Total synthesis of milbemycin E: resolution of the C(1)–C(10) fragment and final assembly

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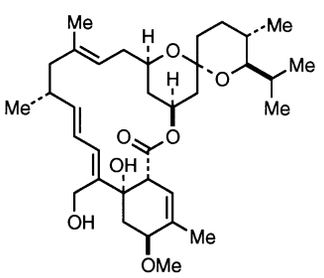
The racemic hydroxycyclohexanone (±)-7, prepared by the Robinson addition of the keto ester 5 to 3-methylbut-3-enone 6, has been reduced stereoselectively to give the racemic cyclohexanediol (±)-8. This has been resolved by fractional crystallisation of the acetylmandelate esters 10 and 11. With (*S*)-acetyl mandelic acid 9, diastereoisomer 11 crystallises out. The required, dextrorotatory, enantiomer of the cyclohexanediol (±)-8 has been obtained by selective saponification of the mixture of the diastereoisomers 10 and 11, to give the mandelates 12 and 13, followed by crystallisation of the required diastereoisomer 12. Saponification of 12 gives the dextrorotatory enantiomer of the cyclohexanediol (+)-8 [which could alternatively have been obtained directly from the racemic diol (±)-8 using (*R*)-acetylmandelate *ent*-9]. Oxidation of the dextrorotatory diol (+)-8 gives the laevorotatory hydroxy ketone (−)-7. The 3,4-double bond has been introduced into this ketone by regioselective enol trimethylsilyl ether formation, phenylselanation and oxidative elimination, followed by reduction to give the cyclohexenediol 18. Methylation, saponification and re-esterification give the 2-furylcyclohexenoate 23, which on oxidation using singlet oxygen is converted into the hydroxybutenolide 3. The dextrorotatory diol (+)-8 has also been converted into the hydroxybutenolide 29 which lacks the 3,4-double bond. Conditions have been developed for the Wittig reactions between the hydroxybutenolides 29 and 3 and the phosphonium salt 2 to give the esters 32 and 37 after esterification using diazomethane and iodine induced isomerisation of the 10,11-double bond. Deprotection gives the hydroxy acids 33 and 39 which have been cyclised to give the macrolides 34 and 40. Selective reduction of these methyl esters gives 3,4-dihydromilbemycin E 35 and milbemycin E 1.

A convergent approach to non-aromatic β-milbemycins, *e.g.* milbemycin E **1**, has been proposed in which a key step is the Wittig reaction between the phosphonium salt **2** and the hydroxybutenolide **3**.[1] We have reported syntheses of the phosphonium salt **2**[2] and the racemic hydroxybutenolide (±)-**4**,[3] and shown that this hydroxybutenolide can be used in Wittig condensations. We now describe the resolution of a synthetic precursor of hydroxybutenolide **3**, and the completion of a total synthesis of milbemycin E **1**.[4]



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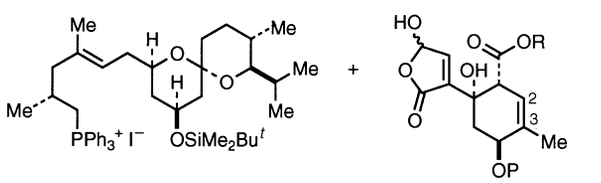

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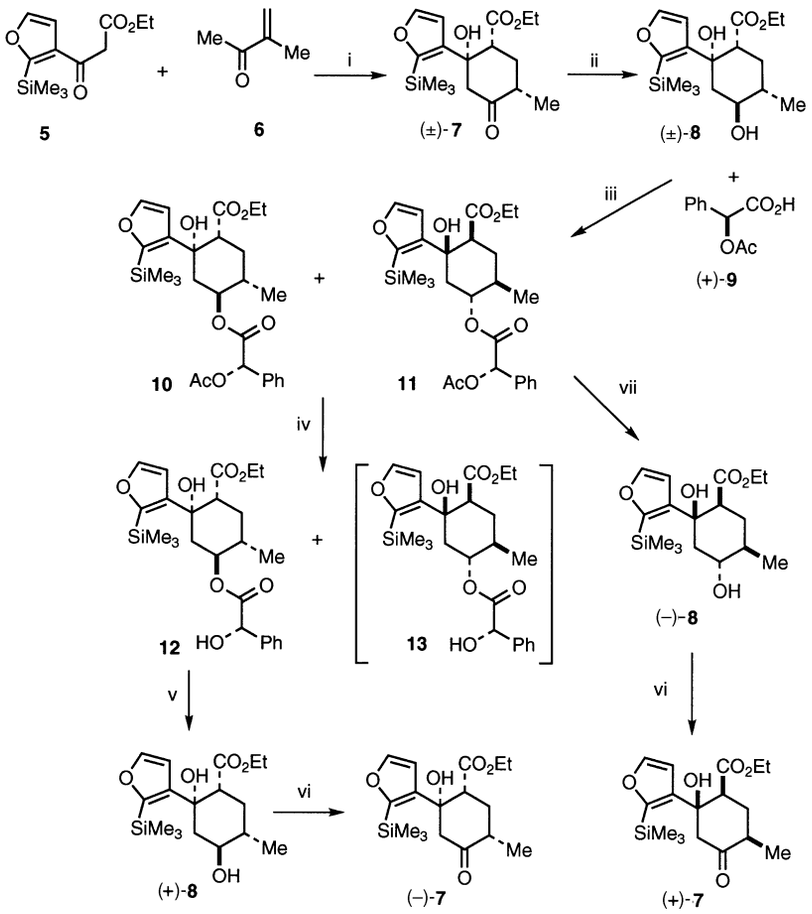
3 P = Me, R = $CH_2CH_2SiMe_3$
4 P = $SiMe_2Bu^t$, R = CH_2CH_3

Results and discussion

The racemic hydroxycyclohexanone (±)-**7** was prepared from the keto ester **5** and 3-methylbut-3-enone **6** (Scheme 1).[3] Preliminary attempts at resolution by saponification to the corresponding acid and esterification using a chiral alcohol, *e.g.* menthol or borneol, were unsuccessful. However, reduction using sodium triacetoxyborohydride[5] gave the racemic cyclohexanediol (±)-**8** which was esterified with (*S*)-(+)-acetylmandelic acid **9** to give the diastereoisomers **10** and **11**.[6] One of these diastereoisomers, the isomer **11**, crystallised out on trituration of the mixture with hexane. A sample of the other isomer **10** was isolated as an oil by chromatography.

The structures of isomers **10** and **11**, and hence the absolute configurations of products derived from them, were assigned by ^{1}H NMR spectroscopy. In particular, the 5-CH_3 for the crystalline isomer was observed at δ 1.03, whereas it was observed at δ 0.63 for the non-crystalline isomer.[6] Following the mnemonic for the assignment of absolute configuration to secondary alcohols from the relative chemical shifts of their acetylmandelates,[7] it followed that the crystalline isomer was **11**, the non-crystalline isomer being **10**. These assignments were confirmed by the successful incorporation of the laevorotatory hydroxycyclohexanone (−)-**7** into a total synthesis of milbemycin E **1**. (Indeed, had the wrong enantiomer of this hydroxy



Scheme 1 *Reagents:* i, NaOH, ethanol (58%);[3] ii, $NaBH(OAc)_3$, acetic acid (94%);[3] iii, dicyclohexylcarbodiimide, 4-dimethylaminopyridine (83% of the mixture of **10** and **11**, 33% of **11** after recrystallisation); iv, K_2CO_3, ethanol, 0 °C, 2 h (39% of **12** from the 1:1 mixture of acetates **10** and **11**); v, K_2CO_3, ethanol, room temperature, 16 h (99%); vi, oxalyl chloride, dimethyl sulfoxide, triethylamine [(−)-**7**, 85%; (+)-**7**, 82%]; vii, K_2CO_3, ethanol, room temperature, 16 h (97%)

ketone been taken through the synthesis, the macrocyclisation reaction would have been unsuccessful.[1])†

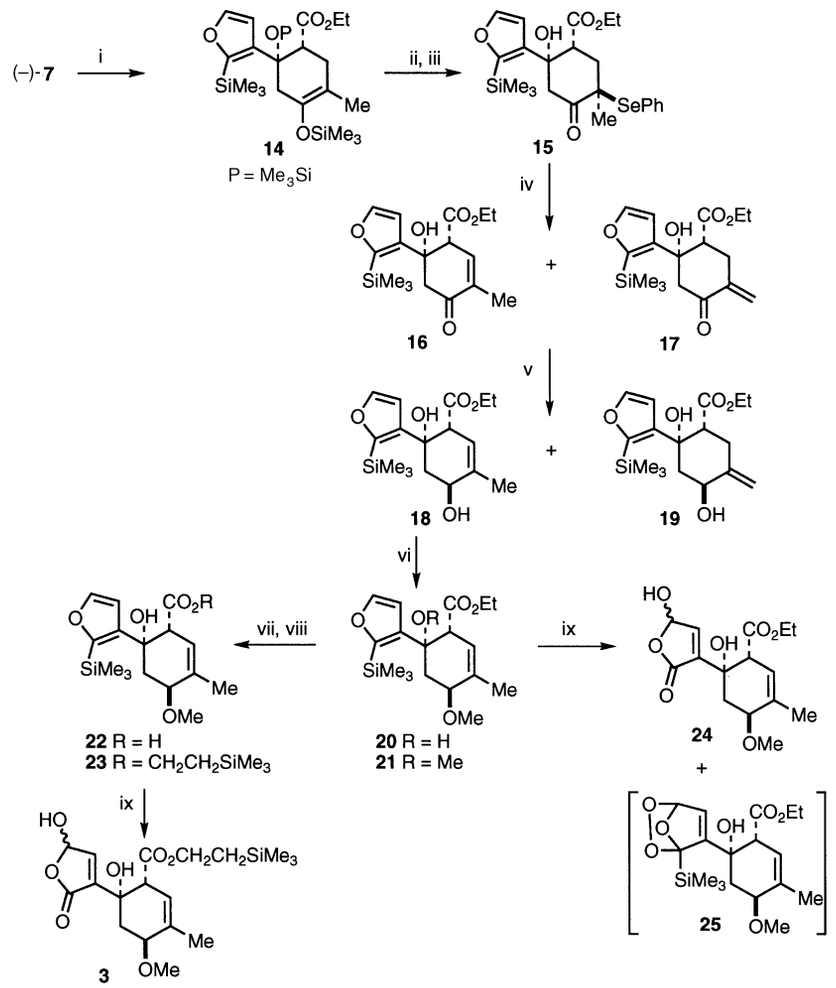
Selective saponification of the acetylmandelate **10**, containing *ca.* 20% of its isomer **11**, gave the mandelate esters **12** and **13**. In this case, the required diastereoisomer **12** could be crystallised out of the mixture, and further treatment with potassium carbonate in ethanol gave the required diol, which turned out to be the dextrorotatory, enantiomer of the cyclohexanediol (+)-**8**. Oxidation of (+)-**8** using Swern conditions[8] gave the laevorotatory hydroxycyclohexanone (−)-**7**. Saponification of the crystalline acetylmandelate **11** gave the laevorotatory cyclohexanediol (−)-**8** which gave the dextrorotatory ketone (+)-**7** on oxidation. [Following the confirmation of structures for the acetylmandelates, (*R*)-acetylmandelic acid *ent*-**9** was used for the resolution of the cyclohexanediol (±)-**8**, since the crystalline acetylmandelate *ent*-**11** could be saponified directly to the required enantiomer (+)-**8**.]

The laevorotatory hydroxycyclohexanone (−)-**7** was converted into its enol trimethylsilyl ether (−)-**14** which gave the phenylselanyl ketone (−)-**15** after sequential treatment with phenylselenenyl chloride and tetrabutylammonium fluoride (Scheme 2).[3] Oxidative elimination gave a mixture of the endo- and exo-cyclic alkenes **16** and **17** which was reduced to give the cyclohexenediol (−)-**18** together with the isomeric methylenecyclohexanediol **19**. The ratio of these two isomers tended to vary with scale, being 90:10 in favour of the endo-isomer **18** on a small scale, but dropping to 78:22 on a multi-gram scale.[3] Spectroscopic data for the enantiomerically enriched products prepared along this sequence were identical to those obtained earlier for the racemic compounds.

At this stage it was necessary to effect selective methylation of the 5-hydroxy group (milbemycin numbering). During model work this had been achieved using trimethyloxonium tetrafluoroborate in the presence of potassium carbonate.[1] However, during the present work this procedure gave mixtures of products including the bis-methyl ether **21**. Conditions for this and subsequent steps were first developed using the racemic alcohol (±)-**18**.[3]

Selective monomethylation to the methyl ether (±)-**20** was achieved using silver oxide which had been freshly prepared, stored in the dark, and rigorously dried under reduced pressure together with methyl iodide which was filtered through silica gel before use. The ethyl ester (±)-**20** was then converted into the 2-trimethylsilylethyl ester (±)-**23** in anticipation of the macrocyclisation step which would require prior deprotection of the acid at C(1) in the presence of the methoxycarbonyl group at C(8).[1] The transesterification was carried out by saponification

† The structures assigned to the acetylmandelates **10** and **11**, and hence the absolute configurations of the cyclohexanediols (+)-**8** and (−)-**8** and the hydroxycyclohexanones (−)-**7** and (+)-**7**, were confirmed by X-ray crystallography of the crystalline acetylmandelate **11** (carried out by O. S. Mills). Fig. 1 shows a projection of the molecular structure of **11** as established by the crystal structure determination. *Crystal data:* $C_{27}H_{36}O_8Si$. $M_r = 516.36$, monoclinic, spacegroup $P2_1$, $Z = 2$. At $T = 293$ K, $a = 10.034(8)$, $b = 11.837(7)$, $c = 12.640(9)$ Å, $\beta = 102.18(3)°$, $V = 1467.5(3)$ Å^3, λ(Mo-Kα) = 0.710 69 Å, $D_x = 1.18$ g cm^{-3}, $\mu = 1.28$ cm^{-1}. Colourless needles, crystal dimensions 0.3 × 0.15 × 0.15 mm. Reflection intensities were collected on a CAD4 diffractometer using the θ–2θ scan method. Index limits were $0 \le h \le 13$, $0 \le k \le 16$ and $-16 \le l \le 17$. The structure was solved by direct methods (MULTAN[16]) and difference Fourier series. The structure was refined by our own full-matrix, least squares program and converged to a final $R = 7.0\%$ for 2628 reflections, $|F| > 3\sigma(|F|)$, for 324 parameters (anisotropic thermal parameters for non-H atoms and fixed parameters for H with $B = 4.5$ Å^2).

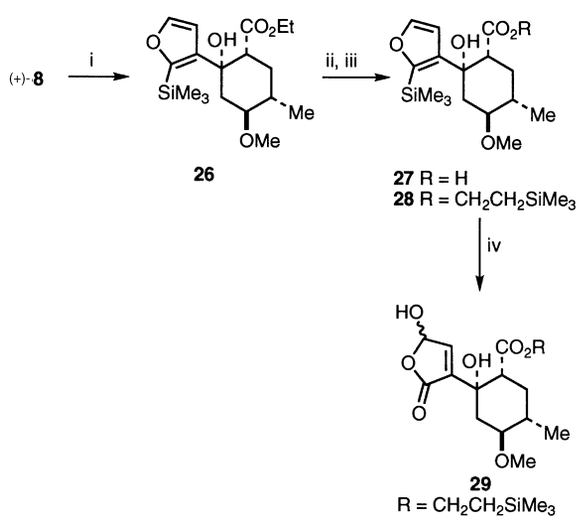


Scheme 2 *Reagents:* i, triethylamine, trimethylsilyl trifluoromethanesulfonate, carbon tetrachloride (85%); ii, phenylselenenyl chloride, tetrahydrofuran (82%); iii, tetrabutylammonium fluoride, tetrahydrofuran (93%); iv, 30% hydrogen peroxide, dichloromethane, room temperature, 30 min; v, sodium triacetoxyborohydride, acetic acid (**18**, 57%; **19**, 17% from **15**); vi, silver(I) oxide, methyl iodide (79%); vii, aqueous sodium hydroxide, ethanol (75%); vii, 2-trimethylsilylethanol, 4-dimethylaminopyridine, dicyclohexylcarbodiimide (78%); ix, oxygen, tetraphenylporphyrin, dichloromethane, methanol (**24**, 98%; **3**, 95%)

of the ethyl ester using sodium hydroxide in ethanol to give the carboxylic acid (±)-**22**, followed by esterification of the acid using 2-trimethylsilylethanol and dicyclohexylcarbodiimide. This synthesis of the racemic trimethylsilyl ester (±)-**23** was followed by a synthesis of the homochiral material (−)-**23** from the laevorotatory cyclohexenol (−)-**18**.

The final step for the synthesis of the required hydroxybutenolide **3** was the oxidation of the furan using singlet oxygen.[9] Previously, this had been carried out using dichloromethane as solvent. When this procedure was followed using the racemic 2-trimethylsilylfuran (±)-**20**, two products were isolated which were separated and identified as the required hydroxybutenolide (±)-**24** together with the Diels–Alder adduct (±)-**25**. The isolation of this latter product was avoided using a mixture of dichloromethane and methanol as solvent.[10] Repetition of this procedure with the laevorotatory 2-trimethylsilylethyl ester (−)-**23** gave the required hydroxybutenolide **3** (95%).

It was decided to synthesise 3,4-dihydromilbemycin E as a more accessible interim target in order to develop conditions for the later stages of the synthesis of milbemycin E. The dextrorotatory cyclohexanediol (+)-**8** was monomethylated to give the methyl ether (+)-**26** (Scheme 3). This was saponified to give the acid **27** which was coupled with 2-trimethylsilylethanol to give the ester (+)-**28**. Oxidation with singlet oxygen in dichloromethane and methanol gave the hydroxybutenolide **29** which lacked the crucial double bond, but which was more readily available than its unsaturated analogue **3**, and was used in studies to establish conditions for the Wittig reaction and macrocyclisation.

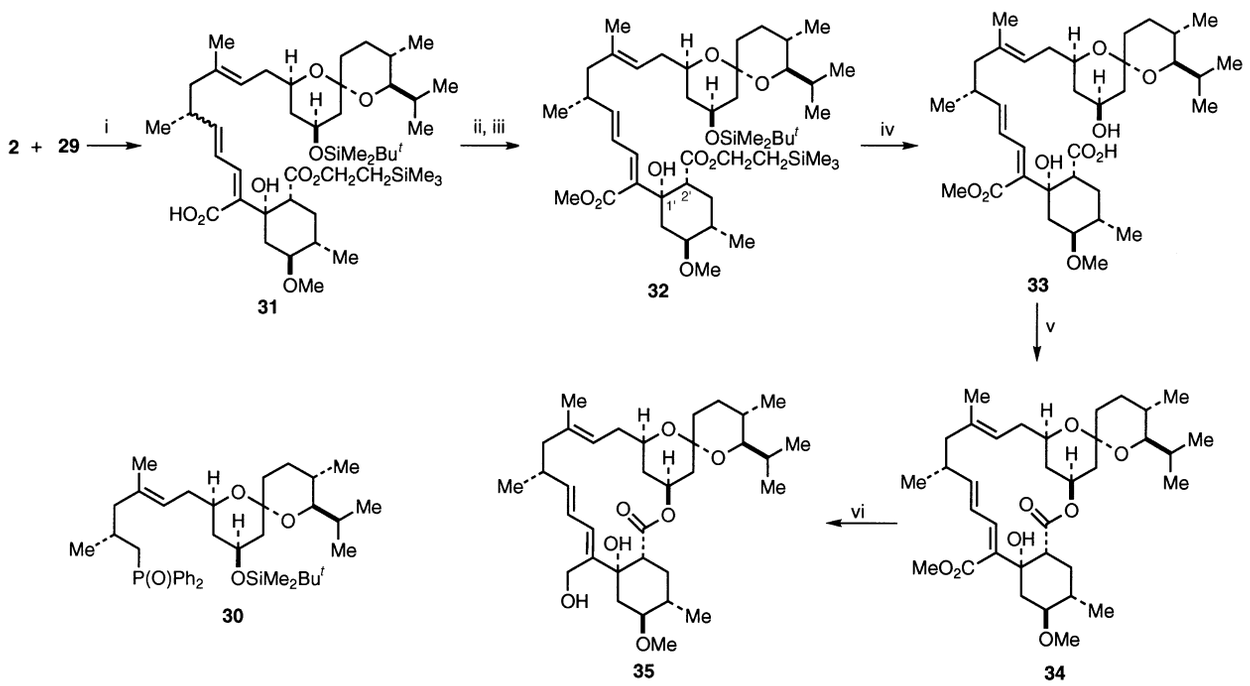


Scheme 3 *Reagents:* i, silver(I) oxide, methyl iodide (100%); ii, sodium hydroxide, ethanol (99%); iii, 2-trimethylsilylethanol, 4-dimethylaminopyridine, dicyclohexylcarbodiimide (82%); iv, oxygen, tetraphenylporphyrin, dichloromethane, ethanol (91%)

Preliminary attempts at the Wittig condensation between the phosphonium salt **2** and the hydroxybutenolide **29** were carried out by treatment of the phosphonium salt with either butyllithium or lithium hexamethyldisilazide at 0 °C, followed by the addition of two mole equivalents of lithium hexamethyl-

disilazide, and the addition of the mixture to the hydroxybutenolide. However, the major product under these conditions was the phosphine oxide **30** together with only traces of the required Wittig product. Slightly better results were obtained using *tert*-butyllithium at −40 °C. The addition of *tert*-butyllithium to the phosphonium salt **2** at −40 °C gave a red solution. Two mole equivalents of lithium hexamethyldisilazide were added and the solution was added to the hydroxybutenolide **29** at −78 °C. The mixture was then allowed to warm to −15 °C before being quenched. The crude product, presumably the acid **31**, was immediately treated with diazomethane and isomerised using a trace of iodine in benzene to give the methyl ester **32** as a single diastereoisomer in 54% overall yield from the phosphonium salt (Scheme 4). Treatment with tetrabutylammonium fluoride[11] gave the hydroxy acid **33** which was cyclised using dicyclohexylcarbodiimide and 4-dimethylaminopyridine to give the macrolide **34** in 34% yield over the two steps.[12] Reduction using Red-Al®, which had been used successfully in model studies, gave 3,4-dihydromilbemycin E **35** which was identified on the basis of its spectroscopic data.

However, attempts to carry out the Wittig reaction following the above procedure, but using the unsaturated hydroxybutenolide **3**, gave only low yields of products and were non-reproducible. An alternative, somewhat simpler, procedure was therefore developed in which three mole equivalents of lithium hexamethyldisilazide were added to a mixture of the phosphonium salt **2** and the hydroxybutenolide **3** at −78 °C and the mixture allowed to warm to −15 °C, before being quenched to give the dienyl acid **36** as a mixture of (*E*)- and (*Z*)-isomers, ratio (*E*):(*Z*) *ca.* 1:2 (Scheme 5). The crude acid was treated with diazomethane and isomerised using a trace of iodine to give the ester **37** together with a trace of an aromatic side-product, possibly **38**, formed by elimination from the hydroxycyclohexenoate. Deprotection and macrocyclisation were carried out as before to give the macrolide **40** in a 37% yield over the two steps.



Scheme 4 *Reagents:* i, *tert*-butyllithium, lithium hexamethyldisilazide; ii, diazomethane; iii, iodine (cat.), benzene (54% of **32** based on **2**); iv, tetrabutylammonium fluoride, tetrahydrofuran; v, 4-dimethylaminopyridine, dicyclohexylcarbodimide (34% of **34** based on **32**); vi, sodium bis(2-methoxyethoxy)aluminium hydride (68%)

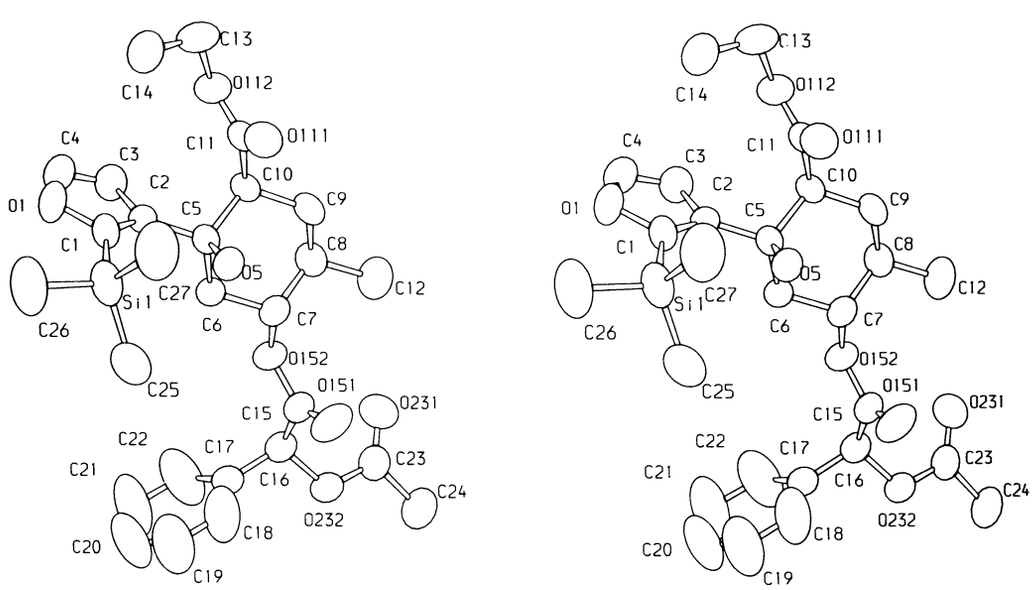
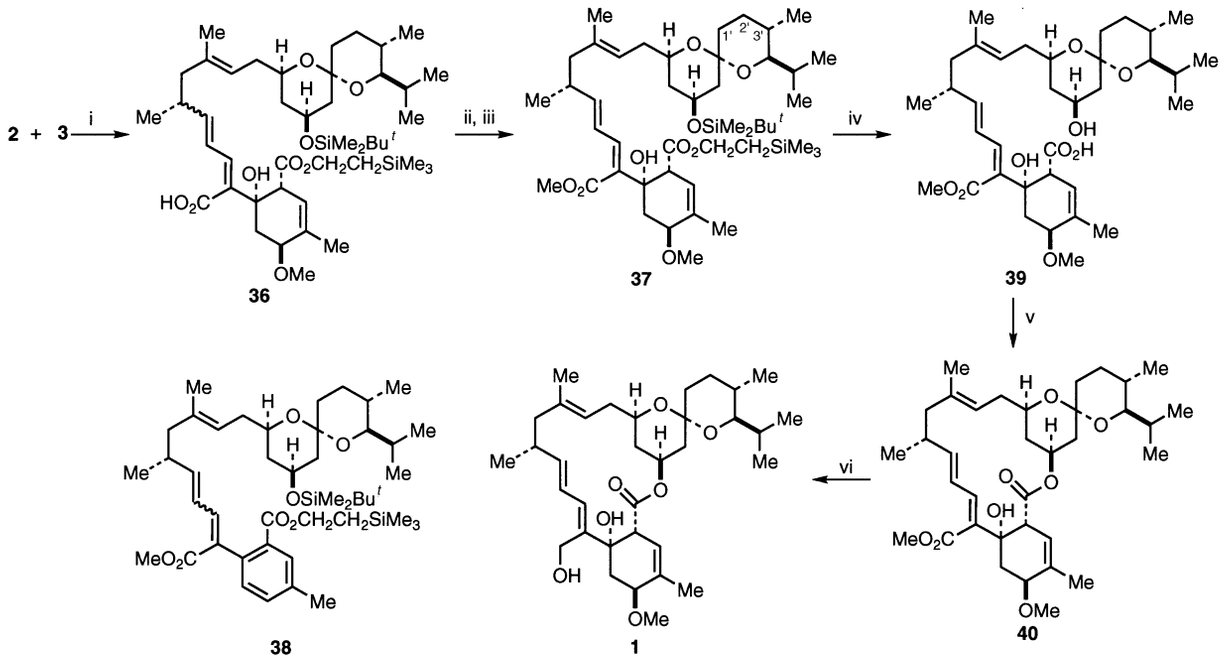


Fig. 1 Projection of the molecular structure of acetylmandelate **11** showing the crystallographic numbering scheme used



Scheme 5 *Reagents:* i, lithium hexamethyldisilazide; ii, diazomethane; iii, iodine (cat.), benzene (42% of **37** based on **2**); iv, tetrabutylammonium fluoride, tetrahydrofuran; v, 4-dimethylaminopyridine, dicyclohexylcarbodiimide (37% of **40** based on **37**); vi, diisobutylaluminium hydride (87%)

It now remained to reduce the methoxycarbonyl substituent to complete a synthesis of milbemycin E **1**. Attempts to effect this transformation using Red-Al®, which had proved successful for the preparation of the dihydromilbemycin E **35**, were unsuccessful and gave rise to the formation of complex mixtures of products; perhaps the Red-Al® is too basic. Diisobutylaluminium hydride in hexane and tetrahydrofuran gave no reaction, but the use of diisobutylaluminium hydride in toluene gave rise to the formation of a single product which was isolated in a yield of 87% and identified as milbemycin E **1** by comparison of its chromatographic and spectroscopic data with a sample of the authentic material.

This work completed a total synthesis of the non-aromatic milbemycin, milbemycin E **1**, by a convergent approach in which the labile 3,4-double bond is introduced early in the synthesis. The Wittig reaction between the phosphonium salt **2** and the hydroxybutenolide **3** is the key step. By having the nucleophilic component of this coupling step in the C(11)–C(25) fragment, the use of protecting groups is minimised. The ylide reacts selectively with the aldehyde derived from the hydroxybutenolide component of **3** rather than with the alkoxycarbonyl group at C(1). This selectivity is important since it means that the alkoxycarbonyl group at C(1) can be introduced early in the synthesis and avoids problems associated with migration of the 3,4-double bond which complicate attempts to oxidise either a hydroxymethyl or formyl group at C(1).[12]

The preferred procedure for the Wittig reaction is that in which lithium hexamethyldisilazide is added to a mixture of the hydroxybutenolide and the phosphonium salt at −78 °C. It would appear that the ylide derived from the phosphonium salt has to be generated in the presence of the aldehyde or else it fragments to give the phosphine oxide **30**. The early successes in using *tert*-butyllithium as base during condensations with the hydroxybutenolide **29** were probably due to formation of the ylide by the lithium hexamethyldisilazide in the presence of the hydroxybutenolide and not by the *tert*-butyllithium itself.

By completing a synthesis of milbemycin E **1**, we had achieved what we had originally set out to accomplish in this area. However, the biological activities of the α-milbemycins and avermectins are more interesting and useful than those of the β-milbemycins and so the strategy for milbemycin synthesis reported in this paper has been adapted to complete a total synthesis of an α-milbemycin, milbemycin G.[13,14] Work on completing a synthesis of the aglycone of an avermectin is in progress.[15]

Experimental

For general experimental details, see the first paper in this series.[2]

The following compounds were prepared as described previously[1,3] but starting with the laevorotatory ketone (−)-**7**; ethyl (1*R*,6*S*)-4,6-bis(trimethylsilyloxy)-3-methyl-6-(2-trimethylsilyl-3-furyl)cyclohex-3-enecarboxylate (−)-**14**, $[\alpha]_D$ −35.0 (*c* 0.98 in $CHCl_3$); ethyl (1*R*,2*S*,5*R*)-5-methyl-4-oxo-5-phenylselanyl-2-trimethylsilyloxy-2-(2-trimethylsilyl-3-furyl)-cyclohexanecarboxylate, $[\alpha]_D$ −57.1 (*c* 0.38 in $CHCl_3$); ethyl (1*R*,2*S*,5*R*)-2-hydroxy-5-methyl-4-oxo-5-phenylselanyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate (−)-**15**, $[\alpha]_D$ −109 (*c* 0.445 in $CHCl_3$); ethyl (1*R*,4*S*,6*S*)-2,6-dihydroxy-3-methyl-6-(2-trimethylsilyl-3-furyl)cyclohex-2-enecarboxylate (−)-**18**, $[\alpha]_D$ −112.9 (*c* 0.89 in $CHCl_3$).

Ethyl (1*R*,2*S*,4*S*,5*S*)-4-[(2*S*)-2-acetoxy-2-phenylacetoxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate 10 and ethyl (1*S*,2*R*,4*R*,5*R*)-4-[(2*S*)-2-acetoxy-2-phenylacetoxy]-2-hydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate 11

Dicyclohexylcarbodiimide (4.45 g, 21.6 mmol) in dichloromethane (35 cm^3) was added to the cyclohexanediol (±)-**8**[1,3] (7 g, 20.6 mmol), (*S*)-(+)-acetylmandelic acid **9** (4.8 g, 24.7 mmol) and 4-dimethylaminopyridine (DMAP) (246 mg, 2 mmol) in dichloromethane (75 cm^3) at 0 °C. The reaction mixture was stirred for 16 h at ambient temperature, filtered and the residue washed with ether (3 × 50 cm^3). Concentration under reduced pressure and chromatography of the residue using light petroleum–ether (4:1) as eluent, gave the two diastereoisomers **10** and **11** as a thick gum (8.86 g, 83%). Warm hexane (100 cm^3) was added and the mixture triturated at ambient temperature to induce crystallisation. Filtration gave the *title compound* **11** (3.6 g, 33%) as white crystals, mp 131–134 °C (Found: C, 62.75; H, 7.3. $C_{27}H_{36}O_8Si$ requires C, 62.77; H, 7.02%); $[\alpha]_D$ +27.7 (*c* 0.88 in $CHCl_3$); ν_{max}/cm^{-1} 3470, 1745, 1709, 1374, 1233, 1210, 1181,

1094, 1056 and 843; δ_H 0.3 [9 H, s, $Si(CH_3)_3$], 1.03 (3 H, d, *J* 6, 5-CH_3), 1.10 (3 H, t, *J* 6, CH_2CH_3), 1.29 (1 H, m, 3-H_{ax}), 1.72 (1 H, m, 5-H), 1.87 (2 H, m, 6-H_2), 2.02 (1 H, dd, *J* 14, 5, 3-H_{eq}), 2.2 (3 H, s, CH_3CO), 2.81 (1 H, m, 1-H), 4.01 (2 H, m, CH_2CH_3), 4.32 (1 H, br s, 2-OH), 5.03 (1 H, td, *J* 10, 7, 4-H), 5.86 (1 H, s, C*H*Ph), 6.10 (1 H, d, *J* 2, 4′-H), 7.37 (5 H, m, aromatic H) and 7.42 (1 H, d, *J* 2, 5′-H); *m/z* (EI) 516 (M^+, 4.5%) and 501 (12). Chromatography of a small portion of the residue, using light petroleum–ether (4:1) as eluent, gave the *title compound* **10** as a viscous oil (Found: M^+, 516.2180. $C_{27}H_{36}O_8Si$ requires *M*, 516.2179); $[\alpha]_D$ +55.2 (*c* 0.42 in $CHCl_3$); ν_{max}/cm^{-1} 3360, 1746, 1709, 1383, 1233, 1181, 1095, 1057 and 843; δ_H 0.31 [9 H, s, $Si(CH_3)_3$], 0.63 (3 H, d, *J* 6, 5-CH_3), 1.11 (3 H, t, *J* 7.5, CH_2CH_3), 1.48 (1 H, m, 3-H_{ax}), 1.63 (1 H, m, 5-H), 1.84 (2 H, m, 6-H_2), 2.18 (3 H, s, CH_3CO), 2.32 (1 H, dd, *J* 14, 4.5, 3-H_{eq}), 2.83 (1 H, m, 1-H), 3.97 (2 H, m, CH_2CH_3), 4.32 (1 H, d, *J* 2, 2-OH), 4.91 (1 H, td, *J* 11.3, 4.5, 4-H), 5.85 (1 H, s, C*H*Ph), 6.15 (1 H, d, *J* 2, 4′-H), 7.41 (5 H, m, aromatic H) and 7.53 (1 H, d, *J* 2, 5′-H); *m/z* (CI) 534 (M^+ + 18, 2%), 516 (M^+, 0.2), 323 (80), 305 (31) and 233 (100).

Ethyl (1*R*,2*S*,4*S*,5*S*)-2-hydroxy-4-[(2*S*)-2-hydroxy-2-phenylacetoxy]-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate 12 and ethyl (1*S*,2*R*,4*R*,5*R*)-2-hydroxy-4-[(2*S*)-2-hydroxy-2-phenylacetoxy]-5-methyl-2-(2-trimethylsilyl-3-furyl)-cyclohexanecarboxylate 13

The mixture of acetates **10** and **11** (5 g, 9.69 mmol) recovered from crystallisation of **11**, ratio **10**:**11** = *ca.* 5:1, was dissolved in ethanol (90 cm^3) and potassium carbonate (7 g, 50 mmol) was added. The mixture was stirred for 2 h at 0 °C, diluted with ether (150 cm^3) and washed with water (2 × 75 cm^3). The aqueous phase was extracted with ether (3 × 100 cm^3) and the organic extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue crystallised on trituration with warm hexane (70 cm^3) and the crystals were washed with cold hexane (50 cm^3) to give the alcohol **12** (2.4 g, 52%). Chromatography of the mother liquor using light petroleum–ether (4:1) as eluent gave a second crop of the alcohol **12** (0.75 g, 16%). The two batches of alcohol were combined to give the *title compound* **12** (3.15 g, 68%; 39% from the 50:50 mixture of acetates **10** and **11**), mp 78–82 °C (Found: C, 63.0; H, 6.95. $C_{25}H_{34}O_7Si$ requires C, 63.27; H, 7.22%); $[\alpha]_D$ +14.3 (*c* 0.83 in $CHCl_3$); ν_{max}/cm^{-1} 3380, 1733, 1715, 1383, 1250, 1185, 1096, 1030 and 843; δ_H 0.32 [9 H, s, $Si(CH_3)_3$], 0.52 (3 H, d, *J* 7.5, 5-CH_3), 1.11 (3 H, t, *J* 7.5, CH_2CH_3), 1.52 (2 H, m, 3-H_{ax} and 5-H), 1.79 (2 H, m, 6-H_2), 2.32 (1 H, dd, *J* 13.5, 5, 3-H_{eq}), 2.83 (1 H, m, 1-H), 3.50 (1 H, br s, OH), 4.0 (2 H, m, CH_2CH_3), 4.36 (1 H, d, *J* 2, 2-OH), 4.97 (1 H, td, *J* 11.3, 4.5, 4-H), 5.07 [1 H, s, C*H*(OH)Ph], 6.13 (1 H, d, *J* 2, 4′-H), 7.28–7.42 (5 H, m, aromatic H) and 7.49 (1 H, d, *J* 2, 5′-H); *m/z* (EI) 474 (M^+, 2.3%) and 459 (13). A sample of the other isomer **13** of the *title compound* (550 mg, 12%) was isolated from the column (Found: M^+, 474.2074. $C_{25}H_{34}O_7Si$ requires *M*, 474.2079); $[\alpha]_D$ −8.5 (*c* 0.71 in $CHCl_3$); ν_{max}/cm^{-1} 3340, 1735, 1715, 1384, 1250, 1185, 1096, 1031 and 843; δ_H 0.3 [9 H, s, $Si(CH_3)_3$], 1.02 (3 H, d, *J* 7, 5-CH_3), 1.11 (3 H, t, *J* 7.5, CH_2CH_3), 1.24 (1 H, m, 3-H_{ax}), 1.70 (1 H, m, 5-H), 1.86 (2 H, m, 6-H_2), 2.06 (1 H, dd, *J* 14.3, 5, 3-H_{eq}), 2.79 (1 H, m, 1-H), 3.5 (1 H, br s, OH), 4.0 (2 H, m, CH_2CH_3), 4.36 (1 H, d, *J* 2, 2-OH), 5.04 (1 H, td, *J* 11.3, 4.5, 4-H), 5.13 [1 H, s, C*H*(OH)Ph], 6.10 (1 H, d, *J* 2, 4′-H), 7.34 (5 H, m, aromatic H) and 7.45 (1 H, d, *J* 2, 5′-H); *m/z* (EI) 474 (M^+, 2.7%) and 459 (10). A sample of the cyclohexanediol **8** (230 mg, 7%) was also isolated from the column.

Ethyl (1*R*,2*S*,4*S*,5*S*)-2,4-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate (+)-8

The mandelate **12** (3.15 g, 6.6 mmol) was dissolved in ethanol (70 cm^3) and potassium carbonate (7 g, 50 mmol) was added. The mixture was stirred for 16 h at ambient temperature and the solvent removed under reduced pressure. The residue was dissolved in ether (100 cm^3) and washed with water (2 × 50 cm^3). The aqueous phase was extracted with ether (3 × 50 cm^3) and the organic extracts washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled using a Kugelrohr at 130 °C/0.05 mmHg to leave behind the title compound (+)-**8** (2.25 g, 99%) which was used without further purification, $[\alpha]_D$ +14.18 (*c* 0.51 in $CHCl_3$); all spectroscopic data were identical to those of the racemic compound.[3]

Ethyl (1*S*,2*R*,4*R*,5*R*)-2,4-dihydroxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate (−)-8

Following the procedure used for the synthesis of the dextrorotatory cyclohexanediol (+)-**8**, the acetylmandelate **11** (2.9 g, 5.6 mmol) gave the laevorotatory enantiomer (−)-**8** (1.85 g, 97%), $[\alpha]_D$ −14.6 (*c* 0.9 in $CHCl_3$).[3]

Ethyl (1*R*,2*S*,5*S*)-2-hydroxy-5-methyl-4-oxo-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate (−)-7

Dimethyl sulfoxide (1.70 cm^3, 24 mmol) in dichloromethane (10 cm^3) was added to oxalyl chloride (1.21 cm^3, 13.9 mmol) in dichloromethane (10 cm^3) at −78 °C. After 15 min, the cyclohexanediol (+)-**8** (4.28 g, 12.6 mmol) in dichloromethane (30 cm^3) was added. After a further 30 min, triethylamine (8.8 cm^3, 63 mmol) was added, and the mixture stirred for 15 min, before warming to room temperature over a period of 1 h. Dilution with ether (100 cm^3) was followed by washing with saturated aqueous ammonium chloride (2 × 50 cm^3). The aqueous phase was extracted with ether (3 × 75 cm^3) and the organic extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (4:1) as eluent, gave the title compound (−)-**7** (3.6 g, 85%), $[\alpha]_D$ −16.7 (*c* 0.4 in $CHCl_3$), with spectroscopic data identical to those of the racemic compound.[3]

Following the same procedure the laevorotatory cyclohexanediol (−)-**8** (200 mg, 0.59 mmol) gave the dextrorotatory cyclohexanone (+)-**7** (164 mg, 82%), $[\alpha]_D$ +15.98 (*c* 1.77 in $CHCl_3$).

Ethyl (1*RS*,4*SR*,6*SR*)-6-hydroxy-4-methoxy-3-methyl-6-(2-trimethylsilyl-3-furyl)cyclohex-2-enecarboxylate (±)-20

Aqueous sodium hydroxide (4 M; 40 cm^3) was added to silver nitrate (8 g, 47 mmol) in water (80 cm^3), and the mixture stirred vigorously in the absence of light for 30 min. The mixture was filtered, and the fine brown powder washed sequentially with water (100 cm^3), acetone (100 cm^3) and ether (200 cm^3) before being dried under reduced pressure in the dark for 48 h to give silver oxide (5 g, 92%).

The cyclohexanediol (±)-**18** (750 mg, 2.22 mmol) was dissolved in methyl iodide (42 cm^3) which had been dried by passing through silica gel, and silver(I) oxide (4 g, 17.4 mmol) was added. The mixture was stirred vigorously, whilst being heated under reflux, in the absence of light, for 48 h. After cooling, the silver(I) oxide was removed by filtration through Celite and was washed with ether (4 × 50 cm^3). Concentration under reduced pressure gave a residue, which was chromatographed, using light petroleum–ether (5:1) as eluent, to give the *title compound* (±)-**20** (620 mg, 79%) as white crystals, mp 78–70 °C (Found: C, 61.3; H, 8.2. $C_{18}H_{28}O_5Si$ requires C, 61.33; H, 8.01%); ν_{max}/cm^{-1} 3450, 1705, 1370, 1330, 1180, 1090 and 840; δ_H 0.35 [9 H, s, $Si(CH_3)_3$], 1.17 (3 H, t, *J* 7, CH_2CH_3), 1.68 (1 H, m, 5-H_{ax}), 1.84 (3 H, br s, 3-CH_3), 2.41 (1 H, dd, *J* 13, 6, 5-H_{eq}), 3.37 (3 H, s, 4-OCH_3), 3.61 (1 H, m, 1-H), 4.10 (2 H, q, *J* 7, CH_2CH_3), 4.13 (1 H, m, 4-H), 4.66 (1 H, d, *J* 2, 6-OH), 5.35 (1 H, m, 2-H), 6.20 (1 H, d, *J* 2, 4′-H) and 7.53 (1 H, d, *J* 2, 5′-H); *m/z* (CI) 370 (M^+ + 18, 1%), 353 (M^+ + 1, 3), 352 (M^+, 2) and 335 (100).

The (1*R*,4*S*,6*S*)-enantiomer (−)-**20** was similarly prepared and had $[\alpha]_D$ −90.48 (*c* 2.48 in $CHCl_3$).

(1*RS*,4*SR*,6*SR*)-6-Hydroxy-4-methoxy-3-methyl-6-(2-trimethylsilyl-3-furyl)cyclohex-2-enecarboxylic acid (±)-22

Aqueous sodium hydroxide (15 M, 1.4 cm^3) diluted with ethanol (3 cm^3) was added to the ethyl ester (±)-**20** (760 mg, 2.16 mmol) in ethanol (7 cm^3) at 0 °C. The resulting orange solution was stirred at 0 °C for 16 h, diluted with ether (20 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (5 × 10 cm^3). The aqueous extracts were acidified to pH 2 using 3 M hydrochloric acid and extracted with ethyl acetate (4 × 30 cm^3). The organic extracts were washed with brine (2 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was further dried by azeotropic distillation with benzene (3 × 25 cm^3) to give the *title compound* (±)-**22** (533 mg, 75%), as a pale yellow solid, which was used without further purification, mp 138–40 °C; ν_{max}/cm^{-1} 3600–2400, 2880, 1700, 1090 and 840; δ_H 0.30 [9 H, s, $Si(CH_3)_3$], 1.70 (1 H, m, 5-H_{ax}), 1.85 (3 H, br s, 3-CH_3), 2.38 (1 H, dd, *J* 13, 5, 5-H_{eq}), 3.37 (3 H, s, 4-OCH_3), 3.66 (1 H, m, 1-H), 4.10 (2 H, m, 4-H and CO_2H), 4.30 (1 H, br s, 6-OH), 5.40 (1 H, m, 2-H), 6.20 (1 H, d, *J* 2, 4′-H) and 7.53 (1 H, d, *J* 2, 5′-H); *m/z* (CI) 324 (M^+, 4%), 303 (33) and 275 (18). The ether phase was washed with brine (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give ethyl 5-methyl-2-(2-trimethylsilyl-3-furyl)benzoate (126 mg, 19%).

The (1*R*,4*S*,6*S*)-enantiomer (−)-**22** was similarly prepared and had $[\alpha]_D$ −85.06 (*c* 0.79 in $CHCl_3$).

2-Trimethylsilylethyl (1*RS*,4*SR*,6*SR*)-6-hydroxy-4-methoxy-3-methyl-6-(2-trimethylsilyl-3-furyl)cyclohex-2-enecarboxylate (±)-23

2-Trimethylsilylethanol (1.1 cm^3, 7.7 mmol) was added to the crude acid (±)-**22** (533 mg, 1.65 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) in dichloromethane (5.7 cm^3) and the mixture cooled to 0 °C. Dicyclohexylcarbodiimide (445 mg, 2.16 mmol) in dichloromethane (3.7 cm^3) was added dropwise, and the resultant mixture stirred at ambient temperature for 16 h. The reaction mixture was diluted with ether (20 cm^3), filtered through Celite and the solvent removed under reduced pressure. The residue was purified by flash chromatography, using light petroleum–ether (20:1) as eluent, to give the *title compound* (±)-**23** (548 mg, 78%) as a viscous oil (Found: C, 59.55; H, 8.85. $C_{21}H_{36}O_5Si_2$ requires C, 59.39; H, 8.55%); ν_{max}/cm^{-1} 3420, 1700, 1375, 1330, 1085 and 835; δ_H 0.02 and 0.34 [each 9 H, s, $Si(CH_3)_3$], 0.90 [2 H, m, $CH_2Si(CH_3)_3$], 1.66 (1 H, m, 5-H_{ax}), 1.84 (3 H, br s, 3-CH_3), 2.40 (1 H, dd, *J* 13, 6, 5-H_{eq}), 3.37 (3 H, s, 4-OCH_3), 3.58 (1 H, m, 1-H), 4.12 [3 H, m, 4-H and $CH_2CH_2Si(CH_3)_3$], 4.73 (1 H, d, *J* 2, 6-OH), 5.34 (1 H, m, 2-H), 6.18 (1 H, d, *J* 2, 4′-H) and 7.52 (1 H, d, *J* 2, 5′-H); *m/z* (CI) 424 (M^+).

The (1*R*,4*S*,6*S*)-enantiomer (−)-**23** was similarly prepared and had $[\alpha]_D$ −78.68 (*c* 0.91 in $CHCl_3$).

Ethyl (1*RS*,4*SR*,6*SR*)-6-hydroxy-6-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-4-methoxy-3-methylcyclohex-2-enecarboxylate (±)-24

A solution of the 2-trimethylsilylfuran (±)-**20** (87 mg, 0.25 mmol) in dichloromethane–methanol (50:50; 10 cm^3) containing a trace of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (tetraphenylporphyrin) was cooled to −78 °C and irradiated for 20 min by a 250 W tungsten light source whilst oxygen was bubbled through the solution. The reaction was allowed to warm to room temperature, then concentrated under reduced pressure to give a residue which was taken up in ether. The mixture was filtered and the filtrate concentrated under reduced pressure. Chromatography of the resultant gum using gradient elution with light petroleum–ether (66:34 to 25:75) as eluent, gave the *title compound* (±)-**24** (75 mg, 98%) as a mixture of epimers; ν_{max}/cm^{-1} 3570–3160, 1764, 1705, 1442, 1369, 1382, 1305, 1194, 1103, 1055 and 1018; δ_H 1.27 (3 H, m, OCH_2CH_3), 1.83 (3 H, s, 3-CH_3), 2.24 (2 H, d, *J* 7, 5-H_2), 3.56 (3 H, s, OCH_3), 3.69 (0.5 H, m, 1-H), 4.08 (4.5 H, m, 1-H, OCH_2CH_3, 4-H, OH), 4.25 and 4.56 (each 0.5 H, d, *J* 2.5, 6-OH), 5.42 (1 H, m, 2-H), 6.09 (1 H, m, 5′-H) and 7.23 and 7.15 (each 0.5 H, s, 4′-H); *m/z* (CI) 330 (M^+ + 18, 43%), 313 (M^+ + 1, 23) and 281 (100).

2-Trimethylsilylethyl (1*R*,4*S*,6*S*)-6-hydroxy-6-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-4-methoxy-3-methylcyclohex-2-enecarboxylate 3

Following the procedure outlined for the synthesis of hydroxybutenolide (±)-**24**, the 2-trimethylsilylfuran (−)-**23** (210 mg, 0.495 mmol) gave, after chromatography, the hydroxybutenolide **3** as a hygroscopic gum. This was recrystallised from hexane–dichloromethane to yield the *title compound* **3** (181 mg, 95%) as a mixture of epimers; ν_{max}/cm^{-1} 3391, 1767, 1735, 1251, 1177, 1112, 1073, 929, 861 and 838; δ_H 0.06 [9 H, s, $Si(CH_3)_3$], 0.98 [2 H, m, $CH_2Si(CH_3)_3$], 1.80 (3 H, br s, 3-CH_3), 2.15 (2 H, m, 5-H_2), 3.36 (3 H, s, 4-OCH_3), 3.63 and 3.73 (each 0.5 H, d, *J* 9, 5′-OH), 4.06 [4 H, m, $CH_2CH_2Si(CH_3)_3$, 1-H and 4-H], 4.33 and 4.65 (each 0.5 H, s, 6-OH), 5.37 and 5.42 (each 0.5 H, d, *J* 2, 2-H), 6.1 (1 H, m, 5′-H) and 7.16 and 7.22 (each 0.5 H, s, 4′-H); *m/z* (CI) 402 (M^+ + 18, 45%), 384 (M^+, 8.4) and 357 (20).

Ethyl (1*R*,2*S*,4*S*,5*S*)-2-hydroxy-4-methoxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate (+)-26

Following the procedure outlined for the synthesis of the methyl ether **20**, the diol (+)-**8** (354 mg, 1.04 mmol) gave the *title compound* (+)-**26** (370 mg, 100%) as a white crystalline solid, mp 83–85 °C (Found: C, 61.0; H, 8.6. $C_{18}H_{30}O_5Si$ requires C, 60.98; H, 8.53%); $[\alpha]_D$ +34.1 (*c* 0.9 in $CHCl_3$); ν_{max}/cm^{-1} 3471, 1711, 1464, 1376, 1249, 1184, 1102 and 844; δ_H 0.32 [9 H, s, $Si(CH_3)_3$], 1.10 (3 H, d, *J* 7.5, 5-CH_3), 1.12 (3 H, t, *J* 7, CH_2CH_3), 1.28 (1 H, m, 3-H_{ax}), 1.52 (1 H, m, 5-H), 1.8 (2 H, m, 6-H_2), 2.34 (1 H, dd, *J* 13.5, 4.5, 3-H_{eq}), 2.84 (1 H, m, 1-H), 3.23 (1 H, td, *J* 11.3, 4.5, 4-H), 3.33 (3 H, s, 4-OCH_3), 4.02 (2 H, m, CH_2CH_3), 4.43 (1 H, br s, 2-OH), 6.18 (1 H, d, *J* 2, 4′-H) and 7.50 (1 H, d, *J* 2, 5′-H); *m/z* (EI) 354 (M^+, 9%), 339 (14) and 307 (11).

(1*R*,2*S*,4*S*,5*S*)-2-Hydroxy-4-methoxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylic acid (+)-27

Following the procedure used for the preparation of the carboxylic acid **22**, the ester (+)-**26** (220 mg, 0.62 mmol) after 48 h at 5 °C, gave the *title compound* (+)-**27** (200 mg, 99%) as a pale yellow crystalline solid, mp 122–125 °C; $[\alpha]_D$ +35.7 (*c* 0.92 in $CHCl_3$); ν_{max}/cm^{-1} 3440–2520, 1710, 1383, 1249, 1182, 1097 and 843; δ_H 0.3 [9 H, s, $Si(CH_3)_3$], 1.08 (3 H, d, *J* 7.5, 5-CH_3), 1.27 (1 H, dd, *J* 14, 11, 3-H_{ax}), 1.54 (1 H, m, 5-H), 1.82 (3 H, m, 6-H_2 and CO_2H), 2.31 (1 H, dd, *J* 14, 5, 3-H_{eq}), 2.91 (1 H, dd, *J* 14, 3.7, 1-H), 3.23 (1 H, td, *J* 11, 5, 4-H), 3.33 (3 H, s, 4-OCH_3), 4.2 (1 H, br s, 2-OH), 6.19 (1 H, d, *J* 2, 4′-H) and 7.50 (1 H, d, *J* 2, 5′-H); *m/z* (EI) 326 (M^+, 14%), 293 (13) and 225 (100).

2-Trimethylsilylethyl (1*R*,2*S*,4*S*,5*S*)-2-hydroxy-4-methoxy-5-methyl-2-(2-trimethylsilyl-3-furyl)cyclohexanecarboxylate-(+)-28

Following the procedure outlined for the preparation of the ester **23**, the carboxylic acid (+)-**27** (145 mg, 0.445 mmol) gave, after chromatography using light petroleum–ether (12:1) as eluent, the *title compound* (+)-**28** (155 mg, 82%) as a viscous oil (Found: M^+, 426.2258. $C_{21}H_{38}O_5Si$ requires *M*, 426.2258); $[\alpha]_D$ +31.68 (*c* 1.25 in $CHCl_3$); ν_{max}/cm^{-1} 3463, 1709, 1385, 1251, 1173, 1102 and 841; δ_H 0.00 and 0.33 [each 9 H, s, $Si(CH_3)_3$], 0.85 [2 H, m, $CH_2Si(CH_3)_3$], 1.08 (3 H, d, *J* 7.5, 5-CH_3), 1.27 (1 H, m, 3-H_{ax}), 1.55 (1 H, m, 5-H), 1.8 (2 H, m, 6-H_2), 2.32 (1 H, dd, *J* 14.3, 4, 3-H_{eq}), 2.82 (1 H, dd, *J* 12, 4.5, 1-H), 3.23 (1 H, td, *J* 10, 4, 4-H), 3.33 (3 H, s, 4-OCH_3), 4.03 [2 H, m, $CH_2CH_2Si(CH_3)_3$], 4.50 (1 H, s, 2-OH), 6.18 (1 H, d, *J* 2,

4′-H) and 7.50 (1 H, d, *J* 2, 5′-H); *m/z* (EI) 426 (M^+, 5%), 383 (8), 351 (7) and 225 (75).

2-Trimethylsilylethyl (1*R*,2*S*,4*S*,5*S*)-2-hydroxy-2-(5-hydroxy-2-oxo-1-oxacyclopent-3-en-3-yl)-4-methoxy-5-methylcyclohexanecarboxylate 29

Following the procedure outlined for the preparation of the hydroxybutenolide **24**, the 2-trimethylsilylfuran (+)-**28** (200 mg, 0.47 mmol) gave, after chromatography with gradient elution using light petroleum–ether (2:1 to 1:3) as eluent, the *title compound* **29** (165 mg, 91%), a mixture of epimers, as a highly crystalline solid (Found: C, 56.1; H, 7.9. $C_{18}H_{30}O_7Si$ requires C, 55.94; H, 7.82%); ν_{max}/cm^{-1} 3620–3200, 1765, 1705, 1252, 1176, 1106, 1013 and 838; δ_H 0.02 [9 H, s, $Si(CH_3)_3$], 0.92 [2 H, m, $CH_2Si(CH_3)_3$], 1.07 (3 H, d, *J* 7, 5-CH_3), 1.67 (3 H, m, 6-H, 3-H_{ax} and 5-H), 1.88 (1 H, m, 6-H), 2.10 (1 H, m, 3-H_{eq}), 3.17 (1 H, td, *J* 11.3, 4.5, 4-H), 3.25 and 3.3 (each 0.5 H, m, 1-H), 3.32 and 3.33 (each 1.5 H, s, 4-OCH_3), 3.65 and 3.73 (each 0.5 H, m, 5′-OH), 4.10 [2 H, m, $CH_2CH_2Si(CH_3)_3$], 4.45 and 4.57 (each 0.5 H, d, *J* 2, 2-OH), 6.03 and 6.07 (each 0.5 H, d, *J* 6, 5′-H) and 7.18 and 7.2 (each 0.5 H, s, 4′-H); *m/z* (CI) 359 (100%) and 341 (82).

Methyl (6*R*,2*Z*,4*E*,8*E*)-6,8-dimethyl-2-[(1*S*,2*R*,4*S*,5*S*)-1-hydroxy-5-methoxy-4-methyl-2-(2-trimethylsilylethoxycarbonyl)-cyclohexan-1-yl]-10-{(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspiro[5.5]undecan-2-yl}-deca-2,4,8-trienoate 32

tert-Butyllithium (0.27 mmol) was added to a solution of the phosphonium salt **2** (200 mg, 0.24 mmol) in tetrahydrofuran (3 cm^3) at −40 °C and the solution stirred at this temperature for 0.5 h. Lithium hexamethyldisilazide (0.61 mmol) in tetrahydrofuran (2 cm^3) was added, and the mixture cooled to −78 °C and added to a solution of the hydroxybutenolide **29** (120 mg, 0.31 mmol) in tetrahydrofuran (2 cm^3) at −78 °C. The mixture was warmed to −15 °C over 3 h, and saturated aqueous ammonium chloride (5 cm^3) and ether (10 cm^3) were added. The ethereal extract was washed with water (5 cm^3), the aqueous phase extracted with ether (3 × 5 cm^3) and the organic extracts washed with brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether–acetic acid (1:1:0.01) as eluent gave the acid **31** as a mixture of *E*- and *Z*-isomers. This was dissolved in ether (10 cm^3) and diazomethane in ether added until a yellow colour persisted. Acetic acid was added to remove the excess of diazomethane and the solution concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (6:1) as eluent, gave the esters as a mixture of *E*- and *Z*-isomers. This was dissolved in benzene (3 cm^3) and iodine (6 mg, 0.024 mmol) in benzene (1 cm^3) was added, and the mixture exposed to sunlight for 8 h. Ether (5 cm^3) was added, and the solution washed with saturated aqueous sodium thiosulfate (5 cm^3) and extracted with ether (3 × 5 cm^3). The organic extracts were washed with brine (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (8:1) as eluent gave the *title compound* **32** (108 mg, 54%) as a viscous oil (Found: M^+, 834.5445. $C_{46}H_{82}O_9Si_2$ requires *M*, 834.5497: Found: $M^+ - H_2O$, 816.5406. $C_{46}H_{80}O_8Si_2$ requires *M*, 816.5391); $[\alpha]_D$ +42.8 (*c* 0.6 in $CHCl_3$); ν_{max}/cm^{-1} 3408, 1712, 1630, 1462, 1385, 1252, 1173, 1091 and 1012; δ_H 0.02 [9 H, s, $Si(CH_3)_3$], 0.05 [6 H, s, $Si(CH_3)_2$], 0.78 (3 H, d, *J* 6, 9″-CH_3), 0.82 (3 H, d, *J* 7, CH_3CHCH_3), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.92 [8 H, m, $CH_2Si(CH_3)_3$, CH_3CHCH_3, 6-CH_3], 1.05 (3 H, d, *J* 6, 4′-CH_3), 1.25 (3 H, m, 3″-H, 5″-H and 6′-H), 1.59 (3 H, s, 8-CH_3), 1.38–1.73 (7 H, overlapping m, 9″-H, 10″-H_2, 11″-H_2, 3′-H and 4′-H), 1.74–1.91 (5 H, overlapping m, 7-H, 3′-H′, 3″-H′, 5″-H′ and 8″-CH), 2.15 (4 H, m, 7-H′, 6′-H_{eq} and 10-H_2), 2.41 (1 H, m, 6-H), 3.05 (2 H, m, 8″-H and 2′-H), 3.17 (1 H, td, *J* 10, 5, 5′-H), 3.35 (3 H, s, 5′-OMe), 3.52 (1 H, m, 2″-H), 3.78 (3 H, s, CO_2CH_3), 4.1 [3 H, m, $CH_2CH_2Si(CH_3)_3$ and 4″-H], 4.36 (1 H, d, *J* 2, 1′-OH), 5.22 (1 H, br t, *J* 7, 9-H), 5.92 (1 H, dd, *J* 15, 7, 5-H), 6.36 (1 H, dd, *J* 15, 11, 4-H) and 6.68 (1 H, d, *J* 11, 3-H); *m/z* (CI) 852 (M^+ + 18, 4%), 835 (M^+ + 1, 5), 834 (M^+, 5), 817 (5), 703 (18) and 685 (31).

(1*R*,2*S*,4*S*,5*S*)-2-{(6*R*,2*Z*,4*E*,8*E*)-6,8-Dimethyl-10-[(2*R*,4*S*,6*R*,-8*R*,9*S*)-4-hydroxy-9-methyl-8-isopropyl-1,7-dioxaspirol[5.5]-undecan-2-yl]-1-methoxy-1-oxodeca-2,4,8-trien-2-yl}-2-hydroxy-4-methoxy-5-methylcyclohexanecarboxylic acid 33

Tetrabutylammonium fluoride (1 M in tetrahydrofuran; 0.55 cm^3, 0.55 mmol) was added to the ester **32** (90 mg, 0.108 mmol) in tetrahydrofuran (5 cm^3) at 0 °C. The solution was stirred at room temperature for 10 h, and ethyl acetate (15 cm^3) and aqueous hydrogen chloride (3 M; 5 cm^3) were added. The aqueous layer was extracted with ethyl acetate (3 × 5 cm^3) and the organic extracts were washed with brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether–propan-2-ol–acetic acid (1:1:0.02:0.01) as eluent, gave the *title compound* **33** (67 mg, ~100%) (Found: $M^+ - H_2O$, 602.3824. $C_{35}H_{56}O_9$ requires *M*, 602.3818); ν_{max}/cm^{-1} 3630–2540, 1712, 1680, 1631, 1553, 1384, 1092 and 1011; δ_H 0.78 (3 H, d, *J* 6, 9″-CH_3), 0.82 and 0.95 (each 3 H, d, *J* 7, CH_3CHCH_3), 1.05 (6 H, m, 5-CH_3 and 6′-CH_3), 1.15–1.39 (3 H, overlapping m, 3-H_{ax}, 3″-H_{ax} and 5″-H_{ax}), 1.60 (3 H, br s, 8′-CH_3), 1.39–1.76 (8 H, overlapping m, 5-H, 6-H_2, 9″-H, 10″-H_2 and 11″-H_2), 1.76–2.03 (4 H, m, 7′-H, 3″-H_{eq}, 5″-H_{eq} and 8″-CH), 2.03–2.36 (4 H, m, 3-H_{eq}, 7′-H′ and 10′-H_2), 2.48 (1 H, m, 6′-H), 3.03 (1 H, d, *J* 10, 8″-H), 3.17 (2 H, m, 1-H and 4-H), 3.35 (3 H, s, 4-OCH_3), 3.51 (1 H, m, 2″-H), 3.81 (3 H, s, CO_2CH_3), 4.18 (1 H, m, 4″-H), 4.45–4.76 (3 H, br s, 2-OH, 4″-OH and CO_2H), 4.98 (1 H, m, 9′-H), 5.73 (1 H, dd, *J* 15, 7.5, 5′-H), 6.32 (1 H, dd, *J* 15, 11, 4′-H) and 6.66 (1 H, d, *J* 11, 3′-H); *m/z* (CI) 620 (M^+, 3.5%), 602 ($M^+ - 18$, 99) and 585 (100).

(4*S*)-8-Methoxycarbonyl-3,4-dihydro-8-norhydroxymethylmilbemycin E 34

The hydroxy acid **33** (36 mg, 0.058 mmol) and 4-dimethylaminopyridine (0.72 mg, 5.8 μmol) in dichloromethane (5 cm^3) were added, over a period of 5 h using a syringe pump, to dicyclohexylcarbodiimide (18 mg, 0.088 mmol) in dichloromethane (10 cm^3) at 0 °C. On completion of the addition, the reaction was stirred at 5 °C for 16 h, and the solvent removed under reduced pressure. The residue was dissolved in ether (2 cm^3), filtered and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (4:1) as eluent gave the *title compound* **34** (12 mg, 34%) (Found: M^+, 602.3817. $C_{35}H_{54}O_8$ requires *M*, 602.3818); $[\alpha]_D$ +183.6 (*c* 0.61 in $CHCl_3$); ν_{max}/cm^{-1} 3452, 1707, 1458, 1376, 1333, 1275, 1181, 1117, 1094 and 1010; δ_H 0.72 (1 H, q, *J* 12, 18-H_{ax}), 0.79 (3 H, d, *J* 6.5, 24-CH_3), 0.83 and 1.01 (each 3 H, d, *J* 7, CH_3CHCH_3), 1.05 and 1.04 (each 3 H, d, *J* 6.55, 4-CH_3 and 12-CH_3), 1.43–1.53 (6 H, overlapping m), 1.57 (3 H, s, 14-CH_3), 1.58–1.91 (8 H, overlapping m), 2.12–2.30 (4 H, m, 6-H, 13-H, 16-H_2), 2.47 (1 H, m, 12-H), 3.06 (1 H, dd, *J* 10, 2, 25-H), 3.21 (2 H, m, 2-H and 5-H), 3.34 (3 H, s, 5-OCH_3), 3.60 (1 H, m, 17-H), 3.78 (3 H, s, CO_2CH_3), 4.70 (1 H, d, *J* 2.5, 7-OH), 4.82 (1 H, d, *J* 9, 15-H), 5.27 (1 H, m, 19-H), 5.60 (1 H, dd, *J* 15, 10, 11-H), 6.27 (1 H, dd, *J* 15, 11, 10-H) and 6.56 (1 H, d, *J* 11, 9-H); *m/z* (CI) 620 (M^+ + 18, 4%), 602 (M^+, 24), 601 (47), 585 (98) and 408 (100).

(4*S*)-3,4-Dihydromilbemycin E 35

Red-Al® [Sodium bis(2-methoxyethoxy)aluminium hydride; 0.085 M; 0.5 cm^3, 0.042 mmol] was added to the ester **34** (4.6 mg, 7.6 μmol) in toluene (0.2 cm^3) at 0 °C. The mixture was stirred for 2 h at 0 °C, and saturated aqueous ammonium chloride (0.5 cm^3) and ether (5 cm^3) were added. The aqueous phase was extracted with ether (3 × 2 cm^3) and the organic extracts washed with brine (3 cm^3), dried ($MgSO_4$) and concentrated

under reduced pressure. Chromatography of the residue using light petroleum–ether (1:1) as eluent, gave the *title compound* **35** (3 mg, 68%) (Found: M^+, 574.3868. $C_{34}H_{54}O_7$ requires *M*, 574.3869); $[\alpha]_D$ +189.7 (*c* 0.66 in $CHCl_3$); ν_{max}/cm^{-1} 3453, 1706, 1457, 1375, 1276, 1176, 1095 and 1009; δ_H 0.70 (1 H, q, *J* 11.7, 18-H_{ax}), 0.80 (3 H, d, *J* 6.5, 24-CH_3), 0.83 and 1.01 (each 3 H, d, *J* 7, CH_3CHCH_3), 1.04 (3 H, d, *J* 6.5, 12-CH_3), 1.06 (3 H, d, *J* 6.5, 4-CH_3), 1.27 (1 H, br s, CH_2OH), 1.38–1.67 (8 H, m, 4-H, 6-H, 20-H, 24-H, 22-H_2 and 23-H_2), 1.60 (3 H, s, 14-CH_3), 1.81 (6 H, m, 3-H_2, 13-H, 18-H, 20-H and 25-CH), 2.21 (4 H, m, 6-H, 13-H and 16-H_2), 2.47 (1 H, m, 12-H), 2.70 (1 H, m, 2-H), 3.06 (1 H, dd, *J* 10, 2, 25-H), 3.24 (1 H, td, *J* 10, 4, 5-H), 3.36 (3 H, s, 5-OCH_3), 3.61 (1 H, m, 17-H), 4.12 (1 H, d, *J* 2.5, 7-OH), 4.2 (2 H, m, CH_2OH), 4.83 (1 H, m, 15-H), 5.33 (1 H, m, 19-H), 5.49 (1 H, dd, *J* 15, 10, 11-H), 6.21 (1 H, dd, *J* 15, 11, 10-H) and 6.31 (1 H, d, *J* 11, 9-H); *m/z* (CI) 575 (M^+ + 1, 6%), 574 (M^+, 2), 558 (46), 557 (100) and 539 (28).

Methyl (6*R*,2*Z*,4*E*,8*E*)-6,8-dimethyl-2-[(1*S*,2*R*,5*S*)-1-hydroxy-5-methoxy-4-methyl-2-trimethylsilylethoxycarbonylcyclohex-3-en-1-yl]-10-{(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspirol[5.5]undecan-2-yl}deca-2,4,8-trienoate 37

Lithium hexamethyldisilazide (0.72 mmol) in tetrahydrofuran (2 cm^3) was added *via* a cannula to the phosphonium salt **2** (138 mg, 0.166 mmol) and the hydroxybutenolide **3** (90 mg, 0.28 mmol) in tetrahydrofuran (3 cm^3) at −78 °C. The resulting orange solution was warmed to −15 °C over 1 h and stirred at this temperature a further 1 h. (The disappearance of the orange colour was noted at −20 °C.) Saturated aqueous ammonium chloride (3 cm^3) and ether (5 cm^3) were added. The organic layer was washed with water (5 cm^3) and the aqueous phase extracted with ether (3 × 10 cm^3). The organic extracts were washed with brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum–ether–acetic acid (1:1:0.01) as eluent, gave a residue which was treated separately with diazomethane and iodine, as outlined above for the synthesis of the ester **32**, to give the *title compound* **37** (58 mg, 42%) as a viscous oil (Found: $M^+ - H_2O$, 814.5220. $C_{48}H_{78}O_8Si_2$ requires *M*, 814.5235); $[\alpha]_D$ −8.75 (*c* 0.64 in $CHCl_3$); ν_{max}/cm^{-1} 3590, 1714, 1460, 1384, 1252, 1216, 1189, 1170, 1089, 1067, 1009, 983 and 837; δ_H 0.02 [9 H, s, $Si(CH_3)_3$], 0.07 [6 H, s, $Si(CH_3)_2$], 0.76 (3 H, d, *J* 6, 9″-CH_3), 0.81 (3 H, d, *J* 7, CH_3CHCH_3), 0.86–1.01 [17 H, overlapping m, CH_2Si$(CH_3)_3$, CH_3CHCH_3, Si$C(CH_3)_3$, 6-CH_3], 1.21 (2 H, m, 3″-H_{ax} and 5″-H_{ax}), 1.60 (3 H, s, 8-CH_3), 1.40–1.69 (5 H, overlapping m, 9″-H, 10″-H_2 and 11″-H_2), 1.80 (3 H, s, 4′-CH_3), 1.89 (5 H, m, 8″-CH, 7-H, 6′-H_{ax}, 3″-H_{eq} and 5″-H_{eq}), 2.09–2.33 (4 H, m, 7-H′, 10-H_2 and 6′-H_{eq}), 2.44 (1 H, m, 6-H), 3.01 (1 H, m, 8″-H), 3.36 (3 H, s, 5′-OCH_3), 3.51 (1 H, m, 2″-H), 3.80 (3 H, s, CO_2CH_3), 3.83 (1 H, m, 2′-H), 4.12 [4 H, m, CH_2CH_2Si$(CH_3)_3$, 5′-H and 4″-H], 4.71 (1 H, br s, 1′-OH), 5.22 (1 H, br t, *J* 7, 9-H), 5.31 (1 H, m, 3′-H), 5.98 (1 H, dd, *J* 15, 7.5, 5-H), 6.43 (1 H, dd, *J* 15, 12, 4-H) and 6.79 (1 H, d, *J* 12, 3-H); *m/z* (CI) 850 (M^+ + 18, 4.5%), 832 (M^+, 1.5), 815 (7) and 683 (80).

(1*R*,4*S*,6*S*)-6-{(6*R*,2*Z*,4*E*,8*E*)-6,8-Dimethyl-10-[(2*R*,4*S*,6*R*,8*R*,9*S*)-4-hydroxy-9-methyl-8-isopropyl-1,7-dioxaspirol[5.5]-undecan-2-yl]-1-methoxy-1-oxodeca-2,4,8-trien-2-yl}-6-hydroxy-4-methoxy-3-methylcyclohex-2-enecarboxylic acid 39

Following the procedure outlined above for the synthesis of the carboxylic acid **33**, the ester **37** (20 mg, 0.024 mmol) gave the *title compound* **39** (15 mg, 100%); ν_{max}/cm^{-1} 3600–2400, 1714, 1636, 1385, 1261, 1191, 1090, 1011 and 983; δ_H 0.78 (3 H, d, *J* 6, 9″-CH_3), 0.82 and 0.95 (each 3 H, d, *J* 7, CH_3CHCH_3), 1.03 (3 H, d, *J* 7.5, 6′-CH_3), 1.27 (2 H, m, 3″-H_{ax} and 5″-H_{ax}), 1.60 (3 H, br s, 8′-CH_3), 1.40–1.75 (5 H, overlapping m, 9″-H, 10″-H_2 and 11″-H_2), 1.81 (3 H, br s, 3-CH_3), 1.81–2.02 (5 H, overlapping m, 5-H_{ax}, 7′-H, 8″-CH, 3″-H_{eq} and 5″-H_{eq}), 2.02–2.34 (4 H, overlapping m, 5-H_{eq}, 7′-H′ and 10′-H_2), 2.47 (1 H, m, 6′-H), 3.04 (1 H, m, 8″-H), 3.37 (3 H, s, 4-OCH_3), 3.53 (1 H, m, 2″-H), 3.80 (3 H, s, CO_2CH_3), 3.91 (1 H, m, 1-H), 4.08 (1 H, m, 4-H), 4.20 (1 H, m, 4″-H), 4.50–4.75 (3 H, br s, 6-OH, 4″-OH and CO_2H), 5.0 (1 H, m, 9′-H), 5.36 (1 H, m, 2-H), 5.78 (1 H, dd, *J* 15, 8.6, 5′-H), 6.40 (1 H, dd, *J* 15, 12, 4′-H) and 6.76 (1 H, d, *J* 12, 3′-H); *m/z* (FAB) 600 (M^+ − 18, 10%).

8-Methoxycarbonyl-8-norhydroxymethylmilbemycin E 40

Following the procedure outlined above for the synthesis of the lactone **34**, the hydroxy acid **39** (15 mg, 0.024 mmol) gave the *title compound* **40** (5.3 mg, 37%) (Found: M^+, 600.3666. $C_{35}H_{52}O_8$ requires *M*, 600.3662); $[\alpha]_D$ +152.4 (*c* 0.37 in $CHCl_3$); ν_{max}/cm^{-1} 3445, 1707, 1625, 1339, 1192, 1120, 1098, 1067 and 1010; δ_H 0.78 (1 H, q, *J* 12, 18-H_{ax}), 0.79 (3 H, d, *J* 6, 24-CH_3), 0.85 and 1.01 (each 3 H, d, *J* 7, CH_3CHCH_3), 1.04 (3 H, d, *J* 6.8, 12-CH_3), 1.46 (1 H, t, *J* 12, 20-H_{ax}), 1.40–1.75 (9 H, overlapping m, 6-H_{ax}, 14-CH_3, 22-H_2, 23-H_2 and 24-H), 1.80 (3 H, s, 4-CH_3), 1.87 (3 H, m, 25-CH, 18-H_{eq} and 20-H_{eq}), 2.04 (1 H, m, 13-H), 2.21 (4 H, m, 6-H_{eq}, 13-H and 16-H_2), 2.5 (1 H, m, 12-H), 3.05 (1 H, m, 25-H), 3.35 (3 H, s, 5-OCH_3), 3.60 (1 H, m, 17-H), 3.80 (3 H, s, CO_2CH_3), 3.92 (1 H, m, 2-H), 4.06 (1 H, m, 5-H), 4.52 (1 H, d, *J* 2, 7-OH), 4.84 (1 H, d *J* 7.5, 15-H), 5.28 (1 H, s, 3-H), 5.32 (1 H, m, 19-H), 5.63 (1 H, dd, *J* 13.5, 8.3, 11-H), 6.39 (1 H, dd, *J* 13.5, 11.3, 10-H) and 6.71 (1 H, d, *J* 11.3, 9-H); *m/z* (EI) 600 (M^+, 1%).

Milbemycin E 1

The ester **40** (3 mg, 5 μmol) was dissolved in toluene (0.3 cm^3) and cooled to −78 °C. Diisobutylaluminium hydride (1 M in toluene; 50 μl) was added and the reaction stirred at −78 °C for 1 h. Water (0.1 cm^3) and ethyl acetate (3 cm^3) were added and the mixture allowed to warm to room temperature. Aqueous hydrogen chloride (3 M; 0.5 cm^3) was added and the aqueous phase was extracted with ethyl acetate (3 × 2 cm^3). The organic extracts were washed with brine (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave milbemycin E **1** (2.5 mg, 87%) as an amorphous glass, $[\alpha]_D$ +153 (*c* 0.15 in acetone) {lit.,[14] $[\alpha]_D$ +157 (*c* 0.25 in acetone)}; ν_{max}/cm^{-1} 3470, 1709, 1460, 1377, 1165, 1099 and 1010; δ_H(500 MHz) 0.77 (1 H, q, *J* 12, 18-H_{ax}), 0.80 (3 H, d, *J* 7, 24-CH_3), 0.83 and 1.02 (each 3 H, d, *J* 7.5, CH_3CHCH_3), 1.04 (3 H, d, *J* 7, 12-CH_3), 1.38 (1 H, t, *J* 12, 20-H_{ax}), 1.42–1.69 (5 H, overlapping m, 22-H_2, 23-H_2 and 24-H), 1.59 (3 H, br s, 14-CH_3), 1.73–1.95 (5 H, m, 6-H, 13-H, 18-H_{eq}, 20-H_{eq} and 25-CH), 1.82 (3 H, br s, 4-CH_3), 2.22 (4 H, m, 6-H, 13-H, 16-H_2), 2.48 (1 H, m, 12-H), 3.04 (1 H, dd, *J* 10, 2, 25-H), 3.38 (3 H, s, 5-OCH_3), 3.50 (1 H, m, 2-H), 3.60 (1 H, m, 17-H), 3.75 (1 H, d, *J* 2, 7-OH), 4.03 (1 H, m, 5-H), 4.18 and 4.27 (each 1 H, d, *J* 13.5, C*H*HOH), 4.85 (1 H, m, 15-H), 5.33 (1 H, narrow m, 3-H), 5.36 (1 H, m, 19-H), 5.51 (1 H, dd, *J* 14, 10, 11-H), 6.25 (1 H, dd, *J* 14, 11, 10-H) and 6.42 (1 H, d, *J* 11, 9-H); *m/z* (EI) 572 (M^+, 23%).

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