J* 7, CH_2CH_3), 1.51–1.68 (2 H, m, 5-H, 6-H), 1.91 (1 H, q, *J* 13, 6-H), 2.20 (3 H, s, OAc), 2.72 (1 H, dd, *J* 13, 4, 1-H), 3.42 (1 H, d, *J* 9, 3-H), 3.65 (1 H, s, 2-OH), 3.92 (3 H, m, CH_2CH_3, Ph*H*CHO), 4.41 (1 H, d, *J* 10.5, PhHC*H*O), 5.13 (1 H, t, *J* 9, 4-H), 5.95 (1 H, s, 2″-H), 6.31 (1 H, d, *J* 2, 4′-H), 6.90–7.45 (10 H, m, ArH) and 7.65 (1 H, d, *J* 2, 5′-H); *m*/*z* (EI) 622 (M^+, 0.5%), 174 (75), 167 (26) and 91 (100). Chromatography of the mother liquor, using light petroleum–ether (4 : 1) as eluant gave the more polar isomer **43** as a white crystalline solid, mp 130–132 °C. (Found: C, 65.6; H, 7.3. $C_{34}H_{42}O_9Si$ requires C, 65.6; H, 6.8%); $[\alpha]_D$ −84 (*c* 0.83 in $CHCl_3$); ν_{max} (film) 3468, 1743, 1712, 1456, 1374, 1349, 1235, 1209, 1182, 1049 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.0 [9 H, s, $Si(CH_3)_3$], 1.01 (3 H, t, *J* 7.5, CH_2CH_3), 1.08 (3 H, d, *J* 7, 5-CH_3), 1.70–1.90 (2 H, m, 5-H, 6-H), 1.98 (1 H, q, *J* 13, 6-H′), 2.20 (3 H, s, OAc), 2.77 (1 H, dd, *J* 13, 4, 1-H), 3.30 (1 H, d, *J* 9, 3-H), 3.39 and 3.48 (each 1 H, d, *J* 10.5, PhHC*H*O), 3.58 (1 H, s, 2-OH), 3.93 (2 H, m, CH_2CH_3), 5.20 (1 H, t, *J* 9, 4-H), 5.92 (1 H, s, 2″-H), 6.22 (1 H, d, *J* 2, 4′-H), 6.43–7.48 (10 H, m, ArH) and 7.52 (1 H, d, *J* 2, 5′-H); *m*/*z* (EI) 622 (M^+, 1%), 174 (81), 167 (32) and 91 (100).

Using the diol **42** (690 mg, 1.55 mmol) and (*S*)-acetylmandelic acid, the enantiomeric esters ent-**43** and ent-**44** (0.81 g, 84%) were obtained. Recrystallization of the mixture (400 mg, 0.643 mmol) from hot hexane gave ent-**44** (140 mg, 35%) as a white crystalline solid, mp 133–135 °C (85–87 °C phase change). (Found C, 65.3; H, 7.1. $C_{34}H_{43}O_9Si$ requires C, 65.6; H, 6.8%); $[\alpha]_D$ −7.9 (*c* 1.01 in $CHCl_3$); all other data were identical to those reported for **44**. Chromatography of the mother liquor yielded the more polar isomer ent-**43** as a white crystalline solid, mp 128–133 °C. (Found: C, 66.0; H, 7.0. $C_{34}H_{42}O_9Si$ requires C, 65.6; H, 6.8%); $[\alpha]_D$ +77 (*c* 1.03 in $CHCl_3$); all other data were identical to those of **43**.

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-3-benzyloxy-2-hydroxy-5-methyl-4-phenylethanoyloxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 45

Following the procedure outlined for the preparation of esters **43** and **44**, the diol **42** (2.5 g, 5.6 mmol) and phenylacetic acid (1.14 g, 8.38 mmol) gave the *title compound* **45** (2.70 g, 85%) as a white crystalline solid, after chromatography using light petroleum–ether (4 : 1) as eluant, mp 81–83 °C. (Found: C, 68.2; H, 7.2; M^+, 564.2548. $C_{32}H_{40}O_7Si$ requires C, 68.05; H, 7.15%; M, 564.2543); ν_{max} (film) 3464, 1736, 1708, 1250, 1188 and 842 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.18 [9 H, s, $Si(CH_3)_3$], 0.9 (3 H, d, *J* 6, 5-CH_3), 1.01 (3 H, t, *J* 7.5, CH_2CH_3), 1.73 (2 H, m, 5-H and 6-H), 1.97 (1 H, q, *J* 13, 6-H′), 2.80 (1 H, dd, *J* 13, 4, 1-H), 3.39 (1 H, d, *J* 9, 3-H), 3.47 (2 H, s, $PhCH_2$), 3.72 (1 H, s, 2-OH), 3.95 (4 H, m, CH_2CH_3 and $PhCH_2O$), 5.18 (1 H, t, *J* 9, 4-H), 6.30 (1 H, s, 4′-H), 6.9–7.22 (10 H, m, ArH) and 7.61(1 H, d *J* 2, 5′-H); *m*/*z* (EI) 564 (M^+, 0.1%), 174 (29) and 91 (100); (CI; NH_3) 582 (M^+ + 18, 100%).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*,5*SR*)-2,3-dihydroxy-5-methyl-4-phenylethanoyloxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 46

A mixture of the esters **43** and **44** (400 mg, 0.64 mmol) was dissolved in ethanol (10 cm^3) with a suspension of 10% palladium on charcoal (68 mg, 0.064 mmol). The mixture was stirred vigorously under an atmosphere of hydrogen until complete consumption of starting material (several days). The reaction mixture was diluted with dichloromethane (20 ml), filtered through celite, and the filter cake was washed with dichloromethane (3 × 10 cm^3). The solvent was removed under reduced pressure and chromatography of the residue, using light petroleum–ether (4 : 1) as eluant, gave the *title compound* **46** (220 mg, 73%) as a white crystalline solid, mp 102–103 °C. (Found: C, 63.0; H, 7.3. $C_{25}H_{34}O_7Si$ requires C, 63.25; H, 7.20%); ν_{max} (film) 3460, 1735, 1709, 1379, 1250, 1188, 1044, 1003 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.31 [9 H, s, $Si(CH_3)_3$], 0.91 (3 H, d, *J* 6, 5-CH_3), 1.06 (3 H, t, *J* 7.5, CH_2CH_3), 1.58 (1 H, br. s, 3-OH), 1.72–1.93 (3 H, m, 5-H, 6-H_2), 2.82 (1 H, m, 1-H), 3.39 (1 H, d, *J* 9, 3-H), 3.68 (2 H, s, $PhCH_2$), 4.0 (2 H, m, CH_2CH_3), 4.48 (1 H, d, *J* 1.5, 2-OH), 5.03 (1 H, t, *J* 9, 4-H), 6.20 (1 H, d, *J* 2, 4′-H), 7.30 (5 H, m, ArH) and 7.56 (1 H, d, *J* 2, 5′-H); *m*/*z* (CI; NH_3) 492 (M^+ + 18, 16%), 474 (M^+, 2), 462 (84), 457 (33), 402 (27), 356 (26), 339 (28), 337 (62), 327 (67), 321 (34), 255 (30) and 249 (100).

Following this procedure, the benzyl ether **45** (2.70 g, 4.8 mmol) gave the diol **46** (2.07 g, 91%).

Ethyl (1*RS*,2*SR*,4*RS*,5*SR*)-2-hydroxy-5-methyl-4-phenylethanoyloxy-2-(2-trimethylsilyl-3-furyl)-3-oxo-cyclohexane-1-carboxylate 47

The diol **46** (2 g, 4.2 mmol) was oxidized at −50 °C using the procedure outlined for alcohol **25** with chromatography using light petroleum–ether (3 : 1) as eluant to give the *title compound* **47** (2 g, *ca.* 100%) as a white crystalline solid, mp 148–150 °C. (Found: C, 63.3; H, 6.8. $C_{25}H_{32}O_7Si$ requires C, 63.55; H, 6.8%); ν_{max} (film) 3444, 1739, 1709, 1457, 1378, 1343, 1249, 1190, 1140 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.25 [9 H, s, $Si(CH_3)_3$], 1.10 (3 H, d, *J* 7, 5-CH_3), 1.12 (3 H, t, *J* 7.5, CH_2CH_3), 1.92–2.10 (2 H, m, 5-H, 6-H), 2.26 (1 H, q, *J* 13, 6-H′), 3.02 (1 H, dd, *J* 13, 4, 1-H), 3.72 (2 H, s, $PhCH_2$), 4.07 (2 H, m, CH_2CH_3), 4.83 (1 H, s, 2-OH), 5.68 (1 H, d, *J* 11, 4-H), 6.19 (1 H, d, *J* 2, 4′-H), 7.18 (5 H, m, ArH) and 7.57 (1 H, d, *J* 2, 5′-H); *m*/*z* (CI; NH_3) 490 (M^+ + 18, 40%), 473 (M^+ + 1, 39), 400 (32), 383 (36), 337 (76) and 247 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2,3-dihydroxy-5-methyl-4-phenylethanoyloxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 48

The ketone **47** (2 g, 4.24 mmol) was dissolved in acetonitrile (15 cm^3) and acetic acid (15 cm^3). Tetramethylammonium triacetoxyborohydride (5 g, 19 mmol) was added and the mixture stirred for 16 h. Work-up as outlined for the preparation of diol **42**, with chromatography using light petroleum–ether (4 : 1) as eluant, gave the *title compound* **48** (1.99 g, 99%) as a white crystalline solid, mp 90–92 °C. (Found C, 63.2; H, 7.3. $C_{25}H_{34}O_7Si$ requires C, 63.25; H, 7.20%); ν_{max} (film) 3465, 1730, 1709, 1260, 1186, 1097, 1016, 841 and 799 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.30 [9 H, s, $Si(CH_3)_3$], 0.91 (3 H, d, *J* 7, 5-CH_3), 1.11 (3 H, t, *J* 7.5, CH_2CH_3), 1.65 (1 H, br. s, 3-OH), 1.81 (2 H, m, 6-H_2), 2.13 (1 H, m, 5-H), 3.25 (1 H, dd, *J* 13, 7, 1-H), 3.65 (2 H, s, $PhCH_2$), 3.80 (1 H, d, *J* 2, 3-H), 4.01 (2 H, m, CH_2CH_3), 4.46 (1 H, s, 2-OH), 5.16 (1 H, dd, *J* 11, 2, 4-H), 6.31 (1 H, s, 4′-H), 7.30 (5 H, m, ArH) and 7.52 (1 H, s, 5′-H); *m*/*z* (EI) 474 (M^+, 6%), 459 (22), 255 (64), 167 (30), 137 (34) and 91 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2-hydroxy-5-methyl-4-phenylethanoyloxy-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 49

The diol **48** (1 g, 2.1 mmol) and diisopropylethylamine (1 cm^3, 5.75 mmol) were dissolved in dichloromethane (2 cm^3) at 0 °C and 2-trimethylsilylethoxymethyl chloride (0.6 cm^3, 3.39 mmol) was added. The reaction mixture was stirred for 16 h at ambient temperature, quenched with water (2 cm^3) and diluted with ether (5 cm^3). The aqueous layer was extracted with ether (3 × 5 cm^3) and the combined organic phases washed with brine (10 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (10 : 1) as eluant, gave the *title compound* **49** (1.16 g, 91%) as a viscous oil. [Found (EI): M^+, 604.2898. $C_{31}H_{48}O_8Si_2$ requires M, 604.2888]; ν_{max} (film) 3467, 1737, 1710, 1250, 1186, 1156, 1098, 1013 and 839 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.0 [9 H, s, $Si(CH_3)_3$], 0.31 (9 H, s, 2′-TMS), 0.81 (2 H, m, CH_2Si), 0.83 (3 H, d, *J* 7, 5-CH_3), 1.13 (3 H, t, *J* 7, CH_2CH_3), 1.77

(2 H, m, 6-H_2), 2.12 (1 H, m, 5-H), 3.19 (1 H, m, 1″-H), 3.25 (1 H, dd, *J* 9, 4, 1-H), 3.43 (1 H, m, 1′-H), 3.64 (2 H, s, $PhCH_2$), 3.79 (1 H, d, *J* 3, 3-H), 4.02 (2 H, q, *J* 7, CH_2CH_3), 4.09 and 4.37 (each 1 H, d, *J* 6, O*H*CHO), 4.38 (1 H, s, 2-OH), 5.15 (1 H, dd, *J* 11, 3, 4-H), 6.28 (1 H, d, *J* 2, 4′-H), 7.30 (5 H, m, ArH) and 7.46 (1 H, d, *J* 2, 5′-H); *m*/*z*. (EI) 604 (M^+, 5%), 413 (53), 337 (48), 277 (43), 249 (57), 193 (27), 167 (37), 156 (85), 91 (92) and 73 (100).

Ethyl (l*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2,4-dihydroxy-5-methyl-3-(2-trimethylsilylethoxymethoxy)-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 50

The ester **49** (3.6 g, 5.96 mmol) was dissolved in ethanol (51 cm^3) and anhydrous potassium carbonate (8 g, 57.9 mmol) was added. The mixture was stirred at ambient temperature for 48 h, the solvent removed under reduced pressure, and the residue partitioned between ether (100 cm^3) and water (50 cm^3). The aqueous phase was extracted with ether (3 × 30 cm^3) and the combined organic phases were washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated. Chromatography of the residue using light petroleum–ether (20 : 1 then 4 : 1) as eluant, gave the *title compound* **50** (2.03 g, 70%) as a white crystalline solid, mp 83–85 °C. (Found: C, 56.95; H, 8.9. $C_{23}H_{42}O_7Si_2$ requires C, 56.75; H, 8.7%); ν_{max} (film) 3457, 1709, 1376, 1250, 1185, 1099, 1061, 1020 and 841 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.01 [9 H, s, $Si(CH_3)_3$], 0.31 (9 H, s, 2′-TMS), 0.92 (2 H, m, CH_2TMS), 1.11 (3 H, d, *J* 7, 5-CH_3), 1.12 (3 H, t, *J* 7, CH_2CH_3), 1.75 (3 H, m, 5-H, 6-H_2), 3.18 (1 H, m, 1-H), 3.33 (1 H, d, *J* 9, 4-OH), 3.45 (1 H, m, 1″-H), 3.51 (1 H, d, *J* 3, 3-H), 3.71 (2 H, m, 4-H, 1″-H), 4.01 (2 H, q, *J* 7, CH_2CH_3), 4.04 (1 H, d, *J* 5.5, O*H*CHO), 4.48 (1 H, s, 2-OH), 4.57(1 H, d, *J* 5.5, OHC*H*O), 6.28 (1 H, d, *J* 1.5, 4′-H) and 7.5 (1 H, d, *J* 1.5, 5′-H); *m*/*z* (EI) 486 (M^+, 1%), 370 (25), 267 (35), 249 (37), 167 (39) and 156 (100). Some of the ester **49** (1.08 g, 30%) was recovered and resubjected to the reaction conditions to yield further alcohol **50** (500 mg, 17%; total yield 2.53 g, 87%).

Ethyl (l*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxymethoxy)-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 51

To silver nitrate (16 g, 94 mmol) in water (80 cm^3) was added aqueous sodium hydroxide (4 M, 160 cm^3) and the mixture stirred in the absence of light for 0.5 h. The mixture was filtered and the brown powder washed with water (200 cm^3), acetone (200 cm^3) and ether (400 cm^3) before being dried under reduced pressure in the dark for 48 h to give silver oxide (10 g, 92%).

The alcohol **50** (2.5 g, 4.12 mmol) was dissolved in methyl iodide (78 cm^3) which had been dried by passing through silica gel and silver(I) oxide (7.42 g, 32.2 mmol) was added. The mixture was stirred while heating under reflux in the absence of light for 48 h then cooled and filtered through celite. The residue was washed with ether and the organic extracts combined and concentrated under reduced pressure. Chromatography using light petroleum–ether (20 : 1 then 4 : 1) as eluant, gave the *title compound* **51** (1.59 g, 62%) as a white crystalline solid, mp 52–54 °C. (Found: C, 57.55; H, 8.9; M^+, 500.2624. $C_{24}H_{44}O_7Si_2$ requires C, 57.55, H, 8.85%; M, 500.2625); ν_{max} (film) 3468, 1710, 1376, 1240, 1183, 1106 1032 and 841 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.02 (9 H, s, TMS), 0.32 (9 H, s, 2′-TMS), 0.76 (2 H, m, CH_2TMS), 1.04 (3 H, d, *J* 7, 5-CH_3), 1.13 (3 H, t, *J* 7, CH_2CH_3), 1.67 (1 H, q, *J* 12.5, 6-H), 1.80 (1 H, dt, *J* 12.5, 4.5, 6-H′), 1.97 (1 H, m, 5-H), 3.12 (1 H, m, 1″-H), 3.25 (1 H, dd, *J* 12.5, 4.5, 1-H), 3.40 (3 H, s, 4-OCH_3), 3.32–3.48 (2 H, m, 4-H, 1″-H), 3.92 (1 H, d, *J* 3, 3-H), 4.02 (2 H, q, *J* 7, CH_2CH_3), 4.22 (1 H, d, *J* 5.5, O*H*CHO), 4.4 (1 H, s, 2-OH), 4.62 (1 H, d, *J* 5.5, OHC*H*O), 6.30 (1 H, d, *J* 1.5, 4′-H and 7.48 (1 H, d, *J* 1.5, 5′-H); *m*/*e* (EI) 500 (M^+, 1%), 231 (35), 179 (24), 167 (36), 156 (65) and 73 (100). Some alcohol **50** (0.53 g, 21%) was also recovered.

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 35 *via* acid 52

The ethyl ester **51** (1.55 g, 3.1 mmol) was dissolved in ethanol (10 cm^3) and aqueous sodium hydroxide (15 M, 2.16 cm^3) diluted with ethanol (5.5 cm^3) was added. The mixture was stirred at ambient temperature for 48 h then acidified to pH 2 with aqueous hydrogen chloride (3 M). The aqueous phase was extracted with ethyl acetate (5 × 25 cm^3) and the combined organic phase washed with brine (2 × 30 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Azeotropic distillation with benzene (3 × 50 cm^3) gave the carboxylic acid **52** (1.45 g, 99%) as a sticky gum; ν_{max} (film) 3600–2400, 1711, 1249, 1183, 1155, 1104, 1058, 1020 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.02 [9 H, s, $Si(CH_3)_3$], 0.31 [9 H, s, 2′-$Si(CH_3)_3$], 0.76 (2 H, m, CH_2Si), 1.03 (3 H, d, *J* 7, 5-CH_3), 1.65 (1 H, q, *J* 13, 6-H), 1.87 (1 H, dt, *J* 13, 4.5, 6-H), 1.98 (1 H, m, 5-H), 3.11 (1 H, m, 1″-H), 3.28 (1 H, dd, *J* 13, 4.5, 1-H), 3.35 (1 H, m, 4-H), 3.38 (3 H, s, 4-OCH_3), 3.43 (1 H, m, 1′-H), 3.91 (1 H, d, *J* 2, 3-H), 4.10 (1 H, s, 2-OH), 4.20 and 4.61 (each 1 H, d, *J* 7, O*H*CHO), 6.29 (1 H, d, *J* 1.5, 4′-H) and 7.49 (1 H, d, *J* 1.5, 5′-H); *m*/*z* (FAB) 495 (M^+ + 23, 2%), 472 (M^+, 4), 247 (36), 226 (93), 203 (25), 175 (26) and 167 (100).

Acid **52** (1.4 g, 2.9 mmol), 2-trimethylsilylethanol (2.12 cm^3, 14.8 mmol) and DMAP (18 mg, 0. 15 mmol) were dissolved in dichloromethane (10 cm^3) at 0 °C, and dicyclohexylcarbodiimide (737 mg, 3.6 mmol) in dichloromethane (6.6 cm^3) was added. Stirring was continued at ambient temperature for 16 h and the reaction mixture diluted with ether (30 cm^3) and washed with water (15 cm^3). The aqueous phase was extracted with ether (3 × 15 cm^3) and the combined organic phases washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (10 : 1) as eluant gave the *title compound* **35** (1.35 g, 80%) as a viscous oil. [Found (CI): M^+ + H, 573.3072. $C_{27}H_{53}O_7Si_3$ requires M, 573.3099]; ν_{max} (film) 3464, 1708, 1250, 1172, 1106, 1036 and 839 cm^{-1}; *m*/*z* (FAB) 573 (M^+ + 1, 0.2%), 226 (7), 167 (7) and 73 (100). All other data were identical to those of a sample prepared from the alcohol **33**, *vide supra*.

(2*Z*,4*Z*,8*E*)-10-[(1*RS*,3*RS*)-1-*tert*-Butyldimethylsilyloxycyclohexan-3-yl]-2-[(1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2-hydroxy-4-methoxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)-3-(2-trimethylsilylethoxy)methoxycyclohexan-2-yl]-8-methyldeca-2,4,8-trienoic acid 54 and (2*Z*,4*Z*,8*E*)-10-[(1*SR*,3*SR*)-1-*tert*-butyldimethylsilyloxycyclohexan-3-yl]-2-[(1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2-hydroxy-4-methoxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)-3-(2-trimethylsilylethoxy)methoxycyclohexan-2-yl)-8-methyldeca-2,4,8-trienoic acid 56

Following the procedure outlined for the synthesis of the diene **38**, the racemic hydroxybutenolide **37** (0.254 g, 0.48 mmol) and racemic phosphonium salt **53** (0.4 g, 0.57 mmol) gave a mixture of the *title compounds* **54** and **56** (0.353 g, 90%) together with their (4*E*)-isomers, ratio *ca.* 90 : 10, as a viscous oil. [Found (CI): M^+ − H, 823.5039. $C_{43}H_{79}O_9Si_3$ requires M, 823.5032]; ν_{max} ($CHCl_3$) 3800–2400, 1710, 1463, 1386, 1172, 1098, 1030 and 861 cm^{-1}; δ_H (300 MHz, $CDCl_3$) (4*Z*)-isomers: −0.9 and 0.02 [each 9 H, s, $Si(CH_3)_3$], 0.04 [6 H, $Si(CH_3)_2$], 0.8 (1 H, m, 2′-H_{ax}), 0.9 [9 H, s, $SiC(CH_3)_3$], 0.9–1.0 (4 H, m), 1.05 (3 H, d, *J* 6, 5″-CH_3), 1.1–1.38 (6 H, m, 2 × CH_2Si, 2 × CH), 1.63 (3 H, s, 8-CH_3), 1.5–1.9 (5 H, m), 1.95 (2 H, m, 10-H_2), 2.08 (2 H, m, 7-H_2), 2.33 (2 H, m, 6-H_2), 3.05 (1 H, dd, *J* 12.5, 4, 1″-H), 3.25 (1 H, dd, *J* 11, 2, 4″-H), 3.43 (3 H, s, OCH_3), 3.55 (3 H, m, 1′-H, OCH_2CH_2Si), 3.91 (1 H, d, *J* 2, 3″-H), 4.18 (2 H, m, OCH_2CH_2), 4.73 and 4.8 (each 1 H, d, *J* 6, O*H*CHO), 4.8 (1 H, s, 2″-OH), 5.18 (1 H, t, *J* 7.5, 9-H), 5.72 (1 H, m, 5-H), 6.35 (1 H, t, *J* 11.5, 4-H) and 6.85 (1 H, d, *J* 11.5, 3-H); (4*E*)-isomers: 5.95 (1 H, dt, *J* 15, 6, 5-H) and 6.55 (2 H, m, 3-H, 4-H); *m*/*z* (FAB) 823 (M^+ − 1, 100%), 723 (25) and 661 (30).

(2*Z*,4*Z*,8*E*)-10-[(1*RS*,3*RS*)-1-*tert*-Butyldimethylsilyloxycyclohexan-3-yl]-2-[(1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2,3-dihydroxy-4-methoxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)cyclohexan-2-yl]-8-methyldeca-2,4,8-trienoic acid 55 and (2*Z*,4*Z*,8*E*)-10-[(1*SR*,3*SR*)-*tert*-butyldimethylsilyloxycyclohexan-3-yl]-2-[(1*RS*,2*SR*,3*RS*,4*RS*,5*SR*)-2,3-dihydroxy-4-methoxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)cyclohexan-2-yl]-8-methyldeca-2,4,8-trienoic acid 57

Potassium carbonate (70 mg) was added to a solution of the 2-trimethylsilylethoxymethyl ethers **54** and **56** (67 mg, 0.08 mmol) in ether (1 cm^3) and the mixture was stirred vigorously. An ethereal solution of magnesium bromide (1 M, 0.66 cm^3, 0.66 mmol) was added, followed by *n*-butanethiol (29 mg, 0.33 mmol) and the reaction was stirred for 10 min. Water (1 cm^3) was added, the mixture diluted with ether (10 cm^3) and the aqueous phase extracted with ether (3 × 5 cm^3). The combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (2 : 1) and 1% acetic acid as eluant gave a mixture of the *title compounds* **55** and **57** (50 mg, 88%) together with their (4*E*)-isomers, ratio *ca.* 90 : 10, as a viscous oil. [Found (CI): M^+ − H, 693.4230. $C_{37}H_{65}O_8Si_2$ requires M, 693.4218]; ν_{max} ($CHCl_3$) 3583–2400, 1707, 1627, 1450 and 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) (4*Z*)-isomers: −0.9 (9 H, s, TMS), 0.07[6 H, s, $Si(CH_3)_2$], 0.8 (1 H, m, 2′-H_{ax}), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.05 (3 H, d, *J* 6, 5″-CH_3), 0.85–1.4 (8 H, m, CH_2Si, 6 × CH), 1.62 (3 H, s, 8-CH_3), 1.5–1.88 (6 H, m), 1.91 (2 H, m, 10-H_2), 2.1 (2 H, t, *J* 7.5, 7-H_2), 2.49 (2 H, m, 6-H_2), 3.15 (1 H, dd, *J* 12, 4, 1″-H), 3.23 (1 H, dd, *J* 10, 2.5, 4″-H), 3.47 (3 H, s, OCH_3), 3.55 (1 H, m, 1′-H), 3.9 (1 H, d, *J* 2.5, 3″-H), 4.2 (2 H, m, OCH_2CH_2), 4.72 (1 H, br. s, 2′-OH), 5.18 (1 H, t, *J* 7.5, 9-H), 5.75 (1 H, m, 5-H), 6.43 (1 H, t, *J* 11.5, 4-H), 7.1 (1 H, d, *J* 11.5, 3-H); (4*E*)-isomers: 5.98 (1 H, dt, *J* 15, 6, 5-H), 6.57 (1 H, dd, *J* 15, 12, 4-H) and 6.74 (1 H, d, *J* 12, 3-H); *m*/*z* (FAB) 694 (M^+, 100%), 676 (5) and 594 (10).

2-Trimethylsilylethyl (1*SR*,2*RS*,4*SR*,5*RS*,6*RS*,9*Z*)-9-{(2*Z*,6*E*)-8-[(1*RS*,3*RS*)-1-*tert*-butyldimethylsilyloxycyclohexan-3-yl]-6-methylocta-2,6-dienylidene}-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxa-bicyclo[4.3.0]nonane-2-carboxylate 58 and 2-trimethylsilylethyl (1*SR*,2*RS*,4*SR*,5*RS*,6*RS*,9*Z*)-9-{(2*Z*,6*E*)-8-[(1*SR*,3*SR*)-1-*tert*-butyldimethylsilyloxycyclohexan-3-yl]-6-methylocta-2,6-dienylidene}-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylate 59

Following the procedure outlined for the synthesis of the lactone **40**, a mixture of the hydroxy acids **55** and **57** (0.29 g, 0.42 mmol) gave a mixture of the *title compounds* **58** and **59** together with their (2′*E*)-isomers, ratio *ca.* 80 : 20, as a viscous oil (0.226 g, 80%). [Found (CI): M^+ + H, 677.4260. $C_{37}H_{65}O_7Si_2$ requires M, 677.4269]; ν_{max} ($CHCl_3$) 3425, 1763, 1737, 1703, 1648, 1461, 1386, 1349, 1174, 1115 and 976 cm^{-1}; δ_H (300 MHz, $CDCl_3$) (2′*Z*)-isomers: 0.03 (9 H, s, TMS), 0.09 [6 H, s, $Si(CH_3)_2$], 0.8 (1 H, m, 2″-H_{ax}), 0.9 [9 H, s, $SiC(CH_3)_3$], 0.85–1.05 (6 H, m, CH_2Si, 4 × CH), 1.1 (3 H, d, *J* 6, 4-CH_3), 1.15–1.35 (2 H, m), 1.6 (3 H, s, 6′-CH_3), 1.5–1.65 (4 H, m), 1.8–2.0 (3 H, m), 2.08 (2 H, t, *J* 7, 5′-H), 2.36 (2 H, m, 4′-H), 2.61 (1 H, dd, *J* 12, 2.5, 2-H), 3.18 (1 H, dd, *J* 11, 3.5, 5-H), 3.45 (3 H, s, OCH_3), 3.52 (1 H, m, 1″-H), 4.18 (2 H, m, OCH_2CH_2), 4.43 (1 H, d, *J* 4.5, 6-H), 5.16 (1 H, t, *J* 7.5, 7′-H), 5.58 (1 H, br. s, 1-OH), 5.95 (1 H, m, 3′-H), 6.95 (1 H, d, *J* 12, 1′-H) and 7.15 (1 H, t, *J* 12, 2′-H); (2′*E*)-isomers: 5.50 (1 H, br. s, 1-OH), 6.1 (1 H, dt, *J* 15, 7.5, 3′-H), 6.55 (1 H, d, *J* 11, 1′-H) and 7.25 (1 H, dd, *J* 15, 11, 2′-H); *m*/*z* (FAB) 677 (M^+ + 1, 2%), 619 (10) and 499 (6).

2-Trimethylsilylethyl (1*SR*,2*RS*,4*SR*,5*RS*,6*RS*,9*Z*)-9-{(2*E*,6*E*)-8-[(1*RS*,3*RS*)-1-*tert*-butyldimethylsilyloxycyclohexan-3-yl]-6-methylocta-2,6-dienylidene}-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxa-bicyclo[4.3.0]nonane-2-carboxylate 60 and 2-trimethylsilylethyl (1*SR*,2*RS*,4*SR*,5*RS*,6*RS*,9*Z*)-9-{(2*E*,6*E*)-8-[(1*SR*,3*SR*)-1-*tert*-butyldimethylsilyloxycyclohexan-3-yl]-6-methylocta-2,6-dienylidene}-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylate 61

Iodine (1.5 mg, 5.9 × 10^{-3} mmol) in benzene (0.3 cm^3) was added to a solution of the lactones **58** and **59** (77 mg, 0.12 mmol) in benzene (9 cm^3) with potassium carbonate (80 mg) and the reaction stirred in the presence of a sun-lamp for 3 h. The mixture was diluted with ether (25 cm^3), washed with saturated aqueous sodium thiosulfate (2 cm^3) and the aqueous phase was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (6 : 1) as eluant gave a mixture of the *title compounds* **60** and **61** (57 mg, 75%) as a viscous oil. [Found (CI): M^+ + H, 677.4250. $C_{37}H_{65}O_7Si_2$ requires M, 677.4269]; ν_{max} ($CHCl_3$) 3428, 1761, 1703, 1651, 1463, 1379, 1175, 1099, 1056 and 975 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.05 (9 H, s, TMS), 0.08 [6 H, s, $Si(CH_3)_2$], 0.8 (1 H, m, 2″-H_{ax}), 0.9 [9 H, s, $SiC(CH_3)_3$], 0.85–1.05 (6 H, m, CH_2Si, 4 × CH), 1.1 (3 H, d, *J* 6, 4-CH_3), 1.2 (2 H, m), 1.6 (3 H, s, 6′-CH_3), 1.5–1.8 (1 H, m), 1.85 (6 H, m), 2.1 (2 H, t, *J* 7.5, 5′-H_2), 2.3 (2 H, m, 4′-H_2), 2.6 (1 H, dd, *J* 12, 2, 2-H), 3.2 (1 H, dd, *J* 11, 3.5, 5-H), 3.5 (3 H, s, OCH_3), 3.52 (1 H, m, 1″- H), 4.2 (2 H, m, OCH_2CH_2), 4.4 (1 H, d, *J* 3.5, 6-H), 5.15 (1 H, t, *J* 7, 7′-H), 5.5 (1 H, s, 1-OH), 6.1 (1 H, dt, *J* 15, 7.5, 3′-H), 6.55 (1 H, d, *J* 11, 1′-H) and 7.25 (1 H, dd, *J* 15, 11, 2′-H); *m*/*z* 677 (M^+ + 1, 5%), 659 (5), 619 (10) and 499 (20). Minor amounts, *ca.* 1–2%, of the (2′*Z*)-isomers **58** and **59** were detected by ^1H NMR.

(1*SR*,2*RS*,4*SR*,5*RS*,6*RS*,9*Z*)-9-{(2*E*,6*E*)-8-[(1*RS*,3*RS*)-1-hydroxycyclohexan-3-yl]-6-methylocta-2,6-dienylidene}-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylic acid 62 and (1*SR*,2*RS*,4*SR*,5*RS*,6*RS*,9*Z*)-9-{(2*E*,6*E*)-8-[(1*SR*,3*SR*)-1-hydroxycyclohexan-3-yl]-6-methylocta-2,6-dienylidene}-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylic acid 63

Tetrabutylammonium fluoride (1 M in THF, 0.19 cm^3, 0.19 mmol) was added to a solution of the esters **60** and **61** (30 mg, 0.04 mmol) in THF (0.5 cm^3) and the mixture stirred at ambient temperature for 16 h. Aqueous hydrogen chloride (3 M, 0.3 cm^3) and chloroform (10 cm^3) were added and the aqueous phase extracted with more chloroform. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate containing acetic acid (1%) as eluant gave the *title compounds* **62** and **63** (20 mg, 97%) as a viscous oil. [Found (CI): M^+ − H, 461.2545. $C_{26}H_{37}O_7$ requires M, 461.2539]; ν_{max} ($CHCl_3$) 3583–2400, 1757, 1710, 1650, 1446, 1396, 1371, 1166, 1099 and 1039 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.8 (1 H, m, 2″-H_{ax}), 0.85–1.0 (4 H, m), 1.1 (3 H, d, *J* 6, 4-CH_3), 1.15–1.4 (2 H, m), 1.54 and 1.59 (each 1.5 H, s, 6′-CH_3), 1.6–2.45 (11 H, m), 2.65 (1 H, m, 2-H), 3.2 (1 H, dd, *J* 10, 4, 5-H), 3.45 (3 H, s, OCH_3), 3.62 and 3.75 (each 0.5 H, m, 1″-H), 4.42 (1 H, d, *J* 4, 6-H), 4.9–5.2 (4 H, m, 1″-OH, 1-OH, CO_2H, 7′-H), 6.05 (1 H, m, 3′-H), 6.57 and 6.58 (each 0.5 H, d, *J* 11, 1′-H) and 7.25 (1 H, dd, *J* 15, 11, 2′-H); *m*/*z* (FAB) 461 (M^+ − 1, 100%) and 241 (15).

(1*RS*,4*SR*,8*RS*,18*SR*,19*RS*,20*RS*,21*SR*,10*E*,14*E*,16*Z*)-11,21-Dimethyl-18-hydroxy-20-methoxy-3,25-dioxatetracyclo[16.4.0.$1^{4,8}$.$2^{17,19}$]pentacosa-10,14,16-triene-2,24-dione 64

Triethylamine (7.5 µl, 0.05 mmol) and trichlorobenzoyl chloride (7 µl, 0.045 mmol) were added to a solution of the hydroxy acids **62** and **63** (20 mg, 0.04 mmol) in anhydrous xylene (4.4 cm^3)

and the mixture stirred at ambient temperature for 2 days. 4-Dimethylaminopyridine (11 mg, 0.086 mmol) in xylene (4.4 cm^3) was added and the mixture was stirred for a further hour before concentrating under reduced pressure. Chromatography of the residue using light petroleum–ether (1 : 1) as eluant gave the *title compound* **64** (5 mg, 26%, 52% based **62**) as a solid, mp 176–178 °C. [Found (CI): M^+ + H, 445.2565. $C_{26}H_{37}O_6$ requires M, 445.2590]; ν_{max} ($CHCl_3$) 3437, 1759, 1737, 1698, 1652, 1581, 1549, 1454, 1385, 1315, 1277, 1135, 1099, 1059, 982 and 909 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.65 (1 H, q, *J* 12, 23-H_{ax}), 0.8–0.92 (4 H, m), 1.08 (3 H, d, *J* 6, 21-CH_3), 1.2–1.4 (4 H, m), 1.5 (3 H, s, 11-CH_3), 1.55–2.05 (5 H, m), 2.1–2.45 (4 H, m), 2.55 (1 H, dd, *J* 12.5, 3.5, 1-H), 3.2 (1 H, dd, *J* 11, 4, 20-H), 3.5 (3 H, s, OCH_3), 4.45 (1 H, d, *J* 4, 19-H), 4.87 (1 H, m, 4-H), 5.0 (1 H, m, 10-H), 5.13 (1 H, s, 18-OH), 5.9 (1 H, m, 14-H), 6.4 (1 H, d, *J* 11.5, 16-H) and 7.19 (1 H, dd, *J* 11, 15, 15-H); *m/z* (FAB) 445 (M^+ + 1, 6%), 427 (3) and 409 (1).

(1*RS*,4*RS*,6*SR*,7*RS*,8*RS*,9*SR*,19*RS*,10*E*,12*E*,16*E*)-8,9-Dihydroxy-6,16-dimethyl-10-hydroxymethyl-7-methoxy-2-oxatricyclo[17.3.1.0^{4,9}]tricosa-10,12,16-trien-3-one 65

Diisobutylaluminium hydride in toluene (1 M, 0.23 cm^3, 0.23 mmol) was added to a solution of lactone **64** (10 mg, 0.025 mmol) in toluene (1 cm^3) at −78 °C. The reaction was stirred for 30 min then water (1 cm^3) and ether (10 cm^3) were added. The aqueous phase was extracted with ether (6 × 5 cm^3) and the combined organic extracts were dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using ether as eluant gave the *title compound* **65** (7 mg, 70%) as a solid, mp 184–188 °C. [Found (EI): M^+, 448.2845. $C_{26}H_{40}O_6$ requires M, 448.2825]; ν_{max} ($CHCl_3$) 3344, 1705, 1451, 1380, 1173, 1095 and 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.06 (1 H, q, *J* 12, 23-H_{ax}), 0.8 (4 H, m), 1.05 (3 H, d, *J* 6, 6-CH_3), 1.1–1.45 (4 H, m), 1.6 (3 H, s, 16-CH_3), 1.5–2.1 (5 H, m), 2.25 (4 H, m), 3.1 (1 H, dd, *J* 9, 7, 4-H), 3.3 (1 H, dd, *J* 10, 3.5, 7-H), 3.42 (3 H, s, OCH_3), 3.9 (1 H, d, *J* 3.5, 8-H), 3.95 (1 H, s, 9-OH), 4.18 and 4.28 (each 1 H, d, *J* 13, 10-CH), 4.75 (1 H, m, 1-H), 4.9 (1 H, m, 17-H), 5.7 (1 H, m, 13-H) and 6.35 (2 H, m, 11-H, 12-H); *m/z* (EI) 448 (M^+, 3%), 430 (6), 412 (12) and 339 (7).

Methyl (6*R*,2*Z*,4*E*,8*E*)-l0-{(2*R*,3*S*,6*R*,8*R*,l0*S*)-l0-*tert*-butyldimethylsilyloxy-3-methyl-2-(1-methylethyl)-l,7-dioxaspiro[5.5]undecan-8-yl}-2-[(l*R*,2*S*,3*R*,4*R*,5*S*)-1-(2-trimethylsilylethoxycarbonyl)-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy-methoxy)cyclohexan-2-yl]-6,8-dimethyldeca-2,4,8-trienoate (4*E*)-66 and methyl [6*R*,2*Z*,4*E*, 8*E*]-l0-{(2*R*,3*S*,6*R*,8*R*,l0*S*)-l0-*tert*-butyldimethylsilyloxy-3-methyl-2-(1-methylethyl)-l,7-dioxaspiro[5.5]undecan-8-yl}-2-[(l*S*,2*R*,3*S*,4*S*,5*R*)-1-(2-trimethylsilylethoxycarbonyl)-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxymeth-oxy)cyclohexan-2-yl]-6,8-dimethyldeca-2,4,8-trienoate (4*E*)-67

The phosphonium salt **1** (115.6 mg, 0.138 mmol) and the racemic hydroxybutenolide **37** (61 mg, 0.115 mmol) were dissolved in THF (2.5 cm^3) and cooled to −78 °C. Lithium hexamethyldisilazide (0.4 mmol in THF, 1.5 cm^3) was cooled to −78 °C, and added to the reaction mixture *via* a cannula. The orange solution was warmed to −10 °C over 1 h, stirred at this temperature for 0.5 h and then saturated aqueous ammonium chloride (2 cm^3) was added. The aqueous layer was extracted with ether (3 × 5 cm^3) and the combined organic phases washed with brine (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether–acetic acid (1 : 1 : 0.01) as eluant gave trienyl acids which were immediately dissolved in ether (10 cm^3) and treated with an excess of ethereal diazomethane. The residual diazomethane was quenched by the addition of acetic acid (0.5 cm^3) and the reaction mixture concentrated. Chromatography of the residue using light petroleum–ether (4 : 1) as eluant gave the trienyl esters **66** and **67** (74 mg, 66%) as a 2 : 1 mixture of (4*Z*)- and (4*E*)-isomers.

This mixture of (4*Z*)- and (4*E*)-dienyl esters **66** and **67** (70 mg, 0.071 mmol) was dissolved in degassed benzene (l cm^3) and iodine (0.18 cm^3 of an 0.2 M solution in benzene) was added. The reaction mixture was left, without stirring, in sunlight until only the 4*E*-isomers were visible by TLC. The solution was diluted with ether (5 cm^3) and washed with saturated aqueous sodium thiosulfate (5 cm^3). The aqueous phase was extracted with ether (3 × 5 cm^3) and the combined organic phases washed with brine (10 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (5 : 1) as eluant, gave a mixture of the *title compounds* (4*E*)-**66** and (4*E*)-**67** (63 mg, 90%). [Found (FAB): M^+ + Na, 1003.6192. $C_{52}H_{96}NaO_{11}Si_3$ requires M, 1003.6159]; ν_{max} (film) 3467, 1726, 1645, 1385, 1216, 1172, 1090, 1066, 1032, 1011, 861 and 837 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.0 and 0.03 [each 9 H, s, Si(CH_3)$_3$], 0.06 [6 H, s, Si(CH_3)$_2$], 0.75 (3 H, d, *J* 7, 3′-CH_3), 0.82 (3 H, d, *J* 7, CHC*H*$_3$), 0.90 [9 H, s, SiC(CH_3)$_3$], 0.85–1.02 (13 H, m, CHC*H*$_3$, 6-CH_3, 5″-CH_3, 2 × CH_2Si), 1.09–1.70 (10 H, m), 1.59 (3 H, s, 8-CH_3), 1.75–1.95 [5 H, m, 9′-H, 11′-H, C*H*(CH_3)$_2$, 7-H_2], 2.05–2.40 (3 H, m, 10-H_2, 6-H), 3.04 (1 H, d, *J* 9, 2′-H), 3.20 (2 H, m, 1″-H, 4″-H), 3.39 (3 H, s, 4″-OCH_3), 3.42–3.69 (2 H, m, 8′-H, $SiCH_2$*H*CHO), 3.74 (1 H, m, $SiCH_2$HC*H*O), 3.80 (3 H, s, CO_2CH_3), 4.03–4.20 (4 H, m, $SiCH_2$C*H*$_2$O, 10′-H, 3″-H), 4.44 (1 H, s, 2″-OH), 4.69 (2 H, m, OCH_2O), 5.22 (1 H, br. t, *J* 7, 9-H), 5.81 (1 H, m, 5-H), 6.12 (1 H, m, 4-H) and 6.30 (1 H, d, *J* 10.8, 3-H); *m/z* FAB 1004 (M^+ + 23, 2%), 980 (M^+, 1%), 430 (18), 297 (67) and 226 (100).

The 4*Z*-isomers (4*Z*)-**66** and (4*Z*)-**67** could be distinguished by the following peaks; δ_H 2.84 (1 H, m, 6-H), 5.43 (1 H, m, 5-H), 5.92 (1 H, m, 4-H) and 6.58 (1 H, d, *J* 11.5 Hz, 3-H).

(l*R*,2*S*,3*R*,4*R*,5*S*)-2-[(5*R*,1*Z*,3*E*,7*E*)-1-carbomethoxy-5,7-dimethyl-9-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-hydroxy-3-methyl-2-(1-methylethyl)-l,7-dioxaspiro[5.5]undecan-8-yl}-nona-1,3,7-trien-1-yl]-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy-methoxy)cyclohexane-1-carboxylic acid 68 and (l*S*,2*R*,3*S*,4*S*, 5*R*)-2-[(5*R*,1*Z*,3*E*,7*E*)-1-carbomethoxy-5,7-dimethyl-9-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-hydroxy-3-methyl-2-(1-methylethyl)-l,7-dioxaspiro[5.5]undecan-8-yl}-nona-1,3,7-trien-1-yl]-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxymethoxy)-cyclohexane-1-carboxylic acid 69

Tetrabutylammonium fluoride (0.102 cm^3 of a 1 M solution in THF) was added to a solution of the esters (4*E*)-**66** and (4*E*)-**67** (20 mg, 0.02 mmol) in THF (1 cm^3) at 0 °C. The solution was stirred at ambient temperature for 10 h, diluted with ethyl acetate (3 cm^3) and aqueous hydrogen chloride (3 M, 1 cm^3) was added. The aqueous layer was extracted with ethyl acetate (3 × 1 cm^3) and the combined organic phases washed with brine (2 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ether–isopropanol (1 : 0.02 : 0.01) gave a mixture of the *title compounds* **68** and **69** (15.4 mg, 99%). [Found (FAB): M^+ + Na, 789.4550. $C_{41}H_{70}O_{11}NaSi$ requires M, 789.4585]; ν_{max} (film) 3630–2400, 1716, 1648, 1456, 1384, 1250, 1188, 1117, 1092, 1058, 1031, 1011, 980, 861 and 836 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.0 [9 H, s, Si(CH_3)$_3$], 0.72–1.05 [17 H, m, (C*H*$_3$)$_2$CH, 5-CH_3, 5′-CH_3, 3″-CH_3, CH_2Si], 1.1–1.71 (10 H, m), 1.55 and 1.59 (each 1.5 H, s, 7′-CH_3), 1.78–2.10 (5 H, m), 2.10–2.30 (2 H, m, 9′-H_2), 2.47 (1 H, m, 5′-H), 3.04 (1 H, d, *J* 9, 2″-H), 3.09–3.27 (2 H, m, 1-H, 4-H), 3.39 (3 H, s, 4-OCH_3), 3.40–3.80 (3 H, m, 8″-H, $SiCH_2$C*H*$_2$O), 3.82 (3 H, s, CO_2CH_3), 3.99 (0.5 H, d, *J* 2, 3-H), 4.02–4.20 (1.5 H, m, 3-H, 10″-H), 4.60–4.69 (2 H, m, OCH_2O), 5.04 (1 H, m, 8′-H), 5.71 (0.5 H, dd, *J* 15, 8, 4′-H), 5.90 (0.5 H, dd, *J* 15, 7, 4′-H), 5.8–6.38 (3 H, br. s, CO_2H, 2-OH, 10″-OH), 6.09–6.24 (1 H, m, 3′-H), 6.21 (0.5 H, d, *J* 11, 2′-H) and 6.48 (0.5 H, d, *J* 10.5, 2′-H); *m/z* (FAB) 789 (M^+ + 23, 2%), 181 (10), 136 (10) and 73 (100).

Methyl (6*R*,2*Z*,4*E*,8*E*)-10-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-*tert*-butyldimethylsilyloxy-3-methyl-2-(1-methylethyl)-1,7-dioxaspiro[5.5]undecan-8-yl}-2-[(1*R*,2*S*,3*R*,4*R*,5*S*)-1-(2-trimethylsilylethoxycarbonyl)-2,3-dihydroxy-4-methoxy-5-methyl)cyclohexan-2-yl]-6,8-dimethyldeca-2,4,8-trienoate 4*E*-70 and methyl (6*R*,2*Z*,4*E*,8*E*)-10-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-*tert*-butyldimethylsilyloxy-3-methyl-2-(1-methylethyl)-1,7-dioxaspiro[5.5]undecan-8-yl}-2-[(1*S*,2*R*,3*S*,4*S*,5*R*)-1-(2-trimethylsilylethoxycarbonyl)-2,3-dihydroxy-4-methoxy-5-methyl)cyclohexan-2-yl]-6,8-dimethyldeca-2,4,8-trienoate 4*E*-71

A mixture of the unisomerized Wittig products **66** and **67** (50 mg, 0.051 mmol) was dissolved in benzene (1 cm^3) and iodine (14 mg, 0.055 mmol) in benzene (0.4 cm^3) was added. The reaction was stirred vigorously while irradiating with a lamp (250 W) for 1.5 h and was then diluted with ether (5 cm^3) and washed with saturated aqueous sodium thiosulfate (3 cm^3). The aqueous phase was extracted with ether (3 × 5 cm^3), and the combined organic phases were washed with brine (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (2 : 1) as eluant gave a mixture of the *title compounds* (4*E*)-**70** and (4*E*)-**71** (40 mg, 92%) which were used immediately; ν_{max} (film) 3468, 1722, 1645, 1385, 1252, 1217, 1173, 1131, 1089, 1068, 1010, 983, 940, 861 and 837 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.08 [9 H, s, Si(CH_3)$_3$], 0.09 [6 H, s, Si(CH_3)$_2$], 0.78 (3 H, d, *J* 7, 3′-CH_3), 0.81 (3 H, d, *J* 7, CHC*H*$_3$), 0.89 [9 H, s, C(CH_3)$_3$], 0.90–1.0 (8 H, m, C*H*$_3$CH, 6-CH_3, CH_2Si), 1.01 (3 H, d, *J* 7, 5″-CH_3), 1.01–1.71 (10 H, m), 1.60 (3 H, s, 8-CH_3), 1.72–1.90 (5 H, m), 2.0–2.48 (3 H, m, 6-H, 10-H_2), 3.04 (1 H, d, *J* 9, 2′-H), 3.19 (1 H, dd, *J* 10, 3, 4″-H), 3.26 (1 H, dd, *J* 12, 4, 1″-H), 3.40 (3 H, s, 4″-OCH_3), 3.50 (1 H, m, 8′-H), 3.81 (3 H, s, CO_2CH_3), 3.99 (1 H, br. s, 3″-H), 4.05–4.24 (3 H, m, SiCH_2C*H*$_2$O, 10′-H), 4.42 (1 H, s, 2″-OH), 5.23 (1 H, br. t, *J* 7, 9-H), 5.88 (1 H, dd, *J* 15, 7, 5-H), 6.27 (1 H, dd, *J* 15, 11, 4-H) and 6.52 (1 H, d, *J* 11, 3-H); *m/z* (FAB) 874 (M$^+$ + 23).

Trimethylsilylethyl (1*S*,2*R*,4*S*,5*R*,6*R*,9*Z*)-9-[(4*R*,2*E*,6*E*)-8-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-*tert*-butyldimethylsilyloxy-3-methyl-2-(1-methylethyl)-1,7-dioxaspiro[5.5]undecan-8-yl}-4,6-dimethylocta-2,6-dienylidene]-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonan-2-ylcarboxylate 72 and trimethylsilylethyl (1*R*,2*S*,4*R*,5*S*,6*S*,9Z)-9-[(4*R*,2*E*,6*E*)-8-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-*tert*-butyldimethylsilyloxy-3-methyl-2-(1-methylethyl)-1,7-dioxaspiro[5.5]undecan-8-yl}-4,6-dimethylocta-2,6-dienylidene]-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonan-2-ylcarboxylate 73

A mixture of the hydroxy esters (4*E*)-**70** and (4*E*)-**71** (36 mg, 0.042 mol) was dissolved in chloroform (2 cm^3), silica gel (1 g, Merck, Kieselgel 60; 230–400 mesh) was added, and the mixture was stirred for 16 h. The solvent was removed under reduced pressure, and chromatography of the residue, pre-adsorbed onto the silica, using light petroleum–ether (3 : 1) as eluant, gave a mixture of the *title compounds* **72** and **73** (33.8 mg, 98%); ν_{max} (film) 3433, 1763, 1704, 1650, 1459, 1385, 1252, 1175, 1090, 1011, 982, 938 and 837 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.03 [9 H, s, Si(CH_3)$_3$], 0.08 [6 H, s, Si(CH_3)$_2$), 0.79 (3 H, d, *J* 6, 3″-CH_3), 0.81 (3 H, d, *J* 7, CHC*H*$_3$), 0.89 [9 H, s, C(CH_3)$_2$], 0.91–1.01 (8 H, m, CHC*H*$_3$, 4′-CH_3, CH_2Si), 1.09 (3 H, d, *J* 7, 4-CH_3), 1.14–1.70 (10 H, m), 1.6 (3 H, s, 6′-CH_3), 1.75–1.98 (5 H, m), 2.0–2.31 (2 H, m, 8′-H_2), 2.51 (1 H, m, 4′-H), 2.60 (1 H, d, *J* 12, 2-H), 3.03 (1 H, d, *J* 9, 2″-H), 3.19 (1 H, dd, *J* 10, 3, 5-H), 3.47 (3 H, s, 5-OCH_3), 3.51 (1 H, m, 8″-H), 4.11 (1 H, m, 10″-H), 4.19 (2 H, m, SiCH_2C*H*$_2$), 4.40 (1 H, d, *J* 3, 6-H), 5.23 (1 H, m, 7′-H), 5.49 and 5.51 (each 0.5 H, s, 1-OH), 6.07 and 6.09 (each 0.5 H, dd, *J* 15, 8, 3′-H), 6.52 (0.5 H, d, *J* 11, 1′-H), 6.54 (0.5 H, d, *J* 11, 1′-H) and 7.21 (1 H, m, 2′-H); *m/z* (FAB) 841 (M$^+$ + 23, 2%), 761 (3), 209 (9) and 73(100).

(1*S*,2*R*,4*S*,5*R*,6*R*,9*Z*)-9-[(4*R*,2*E*,6*E*)-8-{(2*R*,3*S*,6*R*,8*R*,10*S*)-(10-Hydroxy-3-methyl-2-(1-methylethyl)-1,7-dioxaspiro[5.5]-undecan-8-yl}-4,6-dimethylocta-2,6-dienylidene]-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylic acid 74 and (1*R*,2*S*,4*R*,5*S*,6*S*,9*Z*)-9-[(4*R*,2*E*,6*E*)-8-{(2*R*,3*S*,6*R*,8*R*,10*S*)-(10-hydroxy-3-methyl-2-(1-methylethyl)-1,7-dioxaspiro[5.5]undecan-8-yl}-4,6-dimethylocta-2,6-dienylidene]-1-hydroxy-5-methoxy-4-methyl-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylic acid 75

Deprotection of a mixture of the esters **72** and **73** (33 mg, 0.04 mmol) following the procedure outlined for the deprotection of (4*E*)-**66** and (4*E*)-**67** gave a mixture of the *title compounds* **74** and **75** (19.1 mg, 78%). [Found (CI): M$^+$+ H, 605.3710. $C_{34}H_{53}O_9$ requires M, 605.3689]; ν_{max} (film) 3500–2600, 1742, 1710, 1648, 1457, 1384, 1271, 1116, 1057, 1010, 979, 912 and 734 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.76–0.82 (6 H, m, 3″-CH_3, CHC*H*$_3$), 0.93–1.10 (9 H, m, CHC*H*$_3$, 4-CH_3, 4′-CH_3), 1.15–1.70 (10 H, m), 1.55 and 1.62 (each 1.5 H, s, 6′-CH_3), 1.78–2.04 (5 H, m), 2.11–2.30 (2 H, m, 8′-H_2), 2.51–2.71 (2 H, m, 2-H, 4′-H), 3.04 (1 H, d, *J* 9, 2″-H), 3.20 (1 H, dd, *J* 10.5, 3, 5-H), 3.47 and 3.48 (each 1.5 H, s, 5-OCH_3), 3.60 (1 H, m, 8″-H), 4.13 and 4.29 (each 0.5 H, m, 10″-H), 4.4 (1 H, d, *J* 3, 6-H), 4.91 (0.5 H, m, 7′-H), 4.99 (0.5 H, br. t, *J* 6.6, 7′- H), 5.29 (3 H, br. s, CO_2H, 1-OH, 10″-OH), 5.86 (0.5 H, dd, *J* 15.5, 9, 3′-H), 6.13 (0.5 H, dd, *J* 15.5, 6, 3′-H), 6.53 (0.5 H, d, *J* 11.5, 1′-H), 6.60 (0.5 H, d, *J* 10.5, 1′-H) and 7.21 (1 H, dd, *J* 15.5, 11.5, 2′-H); *m/z* FAB 627 (M$^+$ + 23, 10%), 605 (M$^+$ + 1, 5), 587 (23), 569 (13), 181 (74), 139 (57) and 111 (100).

(4*S*)-3,4-Dihydro-28-oxomilbemycin G 76

The seco-acids **74** and **75** (16 mg, 0.026 mmol) and DMAP (0.32 mg, 2.6 μmol) in dichloromethane (2.7 cm^3) were added over 5 h (syringe pump) to dicyclohexylcarbodiimide (10 mg, 0.049 mmol) in dichloromethane (5.5 cm^3) at 0 °C. Stirring was continued at this temperature for 16 h, and the reaction mixture was concentrated under reduced pressure, dissolved in ether (5 cm^3), filtered and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (4 : 1) as eluant gave the *title compound* **76** (3.6 mg, 23%; 46% based on **74**); ν_{max} (film) 3420, 1762, 1705, 1652, 1456, 1376, 1273, 1242, 1178, 1118, 1095, 1058, 1010 and 981 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.80 (3 H, d, *J* 6, 24-CH_3), 0.85 and 1.03 (each 3 H, d, *J* 7, CHC*H*$_3$), 1.04 (3 H, d, *J* 7, 12-CH_3), 1.10 (3 H, d, *J* 6, 4-CH_3), 1.2–2.10 (15 H, m), 1.53 (3 H, s, 14-CH_3), 2.18–2.28 (2 H, m, 16-H_2), 2.57 (1 H, dd, *J* 12, 3, 2-H), 2.60 (1 H, m, 12-H), 3.08 (1 H, d, *J* 9.5, 25-H), 3.20 (1 H, dd, *J* 10, 3.5, 5-H), 3.48 (3 H, s, 5-OCH_3), 3.60 (1 H, m, 17-H), 4.43 (1 H, d, *J* 3.5, 6-H), 4.93 (1 H, m, 15-H), 5.26 (1 H, s, 7-OH), 5.4 (1 H, m, 19-H), 5.82 (1 H, dd, *J* 15, 10, 11-H), 6.40 (1 H, d, *J* 12, 9-H) and 7.24 (1 H, dd, *J* 15, 12, 10-H); *m/z* (FAB) 609 (M$^+$ + 23, 0.2%), 561 (M$^+$ − 17, 0.5), 503 (2.5), 459 (3), 281 (66), 221 (100) and 207 (90).

(4*S*,6*R*)-6-Hydroxy-3,4-dihydromilbemycin E 77

The lactone **76** (4 mg, 7 μmol) was dissolved in toluene (0.4 cm^3), the solution cooled to −78 °C, and DIBAL-H (70 μl of a 1 M solution in toluene) was added. The reaction was stirred for 1 h, water (0.1 cm^3) was added, and the mixture diluted with ethyl acetate (3 cm^3). Aqueous hydrogen chloride (3 M, 0.5 cm^3) was added and the layers separated. The aqueous phase was extracted with ethyl acetate (3 × 2 cm^3), and the combined organic phase washed with brine (5 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (4 : 1 then 1 : 1) as eluant gave the *title compound* **77** (3 mg, 74%). [Found (CI): M$^+$ − OH, 573.3791. $C_{34}H_{53}O_7$ requires M, 573.3791]; ν_{max} (film) 3455, 1706, 1457, 1376, 1175, 1090 and 1009 cm^{-1}; δ_H (300 MHz; $CDCl_3$)

0.70 (1 H, q, *J* 12, 18-H_{ax}), 0.75 and 0.80 (each 3 H, d, *J* 7.5, 24-CH_3, CHC*H*$_3$), 0.99 (3 H, d, *J* 7.5, CHC*H*$_3$), 1.03 (6 H, d, *J* 7, 4-CH_3, 12-CH_3), 1.41 (1 H, t, *J* 12, 20-H_{ax}), 1.38–1.53 (5 H, m, 22-H_2, 23-H_2, 24-H), 1.60 (3 H, s, 14-CH_3), 1.55–1.97 [8 H, m, $(CH_3)_2$C*H*, 3-H_2, 4-H, 13-H_2, 18-H, 20-H], 2.07–2.35 (3 H, m, 16-H_2, OH), 2.49 (1 H, m, 12-H), 3.04 (1 H, d, *J* 9, 25-H), 3.11 (2 H, m, 2-H, 6-OH), 3.31 (1 H, dd, *J* 9, 3, 5-H), 3.40 (3 H, s, 5-OCH_3), 3.60 (1 H, m, 17-H), 3.87 (2 H, m, 6-H, 7-OH), 4.12 and 4.2 (each 1 H, d, *J* 13, HC*H*OH), 4.78 (1 H, d, *J* 9, 15-H), 5.24–5.38 (1 H, m, 19-H), 5.48 (1 H, dd *J* 15,10, 11-H), 6.27 (1 H, dd, J 15, 11, 10-H) and 6.42 (1 H, d, *J* 11, 9-H); *m*/*z* (FAB) 613 (M^+ + 23, 5%), 573 (M^+ − 17, 28), 307 (35), 289 (28), 209 (37) and 181 (100).

(1*RS*,4*RS*,6*SR*,7*RS*,8*RS*,9*SR*,19*RS*,10*E*,12*E*,16*E*)-10-Chloromethyl-8,9-dihydroxy-6,16-dimethyl-7-methoxy-2-oxatricyclo[17.3.1.0^{4,9}]tricosa-10,12,16-trien-3-one 78

Lithium diisopropylamide (0.6 M, 37 µl, 0.022 mmol) was added to the triol **65** (5 mg, 0.011 mmol) in tetrahydrofuran–hexamethylphosphoric triamide (0.4 cm^3, 3 : 1) at −78 °C and the mixture was stirred for 10 minutes. Toluene *p*-sulfonyl chloride (2.8 mg, 0.013 mmol) in tetrahydrofuran–hexamethylphosphoric triamide (0.1 cm^3, 3 : 1) cooled to −78 °C was added and the mixture warmed to 0 °C over 2 h then stirred at 0 °C for 30 minutes before brine (1 cm^3) was added. The mixture was diluted with diethyl ether (10 cm^3), separated, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3 : 1) as eluant gave the *title compound* **78** (4 mg, 84%) as a crystalline solid, mp 170–172 °C. [Found (FAB): M^+ − Cl, 431.2834. $C_{26}H_{39}O_5$ requires M, 431.2719]; ν_{max} ($CHCl_3$) 3485, 1706, 1454, 1382, 1283, 1175, 1113, 1091,1029, 990, 969, 907 and 729 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.77 (1 H, q, *J* 12), 0.85–0.95 (4 H, m), 1.05 (3 H, d, *J* 6, 6-CH_3), 1.25 (2 H, m), 1.45–1.95 (6 H, m), 1.58 (3 H, s, 16-CH_3), 2.1–2.5 (6 H, m), 3.15 (1 H, dd, *J* 12, 4.5, 4-H), 3.27 (1 H, dd, *J* 10, 3, 7-H), 3.43 (3 H, s, OCH_3), 4.0 (1 H, d, *J* 3, 8-H), 4.3 (1 H, s, 9-OH), 4.33 and 4.52 (each 1 H, d, *J* 12, HC*H*Cl), 4.8 (1 H, m, 1-H), 5.0 (1 H, t, *J* 7, 17-H), 5.73 (1 H, m, 3-H), 6.15 (1 H, d, *J* 11, 11-H) and 6.32 (1 H, dd, *J* 14, 11, 12-H); *m*/*z* (FAB) 468 [M^+(^{37}Cl), 12%], 466 [M^+(^{35}Cl), 36%], 451 [M^+(^{37}Cl) − 17, 16], 449 [M^+(^{35}Cl) − 17, 48), 432 (50) and 414 (50).

(4*S*,6*R*)-28-Chloro-6-hydroxy-28-deoxa-3,4-dihydromilbemycin E 79

Following the procedure outlined for the synthesis of the chloride **78**, the triol **77** (5 mg, 0.0085 mmol) gave the *title compound* **79** (5 mg, 100%). [Found (CI): M^+ − HCl, 572.3712. $C_{34}H_{52}O_7$ requires M, 572.3713]; $[\alpha]_D$ +17.5. (*c* 0.004 in $CHCl_3$); ν_{max} ($CHCl_3$) 3461, 1710, 1462, 1377, 1261, 1098 and 802 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.77 and 0.79 (each 3 H, d, *J* 7, CH_3), 0.84 (1 H, m, 18-H_{ax}), 0.95 (3 H, d, *J* 7.5, CH_3), 1.01 (3 H, d, *J* 7, 12-CH_3), 1.09 (3 H, d, *J* 7, 4-CH_3), 1.4–1.53 (5 H, m, 22-H_2, 23-H_2, 24-H), 1.64 (3 H, s, 14-CH_3), 1.6–1.88 (8 H, m, 25-CH, 3-H_2, 4-H, 13-H_2, 18-H, 20-H), 2.15–2.35 (3 H, m, 16-H_2, 20-H), 2.56 (1 H, m, 12-H), 3.04 (1 H, dd, *J* 10, 2, 25-H), 3.08 (1 H, dd, *J* 12, 4, 2-H), 3.25 (1 H, dd, *J* 10, 3, 5-H), 3.4 (3 H, s, OCH_3), 3.65 (1 H, m, 17-H), 4.01 (1 H, m, 6-H), 4.17 (1 H, s, 7-OH), 4.36 and 4.48 (each 1 H, d, *J* 11, HC*H*Cl), 4.83 (1 H, d, *J* 10, 15-H), 5.32 (1 H, m, 19-H), 5.73 (1 H, dd, *J* 15, 8, 11-H), 6.14 (1 H, d, *J* 11, 9-H) and 6.26 (1 H, dd, *J* 15, 11, 10-H); *m*/*z* (EI) 572 [M^+ − 36(^{35}Cl), 38(^{37}Cl), 30%), 503 (25) and 459 (60).

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