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A total synthesis of milbemycin G: approaches to the C(1)–C(10)-fragment and completion of the synthesis

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A synthesis of the hydroxybutenolide (−)-**6** required for synthesis of α-milbemycins and the completion of a total synthesis of milbemycin G **7** is reported.
Following preliminary studies, an optimised synthesis of the hydroxybutenolide (−)-**6** from the hydroxyketone **38** was developed which involved the resolution of **38** by separation of the 3-(*O*-chloroacetyl)-(*S*)-mandelates **80** and **83**. Ester **80**, which corresponded to the required enantiomer of the hydroxyketone **38**, crystallized from the mixture of the diastereoisomeric esters **80** and **83** giving the (−)-hydroxyketone (−)-**38** in an overall yield of 47% (based on racemic **38**) after ethanolysis. Hydroxyketone (−)-**38** was oxidised to the enolic diketone (−)-**39** and phenylselenation and stereoselective reduction gave the trihydroxycyclohexyl selenide (−)-**43**. The regioselective introduction of the non-conjugated double-bond into the six-membered ring was then achieved by esterification of the 4-hydroxyl group using trichloroacetic acid to give the trichloroacetate (−)-**69**. Oxidative elimination from the trichloroacetate using *tert*-butyl hydroperoxide was highly regioselective and gave the endo- and exocyclic alkenes (−)-**44** and (−)-**46** in a ratio of 95 : 5 after ethanolysis of the trichloroacetates. Selective *O*-methylation of the 4-hydroxyl group *via* the cyclic stannylene **55** and protection of the 3-hydroxyl group as its 2-trimethylsilylethoxymethyl (SEM) ether gave the ester (−)-**57**. Following saponification of the ethyl ester, re-esterification using 2-trimethylsilylethanol and oxidation of the 2-trimethylsilylfuryl fragment using singlet oxygen gave the required hydroxybutenolide (−)-**6**.
The Wittig reaction between the phosphonium salt **2** and the hydroxybutenolide (−)-**6** gave a *ca.* 2 : 1 mixture of the (4*Z*)- and (4*E*)-isomers of the ester **84** which on treatment with a catalytic amount of iodine was converted into the (4*E*)-isomer (**4*E***)-**84**. Deprotection gave the seco-acid **85** but attempts to macrocyclise this were unsuccessful, the elimination product **86** being the only product isolated. The Wittig product **84** was taken through to the butenolide (**2′*E***)-**91** by removal of the SEM group, cyclisation to form the butenolide ring and diene isomerization, but this could not be converted into the corresponding seco-acid **92**. However, removal of the SEM group from the seco-acid **85** gave the trihydroxy-acid **93** which was cyclized under modified Yamaguchi conditions to give the macrolide **94** together with a small amount of the macrocyclic butenolide **95**. Reduction of this mixture using diisobutylaluminium hydride gave (6*R*)-6-hydroxymilbemycin E **96** which was converted to milbemycin G **7** by cyclisation of the primary chloride **97**. The synthetic milbemycin G **7** was identical to a sample prepared by methylation of a commercial sample of milbemycin D **98**, 7-*O*-methylmilbemycin G **99** being a side-product of this methylation.

Introduction

The total synthesis of milbemycins and avermectins has attracted much interest from synthetic chemists.[1] We completed a convergent synthesis of milbemycin E **4**, a non-aromatic β-milbemycin, using the Wittig reaction between the hydroxybutenolide **1** and the ylid derived from the phosphonium salt **2**, as a key step.[2] It was of interest to see whether this approach could be applied to complete a synthesis of the α-milbemycins as represented by milbemycin G **7**.[3] This would require the introduction of an extra oxygen functionality at C(6) and formation of the tetrahydrofuran ring. In the preceding paper,[4] a synthesis of the hydroxybutenolide **3**, which has this additional oxygen functionality but which lacks the 3,4-double-bond (milbemycin numbering), is described, together with its incorporation into a synthesis of (6*R*)-hydroxy-3,4-dihydromilbemycin E **5**. We now report studies leading to the synthesis of the hydroxybutenolide (−)-**6** which has both the oxygen functionality at C(3) (corresponding to C(6) in the milbemycins) and the incipient 3,4-double-bond, and the completion of a synthesis of milbemycin G **7**.[5]

The racemic hydroxybutenolide **3** had been prepared from the keto-ester **8** and the alkoxymethyl isopropenyl ketones **9** (Ar = C_6H_5–, 4-$MeOC_6H_4$–) using Robinson reactions to prepare the 2-hydroxycyclohexan-4-ones **10**. The major products from these reactions had the undesired configuration at C(3) but stereoselective reduction at C(4) and inversion of the configuration at C(3) by deprotection and oxidation–reduction, together with functional group interconversions and oxidation of the 2-trimethylsilylfuran using singlet oxygen, gave the hydroxybutenolide **3**.[4] In the synthesis of hydroxybutenolide **1**, the 3,4-double-bond had been introduced by phenylselenation of the thermodynamic trimethylsilyl enol ether of a Robinson product followed by oxidative elimination. However, the regioselectivity of the oxidative elimination was found to be sensitive to the functionality at C(4). For example, oxidative elimination of the α-phenyl selanyl ketone **11** gave an 85 : 15 mixture of the endo- and exocyclic alkenes **12** and **13** whereas oxidative elimination of the corresponding phenyl selanyl alcohol **14**, albeit at a higher temperature, gave more of the exocyclic alkene, **15** : **16** = 11 : 89.[6]

Results and discussion

Preliminary studies

The Robinson products **10** would appear to be suitable precursors of the required hydroxybutenolide **6** with the inversion of the configuration at C(3) and the introduction of the cyclohexenyl double-bond as key steps. However, in view of the sensitivity of the regioselectivity of the selenoxide elimination to structure, it was decided to check procedures for this process first.

The 3-benzyloxycyclohexan-4-one **17**[4] was converted regioselectively into the silyl enol ether **18**,[2] with concomitant silylation of the 2-hydroxyl group, using an excess of trimethylsilyl trifluoromethanesulfonate and triethylamine in dichloromethane,

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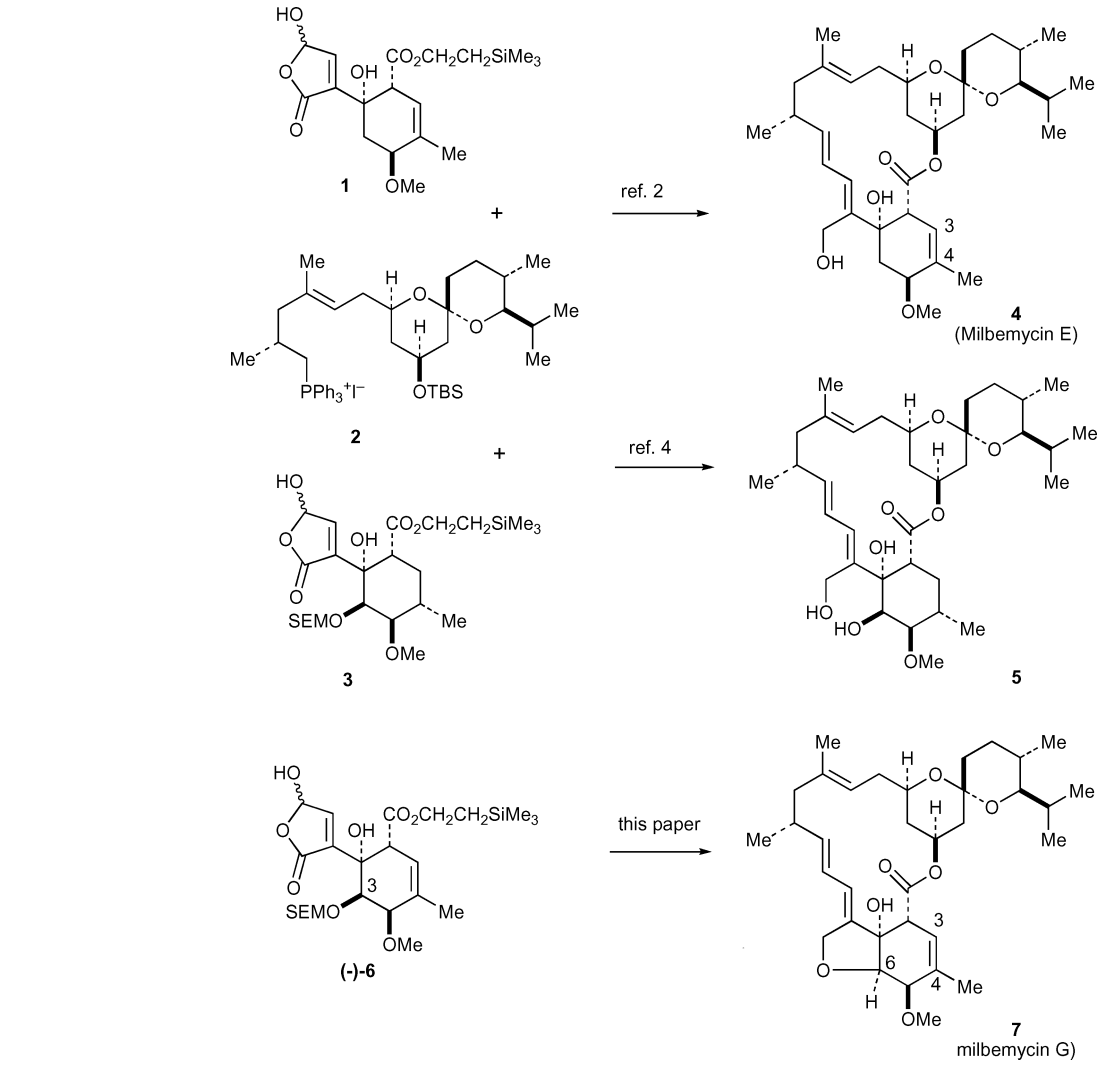
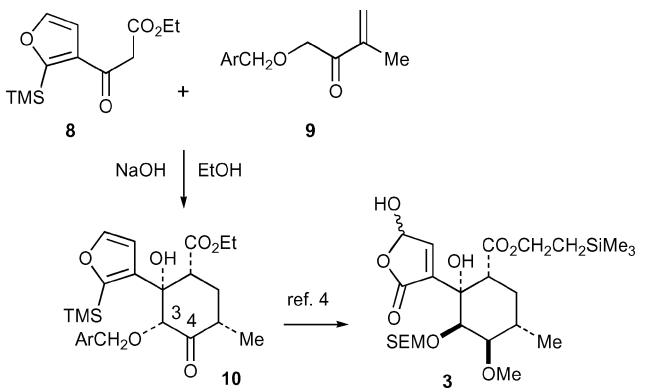
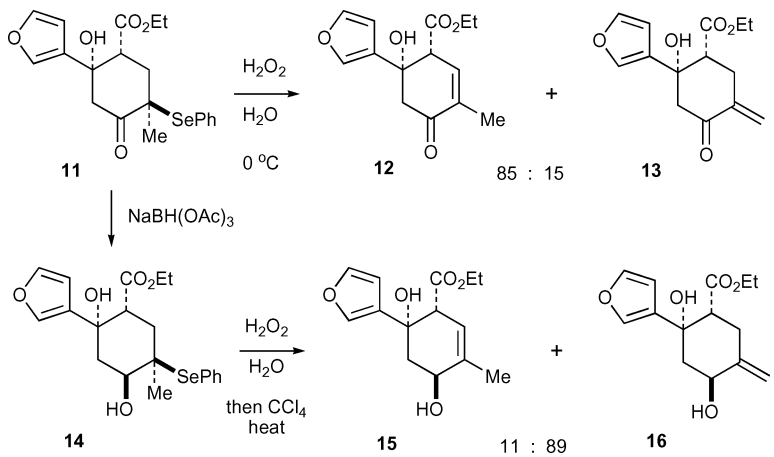
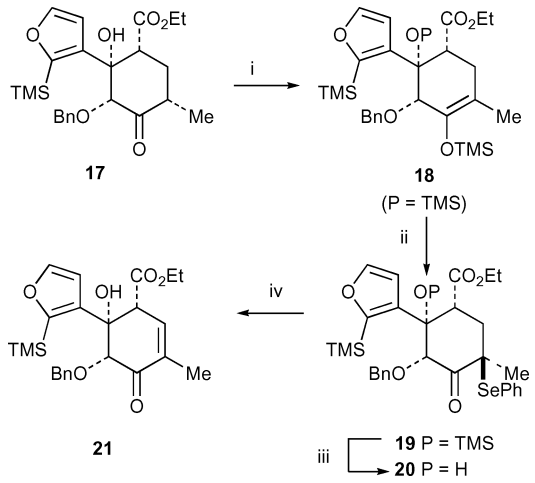




see Scheme 1. Reaction of this silyl enol ether with benzene selenenyl chloride gave the phenyl selanyl ketone **19** as a single diastereoisomer which was desilylated to give the hydroxyketone **20**. Oxidative elimination was then achieved using a two-phase dichloromethane/aqueous hydrogen peroxide system[7] to give the cyclohexenone **21** as the only isolable material in 50% yield, the regioselectivity of elimination being established by ^{1}H NMR (see experimental).

This sequence was then repeated using the 3-*p*-methoxybenzyl protected ketone **22**[4] since procedures were available for removal of the *p*-methoxybenzyl group which should be compatible with the cyclohexenyl double-bond, but attempts to convert the 3-*p*-methoxybenzyloxycyclohexanone **22** into its trimethylsilyl enol





Scheme 1 *Reagents and conditions:* i, TMSOTf, Et_3N, DCM (70%); ii, PhSeCl, DCM (79%); iii, TBAF, THF, −50 °C (87%); iv, 30% aqu. H_2O_2, DCM (50%).

ether using trimethylsilyl trifluoromethanesulfonate and triethylamine led to complex mixtures of products possibly due to loss of the *p*-methoxybenzyl group under the reaction conditions.[8] However, *tert*-butyldimethylsilyl trifluoromethanesulfonate gave the silyl enol ether **23** cleanly with just traces of the corresponding bis-silylated ether, see Scheme 2. The enol ether **23** was treated with phenyl selenenyl chloride to give the phenyl selanyl ketone **24** which could also be obtained, albeit in only modest yield, 36%, by direct phenyl selenation of the ketone **22** using phenyl selenenyl chloride.[9] Oxidative elimination using *tert*-butyl hydroperoxide[10] gave better yields of the cyclohexenone **25** than using hydrogen peroxide but was slow giving only 64% of the product after 72 h at room temperature together with 18% recovered starting material. This was resubjected to the reaction conditions to give an overall yield of 76%.

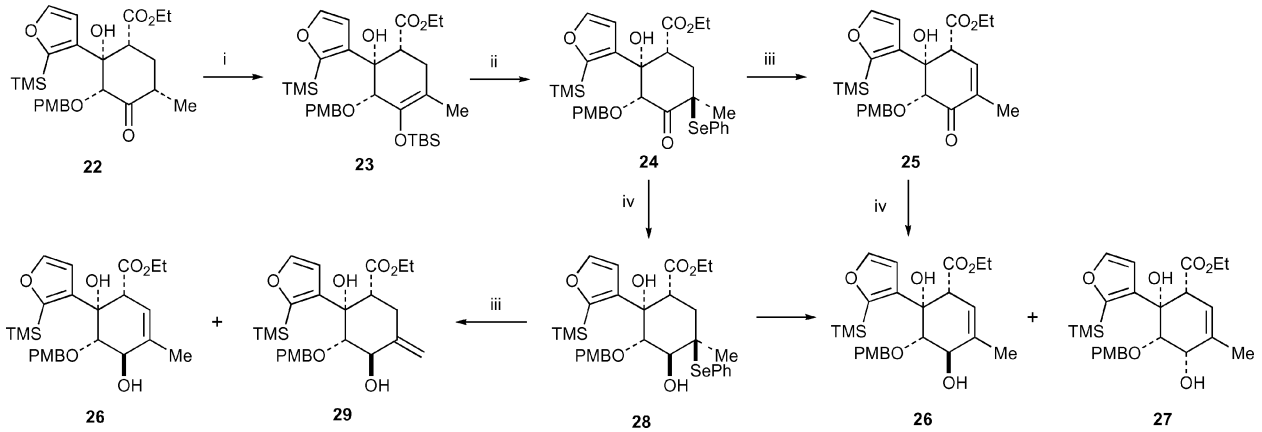
Having prepared the cyclohexenone **25**, the next step was to reduce the ketone to the required alcohol **26**. In earlier work, the reduction of such 2-hydroxycyclohexen-4-ones using sodium and tetramethylammonium triacetoxyborohydride had been highly stereoselective due to intramolecular delivery of the hydride to the ketone from the acetoxyborohydride reagent when co-ordinated to the 2-hydroxyl group.[11] However, in the present case, the reduction using tetramethylammonium triacetoxyborohydride showed only modest stereoselectivity and a *ca.* 2 : 1 mixture of the alcohols **26** and **27**, which were difficult to separate by column chromatography, was obtained, Scheme 2. In contrast, reduction of the phenyl selanyl ketone **24** using tetramethylammonium triacetoxyborohydride was highly stereoselective for directed reduction and gave the alcohol **28** predominantly. As expected,[6] oxidative elimination from the hydroxyselenide **28** gave a mixture of the endo- and exocyclic alkenols **26** and **29**, but the endocyclic alkene **26** was the major product, **26** : **29** = 65 : 35, and the two alcohols **26** and **29** could be separated relatively easily by column chromatography so providing a more convenient route to the alkenol **26**.

These preliminary studies had shown that phenylselenation/oxidative elimination could be used to introduce the incipient 3,4-double-bond into precursors of the hydroxybutenolide **6** albeit with variable regioselectivity. It remained to invert the configuration at C(3). In the synthesis of the hydroxybutenolide **3**, this inversion had been carried out using an oxidation–reduction sequence.[4] However, it was thought this procedure would not be suitable for the present case, *vide infra*, and so a Mitsunobu inversion protocol was investigated first. The 4-hydroxyl group in the diol **26** was protected as its *tert*-butyldimethylsilyl ether **30** and oxidation to the hydroxybutenolide **31** using singlet oxygen[12] confirmed the stability of the cyclohexenyl double-bond to the singlet oxygen reaction conditions, see Scheme 3. A Wittig reaction with 2-methylpropyl(triphenyl)phosphorane then gave a *ca.* 80 : 20 mixture of the (4*Z*)- and (4*E*)-dienyl acids **32**. These were not separated, instead the 3-alcohol was deprotected by oxidative removal[13] of the *p*-methoxybenzyl group to give the (4*Z*)- and (4*E*)-dihydroxy acids **33**, but attempts to cyclise these using a Mitsunobu procedure to the corresponding five-membered lactones with inversion of configuration at C(3), were unsuccessful.

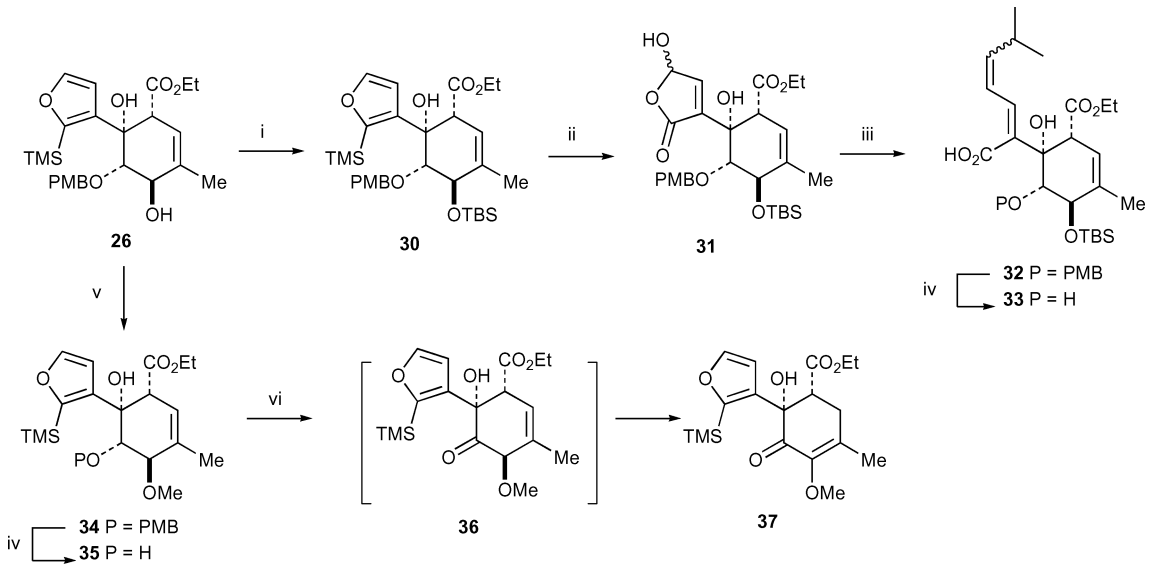
To check the compatibility of the incipient 3,4-double-bond with the oxidation–reduction sequence, the diol **26** was converted into the monomethyl ether **34** and the 3-hydroxyl group deprotected to give the diol **35**. Oxidation using Swern conditions gave the ketone **36** but this was found to be unstable and isomerised on standing to the α,β-unsaturated ketone **37**. Attempts to reduce the non-conjugated ketone **36** were unsuccessful. Tetramethylammonium triacetoxyborohydride in acetic acid–acetonitrile led to rapid double-bond migration giving the conjugated ketone **37** and complex mixtures of products were obtained using other hydride reducing agents. Attempts to convert the alcohol **35** with inversion into the corresponding 4-nitrobenzoate under Mitsunobu conditions[14] were also unsuccessful.

Synthesis and chemistry of the racemic hydroxybutenolide 6

In the preliminary investigations outlined above, useful procedures had been developed for the regioselective introduction of the cyclohexenyl double-bond, but the required inversion of the configuration at C(3) by oxidation–reduction had been hampered by double-bond migration at the ketone stage. It was therefore clear that the configuration at C(3) had to be corrected before the double-bond was introduced. Oxidation



Scheme 2 *Reagents and conditions:* i, TBSOTf, Et_3N, DCM (95%); ii, PhSeCl, DCM (54%); iii, 30% aqu. H_2O_2, r.t., 10 min. (**25**, 27%) or ^{t}BuOOH, DCM (**25**, 64%; recovered **24**, 18%; **26**/**29**, 88%; **26** : **29** = 65 : 35); iv, $NMe_4BH(OAc)_3$, MeCN, AcOH (**26**/**27**, 50%, **26** : **27** = 66 : 34; **28**, 78%).

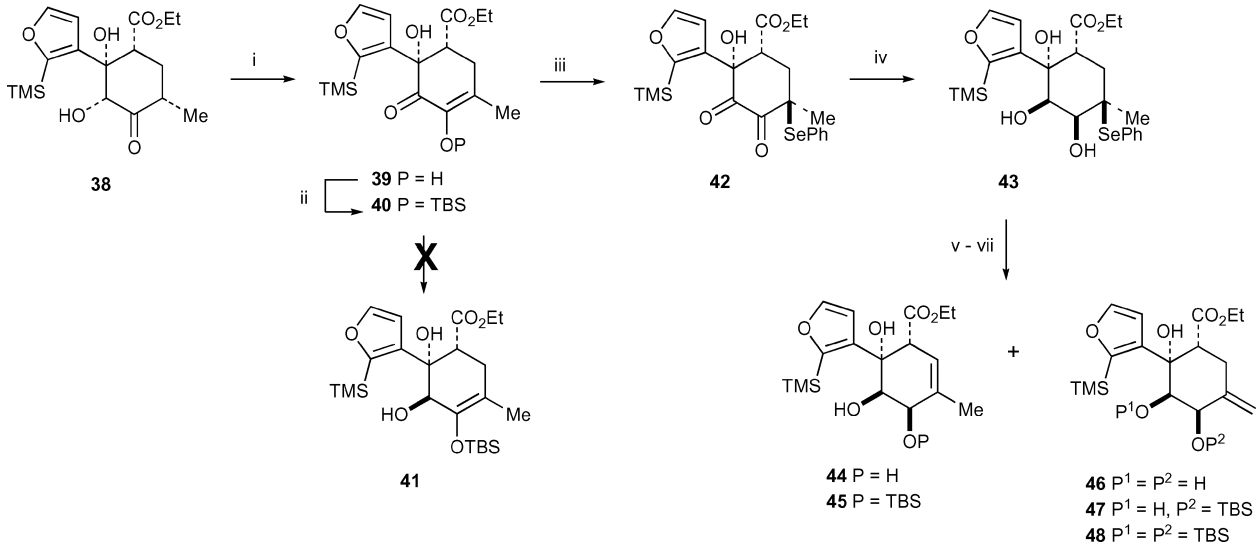


Scheme 3 *Reagents and conditions:* i, TBSOTf, 2,6-lutidine, DCM (97%); ii, O_2, tetraphenylporphine (TPP), MeOH, DCM, hν (96%); iii, $(CH_3)_2CHCH_2PPh_3$, ^{n}BuLi, −78 to −20 °C (68%, 4*E* : 4*Z* = 20 : 80); iv, DDQ (**33**, 78%; **35**, 92%); v, LiHMDS, cetyltrimethylammonium bromide (CTAB), MeI, THF, 0 °C (81%); vi, $(COCl)_2$, DMSO, then Et_3N (77%).

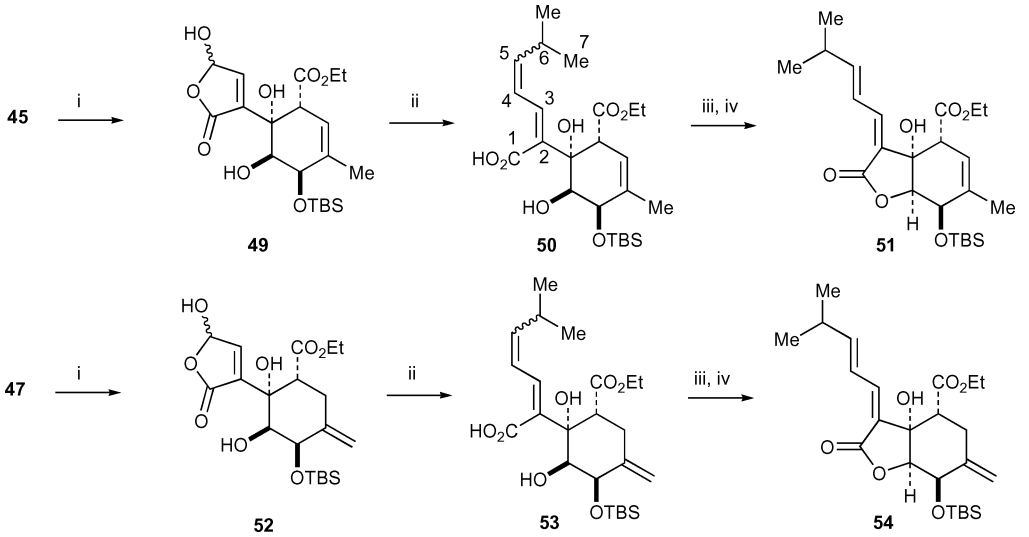
of the hydroxyketone **38**[4] under Swern conditions gave the enol **39** of the α-diketone which was converted into the *tert*-butyldimethylsilyl enol ether **40** using *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine, Scheme 4. It was intended to reduce the ketone moiety in **40** to give the diol **41** which would be protected and the enol ether used to introduce the required double-bond *via* phenylselenation–oxidative elimination, but conditions could not be found for a stereoselective reduction of the ketone to the diol **41**. Mild reducing agents, *e.g.* sodium borohydride–cerium(III) chloride or tetramethylammonium triacetoxyborohydride, gave unchanged starting material and stronger reducing agents gave complex mixtures of products. However, treatment of the enolic α-diketone **39** with phenyl selenenyl chloride gave the phenylselanyl-α-diketone **42** which was reduced using tetramethylammonium triacetoxyborohydride[15] to the triol **43**. This reduction was highly stereoselective, the triol **43** being the only product isolated, but was a little capricious in that freshly prepared reagent was necessary for good yields to be achieved. The *cis*-configuration of the 3- and 4-hydroxyl groups in triol **43** was assigned on the basis of NMR data and was confirmed by the formation of a cyclic derivative, *vide infra*.

Oxidative elimination was then carried out on the trihydroxyselenide **43** and gave a mixture of the endo- and exocyclic alkenes **44** and **46**, ratio *ca.*, 40 : 60, respectively, see Scheme 4. These alkenes were not separated at this stage (but see later). Instead the mixture of alkenes was silylated using *tert*-butyldimethylsilyl trifluoromethanesulfonate to give the monosilyl ethers **45** and **47**. These could be separated by chromatography, but a more convenient procedure was developed which involved prolonged treatment of the triols **44** and **46** with an excess of the silylating agent. Under these conditions, the endo-alkenol **44** was converted into its monosilyl ether **45** but the exocyclic alkene **46** gave the bis-silyl ether **48**, these products being easy to separate by chromatography.

At this point it was decided to check the compatibility of the Wittig chemistry with the functionality present in the cyclohexenediol **45** and its exocyclic isomer **47**, see Scheme 5. Oxidation of the endocyclic alkenol **45** using singlet oxygen[12] gave the hydroxybutenolide **49** which was condensed with 2-methylpropyl(triphenyl)phosphorane to give the dienyl acids **50** as a 75 : 25 mixture of the (4*Z*)- and (4*E*)-isomers. In this reaction, an excess of ylid was used but the additional



Scheme 4 *Reagents and conditions:* i, $(COCl)_2$, DMSO, Et_3N (95%); ii, TBSOTf, Et_3N (*ca.* 100%); iii, PhSeCl, pyridine (96%); iv, $NMe_4BH(OAc)_3$, MeCN, AcOH (82%); v, ^{t}BuOOH, DCM (80%, **44** : **46** = 40 : 60); vi, TBSOTf, 2,6-lutidine, 0 °C, 5.5 h (**45**, 37%); vii, TBSOTf, 2,6-lutidine, r.t., 16 h (**45**, 40%; **48**, 44%).



Scheme 5 *Reagents and conditions:* i, TPP, O_2, −78 °C, hν (**49**, 98%; **52**, 98%); ii, $(CH_3)_2CHCH_2PPh_3Br$, ^{n}BuLi (**50**, 77%); iii, DCC, DMAP; iv, I_2, K_2CO_3, benzene, hν (**51**, 89% from **50**; **54**, 60% from **52**).

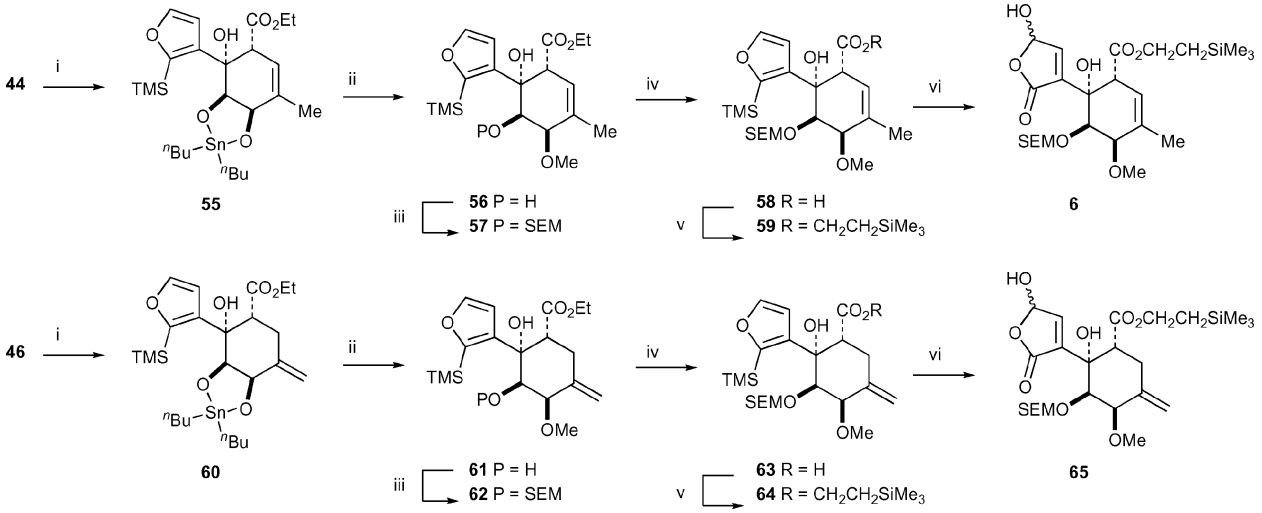
3-hydroxyl group didn't interfere and an acceptable, 77%, yield was obtained. Cyclisation using dicyclohexylcarbodiimide and 4-dimethylaminopyridine followed by iodine catalysed alkene isomerisation[4] gave the lactone **51** in an 89% yield. An analogous series of reactions on the exocyclic alkene **47** gave the isomeric lactone **54**.

In order to complete a synthesis of the racemic hydroxybutenolide **6** from the cyclohexenyl triol **44** it was necessary to convert the 4-hydroxyl group selectively into its methyl ether, protect the 3-hydroxyl group as a 2-trimethylsilylethoxymethyl (SEM) ether and exchange the ethyl ester for a 2-trimethylsilylethyl ester. Firstly, however, an improved separation of the endo- and exocyclic alkenols **44** and **46** had to be achieved. This was carried out by chromatography on silica gel impregnated with silver nitrate. The 4-hydroxyl group of the endocyclic alkenol **44** was then methylated *via* the cyclic stannylene **55**,[16] Scheme 6. This methylation was very regioselective and gave the required dihydroxycyclohexenyl methyl ether **56** in a 96% yield, the regioselectivity of the methylation being checked by oxidation of the alcohol **56** to the ketone **36** which was identical to a sample prepared from the epimeric alcohol **35** (see Scheme 3). The diol **56** was now converted into its SEM-ether **57** which was saponified and the acid **58** so obtained esterified using 2-trimethylsilylethanol to give the ester **59**. Oxidation using singlet oxygen then gave the (racemic) hydroxybutenolide **6**. The exocyclic alkene **46** was similarly taken through to the isomeric hydroxybutenolide **65**, see Scheme 6.

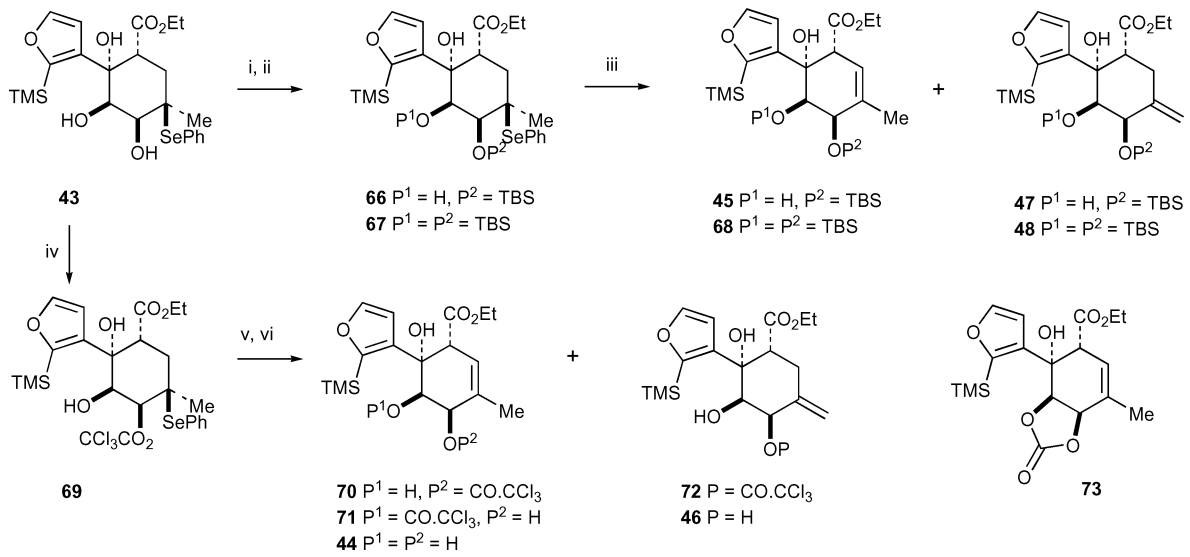
Optimisation of the synthesis of hydroxybutenolide (−)-6

The synthesis of the hydroxybutenolide **6** now needed to be improved since the oxidative elimination used to introduce the 3,4-double-bond had given an unfavourable 40 : 60 mixture of the endo- and exo-isomers **44** and **46**, see Scheme 4. Moreover, a resolution step had to be developed to prepare the enantiomerically enriched **6** for incorporation into a milbemycin synthesis.

The use of different conditions for the oxidative elimination of selenide **43**, *e.g.* the use of *tert*-butyl hydroperoxide or *m*-chloroperoxybenzoic acid at temperatures from −78 °C to ambient temperature did not lead to a significant improvement in the endo–exo ratio of the alkenes **44** and **46**. To evaluate the effect of substituents, the trihydroxyselenide **43** was converted into its mono- and bis-*tert*-butyldimethylsilylated derivatives **66** and **67** but the oxidation of these using *tert*-butyl hydroperoxide also gave more of the exocyclic alkene with endo–exo ratios of, typically, 35 : 65, see Scheme 7. Since improved regioselectivity in favour of the endocyclic alkenes had been observed with ketones rather than alcohols at C(4), it was decided to see whether other electron withdrawing substituents at C(4) would lead to better



Scheme 6 *Reagents and conditions:* i, *n*-Bu_2SnO, MeOH, heat; ii, MeI, Bu_4NI (**56**, 96% from **44**; **61**, 96% from **46**); iii, SEMCl, $^i Pr_2NEt$ (**57**, *ca.* 100%; **62**, 99%); iv, NaOH, EtOH; v, $TMSCH_2CH_2OH$, DCC, DMAP (**59**, 80% from **57**; **64**, 92% from **62**); vi, TPP, O_2, hν, −78 °C (**6**, 99%; **65**, 96%).



Scheme 7 *Reagents and conditions:* i, TBSOTf, 2,6-lutidine, DCM, 0 °C, 1 h (**66**, 82%); ii, TBSOTf, 2,6-lutidine, DCM, r.t., 18 h (**67**, 97%); iii, ^{t}BuOOH, DCM, r.t. (**45**/**47**, 75%; **45** : **47** = 40 : 60; **68**/**48**, 78%; **68** : **48** = 35 : 65); iv, CCl_3COCl, pyr., THF, 0 °C (88%); v, ^{t}BuOOH, benzene, r.t. (81%, **70** : **71** : **72** = 80 : 15 : 5); vi, DMAP, EtOH (99%; **44** : **46** = 95 : 5).

selectivity for the endocyclic alkene. For this reason, the triol **43** was converted into its trichloroacetate **69** and the oxidative elimination investigated on this substrate. *m*-Chloroperoxybenzoic acid in dichloromethane led to the formation of the endo- and exocyclic alkenes **70** and **72** in an indifferent 60 : 40 ratio. However, the use of *tert*-butyl hydroperoxide in benzene gave rise to the formation of three products. These could not be separated but were identified as the two endocyclic alkenes **70** and **71** (in which the trichloroacetate had migrated) and the exocyclic isomer **72**, ratio **70** : **71** : **72** = 80 : 15 : 5. Transesterification of this mixture using 4-dimethylaminopyridine in ethanol removed the trichloroacetyl groups and gave the required alkenes **44** and **46** in an excellent, 99%, yield with a very satisfactory ratio of **44** : **46** = 95 : 5. Interestingly, when lithium hydroxide was used for the attempted saponification of the trichloroacetate, the major product was the cyclic carbonate **73** (47%) together with the required cyclohexenetriol **44** (35%). The formation of the cyclic carbonate **73** confirmed the *cis*-disposition of the 3- and 4-hydroxyl groups in triol **43**.

It remained to find a procedure for the resolution of one of the intermediates in the synthesis of the hydroxybutenolide **6**. A procedure for resolution of the diol **74**, prepared by reduction of the hydroxycyclohexanone **17**, by separating the corresponding 4-(*O*-acetyl)-(*S*)-mandelates, is described in the previous paper. The *p*-methoxybenzyl ether **75**, prepared by reduction of the ketone **22** using tetramethylammonium triacetoxyborohydride, was also resolved using this procedure, the diastereoisomeric esters **76** and **77** being separated by chromatography and recrystallisation. Structure **76** was assigned to the less polar isomer on the basis of the relative chemical shifts of the 5-methyl substituents (5-Me: δ_H 0.52 for **76** and 1.08 for **77**) and was confirmed by a single crystal X-ray structure determination of isomer **76**, see Fig. 1. However, the separation of **76** and **77** was difficult to scale up and as neither of the diols **74** and **75** was now an intermediate in the preferred route to the hydroxybutenolide **6**, see the summary in Scheme 9, it was decided to develop a resolution of the 2,3-dihydroxyketone **38**.

Esterification of the 3-hydroxy group of the diol **38** with (−)-camphanic chloride,[17] endo-bornyloxyacetic acid or D-camphorsulfonyl chloride gave mixtures of diastereoisomers which could not be easily separated. *O*-Acetyl-(*S*)-mandelic acid[18] led to the diastereoisomers **78** and **81** which could be separated by chromatography with the more polar isomer being assigned as structure **78** on the basis of the relative ^{1}H NMR shifts of the 5-methyl substituents.[19] To see whether the non-acetylated mandelic esters **79** and **82** might be easier to separate,

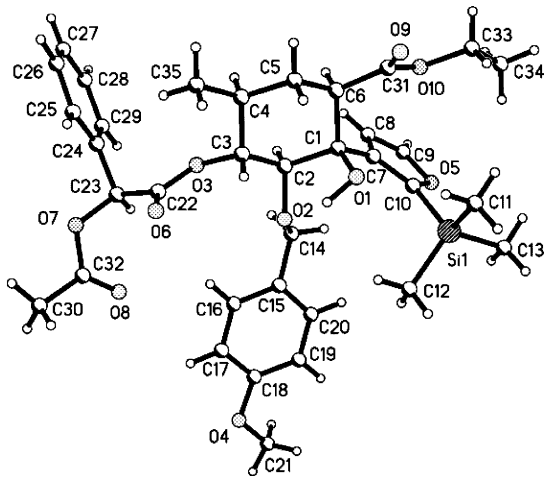
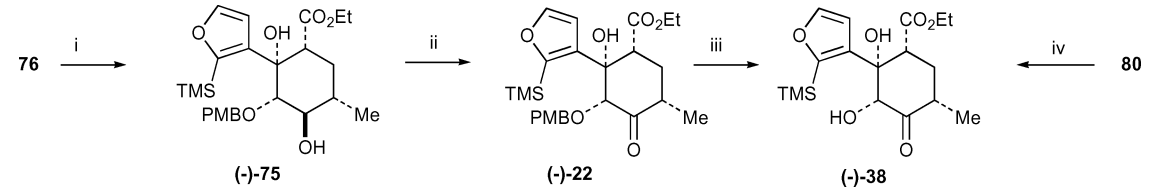


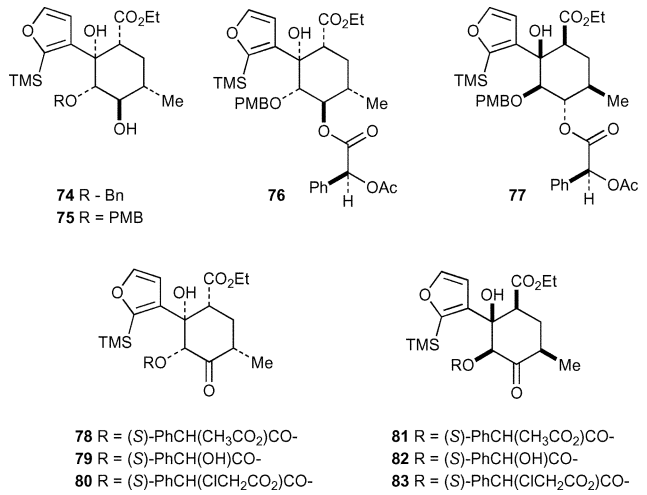
Fig. 1 Projection of the acetylmandelate **76** as determined by X-ray crystallography showing the crystallographic numbering scheme used.

the mixture of esters **78** and **81** was subjected to mild hydrolysis conditions but only the starting hydroxyketone **38** was isolated from this reaction. Since chloroacetates are easier to hydrolyse than the corresponding acetates,[20] the dihydroxyketone **38** was esterified with *O*-chloroacetyl-(*S*)-mandelic acid to give esters **80** and **83** with the intention of studying the selective hydrolysis of the chloroacetyl group to give the free hydroxymandelates. However, this was found not to be necessary since the diastereoisomeric esters **80** and **83** were found to be easy to separate by crystallisation. The required isomer **80** was isolated from the mixture by a single crystallisation from ethyl acetate–light petroleum in 47% yield (based on racemic **38**). Concentration of the filtrate under reduced pressure and chromatography of the residue then gave the other isomer **83** as an amorphous glass.

Structures were initially assigned to the esters **80** and **83** on the basis of the relative ^{1}H NMR chemical shifts of their 5-methyl substituents[19] (5-Me: δ_H 1.11 in **80** and 1.18 in **83**). They were confirmed by correlation with the *O*-acetylmandelates **76**, see Scheme 8. Thus the (−)-enantiomer of dihydroxyketone **38** was obtained by hydrolysis of the 3-chloroacetylmandelate which had been identified as isomer **80** and from the 4-*O*-acetylmandelate **76** by hydrolysis, oxidation and deprotection. The structure of the crystalline chloroacetylmandelate **80** was also finally confirmed by an X-ray structure determination, see Fig. 2.



Scheme 8 *Reagents and conditions:* i, 10% aqu. LiOH, EtOH, r.t., 48 h (97%); ii, $(COCl)_2$, DMSO, then Et_3N (90%); iii, DDQ (88%); iv, K_2CO_3, EtOH, 0 °C (92%).



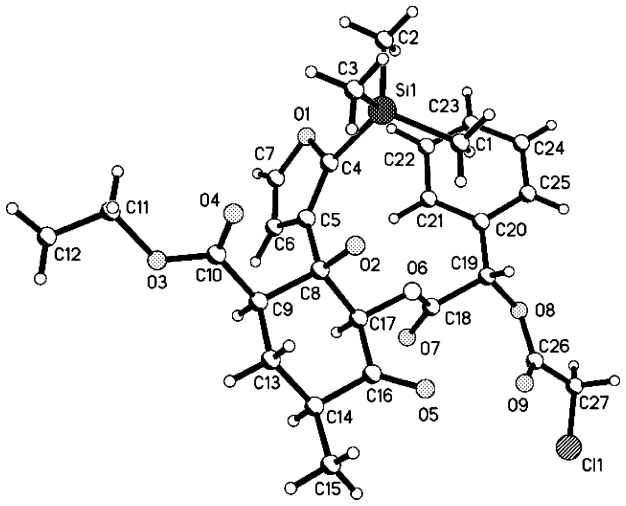


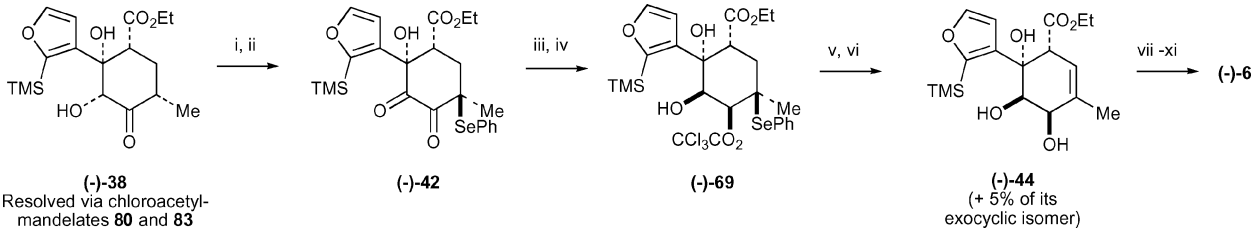
Fig. 2 Projection of the chloroacetylmandelate **80** as determined by X-ray crystallography showing the crystallographic numbering scheme used. Only one of the disordered components of the structure is shown for clarity.

Following the resolution of the dihydroxyketone **38** *via* the chloroacetyl mandelates **80** and **83**, the laevorotatory enantiomer of the ketone **38** was taken through to the laevorotatory hydroxybutenolide **6**, see Scheme 9. Oxidation and phenylselenenylation gave the diketoselenide (−)-**42** which was converted into the trichloroacetate (−)-**69** by reduction and esterification. Regioselective selenoxide elimination and hydrolysis then gave the required cyclohexene triol (−)-**44** and selective methylation of the 4-hydroxyl group followed by protection of the 3-hydroxyl group as its SEM ether gave the required hydroxybutenolide (−)-**6** after ester exchange and oxidation of the 2-trimethylsilylfuran. This synthesis was repeated to give nearly 1.9 grammes of the hydroxybutenolide (−)-**6**.

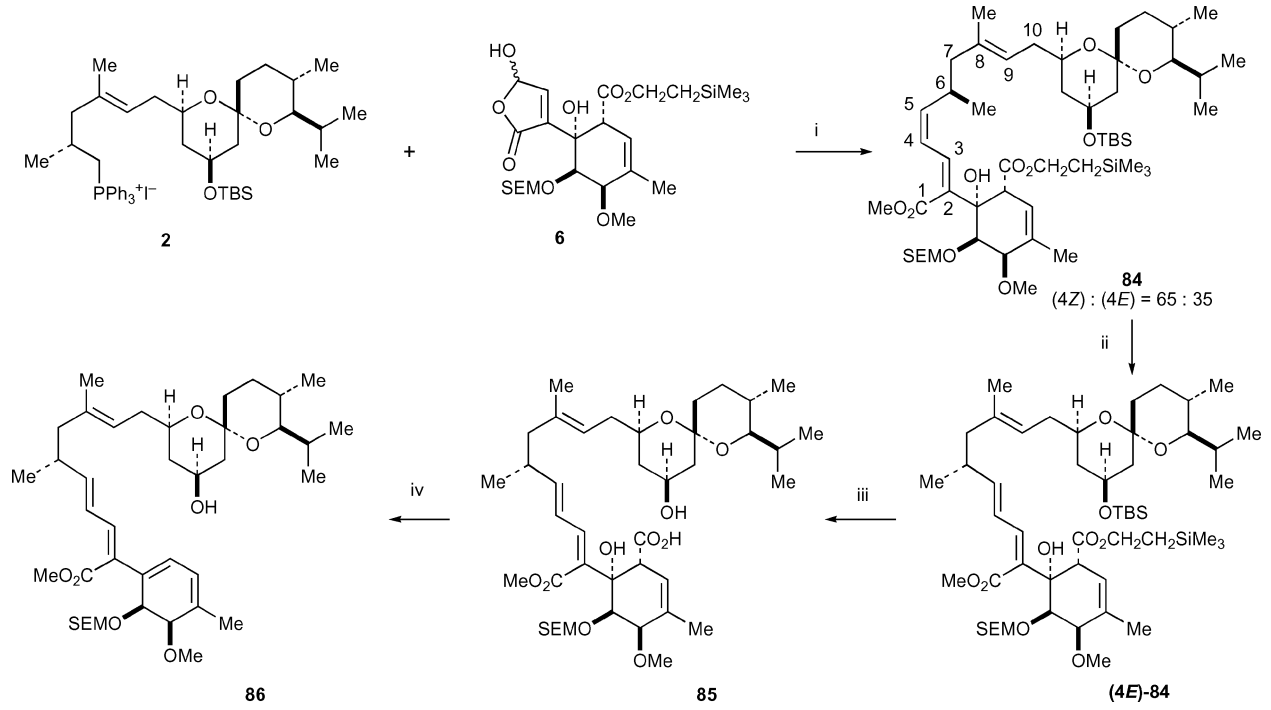
Completion of a synthesis of milbemycin G

The Wittig reaction between the ylid derived from phosphonium salt **2**[2] (10% excess) and the hydroxybutenolide (−)-**6** was carried out using 3.5 molar equivalents of lithium hexamethyldisilazide as base and gave the dienyl ester **84** (48%) as a 2 : 1 mixture of the (4*Z*)- and (4*E*)-isomers (^{1}H NMR) after reaction of the crude product with diazomethane, see Scheme 10. No attempt was made to separate this mixture. Instead treatment with a catalytic amount of iodine in daylight instigated (4*Z*)- to (4*E*)-isomerisation to give the required (4*E*)-isomer (4*E*)-**84**. Removal of the *tert*-butyldimethylsilyl protecting group and cleavage of the 2-trimethylsilylethyl ester was then achieved using tetrabutylammonium fluoride to give the seco-acid **85**. However, attempts to effect macrolactonisation using dicyclohexylcarbodiimide and 4-dimethylaminopyridine in dichloromethane or using 2,4,6-trichlorobenzoyl chloride under the Yamaguchi conditions[21] were unsuccessful, the only product isolated being tentatively identified as the elimination product **86**.

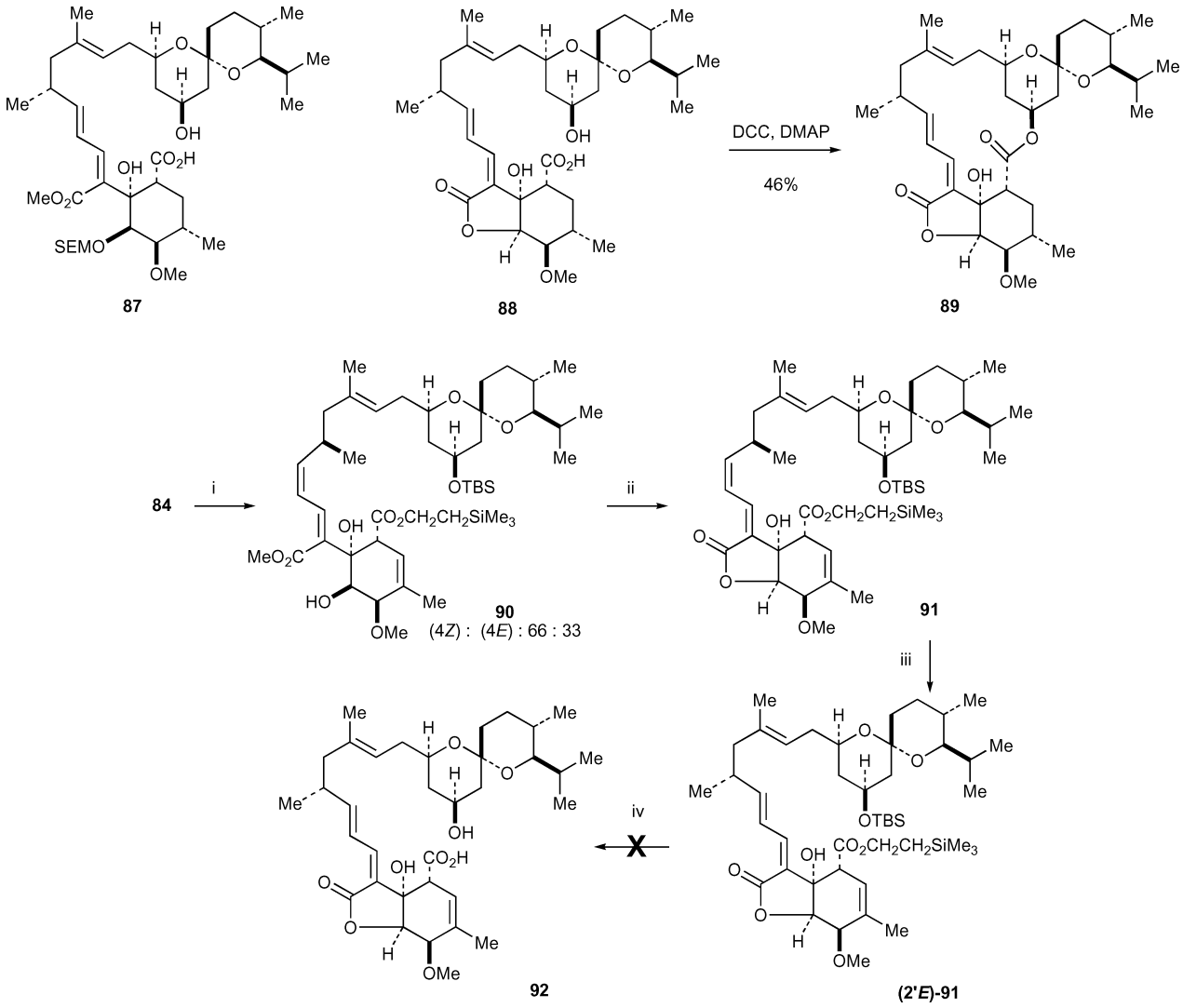
During the synthesis of (6*R*)-3,4-dihydromilbemycin E **5**, it had been observed that macrolactonisation of the 3,4-dihydro seco-acid corresponding to **85**, *i.e.* **87**, was also unsuccessful,[4] and so the difficulties encountered in trying to cyclise **85** were not unexpected. However, in the dihydro-series, macrolactonisation of butenolide **88** using dicyclohexylcarbodiimide gave the macrolide **89** in a 46% yield. The Wittig product **84**, as the mixture of (4*Z*)- and (4*E*)-isomers, was therefore taken through to the protected butenolide **91** by removal of the SEM-group using anhydrous magnesium dibromide and *n*-butanethiol in ether[22] to give the hydroxy-ester **90**, followed by lactonisation to form the butenolide **91** which was carried out using silica gel and 4 Å molecular sieves, see Scheme 11. Iodine catalysed (2′*Z*)- to (2′*E*)-isomerisation was then effected using a trace of iodine in daylight to give (2′***E***)-**91**. However, in this series, attempts to remove the *tert*-butyldimethylsilyl group and the 2-trimethylsilyl ester using tetrabutylammonium fluoride to prepare the seco-acid **92** were unsuccessful, only complex product mixtures being obtained.



Scheme 9 *Reagents and conditions:* i, $(COCl)_2$, DMSO, Et_3N (90%); ii, PhSeCl, py. (88%); iii, $Me_4NBH(OAc)_3$ (75%); iv, CCl_3COCl, py. (87%); v, ^{t}BuOOH, benzene (82%); vi, EtOH, DMAP (94%); vii, ^{n}Bu_2SnO then MeI, Bu_4NI (93%); viii, SEMCl, ^{i}Pr_2NEt (96%); ix, NaOH, EtOH; x, $Me_3SiCH_2CH_2OH$, DCC, DMAP (82% from (−)-**57**); xi, TPP, O_2, hν (98%).



Scheme 10 *Reagents and conditions:* i, (a) LHMDS, −78 °C to r.t., 3 h (b) CH_2N_2, ether, r.t., 20 min (48%); ii, I_2 (5 mol%), benzene (95%); iii, TBAF, THF, r.t., 13 h (93%); iv, DCC, DMAP (cat.), CH_2Cl_2, 5 °C, 69 h (19%) or $Cl_3C_6H_2COCl$, Et_3N, xylene, r.t., 24 h, then DMAP, r.t., 2 h (70%).



Scheme 11 *Reagents and conditions:* i, $MgBr_2$, *n*-BuSH, Et_2O (78%); ii, silica gel, 4A mol. sieves (98%); iii, I_2, benzene (91%); iv, TBAF, THF, r.t.

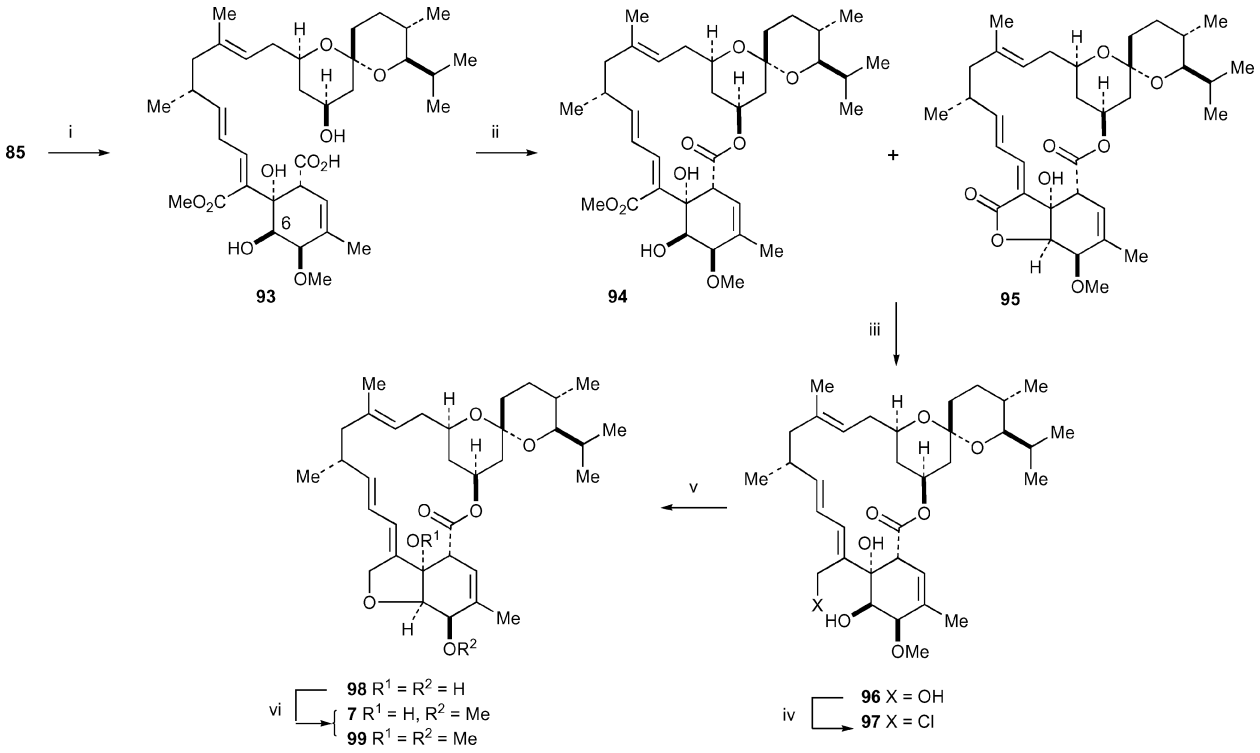
At this point, it was decided to remove the SEM-group from the seco-acid **85**, to see whether macrocyclisation was compatible with a smaller, H-bond donating, group at C(6). This selective deprotection was carried out using anhydrous magnesium bromide and *n*-butanethiol and gave the trihydroxy-acid **93** (90%), see Scheme 12. Fortunately, cyclisation of this acid using the Yamaguchi conditions[21] gave the required macrolide **94** in a 33% yield together with a small amount of the analogous butenolide **95**, ratio **94** : **95** = 80 : 20. Reduction of this mixture using diisobutylaluminium hydride in toluene, with an aqueous quench, gave (6*R*)-6-hydroxymilbemycin E **96** as the only isolable product in a 45% yield.

At this point, it remained to dehydrate the triol **96** to introduce the required tetrahydrofuran ring and complete a synthesis of milbemycin G **7**. The triol was treated with lithium diisopropylamide (2 molar equivalents) followed by the addition of toluene *p*-sulfonyl chloride. Under these conditions it was intended to generate the toluene *p*-sulfonate of the primary alcohol which it was hoped would cyclise under the basic reaction conditions to give milbemycin G. However, the primary chloride **97** was isolated, not milbemycin G **7**. It would appear that displacement of the toluene *p*-sulfonate by the chloride anions in solution had competed with the required cyclisation and that cyclisation by intramolecular displacement of the allylic chloride was slow. Since the displacement of the primary chloride by the hydroxyl group at C(6) would be expected to be promoted by silver(I) salts under basic conditions, the chloride **97** was treated with freshly prepared silver(I) oxide in tetrahydrofuran. Under these conditions, the required displacement did indeed take place to give milbemycin G **7**, $[a]_D$ 101 (*c* 0.195, acetone), lit.[3b] $[a]_D$ 108 (*c* 0.25, acetone), which was isolated in a 71% yield.

The successful completion of a synthesis of milbemycin G was confirmed by comparison of the synthetic material with an authentic sample prepared by *O*-methylation of a commercial sample of milbemycin D **98**. Thus treatment of milbemycin D **98** with an excess of methyl iodide and silver(I) oxide gave milbemycin G **7** (64%), $[a]_D$ 113 (*c* 0.75, acetone) together with a small amount, *ca.* 20%, of 7-*O*-methyl milbemycin G **99**. The sample of milbemycin G **7** prepared by total synthesis was found to be identical to that prepared by methylation of milbemycin D **98** by TLC, MS, IR and ^{1}H NMR.

Summary and conclusions

This work delivered a total synthesis of milbemycin G **7**, an α-milbemycin, by a synthesis in which the 3,4-double-bond was introduced into the C(1)–C(10) fragment before assembly of the macrolide. During this synthesis, no migration of the double-bond was observed nor was any epimerisation at C(2) detected. Of interest is the control of the regioselectivity of the oxidative elimination by use of the trichloroacetate **69**.[23] The origin of the influence of the C(4)-substituent on the regioselectivity of the oxidative elimination of a phenylselanyl group at C(5) was not investigated. These eliminations are believed to be subject to kinetic control and the regioselectivity must be determined at the selenoxide stage. It may be that the 4-substituent influences the diastereoselectivity of selenide oxidation and hence the regioselectivity of elimination. However, configurationally defined selenoxides racemize within minutes at room temperature in the presence of traces of acid and moisture.[24] Although anhydrous *tert*-butyl hydroperoxide in benzene was used for the regioselective oxidative elimination of trichloroacetate **69**, no rigorous precautions were taken to avoid the presence of traces of moisture and so the rapid equilibration of diastereoisomeric selenoxides with different configurations at selenium may well have taken place under our reaction conditions. As an alternative explanation, perhaps through space, dipolar, effects are involved. Such effects have been postulated to explain the regioselectivity of analogous sulfoxide eliminations.[25] The conformation required for elimination to give the exocyclic alkene may introduce a repulsive dipolar interaction with a strongly electron-withdrawing, *cis*-orientated substituent at C(4) which should be more influential for more polar 4-substituents, *i.e.* for ketones and the trichloroacetate, and in less polar solvents, *i.e.* in benzene rather than in dichloromethane. In the conformation required for the endocyclic elimination, this dipolar field effect should be less effective, see Fig. 3, although it may be that half-boat



Scheme 12 *Reagents and conditions:* i, $MgBr_2$, *n*-BuSH, Et_2O (90%); ii, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N then DMAP (33%; **94** : **95** = 80 : 20); iii, DIBAL-H, toluene (45%); iv, LDA, THF–HMPA, *p*-TsCl (74%); v, Ag_2O, THF, r.t. 24 h then heat under reflux, 1 h (71%); vi, Ag_2O, MeI, r.t., 24 h (**7**, 64%; **99**, 20%).

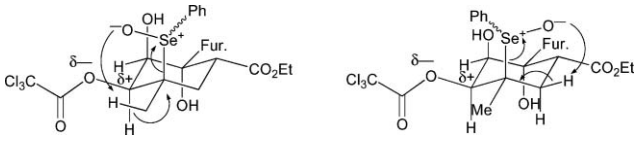


Fig. 3 Transition structures for selenoxide elimination from the trichloroacetate **69**.

conformations are required for the endocyclic process to take place.

Experimental

All IR spectra were recorded as evaporated films and all optical rotations were measured at ambient temperature, *ca.* 20 °C. For other general experimental details see the preceding paper in this issue.[4]

Ethyl (1*RS*,2*SR*,3*RS*)-3-benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-2,4-bis(trimethylsilyloxy)cyclohex-4-ene-1-carboxylate 18

Trimethylsilyl trifluoromethanesulfonate (0.48 cm^3, 2.50 mmol) was added to a solution of cyclohexanone **17** (222 mg, 0.50 mmol) and triethylamine (0.48 cm^3, 3.50 mmol) in dichloromethane (1 cm^3) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 22 h, then diluted with dichloromethane (20 cm^3) and washed with saturated aqueous sodium bicarbonate (20 cm^3). The aqueous phase was extracted with dichloromethane, and the combined organic phase dried (K_2CO_3) and concentrated under reduced pressure. Chromatography of the residue using 25 : 1 light petroleum–ether as eluant gave the *title compound* **18** (205 mg, 70%) as a viscous oil. [Found (FAB): M − CH_3, 573.2515. $C_{29}H_{45}O_6Si_3$ requires M, 573.2524]; ν_{max} 1727, 1250, 1204, 1168 and 840 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.02 [9 H, s, 2-OSi$(CH_3)_3$], 0.19 [9 H, s, 4-OSi$(CH_3)_3$], 0.40 [9 H, s, Si$(CH_3)_3$], 0.98 (3 H, t, *J* 7, CH_2CH_3), 1.49 (3 H, br. s, 5-CH_3), 2.00 (1 H, dd, *J* 16, 5, 6-H_{eq}), 2.63 (1 H, m, 6-H_{ax}), 3.00 (1 H, m, 1-H), 3.81 (2 H, q, *J* 7, CH_2CH_3), 4.22 (1 H, s, 3-H), 4.58 (2 H, m, PhHC*H*O), 6.47 (1 H, d, *J* 2, 4′-H), 7.25 (5 H, m, ArH) and 7.54 (1 H, d, *J* 2, 5′-H); *m*/*z* (FAB) 588 (M^+, 1%), 573 (6), 481 (21), 319 (32), 262 (100) and 171 (99).

Ethyl (1*RS*,2*SR*,3*RS*,5*RS*)-3-benzyloxy-5-methyl-5-phenylselanyl-2-trimethylsilyloxy-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 19

Benzene selenenyl chloride (72 mg, 0.37 mmol) was added to a solution of the silyl enol ether **18** (200 mg, 0.34 mmol) in dichloromethane (5 cm^3) at room temperature and the reaction mixture stirred for 2 h. Saturated aqueous ammonium chloride was added and the mixture diluted with dichloromethane (10 cm^3). The aqueous phase was extracted with dichloromethane and the combined organic phase dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 50 : 1 light petroleum–ether as eluant gave the *title compound* **19** (180 mg, 79%) as a white crystalline solid, mp 88 °C. [Found: C, 58.6; H, 6.6. $C_{33}H_{44}O_6SeSi_2$ requires C, 59.0; H, 6.6%. Found (FAB): M^+–CH_3, 657.1601. $C_{32}H_{41}O_6SeSi_2$ requires M, 657.16071]; ν_{max} 1738, 1714, 1250, 1173 and 841 cm^{-1}; δ_H (300 MHz; $CDCl_3$) − 0.01 [9 H, s, OSi$(CH_3)_3$], 0.48 [9 H, s, Si$(CH_3)_3$], 1.01 (3 H, t, *J* 7, CH_2CH_3), 1.56 (3 H, s, 5-CH_3), 2.13 (1 H, dd, *J* 14, 3, 6-H_{eq}), 2.75 (1 H, dd, *J* 16, 14, 6-H_{ax}), 3.40 (1 H, dd, *J* 14, 3,1-H), 3.88 (2 H, m, CH_2CH_3), 4.42 and 4.99 (each 1 H, d, *J* 12, PhHC*H*O), 5.24 (1 H, s, 3-H), 6.48 (1 H, d, *J* 2, 4′-H), 7.14 (2 H, m, ArH), 7.22 (3 H, m, ArH), 7.30–7.52 (5 H, m, PhSe) and 7.55 (1 H, d, *J* 2, 5′-H); *m*/*z* FAB 672 (M^+, 0.6%), 657 (2), 425 (54), 397 (19), 311 (19) and 167 (100).

Ethyl (1*RS*,2*SR*,3*RS*,5*RS*)-3-benzyloxy-2-hydroxy-5-methyl-5-phenylselanyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 20

Tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.16 cm^3, 0.16 mmol) was added to a solution of the selenide **19** (110 mg, 0.16 mmol) in THF (3 cm^3) at −50 °C and the mixture stirred at −50 °C for 1 h. Saturated aqueous ammonium chloride (2 cm^3) was added and the mixture warmed to room temperature and partitioned between water (5 cm^3) and ether (5 cm^3). The aqueous phase was extracted with ether (3 × 5 cm^3) and the combined organic phase dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 5 : 1 light petroleum–ether as eluant afforded the *title compound* **20** (85 mg, 87%) as an amorphous glass; ν_{max} 3475, 1719, 1377, 1250 and 845 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.23 [9 H, s, Si$(CH_3)_3$], 1.06 (3 H, t, *J* 7, CH_2CH_3], 1.56 (3 H, s, 5-CH_3), 2.20 (1 H, dd, *J* 13, 4, 6-H_{eq}), 2.62 (1 H, dd, *J* 15, 13, 6-H_{ax}), 3.61 (1 H, dd, *J* 13, 4, 1-H), 3.77 (1 H, br. s, 2-OH), 4.00 (2 H, m, CH_2CH_3), 4.23 and 4.56 (each 1 H, d, *J* 12, PhHC*H*O), 4.94 (1 H, s, 3-H), 6.29 (1 H, br. s, 4′-H), 7.01 (3 H, m, ArH), 7.22 (2 H, m, ArH), 7.40 (5 H, m, PhSe) and 7.59 (1 H, d, *J* 2, 5′-H); *m*/*z* (FAB) 599 (M^+ + 1, 0.1%), 443 (4), 353 (7), 167 (26) and 91 (100).

Ethyl (1*RS*,2*SR*,3*RS*)-3-benzyloxy-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohex-5-ene-1-carboxylate 21

Aqueous hydrogen peroxide (30%, 15 cm^3, 1.4 mmol) was added to a solution of selenide **20** (82 mg, 0.14 mmol) in dichloromethane at room temperature. The mixture was stirred for 1.5 h, diluted with ether (10 cm^3) and washed with water. The combined aqueous phase was extracted with ether and the combined organic phase dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 3 : 1 light petroleum–ether gave the *title compound* **21** (30 mg, 50%) as a viscous oil; ν_{max} 3466, 1697, 1249, 1184 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.24 [9 H, s, Si$(CH_3)_3$], 1.11 (3 H, t, *J* 7, CH_2CH_3), 1.81 (3 H, m, 5-CH_3), 3.82 (1 H, m, 1-H), 3.98 (1 H, s, 3-H), 4.07 (2 H, m, CH_2CH_3), 4.20 (1 H, s, 2-OH), 4.43 and 4.74 (each 1 H, d, *J* 12, PhHC*H*O), 6.16 (1 H, d, *J* 2, 4′-H), 6.48 (1 H, m, 6-H), 7.03 (2 H, m, ArH) and 7.22 (3 H, m, ArH), 7.56 (1 H, d, *J* 2, 5′-H); *m*/*z* (Cl) 460 (M^+ + 17, 40%), 335 (54) and 90 (100).

Ethyl (1*RS*,2*SR*,3*RS*)-4-*tert*-butyldimethylsilyloxy-2-hydroxy-3-(4-methoxy)benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohex-4-ene-1-carboxylate 23

tert-Butyldimethylsilyl trifluoromethanesulfonate (2.10 cm^3, 9.00 mmol) was added to a solution of cyclohexanone **22** (854 mg, 1.8 mmol) and triethylamine (1.75 cm^3, 12.6 mmol) in dichloromethane (10 cm^3) at 0 °C and the mixture stirred for 6 h. Saturated aqueous sodium bicarbonate (10 cm^3) was added and the mixture warmed to room temperature. The aqueous phase was extracted with dichloromethane and the combined organic phase dried (Na_2CO_3) and concentrated under reduced pressure. Chromatography of the residue using 39 : 1 light petroleum–ether gave the *title compound* **23** (1.01 g, 95%) as a viscous oil. [Found (FAB): M^+ − OH, 571.2912. $C_{31}H_{47}O_6Si_2$ requires M, 571.2911]; ν_{max} 3530, 1739, 1687, 1515, 1249 and 839 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.14 and 0.16 (each 3 H, s, $SiCH_3$), 0.26 [9 H, s, Si$(CH_3)_3$], 0.98 (3 H, t, *J* 7, CH_2CH_3), 0.99 [9 H, s, SiC$(CH_3)_3$], 1.70 (3 H, s, 5-CH_3), 2.00 (1 H, dd, *J* 15, 4, 6-H_{eq}), 2.69 and 2.77 (each 1 H, m, 1-H, 6-H_{ax}), 3.80 (3 H, s, OCH_3), 3.86 (2 H, q, *J* 7, CH_2CH_3), 3.92 (1 H, s, OH), 4.33 (1 H, s, 3-H), 4.44 and 4.62 (each 1 H, d, *J* 10, ArHC*H*O), 6.32 (1 H, d, *J* 2, 4′-H), 679 and 7.12 (each 2 H, d, *J* 10, ArH) and 7.56 (1 H, d, *J* 2,5′-H); *m*/*z* (FAB) 589 (M^+ + 1, 0.7%), 588 (0.5), 571 (4), 451 (21), 277 (18) and 121 (100).

Ethyl (1*RS*,2*SR*,3*RS*,5*RS*)-2-hydroxy-3-(4-methoxy)benzyloxy-5-methyl-5-phenylselanyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 24

Following the procedure outlined for the preparation of selenide **19**, benzene selenenyl chloride (2.35 g, 12.2 mmol) and the silyl enol ether **23** (3.60 g, 6.12 mmol) in dichloromethane (90 cm^3) at −50 °C for 1.25 h followed by extraction into ether (3 × 25 cm^3) and chromatography using 9 : 1 light petroleum–ether as eluant gave the *title compound* **24** (1.92 g, 50%) as an amorphous glass; ν_{max} 3474, 1717, 1612, 1586, 1513, 1249, 1180, 1032 and 844 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.26 [9 H, s, $Si(CH_3)_3$], 1.06 (3 H, t, *J* 7, CH_2CH_3), 1.51 (3 H, s, 5-CH_3), 2.20 (1 H, dd, *J* 16, 4, 6-H_{eq}), 2.60 (1 H, dd, *J* 16, 14, 6-H_{ax}), 3.60 (1 H, dd, *J* 14, 4, 1-H), 3.75 (1 H, s, OH), 3.79 (3 H, s, OCH_3), 4.00 (2 H, m, CH_2CH_3), 4.20 and 4.44 (each 1 H, d, *J* 12, ArHC*H*O), 4.93 (1 H, s, 3-H), 6.28 (1 H, s, 4′-H), 6.78 and 6.94 (each 2 H, d, *J* 10, ArH), 7.30 (2 H, m, ArH), 7.40 (3 H, m, ArH) and 7.58 (1 H, d, *J* 2, 5′-H); *m*/*z* (FAB) 631 ($M^+ + 1$, 0.2%), 630 (0.1), 456 (1), 337 (7) and 121 (100).

Ethyl (1*RS*,2*SR*,3*RS*)-2-hydroxy-3-(4-methoxy)benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohex-5-ene-1-carboxylate 25

tert-Butyl hydroperoxide (*ca.* 6.5 M in CH_2Cl_2, 1.1 cm^3, 7.3 mmol) was added to a solution of phenyl selenide **24** (461 mg, 0.73 mmol) in dichloromethane (5 cm^3) at 0 °C and the mixture warmed to room temperature and stirred for 72 h. Saturated aqueous sodium sulfite (10 cm^3) was added and the mixture stirred for 30 min then diluted with dichloromethane (5 cm^3). The aqueous phase was extracted with dichloromethane (3 × 10 cm^3) and the combined organic phase dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 6 : 1 light petroleum–ether as eluant gave the *title compound* **25** (222 mg, 64%) as a viscous oil; ν_{max} 3471, 1696, 1613, 1587, 1514, 1249, 1183 and 845 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.24 [9 H, s, $Si(CH_3)_3$], 1.10 (3 H, t, *J* 7, CH_2CH_3), 1.91 (3 H, m, 5-CH_3), 3.77 (3 H, s, OCH_3), 3.81 (1 H, m, 1-H), 3.96 (1 H, s, 3-H), 4.06 (2 H, m, CH_2CH_3), 4.14 (1 H, s, OH), 4.37 and 4.64 (each 1 H, d, *J* 12, ArHC*H*O), 6.14 (1 H, d, *J* 2, 4′-H), 6.48 (1 H, m, 6-H), 6.75 and 6.96 (each 2 H, d, *J* 10, ArH) and 7.56 (1 H, d, *J* 2, 5′-H); *m*/*z* (CI) 490 ($M^+ + 18$, 11%), 455 (18), 335 (39), 319 (10) and 121 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*SR*,5*RS*)-2,4-dihydroxy-3-(4-methoxy)benzyloxy-5-methyl-5-phenylselanyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 28

Tetramethylammonium triacetoxyborohydride (1.92 g, 7.3 mmol) was added to a solution of the phenyl selenide **24** (0.575 g, 0.91 mmol) in acetonitrile (8 cm^3) and acetic acid (8 cm^3) and the mixture stirred at room temperature for 48 h then concentrated under reduced pressure. The residue was dissolved in ether (50 cm^3) and washed with saturated aqueous sodium bicarbonate (2 × 25 cm^3). The combined aqueous phase was extracted with ether (3 × 25 cm^3) and the combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed using 3 : 1 light petroleum–ether as eluant to afford the *title compound* **28** as an amorphous glass (451 mg, 78%); ν_{max} 3476, 1711, 1612, 1586, 1514, 1250, 1182 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.30 [9 H, s, $Si(CH_3)_3$], 1.06 (3 H, t, *J* 7, CH_2CH_3), 1.50 (1 H, dd, *J* 16, 4, 6-H_{eq}), 1.55 (3 H, s, 5-CH_3), 1.62 (1 H, br. s, 4-OH), 1.90 (1 H, dd, *J* 16, 14, 6-H_{ax}), 3.56 (1 H, dd, *J* 14, 4, 1-H), 3.77 (1 H, d, *J* 9, 3-H), 3.79 (3 H, s, OCH_3), 3.83 (1 H, d, *J* 9, 4-H), 3.97 (3 H, m, CH_2CH_3, 2-OH), 4.02 and 4.16 (each 1 H, d, *J* 11, ArHC*H*O), 6.53 (1 H, d, *J* 1, 4′-H), 6.83 and 7.05 (each 2 H, d, *J* 6, ArH), 7.35 (3 H, m, ArH), 7.66 (2 H, m, ArH) and 7.69 (1 H, br. s, 5′-H); *m*/*z* (FAB) 632 (M^+, 0.6%), 457 (1), 321 (2), 249 (22), 167 (69) and 121 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*)-2,4-dihydroxy-3-(4-methoxy)-benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 26 and ethyl (1*RS*,2*SR*,3*SR*,4*RS*)-2,4-dihydroxy-3-(4-methoxy)benzyloxy-5-methylene-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 29

tert-Butyl hydroperoxide (*ca.* 6.5 M in CH_2Cl_2, 1 cm^3, 6.5 mmol) was added to a solution of the hydroxyselenide **28** (420 mg, 0.66 mmol) in dichloromethane (5 cm^3) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6.5 h. Saturated aqueous sodium sulfite (10 cm^3) was added and the mixture stirred for 30 min then diluted with dichloromethane (5 cm^3). The aqueous phase was extracted with dichloromethane (3 × 10 cm^3) and the combined organic phase dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 4 : 1 light petroleum–ether as eluant gave the *title compound* **26** (179 mg, 57%) as a white solid, mp 133–134 °C; ν_{max} 3472, 1713, 1613, 1514, 1249, 1179 and 844 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.29 [9 H, s, $Si(CH_3)_3$], 1.11 (3 H, t, *J* 7, CH_2CH_3), 1.85 (3 H, br. s, 5-CH_3), 2.07 (1 H, br. s, 4-OH), 3.52 (1 H, d, *J* 8, 3-H), 3.65 (1 H, m, 1-H), 3.78 (3 H, s, OCH_3), 4.04 (4 H, m, CH_2CH_3, $ArCH_2O$), 4.28 (1 H, s, 2-OH), 4.42 (1 H, br. d, *J* 8, 4-H), 5.28 (1 H, s, 3-H), 6.33 (1 H, br. s, 4′-H), 6.81 and 7.00 (each 2 H, d, *J* 8, ArH) and 7.63 (1 H, d, *J* 2, 5′-H); *m*/*z* (EI) 474 (M^+, 0.3%), 459 (16), 339 (22), 277 (10), 248 (17) and 121 (100). The *title compound* **29** (98 mg, 31%) was also isolated as a white solid, mp 129–130 °C; ν_{max} (EF) 3475, 1709, 1613, 1587, 1515, 1250, 1186 and 844 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.30 [9 H, s, $Si(CH_3)_3$], 1.06 (3 H, t, *J* 7, CH_2CH_3), 1.65 (1 H, br. s, 4-OH), 2.43 (1 H, m, 6-H_{eq}), 2.80 (2 H, m, 1-H, 6-H_{ax}), 3.22 (1 H, d, *J* 10, 3-H), 3.80 (3 H, s, OCH_3), 4.00 (3 H, m, CH_2CH_3, 2-OH), 4.10 (2 H, s, $ArCH_2O$), 4.49 (1 H, d, *J* 10, 4-H), 4.97 and 5.20 (each 1 H, s, 5-CH), 6.28 (1 H, br. s, 4′-H), 6.81 and 7.00 (2 H, d, *J* 9, ArH) and 7.62 (1 H, d, *J* 2, 5′-H); *m*/*z* (EI) 474 (M^+, 7%), 459 (24), 457 (57), 439 (18), 383 (44) and 121 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*)-4-*tert*-butyldimethylsilyloxy-2-hydroxy-3-(4-methoxy)benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 30

tert-Butyldimethylsilyl trifluoromethanesulfonate (115 μl, 0.5 mmol) was added to a solution of the cyclohexenol **26** (158 mg, 0.33 mmol) and 2,6-lutidine (80 μl, 0.67 mmol) in dichloromethane (3 cm^3) at 0 °C and the mixture stirred for 2 h. Saturated aqueous sodium bicarbonate (3 cm^3) was added and the aqueous phase extracted with dichloromethane (3 × 3 cm^3). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was chromatographed using 9 : 1 light petroleum–ether as eluant to afford the *title compound* **30** (190 mg, 97%) as a viscous oil; ν_{max} 3536, 1714, 1614, 1515, 1249, 1086 and 839 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.11 and 0.15 (each 3 H, s, $SiCH_3$), 0.19 [9 H, s, $Si(CH_3)_3$], 0.94 [9 H, s, $SiC(CH_3)_3$], 1.10 (3 H, t, *J* 7, CH_2CH_3), 1.82 (3 H, s, 5-CH_3), 3.56 (1 H, d, *J* 8, 3-H), 3.63 (1 H, m, 1-H), 3.77 (3 H, s, OCH_3), 3.94 (1 H, d, *J* 10, ArHC*H*O), 4.03 (2 H, m, CH_2CH_3), 4.18 (1 H, s, 2-OH), 4.49 (2 H, m, 4-H, Ar*H*CHO), 5.30 (1 H, br. s, 6-H), 6.34 (1 H, d, *J* 2, 4′-H), 6.74 and 6.79 (each 2 H, d, *J* 10, ArH) and 7.59 (1 H, d, *J* 2,5′-H); *m*/*z* (CI) 589 ($M^+ + 1$, 9%), 339 (47), 137 (19) and 121 (100).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*)-4-*tert*-butyldimethylsilyloxy-2-hydroxy-2-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-3-(4-methoxy)benzyloxy-5-methylcyclohex-5-ene-1-carboxylate 31

A solution of the silylated furan **30** (185 mg, 0.31 mmol) in dichloromethane (5 cm^3) and methanol (5 cm^3) containing a trace amount of tetraphenylporphine was cooled to −78 °C and irradiated for 1.5 h with a 250 W sunlamp whilst a stream of oxygen was passed through the solution. The mixture was concentrated under reduced pressure and the residue chromatographed using 1 : 2 light petroleum–ether as eluant

to give the *title compound* **31** (165 mg, 96%) as a white solid, mp 104–106 °C. [Found: C, 61.4; H, 7.1. $C_{28}H_{40}O_9Si$ requires C, 61.3; H, 7.35%. Found (CI): $M^+ + NH_4$, 566.2754. $C_{28}H_{44}O_9NSi$ requires M, 566.2785]; ν_{max} 3423, 1760, 1740, 1613, 1515, 1250, 1108 and 1020 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.11, 0.12, 0.50 and 0.55 (each 1.5 H, s, $SiCH_3$), 0.97 [9 H, s, $SiC(CH_3)_3$], 1.23 (3 H, m, CH_2CH_3), 1.82 (3 H, s, 5-CH_3), 3.80 (3 H, s, OCH_3), 3.94 (0.55 H, d, *J* 8, 3-H), 3.99 (0.45 H, d, *J* 8, 3-H), 4.05–4.25 (5 H, m, CH_2CH_3, PhHCHO, 4-H, 2-OH), 4.55 (1 H, m, 5-OH), 4.85 (0.45 H, d, *J* 11, ArHCHO), 4.95 (0.55 H, d, *J* 11, ArHCHO), 5.33 and 5.35 (each 0.5 H, br. s, 6-H), 5.65 (0.45 H, s, 5′-H), 5.83 (0.55 H, br. s, 5′-H), 6.84, 6.88, 7.12 and 7.14 (each 1 H, d, *J* 10, ArH), 7.21 (0.45 H, s, 4′-H) and 7.24 (0.55 H, s, 4′-H); *m/z* (CI) 566 (M^+, 7%), 531 (7) and 121 (100).

(2*Z*,4*EZ*)-2-[(1*RS*,2*SR*,3*SR*,4*RS*)-4-*tert*-Butyldimethylsilyloxy-1-ethoxycarbonyl-2-hydroxy-3-(4-methoxy)benzyloxy-5-methylcyclohex-5-en-2-yl]-6-methylhepta-2,4-dienoic acid 32

n-Butyllithium (0.23 cm^3, 1.6 M in hexanes, 0.36 mmol) was added to a solution of 2-methylpropyl(triphenyl)phosphonium bromide (146 mg, 0.36 mmol) in THF (1 cm^3) at 0 °C. The resultant orange solution was stirred at 0 °C for 30 min, cooled to −78 °C and added to a solution of the hydroxybutenolide **31** (40 mg, 0.073 mmol) in THF (1 cm^3) at −78 °C. The resultant solution was warmed to −20 °C over 1 h, then saturated aqueous ammonium chloride was added, and the mixture warmed to room temperature before being extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (65 : 34 : 1 light petroleum–ether–acetic acid) gave the *title compound* **32** (29 mg, 68%), an 80 : 20 mixture of the (4*Z*)- and (4*E*)-isomers, as a white solid, mp 171–172 °C. [Found: C, 65.3; H, 8.3. $C_{32}H_{48}O_8Si$ requires C, 65.28; H, 8.22%. Found (CI): $M^+ - 1$, 587.3041. $C_{32}H_{47}O_8Si$ requires M, 587.3040]; ν_{max} 3371, 1743, 1613, 1514, 1249, 1176 and 1105 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (4*Z*)-isomer: 0.09 and 0.14 (each 3 H, s, $SiCH_3$), 0.98 [9 H, s, $SiC(CH_3)_3$], 1.03 (3 H, d, *J* 7, 6-CH_3), 1.08 (3 H, d, *J* 7, 7-H_3), 1.21 (3 H, t, *J* 7, CH_2CH_3), 1.85 (3 H, s, 5′-CH_3), 2.93 (1 H, m, 6-H), 3.78 (3 H, s, OCH_3), 3.95–4.28 (5 H, m, CH_2CH_3, 3′-H, 4′-H, 1′-H), 4.52 (2 H, br. d, *J* 11, 2-OH, ArCH), 4.69 (1 H, d, *J* 11, ArCH), 5.34 (1 H, s, 6′-H), 5.67 (1 H, t, *J* 11, 5-H), 6.65 (1 H, t, *J* 11, 4-H), 6.79 and 7.18 (each 2 H, d, *J* 8, ArH) and 7.35 (1 H, d, *J* 11, 3-H); (4*E*)-isomer: 2.49 (1 H, m, 6-H), 6.08 (1 H, dd, *J* 15, 7, 5-H), 6.94 (1 H, dd, *J* 15, 11, 4-H); *m/z* (FAB) 588 (M^+, 43%), 587 (100), 437 (54), 393 (80), 347 (39) and 131 (78).

(2*Z*,4*EZ*)-2-[(1*RS*,2*SR*,3*SR*,4*RS*)-4-*tert*-Butyldimethylsilyloxy-1-ethoxycarbonyl-2,3-dihydroxy-5-methylcyclohex-5-en-2-yl]-6-methylhepta-2,4-dienoic acid 33

5,6-Dichloro-2,3-dicyanobenzo-1,4-quinone (29 mg, 0.13 mmol) was added to a solution of the dienyl acid **32** (50 mg, 0.085 mmol) in dichloromethane (0.8 cm^3) and water (0.08 cm^3) and the resultant dark red solution was stirred at room temperature for 5 h. The mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The aqueous phase was extracted with ethyl acetate and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (75 : 24 : 1 light petroleum–ether–acetic acid) gave the *title compound* **33** (31 mg, 78%) as an amorphous glass, mainly the (4*Z*)-isomer. [Found (EI): M^+, 468.2525. $C_{24}H_{40}O_7Si$ requires M, 468.2543]; ν_{max} 3377, 1705, 1691, 1261, 1180, 1164 and 1053 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.14 [6 H, s, $Si(CH_3)_2$], 0.92 [9 H, s, $SiC(CH_3)_3$], 0.97 and 0.98 (each 3 H, d, *J* 7, 6-CH_3, 7-H_3), 1.20 (3 H, t, *J* 7, CH_2CH_3), 1.80 (3 H, br. s, 5′-CH_3), 2.89 (1 H, m, 6-H), 3.86 (1 H, m, 1′-H), 3.95 (1 H, d, *J* 7, 3′-H), 4.05–4.43 (4 H, m, CH_2CH_3, 4′-H, 2′-OH), 5.28 (1 H, br. s, 6′-H), 5.60 (1 H, t, *J* 10, 5-H), 6.43 (1 H, t, *J* 10, 4-H) and 7.09 (1 H, d, *J* 10, 3-H); *m/z* (CI; NH_3) 469 (M^+ + 1, 10%), 468 (20), 451 (45), 433 (76), 319 (50), 301 (100) and 271 (74).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*)-2-hydroxy-4-methoxy-3-(4-methoxy)benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 34

Lithium hexamethyldisilazide (0.56 cm^3, 1.0 M solution in THF, 0.56 mmol) was added dropwise to a solution of the alcohol **26** (53 mg, 0.112 mmol), cetyltrimethylammonium bromide (49 mg, 0.134 mmol) and methyl iodide (0.14 cm^3, 2.24 mmol) in THF (1 cm^3) at 0 °C. The resultant solution was stirred at 0 °C for 25 min then quenched by the addition of saturated aqueous ammonium chloride. The aqueous phase was extracted with ether and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (4 : 1 light petroleum–ether) gave the *title compound* **34** (44 mg, 81%) as a white solid, mp 115–116 °C. [Found: C, 63.7; H, 7.7. $C_{26}H_{36}O_7Si$ requires C, 63.91; H, 7.43%. Found (CI): M^+ + H, 489.2325. $C_{26}H_{37}O_8Si$ requires M, 489.2309]; ν_{max} 3473, 1715, 1613, 1515, 1249, 1189, 1097 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.23 [9 H, s, $Si(CH_3)_3$], 1.09 (3 H, t, *J* 7, CH_2CH_3), 1.85 (3 H, s, 5-CH_3), 3.56 (3 H, s, 4-OCH_3), 3.61 (1 H, m, 1-H), 3.69 (1 H, d, *J* 8, 3-H), 3.78 (3 H, s, $ArOCH_3$), 3.95–4.10 (5 H, m, CH_2CH_3, 2-OH, 4-H, ArCH), 4.37 (1 H, d, *J* 10, ArCH), 5.28 (1 H, br. s, 6-H), 6.32 (1 H, d, *J* 2, 4′-H), 6.77 and 6.98 (each 2 H, d, *J* 9, ArH) and 7.62 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) 0.0, 13.9, 19.3, 51.8, 55.4, 60.2, 75.0, 76.4, 83.1, 85.5, 109.2, 113.4, 117.9, 129.9, 130.6, 138.6, 146.1, 158.9 and 172.9; *m/z* (CI; NH_3) 506 (M^+ + 18, 68%), 489 (28), 339 (100) and 231 (32).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*)-2,3-dihydroxy-4-methoxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 35

5,6-Dichloro-2,3-dicyanobenzo-1,4-quinone (84 mg, 0.37 mmol) was added to a solution of *p*-methoxybenzyl ether **34** (50 mg, 0.085 mmol) in dichloromethane (3 cm^3) and water (0.3 cm^3) and the resultant dark red solution was stirred at room temperature for 2 h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (3 : 1 light petroleum–ether) gave the *title compound* **35** (84 mg, 92%) as a white solid, mp 80.5–82 °C. [Found: C, 59.0; H, 7.6. $C_{18}H_{28}O_6Si$ requires C, 58.67; H, 7.66%. Found (EI): $M^+ + NH_4$, 386.1995. $C_{18}H_{32}NO_6Si$ requires M, 386.1999]; ν_{max} 3460, 1716, 1333, 1249, 1188, 1097 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.32 [9 H, s, $Si(CH_3)_3$], 1.11 (3 H, t, *J* 7, CH_2CH_3), 1.84 (4 H, br. s, 5-CH_3, 3-OH), 3.57 (4 H, br. s, 4-OCH_3, 1-H), 3.77 (1 H, d, *J* 8, 3-H), 3.96 (1 H, br. d, *J* 8, 4-H), 4.05 (2 H, m, CH_2CH_3), 4.38 (1 H, s, 2-OH), 5.29 (1 H, br. s, 6-H), 6.22 (1 H, d, *J* 2, 4′-H) and 7.59 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) 0.0, 13.8, 19.2, 51.1, 59.5, 61.2, 76.5, 77.3, 82.7, 108.0, 118.0, 136.9, 138.2, 147.1, 158.6 and 173.5; *m/z* (CI; NH_3) 386 (M^+ + 18, 14%), 351 (9), 296 (70), 279 (23) and 219 (100).

Ethyl (1*RS*,2*SR*,4*RS*)-2-hydroxy-4-methoxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-3-oxocyclohex-5-ene-1-carboxylate 36

Dimethyl sulfoxide (0.3 cm^3, 4.2 mmol) in dichloromethane (1 cm^3) was added to a solution of oxalyl chloride (0.18 cm^3, 2.1 mmol) in dichloromethane (1 cm^3) at −78 °C and the resultant solution stirred for 10 min. The alcohol **35** (153 mg, 0.42 mmol) in dichloromethane (1.5 cm^3) was added and the mixture stirred at −78 °C for 20 min before triethylamine (1.2 cm^3, 8.4 mmol) was added and the mixture allowed to warm to room temperature. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the

combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 light petroleum–ether) on base-washed silica provided the *title compound* **36** (117 mg, 77%) as an amorphous glass; ν_{max} 3462, 1715, 1249, 1187, 1098, 1020 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.39 [9 H, s, $Si(CH_3)_3$], 1.28 (3 H, t, *J* 7, CH_2CH_3), 1.90 (3 H, s, 5-CH_3), 3.42 (3 H, s, OCH_3), 3.93 (1 H, d, *J* 6, 1-H), 4.15 (2 H, q, *J* 7, CH_2CH_3), 4.45 (1 H, s, 4-H), 4.66 (1 H, s, 2-OH), 5.34 (1 H, br. d, *J* 6, 6-H), 6.40 (1 H, d, *J* 2, 4′-H) and 7.55 (1 H, d, *J* 2, 5′-H).

On standing, the β,γ-unsaturated ketone **36** isomerised to the α,β-unsaturated ketone **37**, an amorphous glass. [Found (CI): M$^+$, 366.1487. $C_{18}H_{26}O_6Si$ requires M, 366.1499]; ν_{max} 3468, 1736, 1688, 1641, 1248, 1189, 1140 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.35 [9 H, s, $Si(CH_3)_3$], 1.24 (3 H, t, *J* 7, CH_2CH_3), 1.99 (3 H, s, 5-CH_3), 2.50 (1 H, dd, *J* 19, 2, 6-H_{eq}), 2.69 (1 H, dd, *J* 19, 6, 6-H_{ax}), 3.28 (1 H, dd, *J* 6, 2, 1-H), 3.78 (3 H, s, OCH_3), 4.17 (2 H, m, CH_2CH_3), 4.30 (1 H, s, 2-OH), 6.18 (1 H, d, *J* 2, 4′-H) and 7.50 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) 0.0, 14.1, 17.5, 31.2, 51.9, 59.8, 61.0, 75.2, 108.5, 135.1, 142.1, 146.0, 147.7, 159.2, 172.2 and 192.7; *m*/*z* (EI) 366 (M$^+$, 8%), 351 (22), 307 (14), 266 (26), 248 (21) and 167 (100).

Ethyl (1*RS*,2*SR*)-2,4-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-3-oxocyclohex-4-ene-1-carboxylate 39

Dimethyl sulfoxide (3.00 cm^3, 42.2 mmol) in dichloromethane (50 cm^3) was added to a solution of oxalyl chloride (1.77 cm^3, 20.2 mmol) in dichloromethane (50 cm^3) at −78 °C and the resultant solution was stirred for 10 min before the hydroxyketone **38** (5.97 g, 16.9 mmol) in dichloromethane (50 cm^3) was added dropwise. The resultant mixture was stirred at −78 °C for 30 min before triethylamine (11.7 cm^3, 84.3 mmol) was added. The mixture was allowed to warm to room temperature, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (2 : 1 light petroleum–ether) gave the *title compound* **39** (5.65 g, 95%) as a white solid, mp 72–73 °C. [Found: C, 57.8; H, 6.9. $C_{17}H_{24}O_6Si$ requires C, 57.93; H, 6.86%. Found (EI): M$^+$, 352.1356. $C_{17}H_{24}O_6Si$ requires M, 352.1342]; ν_{max} 3462, 1735, 1686, 1654, 1248, 1195 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.34 [9 H, s, $Si(CH_3)_3$], 1.21 (3 H, t, *J* 7, CH_2CH_3), 1.97 (3 H, s, 5-CH_3), 2.61 (2 H, m, 6-H_2), 3.27 (1 H, dd, *J* 5, 3, 1-H), 4.14 (2 H, m, CH_2CH_3), 4.19 (1 H, s, 2-OH), 5.93 (1 H, s, 4-OH), 6.11 (1 H, d, *J* 2, 4′-H) and 7.49 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −0.3, 14.0, 16.7, 30.7, 51.9, 61.1, 74.6, 108.6, 127.3, 134.5, 142.7, 146.0, 159.2, 172.5 and 192.2; *m*/*z* (EI) 352 (M$^+$, 4%), 337 (36), 335 (30), 291 (10) and 43 (100).

Following this procedure, the hydroxyketone (−)-**38** (2.95 g, 8.33 mmol) gave the diketone (−)-**39** (2.63 g, 90%), as a white solid, $[\alpha]_D$ −120.8 (*c* 1.23, $CHCl_3$).

Ethyl (1*RS*,2*SR*)-4-*tert*-butyldimethylsilyloxy-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-3-oxocyclohex-4-ene-1-carboxylate 40

tert-Butyldimethylsilyl trifluoromethanesulfonate (30 μl, 0.131 mmol) was added to a solution of the α-diketone **39** (20 mg, 0.057 mmol) and triethylamine (40 μl, 0.288 mmol) in dichloromethane (0.5 cm^3) at room temperature. The resultant mixture was stirred at room temperature for 30 min, then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (19 : 1 light petroleum–ether) gave the *title compound* **40** as a viscous oil (26 mg, 98%). [Found (EI): M$^+$ + NH_4, 484.2547. $C_{23}H_{42}NO_6Si_2$ requires M, 484.2551]; ν_{max} 3463, 1738, 1690, 1251, 1190, 1146 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.17 and 0.20 (each 3 H, s, $SiCH_3$), 0.32 [9 H, s, $Si(CH_3)_3$], 0.98 [9 H, s, $SiC(CH_3)_3$], 1.22 (3 H, t, *J* 7, CH_2CH_3), 1.94 (3 H, s, 5-CH_3), 2.50 (1 H, dd, *J* 19, 1.5, 6-H_{eq}), 2.66 (1 H, ddd, *J* 19, 6, 1.5, 6-H_{ax}), 3.23 (1 H, dd, *J* 6, 3, 1-H), 4.14 (2 H, m, CH_2CH_3), 4.28 (1 H, br. s, 2-OH), 6.15 (1 H, d, *J* 2, 4′-H) and 7.44 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −4.0, −3.7, −0.3, 14.0, 17.9, 18.8, 31.4, 51.8, 60.7, 75.3, 109.0, 134.9, 135.7, 143.7, 145.9, 158.7, 172.6 and 192.6; *m*/*z* (CI; NH_3) 484 (M$^+$ + 18, 48%) and 394 (100).

Ethyl (1*RS*,2*SR*,5*RS*)-2-hydroxy-5-methyl-5-phenylselanyl-2-(2-trimethylsilyl-3-furyl)-3,4-dioxocyclohexane-1-carboxylate 42

Pyridine (1.13 cm^3, 14.0 mmol) was added to a solution of benzene selenenyl chloride (1.34 g, 7.00 mmol) in THF (35 cm^3) at 0 °C and the resultant solution was warmed to room temperature and stirred for 15 min. The enolic α-diketone **39** (2.24 g, 6.36 mmol) in THF (30 cm^3) was added and the resultant mixture was stirred for 5 min before saturated aqueous ammonium chloride was added. The mixture was extracted with ether and the combined organic phase was washed with brine, dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 then 4 : 1 light petroleum–ether) gave the *title compound* **42** (3.10 g, 96%) as a pale yellow solid, mp 140–141 °C. (Found: C, 54.5; H, 5.6. $C_{23}H_{28}O_6SeSi$ requires C, 54.43; H, 5.56%); ν_{max} 3402, 1749, 1710, 1376, 1184 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.25 [9 H, s, $Si(CH_3)_3$], 1.16 (3 H, t, *J* 7, CH_2CH_3), 1.60 (3 H, s, 5-CH_3), 2.30 (1 H, dd, *J* 14, 4, 6-H_{eq}), 2.86 (1 H, dd, *J* 14, 13, 6-H_{ax}), 3.70 (1 H, dd, *J* 13, 4, 1-H), 4.11 (2 H, m, CH_2CH_3), 4.89 (1 H, s, 2-OH), 6.34 (1 H, d, *J* 2, 4′-H), 7.30–7.55 (5 H, m, ArH) and 7.63 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) 0.0, 13.8, 22.2, 30.9, 35.6 46.6, 62.0, 80.3, 108.9, 124.2, 129.5, 130.4, 132.8, 137.7, 146.4, 173.5, 189.4 and 193.1; *m*/*z* (FAB) 509 (M$^+$ + 1, 2%), 389 (4), 351 (18), 198 (20), 167 (67) and 73 (100).

Following this procedure, the α-diketone (−)-**39** (5.39 g, 15.3 mmol) gave the phenyl selanyl diketone (−)-**42** (6.85 g, 88%), as a white solid, $[\alpha]_D$ −188.8 (*c* 1.75, $CHCl_3$).

Ethyl (1*RS*,2*SR*,3*RS*,4*SR*,5*RS*)-5-methyl-5-phenylselanyl-2,3,4-trihydroxy-2-(2-trimethylsilyl-3-furyl)-cyclohexane-1-carboxylate 43

Acetic acid (7.50 cm^3, 172 mmol) was added dropwise to a solution of tetramethylammonium borohydride (5.12 g, 57.5 mmol) in acetonitrile (15 cm^3) at 0 °C. The resultant solution was warmed to room temperature, stirred for 30 min and added to a suspension of the diketone **42** (3.65 g, 7.19 mmol) in acetonitrile (10 cm^3) and acetic acid (17.5 cm^3) at 5 °C. The resultant mixture was warmed to room temperature, stirred for 1 h, diluted with ethyl acetate and slowly poured onto a large volume of saturated aqueous potassium carbonate (*ca.* 750 cm^3) at *ca.* 5 °C. The aqueous phase was extracted with ethyl acetate and the combined organic phase was washed with brine, dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 then 3 : 1 light petroleum–ether) gave the *title compound* **43** as a colourless foam (3.01 g, 82%); ν_{max} 3461, 1707, 1377, 1248, 1186, 1035 and 842 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.40 [9 H, s, $Si(CH_3)_3$], 1.17 (3 H, t, *J* 7, CH_2CH_3), 1.27 (3 H, s, 5-CH_3), 1.95–2.20 (4 H, m, 6-H_2, 3-OH, 4-OH), 3.74 (1 H, d, *J* 3, 3-H), 3.83 (1 H, dd, *J* 10, 6, 1-H), 3.88 (1 H, d, *J* 3, 4-H), 4.08 (2 H, m, CH_2CH_3), 4.49 (1 H, s, 2-OH), 6.45 (1 H, d, *J* 2, 4′-H), 7.25–7.45 (3 H, m, ArH), 7.57 (1 H, d, *J* 2, 5′-H) and 7.83 (2 H, m, ArH); δ_C (75 MHz; $CDCl_3$) −0.1, 14.0, 29.0, 37.6 43.5, 53.2, 61.0, 74.1, 74.7, 110.2, 127.2, 128.8, 128.9, 138.6, 139.4, 146.0, 157.7 and 175.9; *m*/*z* (EI) 512 (M$^+$, 13%), 337 (36), 265 (58), 247 (67), 219 (60) and 167 (100).

Following this procedure, the diketone (−)-**42** (6.54 g, 12.9 mmol) gave the triol (−)-**43** (4.94 g, 75%), as a white solid, $[\alpha]_D$ −68.5 (*c* 0.89, $CHCl_3$).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-5-methyl-2,3,4-trihydroxy-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 44 and ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-5-methylene-2,3,4-trihydroxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 46

tert-Butyl hydroperoxide (2 cm^3, 5 M in dichloromethane, 10 mmol) was added to a solution of the trihydroxyselenide **43** (540 mg, 1.05 mmol) in dichloromethane (10 cm^3) at room temperature and the resultant solution was stirred for 3 h. Saturated aqueous sodium sulfite was added and the resultant mixture was stirred vigorously for 30 min. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (2 : 1 light petroleum–ether) gave the alkenols **44** and **46** (300 mg, 80%), ratio 40 : 60, as an amorphous glass. Chromatography of this mixture on silica gel impregnated with silver nitrate (5% w/w) (2 : 1 light petroleum–ether) gave the *title compound* **44** as a white solid, mp 162–163 °C. (Found: C, 57.45; H, 7.5. $C_{17}H_{26}O_6Si$ requires C, 57.60; H, 7.39%); ν_{max} 3461, 1711, 1248, 1190 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.30 [9 H, s, $Si(CH_3)_3$], 1.17 (3 H, t, *J* 7, CH_2CH_3), 1.86 (3 H, s, 5-CH_3), 2.26 (2 H, br. s, 3-OH, 4-OH), 3.82 (2 H, d, *J* 4, 3-H, 1-H), 4.09 (2 H, q, *J* 7, CH_2CH_3), 4.50 (1 H, m, 4-H), 4.80 (1 H, s, 2-OH), 5.34 (1 H, br. s, 6-H), 6.36 (1 H, d, *J* 2, 4′-H) and 7.54 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −0.1, 14.0, 19.3, 46.2, 61.4, 69.3, 74.7, 75.0, 109.9, 117.7, 137.0, 140.0, 146.2, 157.6 and 174.9; *m*/*z* (CI; NH_3) 355 ($M^+ + 1$, 2%), 337 (11) and 265 (100). Further elution gave the *title compound* **46** (216 mg, 54%) as a colourless foam. [Found (CI): M^+, 354.1502. $C_{17}H_{26}O_6Si$ requires M, 354.1499]; ν_{max} 3454, 1709, 1249, 1187, 1094 and 842 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.33 [9 H, s, $Si(CH_3)_3$], 1.12 (3 H, t, *J* 7, CH_2CH_3), 2.00 (2 H, br. s, 3-OH, 4-OH), 2.50 (1 H, d, *J* 13, 4, 6-H_{eq}), 2.71 (1 H, t, *J* 13, 6-H_{ax}), 3.19 (1 H, dd, *J* 13, 4, 1-H), 3.79 (1 H, d, *J* 3, 3-H), 4.04 (2 H, m, CH_2CH_3), 4.68 (1 H, s, 2-OH), 4.70 (1 H, m, 4-H), 5.09 and 5.19 (each 1 H, br. s, 5-CH), 6.29 (1 H, d, *J* 2, 4′-H) and 7.53 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −0.5, 14.1, 33.3, 46.0, 60.9, 70.0, 75.0, 77.4, 109.4, 110.0, 139.5, 144.4, 146.0, 158.2 and 175.4; *m*/*z* (EI) 354 (M^+, 3%), 336 (9), 290 (18), 247 (24), 173 (72) and 167 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-4-*tert*-butyldimethylsilyloxy-2,3-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 45 and ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-4-*tert*-butyldimethylsilyloxy-2,3-dihydroxy-5-methylene-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 47

tert-Butyldimethylsilyl trifluoromethanesulfonate (0.58 cm^3, 2.53 mmol) was added to a mixture of the alcohols **44** and **46** (300 mg, 0.847 mmol, ratio 40 : 60) and 2,6-lutidine (0.49 cm^3, 4.21 mmol) in dichloromethane (6 cm^3) at 0 °C. The reaction mixture was stirred at 0 °C for 5.5 h, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (49 : 1 hexane–ether) afforded the *title compound* **45** (147 mg, 37%) as a viscous oil. [Found (EI): $M^+ + H$, 469.2444. $C_{23}H_{41}O_6Si_2$ requires M, 469.2442]; ν_{max} 3457, 1712, 1250, 1188 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.12 and 0.19 (each 3 H, s, SiMe), 0.31 [9 H, s, $Si(CH_3)_3$], 0.92 [9 H, s, $SiC(CH_3)_3$], 1.17 (3 H, t, *J* 7, CH_2CH_3), 1.78 (3 H, s, 5-CH_3), 3.74 (1 H, d, *J* 4, 3-H) 3.88 (1 H, m, 1-H), 4.10 (2 H, q, *J* 7, CH_2CH_3), 4.61 (1 H, m, 4-H), 4.84 (1 H, s, 2-OH), 5.35 (1 H, br. s, 6-H), 6.39 (1 H, d, *J* 2, 4′-H and 7.54 (1 H, d, *J* 2, 5′-H); *m*/*z* (CI; NH_3) 469 ($M^+ + 1$, 2%), 451 (5), 379 (60), 247 (44) and 219 (100). Further elution gave the *title compound* **47**. [Found (CI): $M^+ - OH$, 451.2321. $C_{23}H_{39}O_5Si_2$ requires M, 451.2336]; ν_{max} 3467, 1710, 1251, 1185, 1111 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.10 and 0.12 (each 3 H, s, SiMe), 0.32 [9 H, s, $Si(CH_3)_3$], 0.92 [9 H, s, $SiC(CH_3)_3$], 1.13 (3 H, t, *J* 7, CH_2CH_3), 2.34 (1 H, br. s, 3-OH), 2.48 (1 H, dd, *J* 13, 4, 6-H_{eq}), 2.70 (1 H, t, *J* 13, 6-H_{ax}), 3.22 (1 H, dd, *J* 13, 4, 1-H), 3.70 (1 H, d, *J* 3, 3-H), 4.03 (2 H, m, CH_2CH_3), 4.58 (1 H, s, 2-OH), 4.74 (1 H, m, 4-H), 5.05 and 5.15 (each 1 H, br. s, 5-CH), 6.32 (1 H, d, *J* 2, 4′-H) and 7.51 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −5.1, −5.0, 0.0, 13.9, 18.2, 25.8, 32.4, 46.4, 60.9, 71.2, 74.7, 77.9, 110.3, 110.4, 139.9, 143.3, 145.5, 156.8 and 175.7; *m*/*z* (CI; NH_3) 469 ($M^+ + 1$, 1%), 451 (15), 379 (35), 321 (49) and 247 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-3,4-bis(*tert*-butyldimethylsilyloxy)-2-hydroxy-5-methylene-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 48

tert-Butyldimethylsilyl trifluoromethanesulfonate (0.81 cm^3, 3.51 mmol) was added to a solution of the alcohols **44** and **46** (594 mg, 1.68 mmol, ratio 40 : 60) and 2,6-lutidine (0.82 cm^3, 7.02 mmol) in dichloromethane (8 cm^3) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 16 h, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (99 : 1 hexane–ether) afforded the *title compound* **48** (343 mg, 44%) as a white solid, mp 64–65 °C. [Found: C, 60.0; H, 9.5. $C_{29}H_{54}O_6Si_3$ requires C, 59.75; H, 9.34%. Found (CI): $M^+ - OH$, 565.3206. $C_{29}H_{53}O_5Si_3$ requires M, 565.3201]; ν_{max} 3472, 1711, 1250, 1183, 897 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.42, 0.00, 0.10 and 0.11 (each 3 H, s, SiMe), 0.32 [9 H, s, $Si(CH_3)_3$], 0.78 and 0.99 [each 9 H, s, $SiC(CH_3)_3$], 1.16 (3 H, t, *J* 7, CH_2CH_3), 2.45 (1 H, dd, *J* 13, 4, 6-H_{eq}), 2.59 (1 H, t, *J* 13, 6-H_{ax}), 3.23 (1 H, dd, *J* 13, 4, 1-H), 3.60 (1 H, d, *J* 3, 3-H), 4.06 (2 H, q, *J* 7, CH_2CH_3), 4.42 (1 H, s, 2-OH), 4.87 (1 H, m, 4-H), 5.00 and 5.05 (each 1 H, br. s, 5-CH), 6.20 (1 H, d, *J* 2, 4′-H) and 7.41 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −5.1, −4.8, −4.7, −3.2, 0.0, 14.0, 18.4, 18.9, 26.1, 26.4, 33.1, 46.7, 60.7, 72.9, 75.8, 80.6, 109.4, 111.8, 141.1, 143.6, 144.9, 156.8 and 176.1; *m*/*z* (CI; NH_3) 565 ($M^+ - 17$, 44%), 493 (77), 361 (69) and 90 (100). Further elution gave the silyl ether **45** (251 mg, 40%) as a viscous oil.

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-4-*tert*-butyldimethylsilyloxy-2,3-dihydroxy-2-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-5-methylcyclohex-5-ene-1-carboxylate 49

A solution of the 2-silylfuran **45** (89 mg, 0.190 mmol) and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (0.5 mg) in dichloromethane (3 cm^3) and methanol (3 cm^3) was cooled to −78 °C and irradiated with a 250 W sunlamp whilst a stream of oxygen was passed through the solution for 45 min. The reaction mixture was concentrated under reduced pressure and chromatography of the residue (98 : 2 then 95 : 5 chloroform–ether) gave the *title compound* **49** (80 mg, 98%, *ca.* a 1 : 1 mixture of epimers) as a colourless foam. [Found (CI): $M^+ + H$, 429.1941. $C_{20}H_{33}O_8Si$ requires M, 429.1945]; ν_{max} 3427, 1739, 1255, 1113, 1054 and 867 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.15 and 0.17 (each 3 H, s, SiMe), 0.93 [9 H, s, $SiC(CH_3)_3$], 1.27 (3 H, m, CH_2CH_3), 1.79 (3 H, s, 5-CH_3), 3.80 and 3.87 (each 0.5 H, d, *J* 4, 3-H), 3.94 (1 H, m, 1-H), 4.18 (3 H, m, CH_2CH_3, 2-OH), 4.54 (1 H, m, 4-H), 4.85 and 5.08 (each 0.5 H, br. s, 5′-OH), 5.49 (1 H, br. s, 6-H), 6.11 (1 H, m, 5′-H) and 7.32 and 7.38 (each 0.5 H, d, *J* 1, 4′-H); *m*/*z* (CI; NH_3) 429 ($M^+ + 1$, 37%), 411 (19) and 297 (100).

(2*Z*,4*EZ*)-2-[(1*RS*,2*SR*,3*RS*,4*RS*)-4-*tert*-Butyldimethylsilyloxy-2,3-dihydroxy-1-ethoxycarbonyl-5-methylcyclohex-5-en-2-yl]-6-methylhepta-2,4-dienoic acid 50

n-Butyllithium (0.23 cm^3, 1.6 M solution in hexanes, 0.36 mmol) was added to a solution of 2-methylpropyl-(triphenyl)phosphonium bromide (144 mg, 0.36 mmol) in THF (1 cm^3) at 0 °C. The resultant orange solution was stirred for

30 min, cooled to −60 °C and added to a solution of the hydroxybutenolide **49** (31 mg, 0.072 mmol) in THF (0.5 cm^3) at −60 °C. The resultant solution was warmed to −20 °C over 30 min, stirred for 30 min then saturated aqueous ammonium chloride was added. The mixture was warmed to room temperature, extracted with ethyl acetate and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (99 : 1 chloroform–acetic acid) gave the *title compound* **50** (26 mg, 77%), a 75 : 25 mixture of the (4*Z*)- and (4*E*)-isomers, as an amorphous glass; ν_{max} 3450, 1712, 1254, 1189 and 867 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (4*Z*)-isomer: 0.17 and 0.19 (each 3 H, s, SiMe), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.02 (6 H, m, 7-H_3, 6-CH_3), 1.28 (3 H, t, *J* 7, CH_2CH_3), 1.78 (3 H, s, 5′-CH_3), 2.90 (1 H, m, 6-H), 3.54 (1 H, br. s, 3′-OH), 3.80 (2 H, m, 3′-H, 1′-H), 4.21 (2 H, m, CH_2CH_3), 4.55 (1 H, m, 4′-H), 5.08 (1 H, s, 2′-OH), 5.47 (1 H, s, 6′-H), 5.62 (1 H, t, *J* 11, 5-H), 6.39 (1 H, t, *J* 11, 4-H) and 7.12 (1 H, d, *J* 11, 3-H); (4*E*)-isomer: 5.98 (1 H, dd, *J* 15, 6, 5-H), 6.58 (1 H, dd, *J* 15, 11, 4-H) and 6.80 (1 H, d, *J* 11, 3-H); *m/z* (FAB) 469 (M^+ + 1, 1%), 319 (20) and 73 (100).

Ethyl (1*SR*,2*RS*,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]non-3-ene-2-carboxylate 51

A solution of *N*,*N*′-dicyclohexylcarbodiimide (9 mg, 0.045 mmol) in dichloromethane (0.4 cm^3) was added to a solution of the hydroxyacid **50** (7 mg, 0.015 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.2 mg, 0.002 mmol) in dichloromethane (0.6 cm^3) at room temperature. The resultant mixture was stirred for 2 h then concentrated under reduced pressure. The residue was suspended in ether, filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in benzene (1 cm^3) containing iodine (trace) and potassium carbonate (*ca.* 10 mg) and the resultant mixture was vigorously stirred whilst being irradiated with a 250 W sunlamp for 1 h. Saturated aqueous sodium thiosulfate was added and the mixture was extracted with ethyl acetate. The combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (3 : 1 light petroleum–ether) gave the *title compound* **51** as an amorphous glass (6 mg, 89%). [Found (CI): M^+ + H, 451.2514. $C_{24}H_{39}O_6Si$ requires M, 451.2516]; ν_{max} 3389, 1760, 1739, 1641, 1256, 1095 and 1063 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.06 and 0.11 (each 3 H, s, SiMe), 0.81 [9 H, s, $SiC(CH_3)_3$], 1.05 (6 H, d, *J* 7, 5′-H_3, 4′-CH_3), 1.35 (3 H, t, *J* 7, CH_2CH_3), 1.88 (3 H, s, 4-CH_3), 2.51 (1 H, m, 4′-H), 3.78 (1 H, m, 2-H), 3.98 (1 H, br. s, 1-OH), 4.28 (2 H, m, CH_2CH_3), 4.38 (2 H, m, 5-H, 6-H), 5.74 (1 H, m, 3-H), 6.11 (1 H, dd, *J* 15, 7, 3′-H), 7.01 (1 H, d, *J* 11, 1′-H) and 7.45 (1 H, ddd, *J*15, 11, 1, 2′-H); *m/z* (CI; NH_3) 451 (M^+ + 1, 43%) and 271 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-4-*tert*-butyldimethylsilyloxy-2,3-dihydroxy-2-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-5-methylenecyclohexane-1-carboxylate 52

A solution of the 2-silylfuran **47** (107 mg, 0.229 mmol) and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (0.2 mg) in dichloromethane (3 cm^3) and methanol (3 cm^3) was cooled to −78 °C and irradiated with a 250 W sunlamp whilst a stream of oxygen was passed through the solution for 2 h. The reaction mixture was concentrated under reduced pressure and the residue purified by chromatography (98 : 2 chloroform–methanol) to give the *title compound* **52** (96 mg, 98%) as a colourless foam. [Found (CI): M^+ + H, 429.1948. $C_{20}H_{33}O_8Si$ requires M, 429.1945]; ν_{max} 3397, 1741, 1189, 1115 and 864 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.12 [6 H, s, $Si(CH_3)_2$], 0.93 [9 H, s, $SiC(CH_3)_3$], 1.26 (3 H, t, *J* 7, CH_2CH_3), 2.52 (1 H, dd, *J* 13, 4, 6-H_{eq}), 2.67 (1 H, t, *J* 13, 6-H_{ax}), 2.70 (1 H, br. s, 5′-OH), 3.34 (1 H, dd, *J* 13, 4, 1-H), 3.79 (1 H, d, *J* 3, 3-H), 4.14 (2 H, q, *J* 7, CH_2CH_3), 4.65 (1 H, m, 4-H), 4.68 (1 H, s, 2-OH), 5.04 and 5.12 (each 1 H, s, 5-CH), 6.37 (1 H, br. s, 5′-H) and 7.20 (1 H, d, *J* 2, 4′-H); *m/z* (CI; NH_3) 429 (M^+ + 1, 87%), 411 (33), 297 (67), 102 (49) and 75 (100).

(2*Z*,4*EZ*)-2-[(1*RS*,2*SR*,3*RS*,4*RS*)-4-*tert*-Butyldimethylsilyloxy-2,3-dihydroxy-1-ethoxycarbonyl-5-methylenecyclohexan-2-yl]-6-methylhepta-2,4-dienoic acid 53

Following the procedure outlined for the synthesis of the Wittig product **50**, 2-methylpropyl(triphenyl)phosphonium bromide (188 mg, 0.47 mmol) and the hydroxybutenolide **52** (40 mg, 0.093 mmol) gave the *title compound* **53** (30 mg, 69%), an 80 : 20 mixture of the (4*Z*)- and (4*E*)-isomers, as an amorphous glass, after chromatography (99 : 1 chloroform–acetic acid); ν_{max} 3450, 1710, 1253, 1184, 1122 and 867 cm^{-1}; δ_H (200 MHz; $CDCl_3$) (4*Z*)-isomer: 0.12 [6 H, s, $Si(CH_3)_2$], 0.92 [9 H, s, $SiC(CH_3)_3$], 1.02 (6 H, d, *J* 7, 6-CH_3, 7-H_3), 1.28 (3 H, t, *J* 7, CH_2CH_3), 2.67 (2 H, m, 6′-H_2), 2.89 (1 H, m, 6-H), 3.18 (1 H, dd, *J* 13, 4, 1′-H), 3.72 (1 H, d, *J* 4, 3′-H), 4.16 (2 H, m, CH_2CH_3), 4.62 (2 H, br. s, 4′-H, 2′-OH), 5.06 and 5.12 (each 1 H, s, 5′-CH), 5.57 (1 H, t, *J* 11, 5-H), 6.29 (1 H, t, *J* 11, 4-H) and 7.14 (1 H, d, *J* 11, 3-H); (4*E*)-isomer: 5.96 (1 H, dd, *J* 15, 7, 5-H), 6.48 (1 H, dd, *J* 15, 11, 4-H) and 6.75 (1 H, d, *J* 11, 3-H).

Ethyl (1*SR*,2*RS*,5*RS*,6*RS*,9*Z*)-5-*tert*-butyldimethylsilyloxy-1-hydroxy-4-methylene-9-[(2*E*)-4-methyl-pent-2-enylidene]-8-oxo-7-oxabicyclo[4.3.0]nonane-2-carboxylate 54

Following the procedure outlined for the synthesis of the lactone **51**, treatment of the hydroxyacid **53** (25 mg, 0.053 mmol) with *N*,*N*′-dicyclohexylcarbodiimide (33 mg, 0.16 mmol) followed by isomerisation of the crude product with iodine using a sunlamp gave the *title compound* **54** (21 mg, 87%) as an amorphous glass after chromatography (3 : 1 light petroleum–ether). [Found (CI): M^+ + H, 451.2522. $C_{24}H_{39}O_6Si$ requires M, 451.2516]; ν_{max} 3411, 1760, 1738, 1645, 1188 and 1133 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.07 and 0.11 (each 3 H, s, $SiCH_3$), 0.85 [9 H, s, $SiC(CH_3)_3$], 1.05 (6 H, d, *J* 7, 4′-CH_3, 5′-H_3), 1.29 (3 H, t, *J* 7, CH_2CH_3), 2.50 (2 H, m, 3-H_{ax}, 4′-H), 2.68 (1 H, dd, *J* 14, 5, 3-H_{eq}), 3.11 (1 H, dd, *J* 10, 5, 2-H), 4.22 (2 H, q, *J* 7, CH_2CH_3), 4.32 (1 H, d, *J* 4, 5-H), 4.46 (1 H, d, *J* 4, 6-H), 4.75 (1 H, br. s, 1-OH), 5.08 and 5.20 (each 1 H, s, 4-CH), 6.07 (1 H, dd, *J* 16, 7, 3′-H), 6.59 (1 H, d, *J* 11, 1′-H) and 7.33 (1 H, ddd, *J* 16, 11, 1, 2′-H); δ_C (75 MHz; $CDCl_3$) −5.1, −5.0, 14.0, 18.1, 21.8, 25.7, 30.4, 31.8, 46.4, 61.6, 71.4, 75.9, 83.6, 113.6, 122.8, 127.9, 139.1, 141.6, 153.7, 168.2 and 174.7; *m/z* (CI; NH_3) 451 (M^+ + 1, 57%) and 434 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2,3-dihydroxy-4-methoxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 56

A suspension of the triol **44** (316 mg, 0.893 mmol) and di-*n*-butyltin oxide (222 mg, 0.893 mmol) in methanol (18 cm^3) was heated under reflux for 24 h, then cooled, concentrated under reduced pressure and the residue dissolved in benzene (3.5 cm^3). Tetra-*n*-butylammonium iodide (330 mg, 0.893 mmol) and methyl iodide (565 μl, 8,9 mmol) were added and the solution heated under reflux for 36 h. After concentration under reduced pressure, the residue was dissolved in chloroform and the solution washed with saturated aqueous sodium thiosulfate. The aqueous phase was extracted with chloroform and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (4 : 1 light petroleum–ether) gave the *title compound* **56** (312 mg, 96%) as a white solid; mp 158–159 °C. [Found (CI): C, 58.4; H, 7.9; M^+, 368.1650. $C_{18}H_{28}O_6Si$ requires C, 58.67; H, 7.66%; M, 368.1655]; ν_{max} 3461, 1712, 1328, 1248, 1172, 1190, 1095 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.31 [9 H, s, $Si(CH_3)_3$], 1.16 (3 H, t, *J* 7, CH_2CH_3), 1.82 (3 H, s, 5-CH_3), 2.59 (1 H, br. s, 3-OH), 3.47 (3 H, s, OCH_3), 3.88 (1 H, m, 1-H), 3.98 (1 H, d, *J* 4, 3-H), 4.10 (3 H, m, CH_2CH_3, 4-H), 4.77 (1 H, s, 2-OH), 5.36

(1 H, br. s, 6-H), 6.42 (1 H, d, *J* 2, 4′-H) and 7.54 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −0.2, 13.8, 19.1, 46.4, 57.2, 61.1, 70.9, 74.5, 79.1, 110.6, 116.5, 134.7, 140.6, 145.7, 157.4 and 174.7; *m/z* (EI) 368 (M^+, 3%), 171 (24) and 167 (100).

Following this procedure, the cyclohexenol (−)-**44** (630 mg, 1.78 mmol) gave (−)-**56** (606 mg, 93%), as a white solid, $[\alpha]_D$ −85.0 (*c* 1.60, $CHCl_3$).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxymethoxy)-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 57

2-Trimethylsilylethoxymethyl chloride (225 μl, 1.27 mmol) was added to a solution of the diol **56** (312 mg, 0.848 mmol) and ethyldiisopropylamine (440 μl, 2.43 mmol) in dichloromethane (420 μl) at room temperature and the resultant mixture was stirred for 24 h. Methanol (0.5 cm^3) was added and the mixture was stirred for 30 min, then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 light petroleum–ether) gave the *title compound* **57** (417 mg, 99%) as a viscous oil. [Found (EI): $M^+ + NH_4$, 516.2808. $C_{24}H_{46}NO_7Si_2$ requires M, 516.2813]; ν_{max} 3454, 1713, 1327, 1249, 1191, 1176, 1111, 1020 and 841 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.03 and 0.35 [each 9 H, s, $Si(CH_3)_3$], 0.78 (2 H, m, CH_2Si), 1.18 (3 H, t, *J* 7, CH_2CH_3), 1.82 (3 H, s, 5-CH_3), 3.20 (1 H, m, OCH_2OCHH), 3.45 (3 H, s, OCH_3), 3.60 (1 H, m, OCH_2OCHH), 3.88 (1 H, m, 1-H), 4.10 (3 H, m, CH_2CH_3, 3-H), 4.24 (1 H, m, 4-H), 4.34 and 4.67 (each 1 H, d, *J* 7, OHC*H*O), 4.90 (1 H, s, 2-OH), 5.32 (1 H, br. s, 6-H), 6.30 (1 H, d, *J* 2, 4′-H) and 7.44 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −1.5, 0.0, 13.8, 18.1, 19.3, 46.9, 57.8, 61.1, 66.0, 74.5, 76.2, 79.6, 96.2, 110.1, 117.0, 136.8, 140.4, 145.5, 157.6 and 174.8; *m/z* (CI; NH_3) 516 ($M^+ + 18$, 20%), 351 (21), 291 (64) and 90 (100).

Following this procedure, the diol (−)-**56** (180 mg, 0.489 mmol) gave the SEM–ether (−)-**57** (234 mg, 96%), as a viscous oil, $[\alpha]_D$ −73.2 (*c* 1.15, $CHCl_3$).

(1*RS*,2*SR*,3*RS*,4*RS*)-2-Hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohex-5-enoic acid 58

Aqueous sodium hydroxide (0.49 cm^3, 15 M, 7.33 mmol) in ethanol (3 cm^3) was added to a solution of the ethyl ester **57** (365 mg, 0.733 mmol) in ethanol (4 cm^3) at 0 °C. The solution was stirred at 0 °C for 24 h, then diluted with aqueous pH 4 buffer (15 cm^3) and acidified to *ca.* pH 4 by the dropwise addition of 3 M HCl. The mixture was extracted with ethyl acetate and the combined organic phase was washed with brine, dried and concentrated under reduced pressure. Chromatography of the residue (85 : 15 light petroleum–ethyl acetate then 99 : 1 ethyl acetate–acetic acid) gave the *title compound* **58** (325 mg) as a viscous oil. [Found (CI): $M^+ + NH_4$, 488.2502. $C_{22}H_{42}NO_7Si_2$ requires M, 488.2500]; ν_{max} 3407, 1711, 1249, 1195, 1020 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.02 and 0.32 [9 H, s, $Si(CH_3)_3$], 0.78 (2 H, m, CH_2Si), 1.82 (3 H, s, 5-CH_3), 3.20 (1 H, OCH_2OCHH), 3.45 (3 H, s, OCH_3), 3.60 (1 H, m, OCH_2OCHH), 3.91 (1 H, br. s, 1-H), 4.03 (1 H, d, *J* 3, 3-H), 4.27 (1 H, m, 4-H), 4.32 (1 H, d, *J* 7, OHC*H*O), 4.65 (2 H, m, O*H*CHO, 2-OH), 5.32 (1 H, br. s, 6-H), 6.29 (1 H, d, *J* 2, 4′-H) and 7.50 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −1.5, −0.1, 18.0, 19.3, 46.8, 58.0, 65.9, 74.0, 76.1, 79.7, 95.7, 110.3, 116.7, 137.2, 140.6, 145.6, 157.5 and 179.3; *m/z* (CI; NH_3) 488 ($M^+ + 18$, 20%), 225 (42) and 90 (100).

Following this procedure, the ethyl ester (−)-**57** (417 mg, 0.837 mmol) gave the acid (−)-**58** (391 mg), as a colourless foam, $[\alpha]_D$ −57.3 (*c* 1.10, $CHCl_3$).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2-hydroxy-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohex-5-ene-1-carboxylate 59

N,*N*′-Dicyclohexylcarbodiimide (214 mg, 1.04 mmol) in dichloromethane (3 cm^3) was added to the acid **58** (325 mg, 0.691 mmol), 2-trimethylsilylethanol (0.30 cm^3, 2.1 mmol) and 4-*N*,*N*-dimethylaminopyridine (8 mg, 0.07 mmol) in dichloromethane (4 cm^3) and the mixture stirred at room temperature for 18 h then concentrated under reduced pressure. The residue was suspended in ether, filtered and the filtrate concentrated under reduced pressure. Chromatography of the residue (49 : 1 light petroleum–ether) gave the *title compound* **59** (336 mg, 80% from **57**) as a viscous oil. [Found (CI): $M^+ + NH_4$, 588.3192. $C_{27}H_{54}NO_7Si_3$ requires M, 588.3208]; ν_{max} 3452, 1710, 1250, 1170, 1111 and 839 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.02, 0.01 and 0.33 [each 9 H, s, $Si(CH_3)_3$], 0.78 (2 H, m, CH_2Si), 0.92 (2 H, m, $CO_2CH_2CH_2$), 1.84 (3 H, s, 5-CH_3), 3.20 (1 H, m, OCH_2OCHH), 3.45 (3 H, s, OCH_3), 3.60 (1 H, m, OCH_2CHH), 3.85 (1 H, m, 1-H), 4.05 (1 H, d, *J* 3, 3-H), 4.12 (2 H, m, CO_2CH_2), 4.25 (1 H, m, 4-H), 4.33 and 4.67 (each 1 H, d, *J* 7, OHC*H*O), 5.00 (1 H, s, 2-OH), 5.34 (1 H, br. s, 6-H), 6.28 (1 H, d, *J* 2, 4′-H) and 7.49 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −1.4, 0.0, 17.1, 18.0, 19.8, 46.9, 57.9, 63.6, 65.6, 74.2, 77.3, 79.9, 95.6, 110.5, 117.3, 137.0, 140.7, 145.3, 157.6 and 175.1; *m/z* (CI; NH_3) 588 ($M^+ + 18$, 7%), 395 (36), 335 (72) and 90 (100).

Following this procedure, the acid (−)-**58** (391 mg, 0.832 mmol) gave the 2-trimethylsilyl ester (−)-**59** [390 mg, 82% from (−)-**57**], as a viscous oil, $[\alpha]_D$ −60.3 (*c* 0.68, $CHCl_3$).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2-hydroxy-2-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-4-methoxy-5-methyl-3-(2-trimethylsilylethoxy)methoxycyclohex-5-ene-1-carboxylate 6

A solution of the 2-trimethylsilylfuran **59** (330 mg, 0.580 mmol) and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (0.5 mg) in dichloromethane (2 cm^3) and methanol (2 cm^3) was cooled to −78 °C and irradiated with a 250 W sunlamp whilst a stream of oxygen was passed through the solution for 40 min. The reaction mixture was concentrated under reduced pressure and chromatography of the residue (98 : 2 chloroform–methanol) gave the *title compound* **6** (294 mg, 99%) as a colourless foam. [Found (CI): $M^+ + NH_4$, 548.2705. $C_{24}H_{46}NO_9Si_2$ requires M, 548.2711]; ν_{max} 3428, 1767, 1700, 1251, 1192, 1114, 1023, 861 and 838 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.01 and 0.04 [each 9 H, s, $Si(CH_3)_3$], 0.88 [4 H, m, 2 × CH_2Si), 1.80 (3 H, m, 5-CH_3), 3.40–3.70 (5 H, m, OCH_3, OCH_2OCH_2), 3.89 (0.5 H, m, 1-H), 4.00–4.20 (4 H, m, CO_2CH_2, 3-H, 4-H), 4.35 (0.5 H, m, 1-H), 4.55–4.85 (3 H, m, OCH_2O, 2-OH), 5.02 (1 H, br. s, 5′-OH), 5.44 (1 H, br. s, 6-H), 6.01 and 6.05 (each 0.5 H, br. s, 5′-H) and 7.14 and 7.33 (each 0.5 H, d, *J* 1, 4′-H); *m/z* (CI; NH_3) 548 ($M^+ + 18$, 71%), 418 (41), 390 (22), 215 (42) and 90 (100).

Following this procedure, the 2-trimethylsilylfuran (−)-**59** (390 mg, 0.684 mmol) gave the hydroxybutenolide (−)-**6** (356 mg, 98%), as a viscous oil, $[\alpha]_D$ −64.6 (*c* 0.92, $CHCl_3$).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2,3-dihydroxy-4-methoxy-5-methylene-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 61

A suspension of the triol **46** (415 mg, 1.18 mmol) and di-*n*-butyltin oxide (294 mg, 1.18 mmol) in methanol (30 cm^3) was heated under reflux for 24 h. The reaction mixture was cooled, concentrated under reduced pressure and the residue dissolved in benzene (12 cm^3). Tetra-*n*-butylammonium iodide (482 mg, 1.30 mmol) and methyl iodide (740 μl, 11.8 mmol) were added and the resultant solution was heated under reflux for 72 h. The mixture was concentrated under reduced pressure, dissolved in chloroform and washed with saturated sodium thiosulfate solution. The aqueous phase was extracted with chloroform and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue

(4 : 1 light petroleum–ether) gave the *title compound* **61** (415 mg, 96%) as a colourless oil. [Found (EI): M^+, 368.1663. $C_{18}H_{28}O_6Si$ requires M, 368.1665]; ν_{max} 3461, 1707, 1248, 1185, 1072 and 842 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.34 [9 H, s, $Si(CH_3)_3$], 1.14 (3 H, t, *J* 7, CH_2CH_3), 2.07 (1 H, br. s, 3-OH), 2.47 (1 H, dd, *J* 13, 5, 6-H_{eq}), 2.67 (1 H, t, *J* 13, 6-H_{ax}), 3.23 (1 H, dd, *J* 13, 5, 1-H), 3.45 (3 H, s, OCH_3), 3.91 (1 H, d, *J* 3, 3-H), 4.03 (2 H, m, CH_2CH_3), 4.29 (1 H, m, 4-H), 4.58 (1 H, s, 2-OH), 5.07 and 5.14 (each 1 H, m, 5-CH), 6.32 (1 H, d, *J* 2, 4′-H) and 7.50 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) 0.0, 13.9, 32.7, 46.4, 57.2, 60.9, 74.4, 74.6, 79.4, 110.1, 110.4, 139.9, 141.0, 145.6, 156.9 and 176.2; *m/z* (CI; NH_3) 386 ($M^+ + 18$, 4%), 351 (20), 296 (38) and 279 (100).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2-hydroxy-4-methoxy-5-methylene-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 62

2-Trimethylsilylethoxymethyl chloride (217 µl, 1.23 mmol) was added to a solution of the diol **61** (301 mg, 0.822 mmol) and ethyldiisopropylamine (420 µl, 2.47 mmol) in dichloromethane (1.7 cm^3) at room temperature and the mixture was stirred for 24 h. More 2-trimethylsilylethoxymethyl chloride (70 µl, 0.395 mmol) was added, the mixture stirred at room temperature for 24 h then more 2-trimethylsilylethoxymethyl chloride (70 µl, 0.395 mmol) was added and the mixture heated under reflux for 8 h. The mixture was cooled, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 light petroleum–ether) gave the *title compound* **62** (405 mg, 99%) as a viscous oil. [Found (CI): $M^+ + H$, 499.2548. $C_{24}H_{43}O_7Si_2$ requires M, 499.2547]; ν_{max} 3462, 1710, 1249, 1185, 1118, 1020 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.03 and 0.34 [each 9 H, s, $Si(CH_3)_3$], 0.78 (2 H, m, CH_2Si), 1.12 (3 H, t, *J* 7, CH_2CH_3), 2.50 (1 H, dd, *J* 13, 5, 6-H_{eq}), 2.64 (1 H, t, *J* 13, 6-H_{ax}), 3.15 (1 H, m, OCH_2OCHH), 3.24 (1 H, dd, *J* 13, 5, 1-H), 3.45 (3 H, s, OCH_3), 3.56 (1 H, m, OCH_2OCHH), 3.95 (1 H, d, *J* 3, 3-H), 4.02 (2 H, m, CH_2CH_3), 4.17 (1 H, d, *J* 7, OHC*H*O), 4.33 (1 H, m, 4-H), 4.57 (1 H, s, 2-OH), 4.63 (1 H, d, *J* 7, OHC*H*O), 5.04 and 5.10 (each 1 H, m, 5-CH), 6.27 (1 H, d, *J* 2, 4′-H) and 7.45 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −1.5, 0.0, 13.9, 17.9, 33.0, 47.0, 57.4, 60.8, 65.3, 74.8, 79.1, 80.4, 95.3, 108.6, 110.6, 140.2, 141.8, 145.3, 157.1 and 175.8; *m/z* (CI; NH_3) 499 ($M^+ + 1$, 4%), 451 (6), 381 (21), 351 (63), 319 (38), 291 (90) and 90 (100).

(1*RS*,2*SR*,3*RS*,4*RS*)-2-Hydroxy-4-methoxy-5-methylene-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexanoic acid 63

Following the procedure outlined for the preparation of acid **58**, the ethyl ester **62** (450 mg, 0.907 mmol) gave the *title compound* **63** (400 mg) after chromatography of the residue (85 : 15 light petroleum–ethyl acetate then 99 : 1 ethyl acetate–acetic acid) as a viscous oil. [Found (CI): $M^+ + NH_4$, 488.2513. $C_{22}H_{42}NO_7Si_2$ requires M, 488.2500]; ν_{max} 3584, 1712, 1250, 1119, 1022 and 840 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.04 and 0.31 [each 9 H, s, $Si(CH_3)_3$], 0.86 (2 H, m, CH_2Si), 2.52 (2 H, m, 6-H_2), 3.14 (2 H, m, 1-H, OCH_2OCHH), 3.43 (3 H, s, OCH_3), 3.67 (1 H, m, OCH_2OCHH), 3.92 (1 H, d, *J* 3, 3-H), 4.13 (1 H, d, *J* 7, OHC*H*O), 4.29 (1 H, m, 4-H), 4.40 (1 H, br. s, 2-OH), 4.60 (1 H, d, *J* 7, OHC*H*O), 5.03 and 5.10 (each 1 H, m, 5-CH), 6.24 (1 H, br. s, 4′-H) and 7.42 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) −1.5, 0.0, 17.8, 33.1, 46.9, 57.4, 65.4, 74.5, 79.1, 80.2, 95.2, 108.9, 110.5, 118.3, 140.1, 141.4, 145.5, 157.0 and 180.7; *m/z* (CI; NH_3) 488 ($M^+ + 18$, 32%) and 90 (100).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2-hydroxy-4-methoxy-5-methylene-3-(2-trimethylsilylethoxy)methoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 64

A solution of *N*,*N*′-dicyclohexylcarbodiimide (351 mg, 1.70 mmol) in dichloromethane (1.7 cm^3) was added to a solution of the acid **63** (400 mg, 0.851 mmol), 2-trimethylsilylethanol (0.61 cm^3, 4.3 mmol) and 4-*N*,*N*-dimethylaminopyridine (10 mg, 0.09 mmol) in dichloromethane (2.5 cm^3) and the resultant mixture was stirred at room temperature for 3 h then concentrated under reduced pressure. The residue was suspended in ether, filtered and the filtrate concentrated under reduced pressure. Chromatography of the residue (49 : 1 light petroleum–ether) gave the *title compound* **64** (472 mg, 92% from **62**) as a viscous oil. [Found (CI): $M^+ + NH_4$, 588.3214. $C_{27}H_{54}NO_7Si_3$ requires M, 588.3208]; ν_{max} 3455, 1711, 1250, 1169, 1111 and 838 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.02, 0.01 and 0.35 [each 9 H, s, $Si(CH_3)_3$], 0.87 (4 H, m, 2 × CH_2Si), 2.50 (1 H, dd, *J* 13, 5, 6-H_{eq}), 2.63 (1 H, t, *J* 13, 6-H_{ax}), 3.18 (1 H, m, 1-H, OCH_2OCHH), 3.40–3.65 (4 H, m, OCH_3, OCH_2OCHH), 3.96 (1 H, d, *J* 3, 3-H), 4.03 (2 H, m, CO_2CH_2), 4.17 (1 H, d, *J* 7, OHC*H*O), 4.31 (1 H, m, 4-H), 4.62 (1 H, d, *J* 7, OHC*H*O), 4.68 (1 H, s, 2-OH), 5.04 and 5.11 (each 1 H, br. s, 5-CH), 6.35 (1 H, d, *J* 2, 4′-H) and 7.44 (1 H, d, *J* 2, 5′-H); *m/z* (CI; NH_3) 588 ($M^+ + 18$, 1%), 395 (6), 335 (14), 118 (16) and 90 (100).

2-Trimethylsilylethyl (1*RS*,2*SR*,3*RS*,4*RS*)-2-hydroxy-2-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-4-methoxy-5-methylene-(2-trimethylsilylethoxy)methoxycyclohexane-1-carboxylate 65

A solution of the 2-trimethylsilylfuran **64** (450 mg, 0.789 mmol) and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (0.5 mg) in dichloromethane (5 cm^3) and methanol (5 cm^3) was cooled to −78 °C and irradiated with a 250 W sunlamp whilst a stream of oxygen was passed through the solution for 40 min. The reaction mixture was concentrated under reduced pressure then chromatography of the residue (98 : 2 chloroform–methanol) gave the *title compound* **65** (400 mg, 96%, a 1 : 1 mixture of epimers) as a colourless foam. [Found (CI): $M^+ + NH_4$, 548.2696. $C_{24}H_{46}NO_9Si_2$ requires M, 548.2711]; ν_{max} 3417, 1767, 1251, 1191, 1023, 861 and 838 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.01 and 0.06 [each 9 H, s, $Si(CH_3)_3$], 0.75–1.05 (4 H, m, 2 × CH_2Si), 2.45–2.75 (2 H, m, 6-H_2), 3.16 (0.5 H, dd, *J* 13, 5, 1-H), 3.30–3.75 (5.5 H, m, OCH_3, OCH_2OCH_2, 1-H), 3.81 and 3.92 (each 0.5 H, d, *J* 3, 3-H), 4.18 (3 H, m, CO_2CH_2, 4-H), 4.50–4.85 (4 H, m, OCH_2O, 2-OH, 5′-OH), 5.04 (2 H, br. s, 5-CH_2), 6.00 (1 H, s, 5′-H) and 7.07 and 7.32 (each 0.5 H, s, 4′-H); *m/z* (CI; NH_3) 548 ($M^+ + 18$, 5%), 215 (18), 118 (22) and 90 (100).

Preparation and oxidative elimination of ethyl (1*RS*,2*SR*,3*RS*,4*SR*,5*RS*)-4-*tert*-butyldimethylsilyloxy-2,3-dihydroxy-5-methyl-5-phenylselanyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 66

tert-Butyldimethylsilyl trifluoromethanesulfonate (17 µl, 0.076 mmol) was added to a solution of the trihydroxy selenide **43** (26 mg, 0.051 mmol) and 2,6-lutidine (18 µl, 0.15 mmol) in dichloromethane (0.5 cm^3) at 0 °C. The solution was stirred at 0 °C for 1 h, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (49 : 1 light petroleum–ether) gave the *title compound* **66** (26 mg, 82%) as an amorphous glass; ν_{max} 3469, 1711, 1250, 1186, 1110 and 841 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.12 and 0.16 (each 3 H, s, $SiCH_3$), 0.31 [9 H, s, $Si(CH_3)_3$], 0.97 [9 H, s, $SiC(CH_3)_3$], 1.12 (3 H, t, *J* 7, CH_2CH_3), 1.46 (3 H, s, 5-CH_3), 1.68 (1 H, dd, *J* 14, 4, 6-H_{eq}), 1.83 (1 H, dd, *J* 14, 13, 6-H_{ax}), 3.04 (1 H, br. s, 3-OH), 3.73 (2 H, m, 1-H, 3-H), 3.98 (2 H, q, *J* 7, CH_2CH_3), 4.07 (1 H, d, *J* 3, 4-H), 4.38

(1 H, s, 2-OH), 6.45 (1 H, d, *J* 2, 4′-H), 7.33 (3 H, m, ArH), 7.55 (1 H, d, *J* 2, 5′-H) and 7.71 (2 H, m, ArH); δ_C (75 MHz; $CDCl_3$) −4.7, − 4.1, 0.0, 13.9, 18.2, 25.8, 30.8, 35.7, 43.2, 51.2, 60.8, 74.6, 75.8, 77.2, 110.7, 127.0, 128.7, 128.8, 138.9, 140.4, 145.5, 156.7 and 176.0; *m/z* (FAB) 626 (M^+, 2%), 611 (2), 451 (35), 379 (38), 321 (43), 247 (76) and 167 (100).

tert-Butyl hydroperoxide (50 µl, 5 M in dichloromethane, 0.25 mmol) was added to a solution of the selenide **66** (16 mg, 0.026 mmol) in dichloromethane (0.1 cm^3) at room temperature and the mixture was stirred for 1 h. Saturated aqueous sodium sulfite was added and the resultant two-phase mixture stirred vigorously for 30 min. The mixture was partitioned between dichloromethane and water and the aqueous phase extracted with dichloromethane. The combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 light petroleum–ether) gave the alkenes **45** and **47** (9 mg, 75%, ratio 40 : 60) as a viscous oil.

Preparation and oxidative elimination of ethyl (1*RS*,2*SR*,3*RS*,4*SR*,5*RS*)-3,4-bis-(*tert*-butyldimethylsilyloxy)-2-hydroxy-5-methyl-5-phenylselanyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 67

tert-Butyldimethylsilyl trifluoromethanesulfonate (30 µl, 0.13 mmol) was added to a solution of the trihydroxy selenide **43** (27 mg, 0.053 mmol) and 2,6-lutidine (31 µl, 0.26 mmol) in dichloromethane (1 cm^3) at 0 °C. The solution was warmed to room temperature, stirred for 18 h, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (49 : 1 light petroleum–ether) gave the *title compound* **67** (38 mg, 97%) as an amorphous glass; ν_{max} 3475, 1711, 1249, 1183, 1097 and 839 cm^{-1}; δ_H (300 MHz; $CDCl_3$) −0.48, 0.13, 0.17 and 0.18 (each 3 H, s, $SiCH_3$), 0.33 [9 H, s, $Si(CH_3)_3$], 0.90 and 1.07 [each 9 H, s, $SiC(CH_3)_3$], 1.21 (6 H, m, CH_2CH_3, 5-CH_3), 1.90 (2 H, m, 6-H_2), 3.81 (1 H, d, *J* 3, 3-H), 3.98 (1 H, dd, *J* 12, 5, 1-H), 4.07 (2 H, m, CH_2CH_3), 4.25 (2 H, m, 4-H, 2-OH), 6.39 (1 H, d, *J* 2, 4′-H), 7.32 (3 H, m, ArH), 7.48 (1 H, d, *J* 2, 5′-H) and 7.68 (2 H, m, ArH); δ_C (75 MHz; $CDCl_3$) −5.6, −3.8, −1.8, −1.7, −0.1, 14.1, 18.5, 18.8, 26.9, 27.1, 29.9, 38.2, 43.9, 50.0, 60.7, 75.6, 76.5, 79.4, 112.3, 128.2, 128.9, 139.4, 141.3, 145.0, 157.0 and 176.5; *m/z* (FAB) 723 (M^+ − 17, 1%), 683 (4), 525 (6), 493 (3), 451 (35), 215 (35), 167 (85) and 73 (100).

tert-Butyl hydroperoxide (35 µl, 5 M in dichloromethane, 0.18 mmol) was added to a solution of the selenide **67** (13 mg, 0.018 mmol) in dichloromethane (0.1 cm^3) at room temperature and the resultant mixture was stirred for 16 h. Saturated aqueous sodium sulfite was added and the resultant two-phase mixture was stirred vigorously for 30 min. The mixture was partitioned between dichloromethane and water and the aqueous phase extracted with dichloromethane. The combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (98 : 2 light petroleum–ether) gave a mixture of the alkenes **68** and **48** (8 mg, 78%, ratio 35 : 65) as a viscous oil. The endo-isomer **68** was distinguished by the following peaks in the ^1H NMR spectrum of the mixture; δ_H (300 MHz; $CDCl_3$) 1.83 (3 H, s, 5-CH_3), 3.84 (1 H, m, 1-H), 5.34 (1 H, br. s, 6-H) and 6.32 (1 H, d, *J* 2, 4′-H).

Preparation and oxidative elimination of ethyl (1*RS*,2*SR*,3*RS*,4*SR*,5*RS*)-2,3-dihydroxy-5-methyl-5-phenylselanyl-4-trichloroacetoxy-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 69

Trichloroacetyl chloride (65 µl, 0.586 mmol) was added to a solution of the triol **43** (200 mg, 0.391 mmol) and pyridine (95 µl, 1.17 mmol) in THF at 0 °C and the mixture was stirred at 0 °C for 20 min then diluted with ether and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ether and the combined organic phase was washed with brine, dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 light petroleum–ether) gave the *title compound* **69** (226 mg, 88%) as a colourless foam. [Found (FAB): M^+, 656.0080. $C_{25}H_{31}O_7Cl_3SeSi$ requires M, 656.0070]; ν_{max} 3465, 1765, 1710, 1248, 1188, 1129, 1003 and 842 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.34 [9 H, s, $Si(CH_3)_3$], 1.17 (3 H, t, *J* 7, CH_2CH_3), 1.42 (3 H, s, 5-CH_3), 1.93 (1 H, dd, *J* 14, 4, 6-H_{eq}), 2.11 (1 H, dd, *J* 14, 13, 6-H_{ax}), 2.74 (1 H, br. d, *J* 7, 3-OH), 3.85 (1 H, dd, *J* 13, 4, 1-H), 4.05 (3 H, m, CH_2CH_3, 3-H), 4.50 (1 H, s, 2-OH), 5.44 (1 H, d, *J* 3, 4-H), 6.46 (1 H, d, *J* 2, 4′-H), 7.35 (3 H, m, ArH), 7.56 (1 H, d, *J* 2, 5′-H) and 7.72 (2 H, m, ArH); δ_C (75 MHz; $CHCl_3$) −0.2, 14.2, 15.5, 29.4, 36.7, 43.2, 46.8, 61.2, 66.0, 73.8, 74.7, 82.4, 110.3, 126.4, 129.2, 138.9, 146.0, 157.6, 161.3 and 175.4; *m/z* (FAB) 656 (M^+, 11%), 567 (5), 409 (11), 337 (13), 247 (55) and 167 (100).

Following this procedure, the trihydroxy selenide (−)-**43** (578 mg, 1.13 mmol) gave the trichloroacetate (−)-**69** (646 mg, 87%), as a colourless foam, $[\alpha]_D$ −30.3 (*c* 1.19, $CHCl_3$).

3-Chloroperbenzoic acid (0.29 cm^3, 0.25 M in dichloromethane, 0.073 mmol) was added dropwise to the selenide **69** (24 mg, 0.0365 mmol) in dichloromethane (0.4 cm^3) at −78 °C and the mixture was stirred at −78 °C for 20 min then warmed to room temperature over 0.5 h and stirred for 1 h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate and the aqueous phase was extracted with dichloromethane. The combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 light petroleum–ether) gave a mixture of the alkenes **70** and **72** (16 mg, 88%, ratio 40 : 60) as a colourless foam; ν_{max} 3462, 1763, 1712, 1250, 1021 and 844 cm^{-1}; δ_H (300 MHz; $CDCl_3$) endo-isomer **70**: 0.30 [9 H, s, $Si(CH_3)_3$], 1.22 (3 H, t, *J* 7, CH_2CH_3), 1.89 (3 H, br. s, 5-CH_3), 3.95 (1 H, m, 1-H), 4.12 (3 H, m, CH_2CH_3, 3-H), 4.98 (1 H, s, 2-OH), 5.57 (1 H, m, 6-H), 5.94 (1 H, m, 4-H), 6.40 (1 H, d, *J* 2, 4′-H), 7.55 (1 H, d, *J* 2, 5′-H); exo-isomer **72**: 2.48 (1 H, dd, *J* 13, 4, 6-H_{eq}), 2.68 (1 H, t, *J* 13, 6-H_{ax}), 3.20 (1 H, dd, *J* 13, 4 Hz, 1-H), 5.13 and 5.27 (each 1 H, br. s, 5-CH) and 6.30 (1 H, d, *J* 2, 4′-H); *m/z* (CI; NH_3) 516 (M^+ + 18, 2%), 426 (10), 398 (13) and 264 (100).

A solution of *tert*-butyl hydroperoxide (0.82 cm^3, 6 M in benzene, 4.91 mmol) was added to a solution of the selenide **69** (646 mg, 0.982 mmol) in benzene (1 cm^3) at room temperature and the resultant mixture was stirred for 18 h. Saturated sodium sulfite solution was added and the resultant two-phase mixture was stirred vigorously for 30 min, then partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic phase was washed with brine, dried and concentrated under reduced pressure. Chromatography of the residue (9 : 1 light petroleum–ether) gave a mixture of the alkenes **70**, **71** and **72** (453 mg, 92%), ratio 85 : 15 : 5, respectively, as a colourless foam. Partial assignment of the C-3 endo-trichloroacetate **71**: δ_H (300 MHz; $CDCl_3$) 3.83 (1 H, m, 1-H), 5.42 (1 H, m, 6-H), 6.39 (1 H, d, *J* 2, 4′-H) and 7.49 (1 H, d, *J* 2, 5′-H).

Following this procedure, the trichloroacetyl selenide (−)-**69** (1.43 g, 2.17 mmol) gave the alkene (−)-**70** (895 mg, 82%), together with its isomers **71** and **72**, ratio 85 : 15 : 5, respectively, as a colourless foam, $[\alpha]_D$ −83.3 (*c* 0.81, $CHCl_3$).

4-*N*,*N*-Dimethylaminopyridine (22 mg, 0.18 mmol) was added to a mixture of the trichloroacetates **70**, **71** and **72** (895 mg, 1.79 mmol, ratio 80 : 15 : 5, respectively) in ethanol (18 cm^3) at room temperature and the solution was stirred for 16 h. The reaction mixture was concentrated under reduced pressure and the residue chromatographed (2 : 1 light petroleum–ether) to give the cyclohexenetriol **44** (630 mg, 99%), as a white solid, together with a small amount (<5%) of the exo-isomer **46**. All data were in accord with those reported above.

Following this procedure, a mixture of the trichloroacetates (−)-**70**, **71** and **72** (615 mg, 1.23 mmol, ratio 85 : 15 : 5, respectively) gave the triol (−)-**44** (410 mg, 94%), as a white solid, containing less than 5% of the exo-isomer **46**, $[\alpha]_D$ −152.8 (*c* 0.99, $CHCl_3$).

Ethyl (1*RS*,2*SR*,3*RS*,4*RS*)-3,4-carbonyldioxy-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-5-cyclohexene-1-carboxylate 73

Aqueous lithium hydroxide (520 µl, 5% w/v, 1.1 mmol) was added to a solution of the trichloroacetates **70**, **71** and **72** (182 mg, 0.364 mmol, ratio 80 : 15 : 5) in THF at 0 °C. The resultant solution was stirred for 10 min at 0 °C then partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic phase was washed with brine, dried and concentrated under reduced pressure. Chromatography of the residue (3 : 1 light petroleum–ether) gave the *title compound* **73** (65 mg, 47%) as an amorphous glass. [Found (EI): $M^+ + NH_4$, 398.1639. $C_{18}H_{28}NO_7Si$ requires M, 398.1635]; ν_{max} 3451, 1816, 1711, 1249, 1193, 1173, 1094, 1072, 1055, 1018 and 843 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.32 [9 H, s, $Si(CH_3)_3$], 1.16 (3 H, t, *J* 7, CH_2CH_3), 1.95 (3 H, s, 5-CH_3), 3.79 (1 H, m, 1-H), 4.12 (2 H, m, CH_2CH_3), 4.60 (1 H, d, *J* 7, 3-H), 4.89 (1 H, s, 2-OH), 5.08 (1 H, br. d, *J* 7, 4-H), 5.55 (1 H, s, 6-H), 6.40 (1 H, d, *J* 2, 4′-H) and 7.57 (1 H, d, *J* 2, 5′-H); *m*/*z* (CI; NH_3) 398 ($M^+ + 18$, 100%). The endo-allylic alcohol **44** (50 mg, 39%) was also isolated.

Ethyl (1*R*,2*S*,3*S*,4*R*,5*S*)-4-[(*S*)-*O*-acetylmandeloyloxy]-2-hydroxy-3-(4-methoxy)benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate 76

N,*N*′-Dicyclohexylcarbodiimide (3.1 g, 15 mmol) in dichloromethane (14 cm^3) was added slowly to the diol **75** (3.6 g, 7.6 mmol), (*S*)-*O*-acetylmandelic acid (2.92 g, 15 mmol) and 4-*N*,*N*-dimethylaminopyridine (100 mg, 0.8 mmol) in dichloromethane (28 cm^3) at 0 °C. A white suspension formed and the mixture was allowed to warm to ambient temperature and stirred for 16 h before being diluted with ether (60 cm^3). The mixture was filtered through a pad of celite and the filtrate concentrated under reduced pressure. Chromatography of the residue (4 : 1 light petroleum–ether) gave the required ester **76** as the first eluted product and this was recrystallised from light petroleum and ether. Mixed fractions from the column were rechromatographed to give, after final recrystallisation, the *title compound* **76** (1.87 g, 38%), as a white solid, mp 134 °C (ether–light petroleum); $[\alpha]_D$ −12 (*c* 0.95, $CHCl_3$). (Found: C, 64.2; H, 7.0. $C_{35}H_{44}O_{10}Si$ requires C, 64.4; H, 6.8%); ν_{max} 3400, 1745, 1613, 1249, 1209, 1180, 1069, 912 and 844 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.1 [9 H, s, $Si(CH_3)_3$], 0.52 (3 H, d, *J* 5, 5-CH_3), 1.0 (3 H, t, *J* 5, CH_2CH_3), 1.6 (2 H, m, 5-H, 6-H_{eq}), 1.9 (1 H, q, *J* 9, 6-H_{ax}), 2.2 (3 H, s, CH_3CO), 2.7 (1 H, dd, *J* 13, 3, 1-H), 3.42 (1 H, d, *J* 10, 3-H), 3.6 (1 H, s, 2-OH), 3.79 (3 H, s, OCH_3), 3.80–4.05 (3 H, m, CH_2CH_3, Ar*H*CHO), 4.35 (1 H, d, *J* 10, ArHC*H*O), 5.1 (1 H, t, *J* 7.5, 4-H), 6.0 (1 H, s, $PhCHCO_2$), 6.3 (1 H, d, *J* 1, 4′-H), 6.75 and 6.82 (each 2 H, d, *J* 9, ArH), 7.35 (3 H, m, ArH), 7.45 (2 H, m, ArH) and 7.6 (1 H, d, *J* 1, 5′-H); δ_C (75 MHz, $CDCl_3$) 0.0, 13.8, 17.2, 21.0, 30.8, 35.5, 50.5, 55.4, 60.7, 74.5, 75.5, 76.3, 79.2, 84.6, 108.9, 113.5, 127.7, 128.8, 129.3, 130.2, 130.5, 134.4, 138.5, 146.2, 158.4, 159.3, 168.4, 170.1 and 172.7; *m*/*z* (FAB) 653 ($M^+ + 1$, 1%), 441 (4), 250 (4.5) and 121 (100).

Ethyl (1*R*,2*S*,3*R*,5*S*)-3-[(*S*)-*O*-acetylmandeloyloxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 78 and ethyl (1*S*,2*R*,3*S*,5*R*)-3-[(*S*)-*O*-acetylmandeloyloxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 81

N,*N*′-Dicyclohexylcarbodiimide (803 mg, 3.90 mmol) in dichloromethane (2 cm^3) was added to the hydroxyketone **38** (690 mg, 1.95 mmol), (*S*)-(+)-*O*-acetylmandelic acid (382 mg, 2.14 mmol) and 4-*N*,*N*-dimethylaminopyridine (24 mg, 0.195 mmol) in dichloromethane (2 cm^3) at 0 °C. The resultant mixture was warmed to room temperature and stirred for 16 h, then concentrated under reduced pressure. The residue was suspended in ether, filtered and the filtrate concentrated under reduced pressure to give the esters **78** and **81** (1.00 g, 100%) as a colourless foam. Chromatography of the mixture (4 : 1 light petroleum–ether) gave first the *title compound* **81**, as a white solid, mp 110–111 °C (ether–light petroleum); $[\alpha]_D$ +59.3 (*c* 1.19, $CHCl_3$). [Found: C, 61.4; H, 6.5. $C_{27}H_{34}O_9Si$ requires C, 61.11; H, 6.46%. Found (FAB): $M^+ + H$, 531.2056. $C_{27}H_{35}O_9Si$ requires M, 531.2050]; ν_{max} 3460, 1755, 1710, 1250, 1228, 1191, 1096, 1047 and 844 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.35 [9 H, s, $Si(CH_3)_3$], 1.05 (3 H, t, *J* 7, CH_2CH_3), 1.12 (3 H, d, *J* 7, 5-CH_3), 2.12 (5 H, m, 6-H_2, CH_3CO_2), 2.62 (1 H, m, 5-H), 3.41 (1 H, dd, *J* 13, 5, 1-H), 4.02 (2 H, m, CH_2CH_3), 4.38 (1 H, s, 2-OH), 5.40 (1 H, s, 3-H), 5.96 (1 H, s, PhC*H*), 6.18 (1 H, br. s, 4′-H), 7.40 (5 H, m, ArH) and 7.50 (1 H, d, *J* 2, 5′-H); δ_C (75 MHz; $CDCl_3$) 0.0, 13.6, 13.9, 20.8, 32.8, 42.1, 50.0, 61.5, 74.3, 78.6, 81.0, 108.0, 128.1, 128.9, 129.5, 133.4, 135.7, 146.5, 158.1, 167.9, 169.6, 173.4 and 200.1; *m*/*z* (FAB) 531 (MH^+, 7%), 455 (12), 353 (29), 217 (63), 167 (92) and 149 (100). The more polar product was the *title compound* **78**, a white solid, mp 125–126 °C (ether–light petroleum); $[\alpha]_D$ +0.1 (*c* 0.97, $CHCl_3$). [Found: C, 61.5; H, 6.6. $C_{27}H_{34}O_9Si$ requires C, 61.11; H, 6.46%. Found (FAB): $M^+ + H$, 531.2009. $C_{27}H_{35}O_9Si$ requires M, 531.2050]; ν_{max} 3461, 1755, 1739, 1710, 1190, 1049 and 844 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.18 [9 H, s, $Si(CH_3)_3$], 1.03 (3 H, t, *J* 7, CH_2CH_3), 1.19 (3 H, d, *J* 7, 5-CH_3), 2.07 (3 H, s, CH_3CO_2), 2.18 (2 H, m, 6-H_2), 2.68 (1 H, m, 5-H), 3.31 (1 H, dd, *J* 13, 5, 1-H), 4.00 (2 H, m, CH_2CH_3), 4.20 (1 H, s, 2-OH), 5.25 (1 H, s, 3-H), 6.08 (1 H, s, PhC*H*), 6.20 (1 H, br. s, 4′-H), 7.09 (2 H, m, ArH), 7.28 (3 H, m, ArH) and 7.48 (1 H, br. s, 5′-H); δ_C (75 MHz; $CDCl_3$) −0.3, 13.6, 13.7, 20.7, 32.9, 42.2, 50.1, 61.6, 74.3, 78.1, 81.4, 108.0, 128.1, 128.7, 129.0, 133.2, 135.1, 146.6, 157.8, 168.4, 169.6, 173.3 and 199.8; *m*/*z* (FAB) 531 (MH^+, 10%), 217 (35), 167 (71) and 149 (100).

(*S*)-(+)-*O*-Chloroacetylmandelic acid

A mixture of (*S*)-(+)-mandelic acid (10.0 g, 65.8 mmol) and chloroacetyl chloride (26 cm^3, 330 mmol) was stirred at 100 °C for 1 h. The mixture was cooled, diluted with ethyl acetate (300 cm^3) and washed with water (20 × 100 cm^3). The organic phase was dried and concentrated under reduced pressure. Crystallisation of the residue from benzene–hexane gave the *title compound* (11.2 g, 75%) as a white solid, mp 102–103 °C; $[\alpha]_D$ +133.9 (*c* 2.08, acetone). [Found (CI): $M^+ + NH_4$, 246.0532. $C_{10}H_{13}NO_4{}^{35}Cl$ requires M, 246.0533]; ν_{max} 3037 (br), 1738, 1166, 1081 and 1027 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 4.20 (2 H, m, CH_2Cl), 6.02 (1 H, s, PhC*H*) and 7.45 (5 H, m, ArH); δ_C (50 MHz; $CDCl_3$) 41.0, 75.7, 128.2, 129.5, 130.4, 132.8, 167.4 and 174.4; *m*/*z* (CI; NH_3) 246 ($MNH_4{}^+$, 100%), 212 (83) and 154 (58).

Ethyl (1*R*,2*S*,3*R*,5*S*)-3-[(*S*)-*O*-(chloroacetyl)mandeloyloxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 80 and ethyl (1*S*,2*R*,3*S*,5*R*)-3-[(*S*)-*O*-(chloroacetyl)-mandeloyloxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate 83

N,*N*′-Dicyclohexylcarbodiimide (4.86 g, 23.6 mmol) in dichloromethane (100 cm^3) was added to the hydroxyketone **38** (7.60 g, 21.5 mmol), 4-*N*,*N*-dimethylaminopyridine (260 mg, 2.15 mmol) and (*S*)-(+)-*O*-(chloroacetyl)mandelic acid (5.40 g, 23.6 mmol) in dichloromethane (100 cm^3) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h then diluted with ether and filtered. The filtrate was concentrated under reduced pressure to give a mixture of the esters **80** and **83** (12.0 g, 100%). Crystallisation from ethyl acetate–hexane gave the *title compound* **80** (5.72 g, 47%) as a white solid, mp 116–117 °C; $[\alpha]_D$ −1.8 (*c* 1.01, $CHCl_3$). [Found: C, 57.6; H, 6.05;

Cl, 6.4. $C_{27}H_{33}O_9ClSi$ requires C, 57.39; H, 5.89; Cl, 6.27%. Found (CI): $M^+ + NH_4$, 582.1922. $C_{27}H_{37}NO_9{}^{35}ClSi$ requires M, 582.1926]; ν_{max} 3463, 1756, 1737, 1710, 1250, 1191, 1159, 1026 and 844 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.15 [9 H, s, $Si(CH_3)_3$], 1.03 (3 H, t, *J* 7, CH_2CH_3), 1.18 (3 H, d, *J* 7, 5-CH_3), 2.12 (2 H, m, 6-H_2), 2.68 (1 H, m, 5-H), 3.32 (1 H, dd, *J* 13, 5, 1-H), 4.01 (4 H, m, CH_2CH_3, CH_2Cl), 4.22 (1 H, s, 2-OH), 5.27 (1 H, s, 3-H), 6.17 (1 H, s, PhC*H*), 6.21 (1 H, d, *J* 2, 4′-H), 7.07 (2 H, m, ArH), 7.29 (3 H, m, ArH) and 7.49 (1 H, br. s, 5′-H); δ_C (75 MHz; $CDCl_3$) −0.4, 13.6, 13.7, 32.8, 40.4, 42.1, 50.0, 61.4, 75.3, 78.3, 81.7, 107.8, 127.9, 128.7, 129.4, 132.5, 135.5, 146.6, 158.0, 166.2, 167.6, 173.4 and 199.6; *m*/*z* (CI; NH_3) 582 (MNH_4^+, 14%), 356 (28), 321 (53), 249 (61), 225 (82) and 100 (100). Concentration of the filtrate under reduced pressure and chromatography of the residue (4 : 1 light petroleum–ether) gave the *title compound* **83** as an amorphous glass, $[\alpha]_D$ +46.8 (*c* 1.18, $CHCl_3$). [Found (CI): $M^+ + NH_4$, 582.1919. $C_{27}H_{37}NO_9{}^{35}ClSi$ requires M, 582.1926]; ν_{max} 3463, 1757, 1738, 1710, 1251, 1190, 1023 and 845 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.30 [9 H, s, $Si(CH_3)_3$], 1.09 (3 H, t, *J* 7, CH_2CH_3), 1.11 (3 H, d, *J* 7, 5-CH_3), 2.12 (2 H, m, 6-H_2), 2.64 (1 H, m, 5-H), 3.35 (1 H, dd, *J* 13, 5, 1-H), 3.85–4.25 (4 H, m, CH_2CH_3, CH_2Cl), 4.32 (1 H, s, 2-OH), 5.34 (1 H, s, 3-H), 6.02 (1 H, s, PhC*H*), 6.22 (1 H, br. s, 4′-H), 7.32 (5 H, m, ArH) and 7.55 (1 H, br. s, 5′-H); δ_C (75 MHz; $CDCl_3$) −0.1, 13.7, 14.3, 32.9, 40.7, 42.2, 50.1, 61.6, 75.5, 78.4, 81.5, 108.0, 128.3, 128.9, 129.4, 132.8, 135.7, 147.0, 158.2, 166.7, 167.5, 173.8 and 200.0; *m*/*z* (CI; NH_3) 582 (MNH_4^+, 100%) and 548 (31).

Ethyl (1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dihydroxy-3-(4-methoxy)benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexane-1-carboxylate (−)-75

Aqueous lithium hydroxide (10 cm^3, 10% w/v) was added to the acetylmandelate **76** (4.00 g, 6.13 mmol) in ethanol (400 cm^3) at room temperature and the resultant mixture stirred for 48 h. The mixture was diluted with ethyl acetate and washed with water then brine. The organic phase was concentrated under reduced pressure and the residue was chromatographed (2 : 1 light petroleum–ether) to give the diol (−)-**75** (2.83 g, 97%) as a white solid, mp 139–140 °C; $[\alpha]_D$ −95.6 (*c* 0.98, $CHCl_3$). All other data were in accord with those of the racemate.[4]

Ethyl (1*R*,2*S*,3*R*,5*S*)-2-hydroxy-3-(4-methoxy)benzyloxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate (−)-22

Dimethyl sulfoxide (0.935 cm^3, 13.27 mmol) in dichloromethane (25 cm^3) was added to oxalyl chloride (0.632 cm^3, 7.31 mmol) in dichloromethane (25 cm^3) at −78 °C and the mixture stirred for 10 min before the alcohol (−)-**75** (3.16 g, 6.64 mmol) in dichloromethane (25 cm^3) was added. The solution was stirred at −78 °C for 30 min, then triethylamine (4.55 cm^3, 33.12 mmol) was added and the mixture warmed to room temperature, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was dried and concentrated under reduced pressure. Chromatography of the residue (2 : 1 light petroleum–ether) gave the hydroxyketone[4] (−)-**22** (3.10 g, 90%) as a white solid, $[\alpha]_D$ −85.1 (*c* 0.94, $CHCl_3$); mp 125–126 °C. All other data were in accord with those of the racemate.[4]

Ethyl (1*R*,2*S*,3*R*,5*S*)-2,3-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)-4-oxocyclohexane-1-carboxylate (−)-38

Potassium carbonate (1.49 g, 10.7 mmol) was added to a solution of the chloroacetylmandelate **80** (3.00 g, 5.33 mol) in ethanol (25 cm^3) at 0 °C. The mixture was stirred at 0 °C for 1 h, diluted with ethyl acetate and washed with water. The aqueous phase was extracted with ethyl acetate and the combined organic phase was washed with brine, dried and concentrated under reduced pressure. Chromatography of the residue (2 : 1 light petroleum–ether) gave the hydroxyketone (−)-**38** (1.74 g, 92%) as a white solid. $[\alpha]_D$ −13.1 (*c* 1.10, $CHCl_3$). All other data were in accord with the racemate.[4]

Deprotection of the cyclohexanone (−)-**22** (3.10 g, 6.51 mmol) following the procedure outlined for the racemic compound,[4] gave the dihydroxyketone (−)-**38** (2.03 g, 88%), as a white solid, $[\alpha]_D$ −12.7 (*c* 1.10, $CHCl_3$).

Methyl (6*R*,2*Z*,4*EZ*,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*)-2-hydroxy-4-methoxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)-3-(2-trimethylsilylethoxy)methoxycyclohex-5-en-2-yl]-6,8-dimethyldeca-2,4,8-trienoate 84

n-Butyllithium (1.6 M in hexane, 0.31 cm^3, 4.98 mmol) was added to hexamethyldisilazane (0.096 cm^3, 4.59 mmol) in tetrahydrofuran (0.86 cm^3) at 0 °C. After 30 min the solution was cooled to −78 °C and added to the hydroxybutenolide (−)-**6** (69 mg, 1.31 mmol) and the phosphonium salt **2** (124 mg, 1.48 mmol) in tetrahydrofuran (2.5 cm^3) at −78 °C. The reaction mixture was warmed to −10 °C over 1 h and left at this temperature for 2 h. Saturated aqueous ammonium chloride (0.5 cm^3) and ethyl acetate (7 cm^3) were added, and the mixture acidified with aqueous hydrochloric acid (1.2 M) to pH 4. The aqueous layer was extracted with ethyl acetate (6 × 10 cm^3), and the combined organic phases were washed with brine (4 cm^3) and dried ($MgSO_4$). After concentration under reduced pressure, the residue was dissolved in ether (3 cm^3) and an excess of ethereal diazomethane was added over a period of 20 min before glacial acetic acid was added until no further gas evolution was observed. Ether (15 cm^3) was added and the solution washed with saturated aqueous sodium hydrogen carbonate (3 cm^3). The aqueous phase was extracted with ether (2 × 5 cm^3) and the combined organic phases were dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (7 : 1 light petroleum–ether) gave the *title compound* **84** (61 mg, 48%), a *ca.* 65 : 35 mixture of the (4*Z*)- and (4*E*)-isomers, as a viscous oil. [Found (CI): $M^+ + NH_4$, 996.6373. $C_{52}H_{98}NO_{11}Si_3$ requires M, 996.6448]; ν_{max} 3369, 1726, 1457, 1251, 1168, 1072, 861 and 837 cm^{-1}; δ_H (300 MHz, $CDCl_3$) (4*Z*)-isomer 0.02 and 0.07 [each 9 H, s, $Si(CH_3)_3$], 0.09 [6 H, s, $Si(CH_3)_2$], 0.81 (3 H, d, *J* 6, 3′-CH_3), 0.85 (3 H, d, *J* 7, 2′-$CHCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 0.96–1.06 (13 H, m, 6-CH_3, 4′-H_2, 2′-$CHCH_3$, 2 × CH_2Si), 1.19–1.36 (3 H, m, 3′-H, 5′-H_2), 1.46–1.70 (2 H, m, 9′-H_{ax}, 11′-H_{ax}), 1.61 (3 H, s, 8-CH_3), 1.79–1.91 (2 H, m, 9′-H_{eq}, 11′-H_{eq}), 1.82 (3 H, s, 5″-CH_3), 1.99–2.30 (4 H, m, 7-H_2 and 10-H_2), 2.84 (1 H, m, 6-H), 3.06 (1 H, br. d, *J* 9, 2′-H), 3.42–3.59 (2 H, m, 1″-H, $OCHHCH_2Si$), 3.51 (3 H, s, OCH_3), 3.81–3.92 (2 H, m, 8′-H, $OCHHCH_2Si$), 3.84 (3 H, s, CO_2CH_3), 4.11–4.37 (5 H, m, 10′-H, 3″-H, 4″-H, CO_2CH_2), 4.72 and 4.77 (each 1 H, d, *J* 7, OHC*H*O), 5.04 (1 H, s, 2″-OH), 5.25–5.32 (2 H, m, 9-H, 6″-H), 5.48 (1 H, t, *J* 11, 5-H), 5.97 (1 H, t, *J* 11, 4-H) and 6.65 (1 H, d, *J* 11, 3-H); (4*E*)-isomer 5.86 (1 H, dd, *J* 15, 7, 5-H), 6.15 (1 H, dd, *J* 15, 11, 4-H) and 6.38 (1 H, d, *J* 11, 3-H); *m*/*z* (CI/NH_3) 996 (M^+ + 18, 18%), 961 (M^+ − 17, 5), 878 (5), 462 (11), 399 (15) and 295 (100).

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*)-2-hydroxy-4-methoxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)-3-(2-trimethylsilylethoxy)methoxycyclohex-5-en-2-yl]-6,8-dimethyldeca-2,4,8-trienoate (4*E*)-84

To the ester **84** (75 mg, 0.768 mmol) in degassed benzene (2.2 cm^3) was added iodine (0.2 M in benzene, 0.02 cm^3, 0.0384 mmol) and potassium carbonate (50 mg, 3.69 mmol). The suspension was stirred in daylight for 6.5 h then diluted

with ether (10 cm^3) and washed with saturated aqueous sodium thiosulfate (2 cm^3). The aqueous phase was extracted with ether (5 × 5 cm^3) and the combined organic phases were dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (9 : 1 light petroleum–ether) gave the *title compound* (4*E*)-**84** (71 mg, 95%) as a viscous oil. [Found (CI): $M^+ + NH_4$, 996.6387. $C_{52}H_{98}NO_{11}Si_3$ requires M, 996.6448]; $[a]_D^{21}$ +10.6 (*c* 1.28, $CHCl_3$); ν_{max} 3439, 1722, 1643, 1384, 1098 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 and 0.04 [each 9 H, s, $Si(CH_3)_3$], 0.08 [6 H, s, $Si(CH_3)_2$], 0.81 (3 H, d, *J* 6, 3′-CH_3), 0.85 (3 H, d, *J* 7, 2′-CHCH_3), 0.93 [9 H, s, $SiC(CH_3)_3$], 0.94–1.07 (13 H, m, 6-CH_3, 4′-H_2, 2′-C*H*C*H*$_3$, 2 × CH_2Si), 1.19–1.37 (3 H, m, 3′-H and 5′-H_2), 1.46–1.58 (2 H, m, 9′-H_{ax}, 11′-H_{ax}), 1.62 (3 H, s, 8-CH_3), 1.82 (3 H, s, 5″-CH_3), 1.82–1.91 (2 H, m, 9′-H_{eq}, 11′-H_{eq}), 2.12–2.32 (4 H, m, 7-H_2 and 10-H_2), 2.42 (1 H, m, 6-H), 3.07 (1 H, m, 2′-H), 3.45–3.59 (2 H, m, 1″-H, OC*H*HCH_2Si), 3.50 (3 H, s, OCH_3), 3.79–3.86 (2 H, m, 8′-H, OCH*H*CH_2Si), 3.85 (3 H, s, CO_2CH_3), 4.12–4.35 (5 H, m, 10′-H, 3″-H, 4″-H, CO_2CH_2), 4.72 and 4.77 (each 1 H, d, *J* 7, OHC*H*O), 4.97 (1 H, s, 2″-OH), 5.25 (1 H, m, 9-H), 5.33 (1 H, m, 6″-H), 5.86 (1 H, dd, *J* 15, 7, 5-H), 6.15 (1 H, dd, *J* 15, 11, 4-H) and 6.38 (1 H, d, *J* 11, 3-H); δ_C (50 MHz, $CDCl_3$) −4.2, −1.0, −0.9, 14.6, 16.7, 17.8, 18.0, 18.7, 18.8, 19.2, 19.8, 21.4, 24.3, 26.5, 28.7, 28.8, 32.1, 34.9, 35.2, 36.2, 41.8, 45.6, 46.0, 47.4, 52.2, 58.7, 64.2, 66.3, 68.6, 68.7, 74.9, 76.5, 76.9, 78.1, 78.4, 79.9, 80.0, 96.6, 96.7, 97.7, 117.5, 123.6, 124.5, 133.4, 134.9, 135.9, 137.0, 147.4, 169.1 and 175.3; *m/z* (CI/NH_3) 996 (M^+ + 18, 22%), 979 (M^+ + 1, 3), 829 (7), 411 (29) and 90 (100).

(l*R*,2*S*,3*R*,4*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-trimethylsilylethoxy)-methoxycyclohex-5-ene-1-carboxylic acid 85

Tetra-*n*-butylammonium fluoride (1 M in tetrahydrofuran, 0.28 cm^3, 2.82 mmol) was added to the ester (4*E*)-**84** (55 mg, 0.564 mmol) in tetrahydrofuran (2.6 cm^3) at room temperature. After 13 h, aqueous hydrogen chloride (1.2 M, 0.3 cm^3) and saturated aqueous ammonium chloride (2 cm^3) were added. The mixture was diluted with ethyl acetate (10 cm^3), the aqueous phase was extracted with chloroform (5 × 7 cm^3) and the combined organic phases were dried ($MgSO_4$). After concentration under reduced pressure, chromatography (50 : 50 : 1 : 1 light petroleum–ether–methanol–acetic acid) of the residue gave the *title compound* **85** (40 mg, 93%) as a viscous oil. [Found (CI): M^+ − OH, 747.4517. $C_{41}H_{67}O_{10}Si$ requires M, 747.4504]; ν_{max} 3419, 1721, 1435, 1250, 1198, 1121, 1099, 1075, 1057, 1023, 862 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.02 [9 H, s, $Si(CH_3)_3$], 0.82 (3 H, d, *J* 6, 3″-CH_3), 0.85 (3 H, d, *J* 7, 2″-CHC*H*$_3$), 0.95–1.10 (11 H, m, 5′-CH_3, 4″-H_2, CH_2Si, 2″-C*H*C*H*$_3$), 1.28–1.36 (3 H, m, 3″-H, 5″-H_2), 1.48–1.57 (2 H, m, 9″-H_{ax}, 11″-H_{ax}), 1.64 (3 H, s, 7′-CH_3), 1.83 (3 H, s, 5-CH_3), 1.95–2.05 (2 H, m, 9″-H_{eq}, 11″-H_{eq}), 2.24–2.35 (4 H, m, 6′-H_2, 9′-H_2), 2.55 (1 H, m, 5′-H), 3.07 (1 H, m, 2″-H), 3.45–3.52 (2 H, m, 8″-H, OC*H*HCH_2Si), 3.50 (3 H, s, OCH_3), 3.68 (2 H, m, 10″-H, 10″-OH), 3.88–3.96 (2 H, m, 1-H, OCH*H*CH_2Si), 3.91 (3 H, s, CO_2CH_3), 4.14–4.32 (3 H, m, 3-H, 4-H, 2-OH), 4.73 (2 H, s, OCH_2O), 5.08 (1 H, m, 8′-H), 5.34 (1 H, br. s, 6-H), 6.03 (1 H, dd, *J* 15, 7, 4′-H), 6.38 (1 H, dd, *J* 15, 11, 3′-H) and 6.60 (1 H, d, *J* 11, 2′-H); δ_C (50 MHz, $CDCl_3$) −0.9, 14.6, 16.6, 17.9, 18.5, 19.7, 19.9, 21.3, 28.7, 28.7, 30.2, 30.2, 32.0, 32.1, 34.4, 34.8, 36.2, 40.1, 45.2, 46.0, 47.7, 52.6, 58.9, 66.1, 66.3, 66.4, 68.4, 74.2, 76.9, 77.1, 78.1, 78.6, 80.3, 96.3, 97.8, 117.8, 122.8, 124.7, 131.9, 135.3, 136.7, 137.2, 149.2, 170.1, 176.2 and 258.6; *m/z* (CI/NH_3) 765 (M^+ + 1, 7%), 747 (M^+ − 17, 19), 729 (22), 647 (50), 629 (74) and 90 (100).

Methyl (2*Z*,4*E*,8*E*)-10-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-hydroxy-2-(2-methyl)propyl-3-methyl-1,7-dioxaspiro-[5.5]undec-8-yl}-2-[(5*R*,6*S*)-5-methoxy-4-methyl-6-(2-trimethylsilylethoxy)-methoxycyclohexa-1,3-dien-1-yl]-6,8-dimethyldeca-2,4,8-trienoate 86

Triethylamine (0.1 M in xylene, 0.18 cm^3, 0.18 mmol) and 2,4,6-trichlorobenzoyl chloride (0.1 M in xylene, 0.15 cm^3, 0.151 mmol) in xylene (1.3 cm^3) were added to the acid **85** (11 mg, 0.151 mmol) at room temperature. After 44 h, 4-*N*,*N*-dimethylaminopyridine (4.7 mg, 0.341 mmol) in xylene (1.3 cm^3) was added and the reaction mixture was stirred for 2 h. After concentration under reduced pressure, chromatography (2 : 1 light petroleum–ether) of the residue afforded the *title compound* **86** (7.5 mg, 70%) as a viscous oil. [Found (FAB): M^+ + Na-H, 724.4316. $C_{40}H_{65}O_8SiNa$ requires M, 724.4346]; ν_{max} 3399, 1728, 1632, 1454, 1383, 1249, 1196, 1117, 1062, 1011, 980, 860 and 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 [9 H, s, $Si(CH_3)_3$], 0.82 (3 H, d, *J* 6, 3′-CH_3), 0.85 (3 H, d, *J* 7, 2′-CHC*H*$_3$), 0.89–1.12 (11 H, m, 6-CH_3, 4′-H_2, 2′-C*H*C*H*$_3$, CH_2Si), 1.25–1.32 (3 H, m, 3′-H, 5′-H_2), 1.48–1.70 (2 H, m, 9′-H_{ax} 11′-H_{ax}), 1.60 (3 H, s, 8-CH_3), 1.87–2.11 (4 H, m, 10-H_2, 9′-H_{eq}, 11′-H_{eq}), 1.96 (3 H, s, 4″-CH_3), 2.25 (2 H, m, 7-H_2), 2.50 (1 H, m, 6-H), 3.08 (1 H, m, 2′-H), 3.51–3.61 (2 H, m, OC*H*$_2$CH_2Si), 3.54 (3 H, s, OCH_3), 3.68 (1 H, m, 8′-H), 3.85 (3 H, s, CO_2CH_3), 3.99–4.09 (2 H, m, 10′-H, 6″-H), 4.59 (1 H, d, *J* 5, 5″-H), 4.71 and 4.86 (each 1 H, d, *J* 7, OHC*H*O), 5.19 (1 H, m, 9-H), 5.82–5.95 (3 H, m, 5-H, 2″-H, 3″-H), 6.35 (1 H, dd, *J* 15, 11, 4-H) and 6.67 (1 H, d, *J* 11, 3-H); *m/z* (CI/NH_3) 720 (M^+ + 18, 4%), 703 (M^+ + 1, 5), 555 (100) and 537 (92)

The acid **85** (11 mg, 0.146 mmol) and 4-dimethylaminopyridine (0.1 M in dichloromethane, 0.015 cm^3, 0.0146 mmol) in dichloromethane (2.3 cm^3) were added to dicyclohexylcarbodiimide (0.1 M in dichloromethane, 0.22 cm^3, 0.219 mmol) in dichloromethane (2.0 cm^3) at 0 °C *via* a syringe pump over 6 h and the reaction mixture then stirred at 5 °C for 63 h. After concentration under reduced pressure, the residue was dissolved in ether (3 cm^3) and filtered through silica gel. The combined filtrate was then concentrated under reduced pressure and chromatography (1 : 1 light petroleum–ether) of the residue gave the cyclohexadiene **86** (2 mg, 19%) as a viscous oil. Further elution with light petroleum–ether–methanol–acetic acid 50 : 50 : 1 : 1 gave recovered acid **85** (1 mg).

Methyl (6*R*,2*Z*,4*EZ*,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*)-2,3-dihydroxy-4-methoxy-5-methyl-1-(2-trimethylsilylethoxycarbonyl)-cyclohex-5-en-2-yl]-6,8-dimethyldeca-2,4,8-trienoate 90

Magnesium bromide diethyl etherate (65 mg, 2.53 mmol), potassium carbonate (31 mg, 2.21 mmol) and *n*-butanethiol (0.027 cm^3, 2.53 mmol) were added to the 2-trimethylsilylethoxymethyl ether **84** (31 mg, 0.316 mol) in ether (0.9 cm^3) at room temperature. After 2.5 h, water (1.4 cm^3), aqueous hydrogen chloride (1.2 M, 0.2 cm^3) and ether (22 cm^3) were added, the aqueous phase was extracted with ether (6 × 20 cm^3) and the combined organic phases were dried ($MgSO_4$). After concentration under reduced pressure, chromatography (8 : 1 then 2 : 1 light petroleum–ether) of the residue gave the *title compound* **90** (21 mg, 78%), a *ca.* 2 : 1 mixture of the (4*Z*)- and (4*E*)-isomers, as a viscous oil. [Found (CI): $M^+ + NH_4$, 866.5624. $C_{46}H_{84}NO_{10}Si_2$ requires M, 866.5634]; ν_{max} 3369, 1726, 1457, 1168, 1072 and 837 cm^{-1}; δ_H (300 MHz, $CDCl_3$) (4*Z*)-isomer 0.08 [9 H, s, $Si(CH_3)_3$], 0.10 [6 H, s, $Si(CH_3)_2$], 0.81 (3 H, d, *J* 6, 3′-CH_3), 0.85 (3 H, d, *J* 7, 2′-CHC*H*$_3$), 0.93 [9 H, s, $SiC(CH_3)_3$], 0.96–1.07 (11 H, m, 6-CH_3, 4′-H_2, 2′-C*H*C*H*$_3$, CH_2Si), 1.19–1.38 (3 H, m, 3′-H, 5′-H_2), 1.47–1.65 (2 H, m, 9′-H_{ax}, 11′-H_{ax}), 1.63 (3 H, s, 8-CH_3), 1.81 (3 H, s, 5″-CH_3), 1.86–1.92 (2 H, m, 9′-H_{eq}, 11′-H_{eq}), 1.98–2.28 (4 H, m,

7-H_2, 10-H_2), 2.66 (1 H, br. s, 3″-OH), 2.90 (1 H, m, 6-H), 3.07 (1 H, d, *J* 9, 2′-H), 3.50 (3 H, s, OCH_3), 3.53 (1 H, m, 1″-H), 3.82 (3 H, s, CO_2CH_3), 3.83 (1 H, m, 8′-H), 3.97–4.31 (5 H, m, 10′-H, 3″-H, 4″-H, CO_2CH_2), 4.96 (1 H, s, 2″-OH), 5.26 (1 H, m, 9-H), 5.36 (1 H, m, 6″-H), 5.49 (1 H, d, *J* 10, 5-H), 6.03 (1 H, t, *J* 10, 4-H) and 6.91 (1 H, d, *J* 11, 3-H); (4*E*)-isomer 5.92 (1 H, dd, *J* 15, 7, 5-H), 6.19 (1 H, dd, *J* 15, 11, 4-H) and 6.62 (1 H, d, *J* 10, 3-H); *m*/*z* (CI/NH_3) 866 (M^+ + 18, 28), 849 (M^+, 17), 831 (5) and 717 (100).

2-Trimethylsilylethyl (1*S*,2*R*,5*R*,6*R*,9*Z*)-9-[(4*R*,2*Z*,6*E*)-8-{(2*R*,3*S*,6*R*,8*R*,10*S*)-10-*tert*-butyldimethylsilyloxy-3-methyl-2-(1-methylethyl)-l,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]non-3-ene-2-carboxylate 91

Silica gel (350 mg) and powdered molecular sieves 4 Å (1 mg) were added to the hydroxyester **90** (12 mg, 0.147 mmol) in chloroform (0.7 cm^3) at room temperature and the suspension stirred for 29 h before being concentrated under reduced pressure. Chromatography (2 : 1 light petroleum–ether) of the residue gave the *title compound* **91** (11 mg, 98%), mainly the (2′*Z*)-isomers, as a viscous oil. [Found (CI): M^+ + H, 817.5111. $C_{45}H_{77}O_9Si_2$ requires M, 817.5106]; ν_{max} 3421, 1754, 1639, 1459, 1252, 1187, 1122, 1069 and 837 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.10 [9 H, s, $Si(CH_3)_3$], 0.11 [6 H, s, $Si(CH_3)_2$], 0.81 (3 H, d, *J* 6, 3″-CH_3), 0.85 (3 H, d, *J* 7, 2″-CHCH_3) 0.93 [9 H, s, $SiC(CH_3)_3$], 0.97–1.09 (11 H, m, 4′-CH_3, 4″-H_2, 2″-C*H*CH_3, CH_2Si), 1.30 (3 H, m, 3″-H, 5″-H_2), 1.48–1.63 (2 H, m, 9″-H_{ax}, 11″-H_{ax}), 1.59 (3 H, s, 6′-CH_3), 1.81–1.92 (2 H, m, 9″-H_{eq}, 11″-H_{eq}), 1.90 (3 H, s, 4-CH_3), 2.05–2.21 (4 H, m, 5′-H_2, 8′-H_2), 2.98 (1 H, m, 4′-H), 3.06 (1 H, d, *J* 9, 2″-H), 3.46 (3 H, s, OCH_3), 3.53 (2 H, m, 8″-H, 1-OH), 3.64 (1 H, m, 2-H), 4.15 (2 H, m, CO_2CH_2), 4.32 (2 H, m, 5-H, 10″-H), 4.70 (1 H, d, *J* 3, 6-H), 5.28 (1 H, m, 7′-H), 5.71 (1 H, m, 3-H), 5.85 (1 H, m, 3′-H) and 7.38 (2 H, m, 1′-H, 2′-H); *m*/*z* (CI/NH_3) 817 (M^+ + 1, 0.5%), 685 (1), 667 (1) and 215 (100).

2-Trimethylsilylethyl (1*S*,2*R*,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)-l,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]non-3-ene-2-carboxylate (2′*E*)-91

Iodine (0.2 M in benzene, 0.01 cm^3, 0.002 mmol) and potassium carbonate (25 mg, 1.86 mmol) were added to the (2′*Z*)-alkene **91** (32 mg, 0.388 mmol) in degassed benzene (1.1 cm^3) at room temperature and the mixture stirred in the presence of daylight for 6.5 h before being diluted with ether (20 cm^3) and washed with saturated aqueous sodium thiosulfate (1.2 cm^3). The aqueous phase was extracted with ether (3 × 10 cm^3) and the combined organic phases were dried ($MgSO_4$). After concentration under reduced pressure, chromatography (5 : 1 light petroleum–ether) of the residue gave the *title compound* (2′*E*)-**91** (29 mg, 91%), as a viscous oil. [Found (EI): M^+ + H, 817.5112. $C_{45}H_{77}O_9Si_2$ requires M, 817.5106]; $[\alpha]_D^{20}$ −10.6 (*c* 0.34, $CHCl_3$); ν_{max} 3437, 1751, 1734, 1641, 1383, 1251, 1121, 1068, 1009, 983 and 837 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.09 [6 H, s, $Si(CH_3)_2$], 0.10 [9 H, s, $Si(CH_3)_3$], 0.81 (3 H, d, *J* 6, 3″-CH_3), 0.85 (3 H, d, *J* 7, 2″-CHCH_3), 0.93 [9 H, s, $SiC(CH_3)_3$], 0.95–1.11 (11 H, m, 4′-CH_3, 4″-H_2, 2″-C*H*CH_3, CH_2Si), 1.19–1.37 (3 H, m, 3″-H, 5″-H_2), 1.45–1.60 (2 H, m, 9″-H_{ax}, 11″-H_{ax}), 1.63 (3 H, s, 6′-CH_3), 1.81–1.95 (2 H, m, 9″-H_{eq}, 11″-H_{eq}), 1.89 (3 H, s, 4-CH_3), 2.12–2.30 (4 H, m, 5′-H_2, 8′-H_2), 2.58 (1 H, m, 4′-H), 3.07 (1 H, m, 2″-H), 3.47 (3 H, s, OCH_3), 3.52–3.65 (2 H, m, 2-H, 8″-H), 4.10–4.34 (5 H, m, 1-OH, 5-H, 10″-H, CO_2CH_2), 4.75 (1 H, d, *J* 4, 6-H), 5.27 (1 H, m, 7′-H), 5.66 (1 H, m, 3-H), 6.16 (1 H, dd, *J* 15, 7, 3′-H), 6.93 (1 H, d, *J* 11, 1′-H) and 7.54 (1 H, dd, *J* 15, 11, 2′-H); *m*/*z* (CI/NH_3) 817 (M^+ + 1, 66%), 799 (21), 685 (100), 667 (72) and 215 (95).

(1*R*,2*S*,3*R*,4*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]-2,3-dihydroxy-4-methoxy-5-methylcyclohex-5-ene-1-carboxylic acid 93

Following the procedure outlined for the preparation of the diol **90**, the trimethylsilylethoxymethyl ether **85** (40 mg, 0.523 mmol), magnesium bromide diethyl etherate (108 mg, 4.18 mmol), potassium carbonate (50 mg, 3.66 mmol) and *n*-butanethiol (0.022 cm^3, 2.09 mmol) in ether (1.5 cm^3), after chromatography (25 : 25 : 2 : 1 light petroleum–ether–methanol–acetic acid) gave the *title compound* **93** (30 mg, 90%) as a viscous oil. [Found (CI): M^+ − OH, 617.3689. $C_{35}H_{53}O_9$ requires M, 617.3690]; $[\alpha]_D^{22}$ +15.7 (*c* 0.9, $CHCl_3$); ν_{max} 3421, 1715, 1454, 1384, 1198, 1085, 1009, 979, 883 and 737 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.82 (3 H, d, *J* 6, 3″-CH_3), 0.85 (3 H, d, *J* 7, 2″-CHCH_3), 0.92–1.08 (9 H, m, 5′-CH_3, 4″-H_2, 2″-C*H*CH_3), 1.25–1.34 (3 H, m, 3″-H, 5″-H_2), 1.48–1.72 (2 H, m, 9″-H_{ax}, 11″-H_{ax}), 1.61 (3 H, s, 7′-CH_3), 1.80 (3 H, s, 5-CH_3), 1.87–2.02 (2 H, m, 9″-H_{eq}, 11″-H_{eq}), 2.12–2.31 (4 H, m, 6′-H_2, 9′-H_2), 2.51 (1 H, m, 5′-H), 3.07 (1 H, br. d, *J* 8, 2″-H), 3.46 (1 H, m, 1-H), 3.48 (3 H, s, OCH_3), 3.58 (1 H, m, 8″-H), 3.88 (3 H, s, CO_2CH_3), 4.01–4.21 (4 H, m, 3-H, 4-H, 10″-H, 10″-OH), 5.03 (1 H, m, 8′-H), 5.41 (1 H, m, 6-H), 5.84 (1 H, dd, *J* 15, 7, 4′-H), 6.19 (1 H, dd, *J* 15, 11, 3′-H) and 6.68 (1 H, d, *J* 11, 2′-H); *m*/*z* (CI/NH_3) 635 (M^+ + 1, 9%), 617 (8), 585 (7), 401 (90) and 219 (100).

(6*R*)-6-Hydroxymilbemycin E 96

Triethylamine (0.1 M in xylene, 0.62 cm^3, 0.624 mmol) and 2,4,6-trichlorobenzoyl chloride (0.1 M in xylene, 0.52 cm^3, 0.520 mmol) were added to the seco-acid **93** (33 mg, 0.52 mmol) in xylene (4.4 cm^3) at room temperature. After 46 h, 4-*N*,*N*-dimethylaminopyridine (13 mg, 1.12 mmol) in xylene (5.5 cm^3) was added and the mixture stirred for 30 min. After concentration under reduced pressure, chromatography (1 : 1 light petroleum–ether) of the residue gave a mixture of (6*R*)-6-hydroxy-28-(*O*-methyl)-28-oxomilbemycin E **94** and 28-oxomilbemycin G **95** (11 mg, 33%) as a viscous oil. [Found for **94** (CI): M^+ + H, 617.3683. $C_{35}H_{53}O_9$ requires M, 617.3690]; ν_{max} 3428, 1731, 1643, 1454, 1373, 1265, 1178, 1089, 1010, 880 and 805 cm^{-1}; δ_H (200 MHz, $CDCl_3$) for **94** 1.80 (3 H, s, 4-CH_3), 3.46 (3 H, s, OCH_3), 3.80 (3 H, s, CO_2CH_3), 4.85 (1 H, m, 15-H) and 5.40 (1 H, m, 19-H); *m*/*z* (CI/NH_3) 634 (M^+ + 18, 2%), 617 (M^+ + 1, 41) and 585 (M^+ − 31, 100).

Diisobutylaluminium hydride (1 M in toluene, 0.13 cm^3, 1.29 mmol) was added to a mixture of the macrolides **94** and **95** (8 mg, 0.129 mmol) in toluene (0.58 cm^3) at −78 °C. The reaction mixture was warmed to −40 °C over 15 min, stirred for 2 h, then cooled to −78 °C. Water (0.5 cm^3) was added, and the mixture warmed to room temperature and diluted with ether (5 cm^3). The aqueous phase was extracted with ether (3 × 5 cm^3) and dichloromethane (3 × 5 cm^3) and the combined organic phases dried ($MgSO_4$). Concentration under reduced pressure and chromatography (2 : 1 light petroleum–ether) of the residue gave a mixture of the starting macrolides **94** and **95** (1 mg) followed by the *title compound* **96** (3 mg, 45%). [Found (CI): M^+ − OH, 571.3621. $C_{34}H_{51}O_7$ requires M, 571.3635]; $[\alpha]_D^{23}$ +87.3 (*c* 0.47, acetone); ν_{max} 3439, 1711, 1454, 1383, 1333, 1170, 1089, 1009 and 877 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.77 (3 H, d, *J* 6, 24-CH_3), 0.81 (3 H, d, *J* 7, 25-CHCH_3), 0.84 (1 H, m, 18-H_{ax}), 0.97 (3 H, d, *J* 7, 25-CHCH_3), 1.01 (3 H, d, *J* 7, 12-CH_3), 1.37–1.68 (6 H, m, 20-H_{ax}, 22-H_2, 23-H_2, 24-H), 1.58 (3 H, s, 14-CH_3), 1.76 (3 H, s, 4-CH_3), 1.78–1.87 and 2.10–2.24 (7 H, m, 13-H_2, 16-H_2, 18-H_{eq}, 20-H_{eq}, 25-CH), 2.45 (1 H, m, 12-H), 3.03 (1 H, dd, *J* 10, 2, 25-H), 3.26 (1 H, br. s, OH), 3.43 (3 H, s, OCH_3), 3.57 (1 H, m, 2-H), 3.73 (1 H, m, 17-H), 3.79 (1 H, m, OH), 3.81 (1 H, s, OH), 4.00 (2 H, m, 5-H, 6-H), 4.17 and 4.28 (each 1 H, d, *J* 15, 28-H), 4.78 (1 H, m, 15-H), 5.30 (2 H, m, 3-H, 19-H), 5.45 (1 H, dd, *J* 15, 10, 11-H), 6.27 (1 H, dd, *J* 15, 11, 10-H)

and 6.46 (1 H, d, *J* 11, 9-H); *m/z* (CI/NH_3) 588 (M^+, 4%), 571 ($M^+ - 17$, 100) and 553 (42).

(6*R*)-28-Chloro-28-deoxy-6-hydroxymilbemycin E 97

A solution of lithium diisopropylamine (0.6 M in tetrahydrofuran, 0.024 cm^3, 0.0731 mmol) cooled to −78 °C was added to (6*S*)-6-hydroxymilbemycin E **96** (4 mg, 0.0731 mmol) in tetrahydrofuran–hexamethyldisilazane (3 : 1, 0.26 cm^3) at −78 °C. After 10 min, a solution of toluene *p*-sulfonyl chloride (0.08 M in tetrahydrofuran–hexamethyldisilazane 3 : 1, 0.1 cm^3, 0.0877 mmol) cooled to −78 °C was added and the mixture stirred for 10 min. The reaction mixture was warmed to 0 °C over 2 h and left at this temperature for 40 min. Brine (0.6 cm^3) and ether (10 cm^3) were added, the aqueous phase was extracted with ether (3 × 5 cm^3) and the combined organic phases were dried ($MgSO_4$). After concentration under reduced pressure, chromatography (20 : 1 light petroleum–ether) of the residue gave the *title compound* **97** (3 mg, 74%) as a viscous oil. [Found (CI): $M^+ + H$, 607.3393. $C_{34}H_{52}ClO_7$ requires M, 607.3402]; $[a]_D^{25}$ +81.7 (*c* 0.14, acetone); ν_{max} 3456, 1705, 1454, 1383, 1332, 1172, 1120, 1088, 1055, 1009, 878 and 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.77 (3 H, d, *J* 7, 24-CH_3), 0.81 (3 H, d, *J* 7, 25-CHCH_3), 0.85 (1 H, m, 18-H_{ax}), 0.97 (3 H, d, *J* 7, 25-CHCH_3), 1.04 (3 H, d, *J* 7, 12-CH_3), 1.41–1.66 (6 H, m, 20-H_{ax}, 22-H_2, 23-H_2, 24-H), 1.60 (3 H, s, 14-CH_3), 1.72–1.87 (4 H, m, 13-H, 18-H_{eq}, 20-H_{eq}, 25-CH), 1.75 (3 H, s, 4-CH_3), 2.14–2.28 (3 H, m, 13-H′, 16-H_2), 2.53 (1 H, m, 12-H), 2.72 (1 H, s, 6-OH), 3.04 (1 H, dd, *J* 10, 2, 25-H), 3.44 (3 H, s, OCH_3), 3.59 (1 H, m, 17-H), 3.68 (1 H, m, 2-H), 4.02 (1 H, m, 5-H), 4.11 (1 H, d, *J* 4, 6-H), 4.45 (1 H, d, *J* 11, 28-H), 4.55 (1 H, s, 7-OH), 4.56 (1 H, d, *J* 11, 28-H), 4.83 (1 H, d, *J* 10, 15-H), 5.26 (1 H, d, *J* 2, 3-H), 5.33 (1 H, m, 19-H), 5.58 (1 H, dd, *J* 15, 9, 11-H), 6.26 (1 H, dd, *J* 15, 11, 10-H) and 6.38 (1 H, d, *J* 11, 9-H); *m/z* (CI/NH_3) 609 [$M^+ + 1$ (^{37}Cl), 7%], 607 [$M^+ + 1$ (^{35}Cl), 21], 589 ($M^+ - 17$, 21), 571 (41) and 553 (100).

Milbemycin G 7

Freshly prepared silver(I) oxide (17 mg, 0.0247 mmol) was added to a solution of (6*R*)-28-chloro-28-deoxy-6-hydroxymilbemycin G **97** (1.5 mg, 0.0247 mmol) in tetrahydrofuran (0.5 cm^3) at room temperature. The suspension was stirred for 24 h, heated under reflux for 1 h, then cooled and filtered through celite. The filter cake was washed with ether (10 × 1 cm^3) and dichloromethane (10 × 1 cm^3) and the combined organic phases were concentrated under reduced pressure. Chromatography (3 : 1 light petroleum–ether) of the residue gave milbemycin G **7** (1 mg, 71%) as a viscous oil. [Found (EI): M^+, 570.3555. $C_{34}H_{50}O_7$ requires M, 570.3557]; $[a]_D^{26}$ +101 (*c* 0.195, acetone) [lit.[3b] $[a]_D^{27}$ +108 (*c* 0.25, acetone)]; ν_{max} 3461, 1713, 1454, 1367, 1308, 1265, 1165, 1119, 1097, 1010, 869, 805 and 737 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.77 (3 H, d, *J* 7, 24-CH_3), 0.83 (1 H, m, 18-H_{ax}), 0.84 and 0.98 (each 3 H, d, *J* 7, 25-CHCH_3), 1.02 (3 H, d, *J* 7, 12-CH_3), 1.33 (1 H, t, *J* 12, 20-H_{ax}), 1.42–1.64 (5 H, m, 22-H_2, 23-H_2, 24-H), 1.51 (3 H, s, 14-CH_3), 1.74–1.90 (3 H, m, 13-H, 18-H_{eq}, 25-CH), 1.79 (3 H, s, 4-CH_3), 1.98 (1 H, m, 20-H_{eq}), 2.15–2.21 (3 H, m, 13-H′, 16-H_2), 2.40 (1 H, m, 12-H), 3.05 (1 H, dd, *J* 10, 2, 25-H), 3.28 (1 H, m, 2-H), 3.49 (3 H, s, OCH_3), 3.57 (1 H, m, 17-H), 3.96 (1 H, m, 5-H), 4.01 (1 H, d, *J* 6, 6-H), 4.11 (1 H, s, 7-OH), 4.60 and 4.67 (each 1 H, d, *J* 14, 28-H), 4.93 (1 H, t, *J* 8, 15-H), 5.28–5.38 (3 H, m, 3-H, 11-H, 19-H) and 5.69–5.77 (2 H, m, 9-H, 10-H); *m/z* (EI) 570 (M^+, 5%), 552 ($M^+ - 18$, 1), 428 (14), 259 (17), 151 (43) and 49 (100); *m/z* (CI/NH_3) 571 ($M^+ + 1$, 2%), 554 (18), 181 (51) and 55 (100).

Freshly prepared silver(I) oxide (287 mg, 12.4 mmol) was added to a solution of milbemycin D **98** (11 mg, 0.206 mmol) in methyl iodide (3 cm^3) at room temperature. After 24 h, the reaction mixture was filtered through celite. The filter cake was washed with ether (30 cm^3) and the combined organic phases concentrated under reduced pressure. Chromatography (3 : 1 light petroleum–ether) of the residue gave a mixture of milbemycin G **7** and 7-*O*-methylmilbemycin G **99**. Reverse phase HPLC (9 : 1 acetonitrile–water) gave milbemycin G **7** (7.5 mg, 64%) as a viscous oil, $[a]_D^{21}$ +113.2 (*c* 0.75, acetone), all other data were in accord with those recorded above, together with 7-*O*-methylmilbemycin G **99**. [Found (CI): $M^+ + H$, 585.3798. $C_{35}H_{53}O_7$ requires M, 585.3791]; ν_{max} 3391, 1739, 1683, 1171, 1099, 836 and 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.84 (3 H, d, *J* 7, 24-CH_3), 0.87 (3 H, d, *J* 7, 25-CHCH_3), 0.91 (1 H, dd, *J* 7, 5, 18-H_{ax}), 1.01 (3 H, d, *J* 7, 25-CHCH_3), 1.02 (3 H, d, *J* 7, 12-CH_3), 1.15 (1 H, t, *J* 12, 20-H_{ax}), 1.39–1.67 (5 H, m, 22-H_2, 23-H_2, 24-H), 1.53 (3 H, s, 14-CH_3), 1.81 (3 H, s, 4-CH_3), 1.88 (3 H, m, 13-H, 18-H_{eq}, 25-CH), 2.16–2.28 (4 H, m, 13-H′, 16-H_2, 20-H_{eq}), 2.46 (1 H, m, 12-H), 3.04 (1 H, dd, *J* 10, 2, 25-H), 3.26 (3 H, s, 7-OCH_3), 3.35 (1 H, m, 2-H), 3.46 (3 H, s, 5-OCH_3), 3.60 (1 H, m, 17-H), 3.91 (1 H, d, *J* 5, 5-H), 4.11 (1 H, m, 6-H), 4.59 and 4.66 (each 1 H, dd, *J* 14, 2, 28-H), 4.98 (1 H, m, 15-H), 5.0 and 5.52 (each 1 H, m), 5.65 (1 H, br. s, 3-H), 5.70 (1 H, d, *J* 11, 9-H) and 5.81 (1 H, dd, *J* 15, 11, 10-H); *m/z* (CI/NH_3) 585 ($M^+ + 1$, 7%) and 553 ($M^+ - 31$, 100).

Crystal data for acetylmandelate 76

$C_{35}H_{44}O_{10}Si$, $M = 652.81$, orthorhombic, $a = 14.792(2)$, $b = 28.300(4)$, $c = 8.5666(9)$ Å, $U = 3586.1(7)$ Å^3, $T = 293(1)°$, space group $P2_12_12_1$ (no. 19), $Z = 4$, μ(CuKα) = 1.027 mm^{-1}, 3060 unique reflections, 2565 reflections with $I > 3.00\,\sigma(I)$ were used in the final refinement. The final $R(F) = 0.0484$. X-Ray data have been deposited with the Cambridge Crystallographic Data Base, CCDC number 275136.†

Crystal data for chloroacetylmandelate 80

$C_{27}H_{33}ClO_9Si$, $M = 565.09$, hexagonal, $a = 14.153(1)$, $c = 25.881(2)$ Å, $U = 4489.3(7)$ Å^3, space group $P6_1$ (number 169), $Z = 6$, μ(CuKα) = 1.925 mm^{-1}, 2592 reflections measured, 2292 unique reflections ($R_{int} = 0.08139$), 1156 reflections with $I > 3.00\,\sigma(I)$ were used in the final refinement. The final $R(F) = 0.0907$. Since the number of observations was low, only the Cl, Si and O atoms were refined anisotropically. C11 was disordered over two sites each at 50% occupancy. H atoms were included in calculated positions, except that bonded to O2, which could not be located. X-Ray data have been deposited with the Cambridge Crystallographic Data Base, CCDC number 275135.†

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