Synthesis of a Macrocyclic Analogue of Milbemycin β_1; *X*-Ray Structure of (1*RS*, 4*RS*, 6*SR*, 7*SR*, 9*SR*, 19*RS*)-(10*Z*, 12*E*, 16*E*)-6,16-Dimethyl-9-hydroxy-7-methoxy-10-methoxycarbonyl-2-oxatricyclo[17.3.1.$0^{4,9}$]tricosa-10,12,16-trien-3-one

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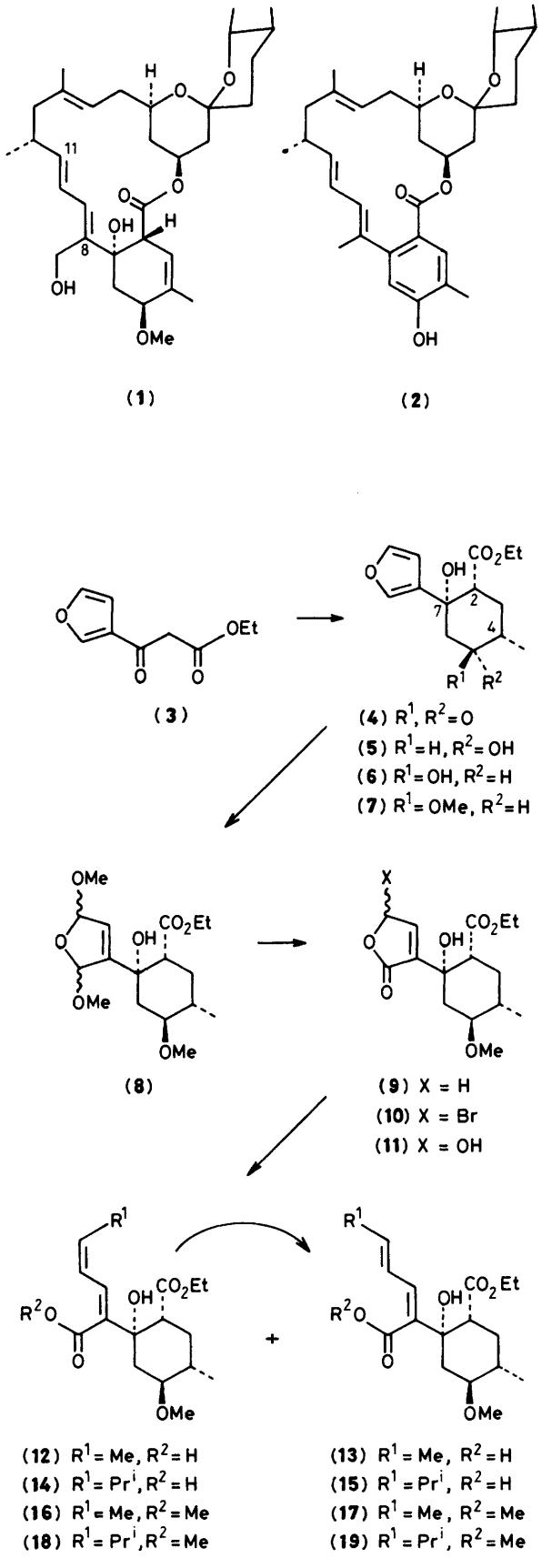
The milbemycin β_1 analogue (**38**) has been prepared by a convergent route involving the Wittig condensation between phosphonium salt (**28**) and 5-hydroxy-5*H*-furan-2-one (**11**), followed by diene isomerization, transprotection, lactonization, and reduction; the structure of the ester intermediate (**37**) was established by *X*-ray crystallography.

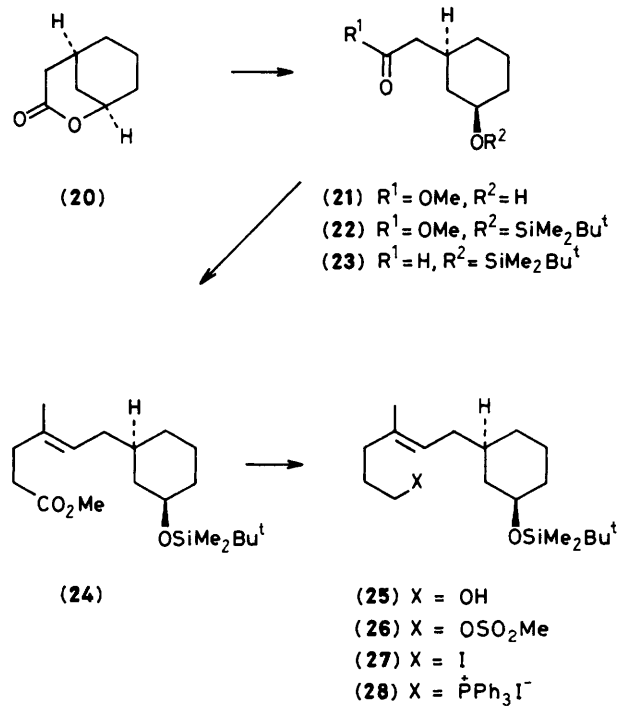
Synthesis of the milbemycins, *e.g.* β_1 (**1**),[1] a group of macrolide antibiotics of current interest because of their potent pesticidal activity, is under intense investigation at present. To date two syntheses of the aromatic milbemycin β_3 (**2**) have been described,[2] together with several approaches to the synthesis of the spiro-acetal 'northern hemisphere'.[3] We report a convergent synthesis of the milbemycin β_1 analogue (**38**) which uses a 3-substituted furan to introduce the 8-hydroxymethyl-(8*E*, 10*E*)-dienyl fragment.

Thus furan-3-carboxylic acid was converted *via* its acid chloride into keto-ester (**3**) which was treated with propen-2-yl methyl ketone and sodium hydroxide in ethanol (20 °C, 18 h) to give hydroxycyclohexanone (**4**) isolated after recrystallization, as a single diastereoisomer (65%).† The C(2)–C(7)

† All new compounds were fully characterized spectroscopically, and whenever possible by analytical data.



Scheme 1



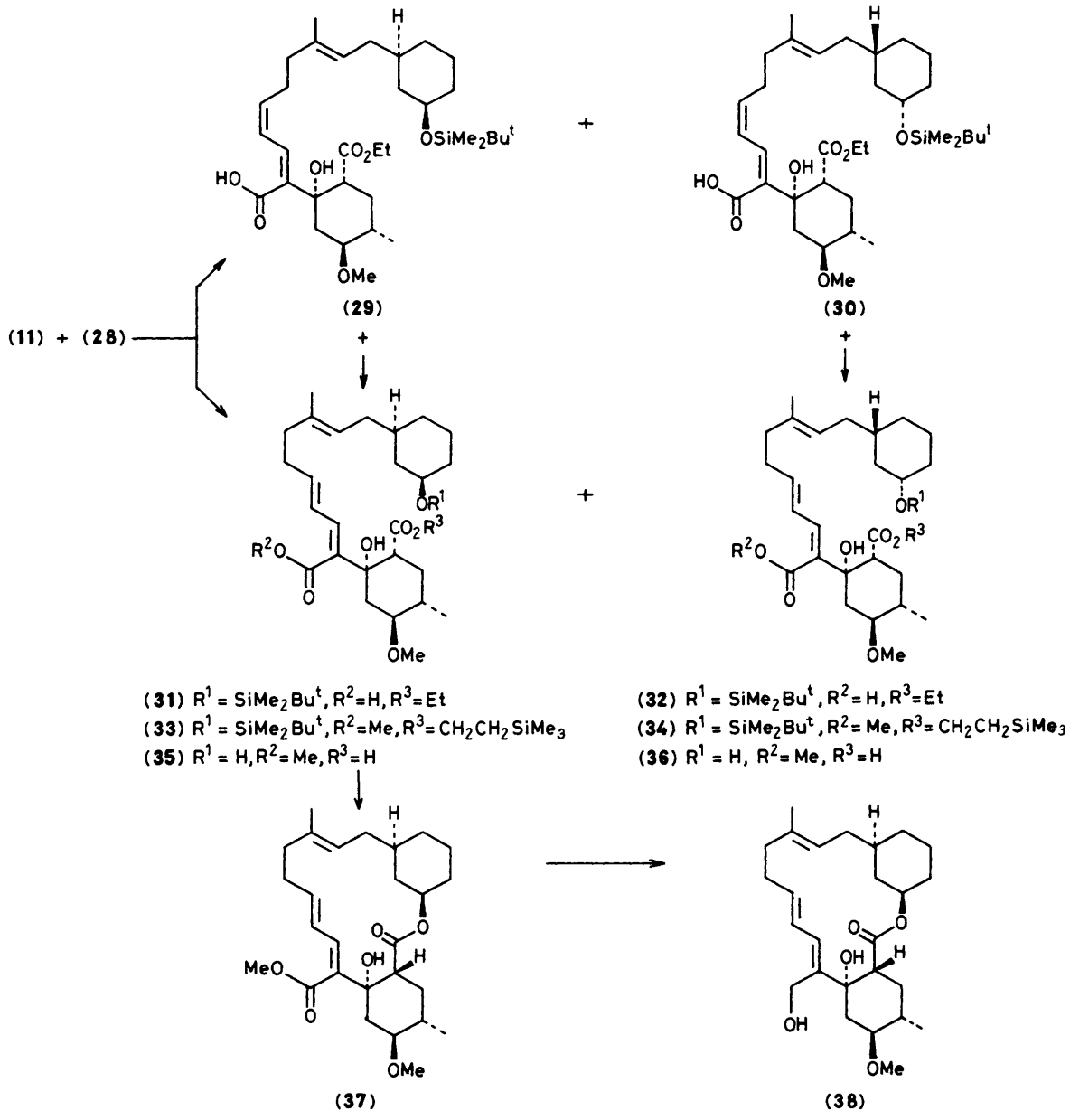
Scheme 2

stereochemistry of adduct (**4**) was assigned by analogy with the literature,[4] and ^{1}H n.m.r. data established the configuration at C(4).‡ Reduction using sodium borohydride gave a mixture of *cis*- and *trans*-diols (**5**) and (**6**), ratio 70:30, however the desired *trans*-diol (**6**) could be obtained stereoselectively using sodium triacetoxyborohydride in acetic acid (95%).[5] Conversion into the methyl ether (**7**) was carried out using trimethyloxonium tetrafluoroborate–potassium carbonate (70%) since conventional conditions (NaH, MeI, tetrahydrofuran, THF) gave preferential methylation of the tertiary alcohol (Scheme 1).

The latent 1,4-dicarbonyl functionality of the furan moiety was now to be released. Treatment of the furan (**7**) with bromine–methanol gave a mixture of 2,5-dimethoxydihydrofurans (**8**) which were hydrolysed (HCl, THF–H_2O) to give the 3-substituted 5*H*-furan-2-one (**9**), in 80% yield from (**7**); none of the isomeric 4-substituted 5*H*-furan-2-one was isolated.[6] The 5*H*-furan-2-one (**9**) was then oxidized to the 5-hydroxy-5*H*-furan-2-one (**11**) *via* bromide (**10**) (*N*-bromosuccinimide, CCl_4, heat, 3 h; acetone, H_2O heat under reflux, 6 h), 75% yield over the two steps.

Having obtained (**11**), it remained to demonstrate its use as an intermediate for milbemycin analogue synthesis; in particular for the stereoselective introduction of the (8*E*, 10*E*)-dienyl fragment. Condensation with triphenylphosphonium methylide and isopropylide was achieved after prior deprotection using lithium di-isopropylamide (2 equiv.), and gave mixtures of the (*Z*,*Z*)- and (*Z*,*E*)-diene esters (**16**)—(**19**) after esterification with diazomethane. The unwanted (*Z*,*Z*)-isomers (**16**) and (**18**) predominated in these mixtures, with a

‡ The milbemycin numbering scheme[1] is used in the text.



Scheme 3

selectivity of *ca.* 3:1. Preliminary attempts to obtain the desired (*Z,E*)-isomers *via* alternative condensation procedures were not encouraging, and were discontinued when it was found that the (*Z,Z*)-diene acids (**12**) and (**14**) could be isomerized cleanly to the (*Z,E*)-isomers (**13**) and (**15**) using a trace of iodine in benzene (25 °C, 24 h), so providing the desired diene acids (**13**) and (**15**) in *ca.* 60% yield from (**11**). Since attempts to reduce these dienyl acids to the corresponding dienyl alcohols gave complex mixtures of products, it was decided to prepare a macrocyclic system to complete the model work.

The protected hydroxy phosphonium salt (**28**), a model for the 'northern hemisphere', was prepared from the known lactone (**20**)[7] as shown in Scheme 2. Methanolysis of this lactone, followed by alcohol protection, and di-isobutyltin hydride reduction, gave aldehyde (**23**) (50% overall), which on treatment with prop-2-enylmagnesium bromide and trimethyl orthoacetate–propanoic acid (xylene, heat, 24 h), gave the (*E*)-alkene (**24**) *via* a Claisen rearrangement. Ester reduction ($LiAlH_4$; 82%) and alcohol displacement *via* methanesulphonate (**26**) gave iodide (**27**) (87%), which could be converted into the hygroscopic phosphonium salt (**28**) using triphenylphosphine (dimethylformamide, DMF, heat under reflux, 4 h). This phosphonium salt was difficult to handle and was used without recrystallization.

The 5-hydroxy-5*H*-furan-2-one (**11**) was now treated with lithium hexamethyldisilazide (2 equiv.) followed by the ylide formed from phosphonium salt (**28**). A mixture of the diene

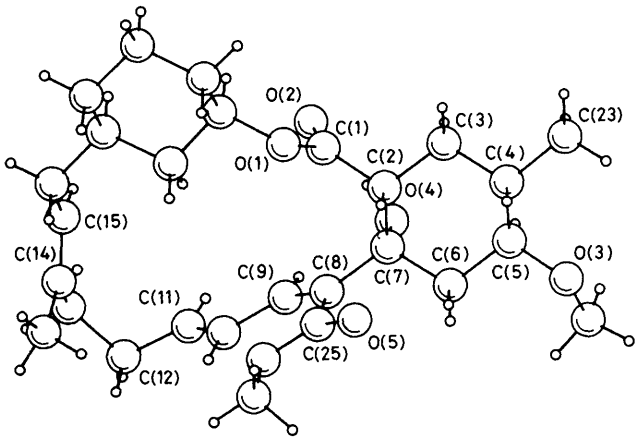


Figure 1. Ball and stick diagram of ester (**37**) showing the crystallographic numbering scheme used.

acids (**29**)—(**32**) was obtained, consisting mainly of the (*Z,Z*)-diene isomers (**29**) and (**30**). Treatment of this mixture with a trace of iodine in benzene (25 °C, 24 h) isomerized the (*Z,Z*)-dienes as before to give a 1 : 1 mixture of (*Z,E*)-isomers (**31**) and (**32**) containing less than 5% of the unwanted (*Z,Z*)-isomers [70% from (**11**)]. The ^{1}H n.m.r. spectrum of this mixture of (*Z,E*)-diene acids was consistent with the presence of a single component, but as both the hydroxyfuranone (**11**) and the phosphonium salt (**28**) were racemic, both (*Z,E*)-diastereoisomers (**31**) and (**32**) were assumed to be present.

Having obtained the macrolide precursors (**31**) and (**32**), it was necessary to exchange protecting groups before attempting cyclization. Transesterification was achieved using 2-trimethylsilylethanol, followed by treatment with diazomethane to give the diesters (**33**) and (**34**) (50%) which were deprotected (F^-, THF–H_2O, 25 °C, 4 h; 1 M HCl, 6 h) to provide the hydroxy acids (**35**) and (**36**), now identifiable as a 1 : 1 mixture by ^{1}H n.m.r. spectroscopy (85%) (Scheme 3).

Cyclization was achieved using *N*-methyl-2-chloropyridinium iodide–triethylamine in CH_2Cl_2 at 20 °C.[8] The high field ^{1}H n.m.r. spectrum of the single crystalline product obtained after chromatography suggested it was a macrocyclic lactone but did not distinguish between adduct (**37**) or the analogous macrolide derived from hydroxy acid (**36**). The structure of this product was then established by *X*-ray crystallography.

Crystal data for macrolide (**37**), $C_{27}H_{40}O_6$, M = 460.61, monoclinic, space group $P2_1/c$, a = 10.583(5), b = 12.774(2), c = 19.481(3) Å, β = 90.36(2)°, U = 2627.4 Å^3, Z = 4, D_c = 1.164 g cm^{-3}, R = 0.043, R_w = 0.058. For observed reflections, $I > 3\sigma(I)$, λ (Mo-K_α) = 0.71069 Å. Data were collected on an Enraf–Nonius CAD4-F diffractometer to $\theta \leq 25°$. The crystal structure was solved by direct methods.[9] Parameters, including those for anistropic thermal vibration, were refined by large-block approximation to full matrix least squares.[10] The majority of the hydrogen atoms were located in difference Fourier syntheses and those not found were included in their theoretical positions.§ Hydrogen atoms were included in the refinement with restraints [11] being applied to the C–H or O–H bonds.

Figure 1 shows that the stereochemistry of the macrocyclic product is as depicted in (**37**), and corresponds to that of the natural milbemycins, *cf.* (**1**). Moreover the *X*-ray structure determination confirms the other structural assignments made during the course of this work. Since the lactone (**37**) was the only macrocyclic product isolated from the cyclization of the 1 : 1 mixture of hydroxy acids (**35**) and (**36**), it would appear that the 'unnatural' hydroxy acid (**36**) does not cyclize under these conditions; in fact no products derived from (**36**) could be characterized. The yield of macrolide (**37**) was 36% based on hydroxy acid (**35**), and *ca.* 35% of a mixture of unchanged hydroxy acids (**35**) and (**36**) was recovered.

To complete the milbemycin model synthesis the methyl ester moiety of macrolide (**37**) was reduced [sodium bis(2-methoxyethoxy)aluminium hydride, Red-Al, THF, 1 h] to give the crystalline alcohol (**38**) (80%). Macrolide (**38**) incorporates many of the structural and stereochemical features of milbemycin β_1 (**1**), in particular the 8-hydroxymethyl-(8*E*, 10*E*)-dienyl unit, and its synthesis shows how the later stages of a milbemycin synthesis could be achieved. Of particular interest is the apparently selective macrolactonization of hydroxy acid (**35**).

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§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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