A Total Synthesis of Milbemycin E

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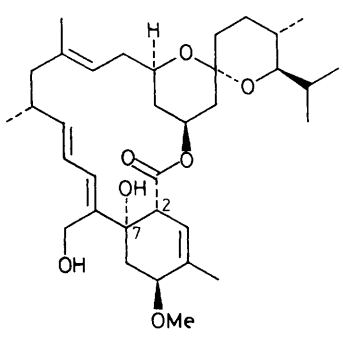
Milbemycin E (**1**) and 3,4-dihydromilbemycin E (**34**) have been synthesized, the C(1)–C(10) fragment being prepared using a stereoselective Robinson annelation.

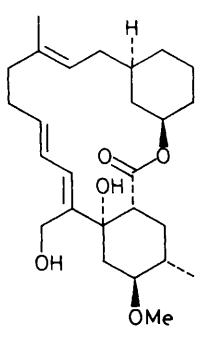
There is considerable interest in the development of syntheses of milbemycins and avermectins because of the potent and useful biological activities of these compounds.[1] Milbemycin β_3, in which the C(2)–C(7) fragment is aromatic, was the first member of the series to be synthesized,[2] and syntheses of avermectin B_{1a} and A_{1a} have since been described.[3] We now report total syntheses of milbemycin E (**1**)[4] and its 3,4-dihydro derivative (**34**) from the spiroacetal (**3**)[5] and the Robinson annelation product (**13**).[6] Our approach was first used to synthesize the milbemycin analogue (**2**).[7]

Following the strategy developed by Baker,[8] alcohol (**10**) was prepared from spiroacetal (**3**),[5] and was converted into phosphonium salt (**12**) as outlined in Scheme 1. Although some nine steps were involved in this conversion, the overall yield was *ca.* 50%, and the reactions could be carried out on multi-gram scale.

Resolution of the racemic Robinson annelation product (**13**)[6] was achieved by reduction to alcohol (**14**) using $NaBH(OAc)_3$, and conversion of this alcohol into a mixture of the diastereoisomeric (*S*)-(+)-acetoxymandelates (**15**) and (**17**), from which the undesired diastereoisomer (**17**) was removed by selective recrystallization from hexane. Partial ethanolysis of the mother liquor [containing a 5 : 1 mixture of (**15**) and (**17**)] gave a mixture of diols (**16**) and (**18**) from which the required diastereoisomer (**16**) was crystallized out. The desired dextrorotatory dihydroxyester (**14**), $[\alpha]_D^{20}$ + 14.2° (*c* 0.51 in EtOH) was then liberated by treatment with K_2CO_3 in ethanol.†



(**1**)

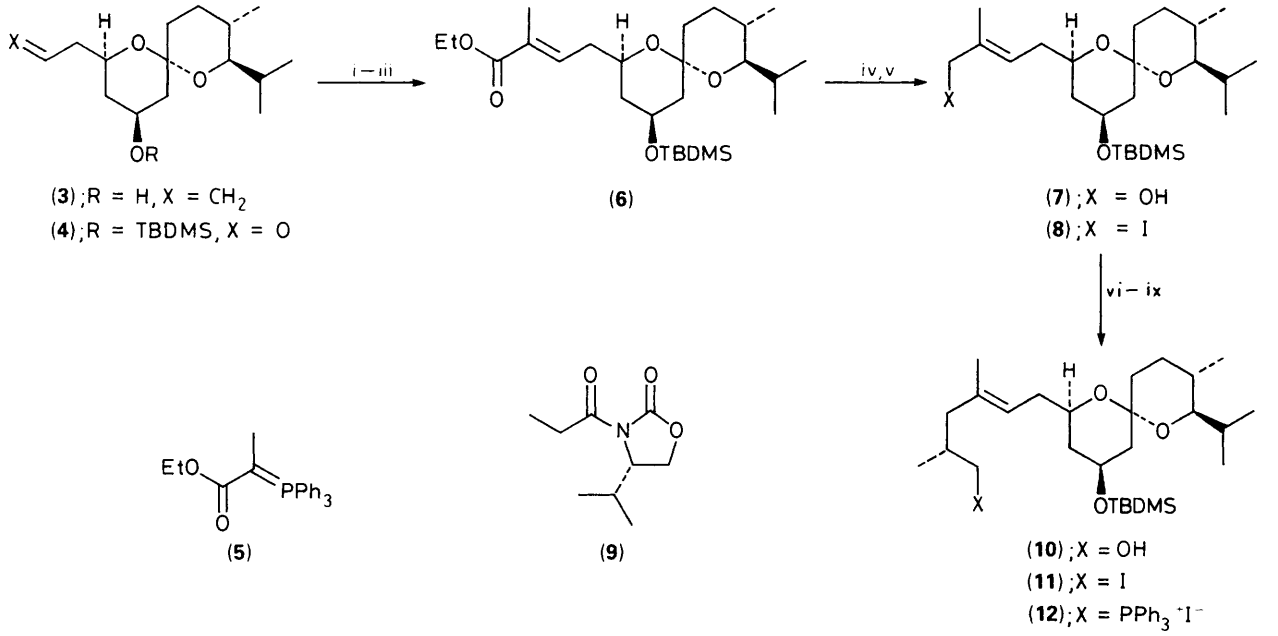


(**2**)

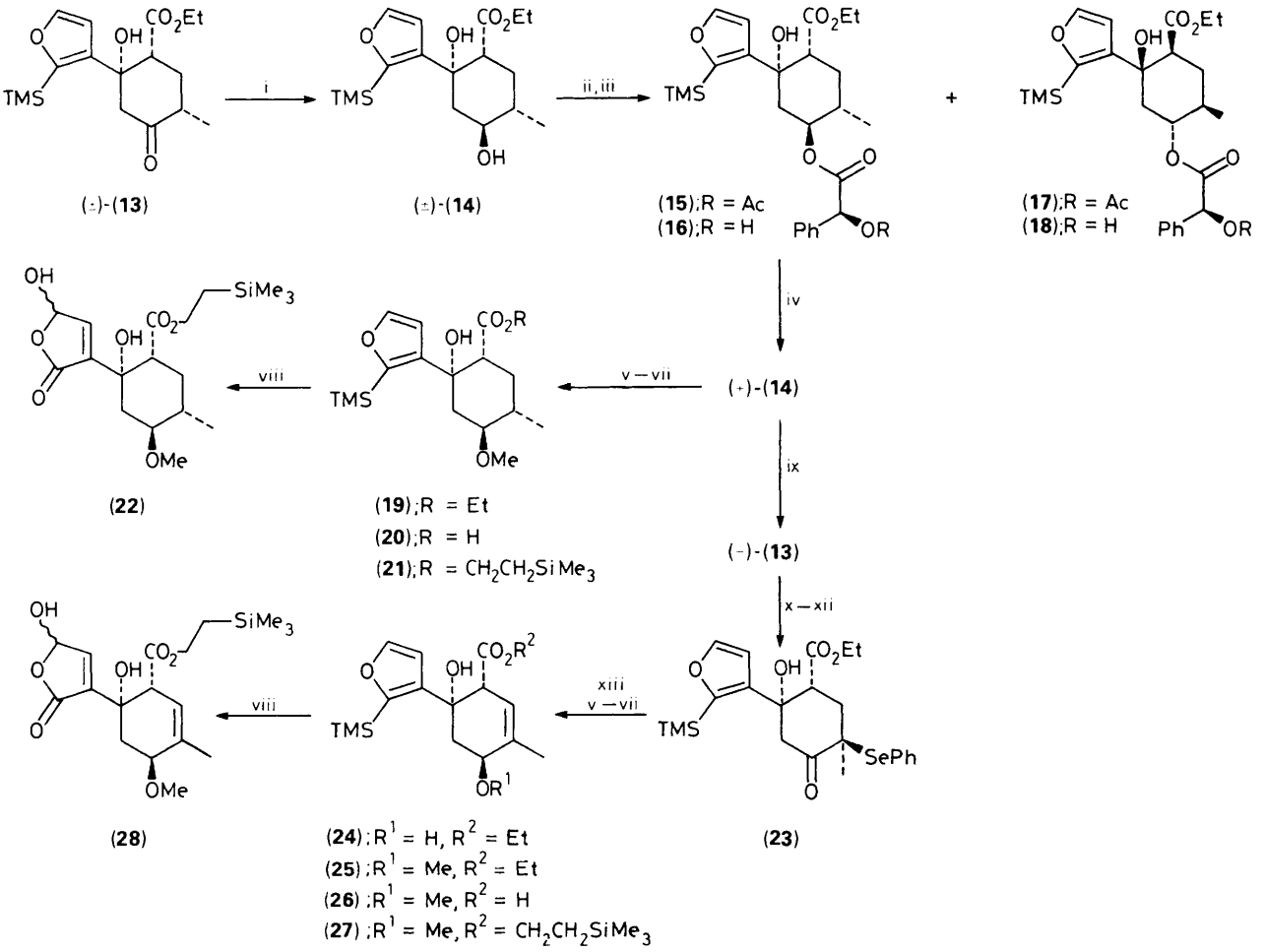
Hydroxybutenolides (**22**) and (**28**) were prepared from alcohol (+)-(**14**) using procedures analogous to those described previously.[6] Thus monomethylation using methyl iodide and freshly prepared Ag_2O, followed by ester exchange and furan oxidation using singlet oxygen in methanol–dichloromethane, gave hydroxybutenolide (**22**) as a highly crystalline solid. Swern oxidation of ester (+)-(**14**), and regioselective phenylselenenylation–oxidative elimination gave the cyclohexenol (**24**) after reduction together with *ca.* 15% of its exocyclic isomer, which were separated by flash chromatography. Selective methylation and ester exchange gave the desired hydroxybutenolide (**28**) as a crystalline solid after singlet oxygen oxidation.

To develop conditions for the Wittig coupling and cyclization steps, the synthesis of 3,4-dihydromilbemycin E (**34**) was investigated. Generation of the ylide (**29**) from the phosphonium salt (**2**) was best achieved using t-butyl-lithium at −40 °C, and the Wittig reaction was carried out by adding a

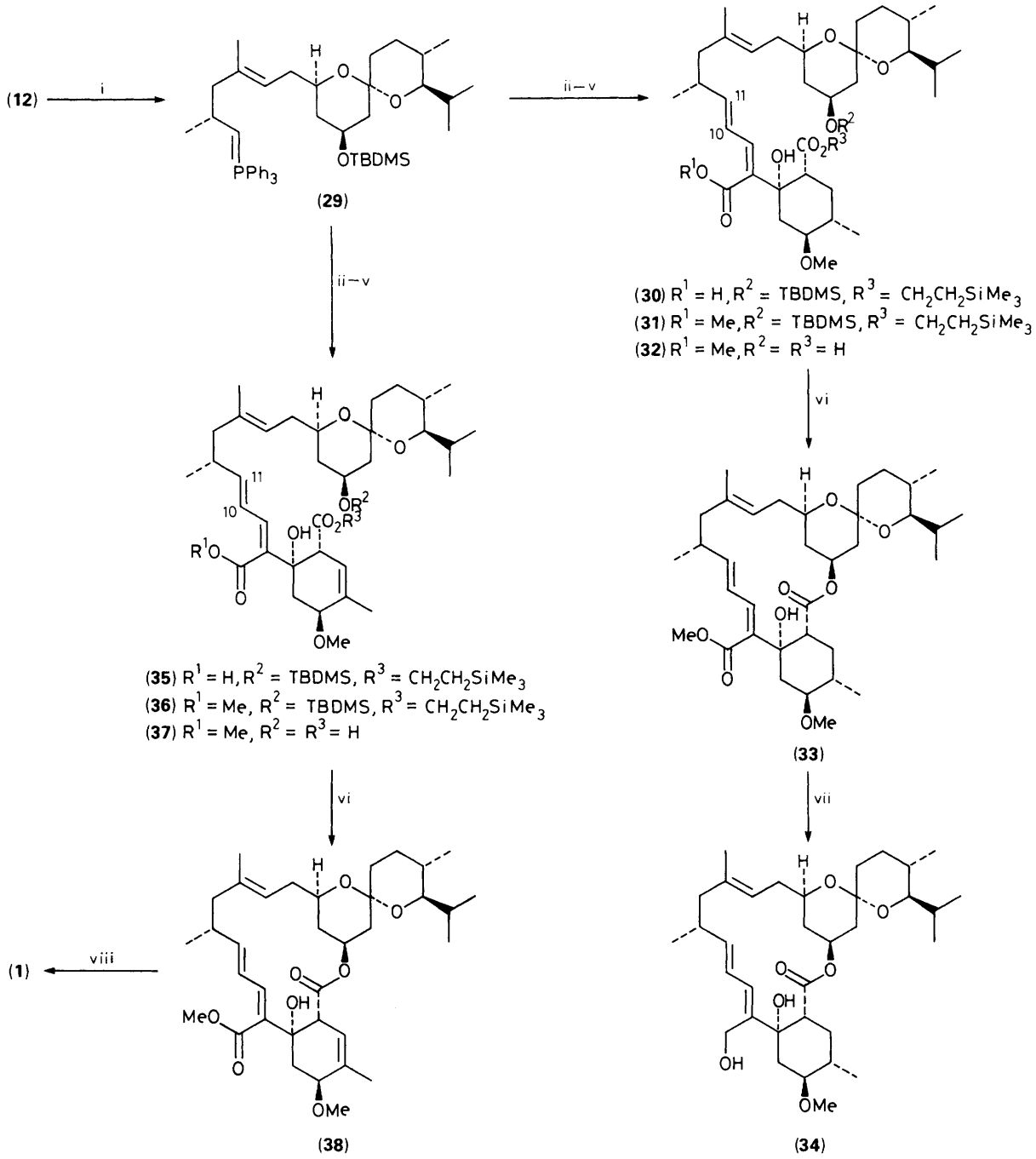
† The structure of diastereoisomer (**17**) and hence the absolute configuration of the dextrorotatory dihydroxyester (+)-(**14**) was established by *X*-ray crystallography (O. S. Mills, University of Manchester, personal communication). Details will be published in a full paper. Clearly in future this resolution would be carried out using (*R*)-(−)-acetoxymandelic acid, which should give the enantiomer of (**17**) and hence the dextrorotatory enantiomer of (**14**) directly.



Scheme 1. *Reagents and conditions*: i, TBDMSCl (TBDMS = t-butyldimethylsilyl), imidazole; ii, O_3, MeOH, then dimethyl sulphide; iii, (**5**), benzene, room temp., 16 h [74% from (**3**)]; iv, DIBAL, −78 °C (99%); v, I_2, PPh_3, imidazole; vi, (**9**)-Li [87% from (**7**)]; vii, $LiAlH_4$ (98%); viii, I_2, PPh_3, imidazole (89%); ix, PPh_3, MeCN, heat under reflux (84%).



Scheme 2. *Reagents and conditions*: i, $NaBH(OAc)_3$, AcOH (98%); ii, (*S*)-(+)-$PhCH(OAc)CO_2H$, DCC, 4-*N*,N-dimethylaminopyridine (DMAP), CH_2Cl_2; iii, K_2CO_3, EtOH, 0 °C, 1 h; iv, K_2CO_3, EtOH, room temp. [35% of (+)-(**14**) from (±)-(**14**)]; v, Ag_2O, MeI, heat under reflux, 48 h; vi, aq. NaOH, EtOH, 0 °C, 16 h; vii, $Me_3SiCH_2CH_2OH$, DCC, DMAP, CH_2Cl_2, 16 h [82% of (**21**) from (**14**); 44% of (**27**) from (**24**)]; viii, O_2, CH_2Cl_2, MeOH, sun lamp, tetraphenylporphyrin, 45 min (90%); ix, $(COCl)_2$, dimethylsulphoxide (DMSO); CH_2Cl_2 (85%); x, TMSOTf ($CF_3SO_3SiMe_3$), Et_3N, CCl_4; xi, PhSeCl, THF, 0 °C, 1 h; xii, Bu^n_4NF, THF, −78 °C, 3 h [71% of (**23**) from (−)-(**13**)]; xiii, H_2O_2, CH_2Cl_2, 20 min, 0 °C then $NaBH(OAc)_3$, AcOH (63%).



Scheme 3. *Reagents and conditions*: i, Bu^{t}Li, THF, −40 °C, 30 min; ii, 2 mol. equiv. $LiN(SiMe_3)_2$, (**22**) or (**28**), −78 to −15 °C, 3 h; iii, CH_2N_2, Et_2O; iv, I_2, benzene [54% of (**31**) and 37% of (**36**) from (**12**)]; v, Bu$^n_4$NF, THF, 10 h; vi, DCC, DMAP, CH_2Cl_2, 0 °C, 16 h [*ca.* 35% for both (**33**) and (**38**) from (**31**) and (**36**)]; vii, Red-Al, toluene, 0 °C, 2 h (67%); viii, DIBAL, toluene, 1 h, −78 °C (90%).

mixture of this ylide and lithium hexamethyldisilazide (2 mol. equiv.) to a solution of the hydroxybutenolide in tetrahydrofuran (THF) at −78 °C. The reaction mixture was then allowed to warm to −15 °C, and was stirred at this temperature for several hours, during which time the red colour of the ylide disappeared. Work-up gave a mixture of the conjugated dienyl acid (**30**) and its C(10)–C(11) (*Z*)-double-bond isomer (milbemycin numbering), ratio *ca.* 1 : 4. This mixture was not separated; instead it was treated with an excess of diazomethane, and the mixture of esters so obtained isomerized using a trace of iodine in benzene to provide the desired (*E*)-ester (**31**) [54% from phosphonium salt (**12**)]. Deprotection was carried out using tetra-n-butylammonium fluoride, and the dihydroxyacid (**32**) cyclized using dicyclohexylcarbodiimide (DCC) at 0 °C to give the large-ring lactone (**33**). Selective reduction of the methyl ester using sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) then gave 3,4-dihydromilbemycin E (**34**). The structure of dihydromilbemycin E (**34**) was not formally established at this stage. However, the structure shown was consistent with spectroscopic data,

and with its synthesis from acetoxymandelate (**15**) and spiroacetal (**3**), *cf.* the synthesis of analogue (**2**),[7] and was confirmed by the synthesis of milbemycin E (**1**), *vide infra.*

The reactions developed for the synthesis of the dihydromilbemycin (**34**) were then applied to a synthesis of milbemycin E (**1**). Addition of ylide (**29**) and lithium hexamethyldisilazide to the cyclohexenylhydroxybutenolide (**28**) gave the acid (**35**) together with its 10,11-(*Z*)-isomer. This mixture was esterified and isomerized as before to give the desired ester (**36**) [37% from the phosphonium salt (**12**)] together with a small amount (*ca.* 10%) of an aromatic side product. Deprotection and cyclization were then carried out as in the dihydro series to give the cyclized methyl ester (**38**). Reduction of this ester using Red-AL gave a mixture of products; however di-isobutylaluminium hydride (DIBAL) in toluene at −78 °C reduced the methyl ester selectively and gave a good yield (*ca.* 90%) of milbemycin E (**1**), identified by comparison (300 MHz ^{1}H n.m.r. and i.r. spectroscopy, m.s., optical rotation, t.l.c.) with an authentic sample of the natural product.

This synthesis of milbemycin E is of interest in that it shows that the hydroxybutenolide approach can be used to prepare non-aromatic milbemycins and that the sensitive C(3)–C(4) double bond can be introduced before the milbemycin skeleton is assembled. Migration of this double bond into conjugation with the C(1) carboxy group was not found to be a problem.[9] However, care had to be taken in handling the C(3)–C(4) unsaturated esters under strongly basic conditions to avoid elimination reactions which gave aromatic side products, *e.g.* during the Wittig reaction.

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