Total Synthesis of Milbemycin G: Assembly and Completion of the Synthesis

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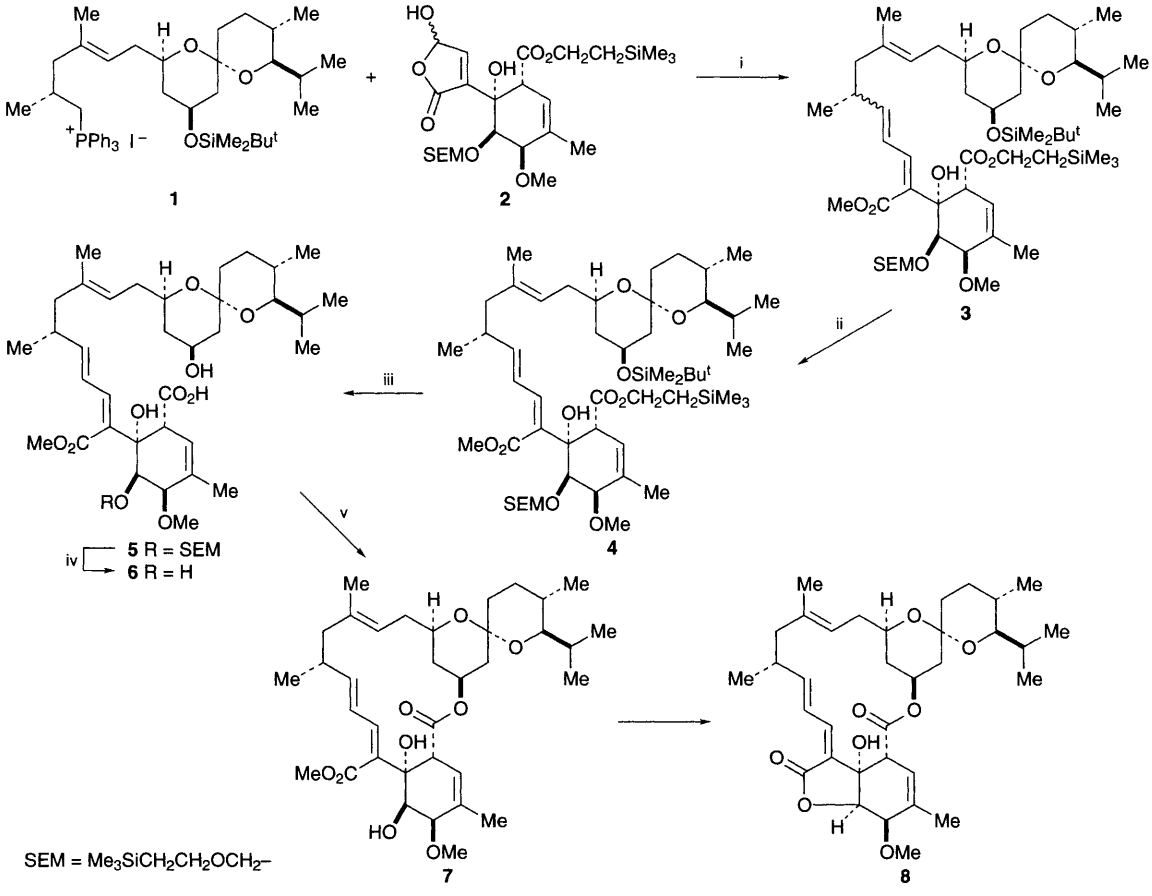
The Wittig reaction between phosphonium salt **1** and the hydroxybutenolide **2** followed by deprotection, macrocyclisation, and reduction gives the 6-hydroxymilbemycin E **9** which by further cyclisation is converted into milbemycin G **11**.

An approach to a convergent total synthesis of the α-milbemycins and avermectins[1] is outlined in the accompanying communication together with a synthesis of the hydroxybutenolide **2**.[2] We now report the completion of a synthesis of milbemycin G **11**[3] from the phosphonium salt **1**[4] and the hydroxybutenolide **2**.

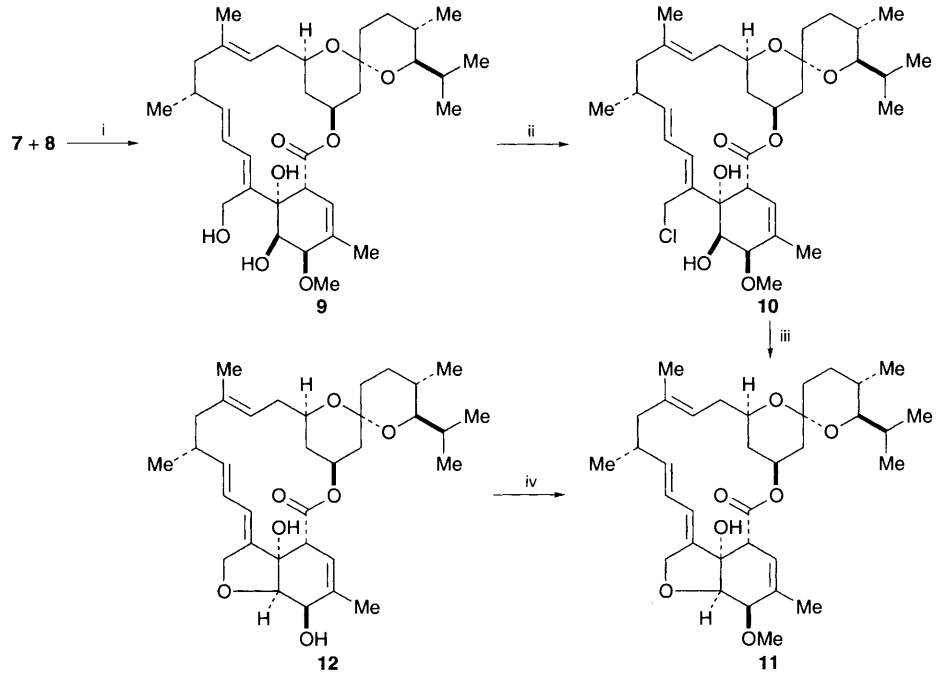
The Wittig condensation between the phosphonium salt **1** and the hydroxybutenolide **2** was carried out using lithium hexamethyldisilazide (Scheme 1).[4] After treatment with diazomethane, the product **3** was isolated as a mixture of 10,11-double bond isomers which was treated with a catalytic quantity of iodine to effect isomerisation to the required 10,11-*E*-isomer **4**. Deprotection gave the dihydroxy acid **5**, but attempts to carry out macrolactonisation using a variety of reagents were unsuccessful. Since the analogous dihydroxy acid lacking the protected hydroxy group at C(6) had been cyclised during our synthesis of milbemycin E,[4] it appeared that the C(6)-substituent was interfering with the macrocyclisation, possibly by steric interaction with the methyl ester in the conformation required for macrocyclisation. Similar problems had been encountered in model studies.[5,6] To reduce this interaction, and possibly to benefit from H-bonding, the 6-hydroxy substituent was deprotected to give the trihydroxy acid **6** which was cyclised with trichlorobenzoyl chloride and 4-dimethylaminopyridine (DMAP),[7] to give the macrolide **7**. This had a tendency to cyclise on standing to give the butyrolactone **8**.

The mixture of hydroxymethyl ester **7** and lactone **8** was reduced using diisobutylaluminium hydride to give the 6-hydroxymilbemycin E **9** (Scheme 2). Model studies had indicated that the remaining cyclisation to give milbemycin G **11** would be achieved using lithium diisopropylamide and toluene-*p*-sulfonyl chloride at low temperature.[6] However, reaction of the 6-hydroxymilbemycin E **9** under these conditions resulted in selective displacement of the primary hydroxy group to give the chloride **10**.† However, it was found that this could be cyclised using an excess of silver oxide in tetrahydrofuran, gently heated under reflux, to give milbemycin G **11**. The structure of the synthetic material was confirmed by comparison (500 MHz ^{1}H NMR, MS, IR, TLC, optical rotation) with a sample prepared by *O*-methylation of a sample of authentic milbemycin D **12**. The physical and spectroscopic data for both samples of milbemycin G were identical to those reported in the literature.[3]

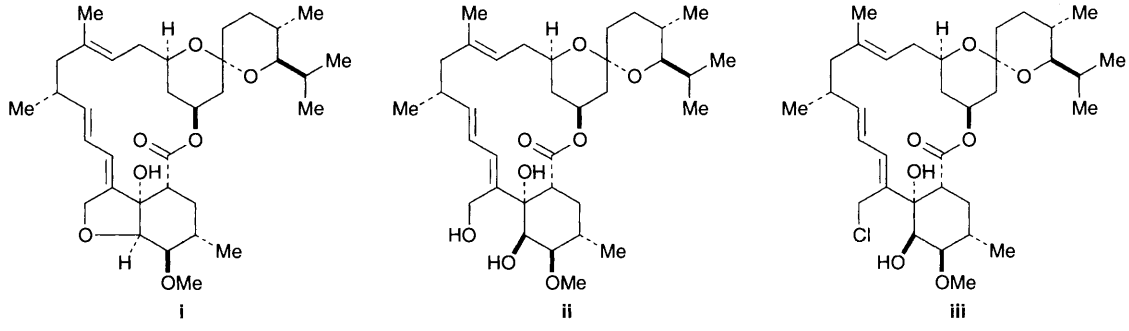
This synthesis of milbemycin G **11** constitutes a convergent synthesis of an α-milbemycin in which the 3,4-double bond has been introduced regioselectively early in the synthesis, avoiding the formation of mixtures of epimers at C(2). At no time during



Scheme 1 *Reagents and conditions*: i, $LiN(SiMe_3)_2$, THF, −78 to −10 °C, followed by treatment of the crude product with an excess of diazomethane, 48%; ii, I_2 (trace), benzene, sunlight, 95%; iii, Bu_4NF, THF, 93%; iv, $MgBr_2.Et_2O$, butanethiol, K_2CO_3, 90%; v, 2,4,6-trichlorobenzoyl chloride, 2 d, then DMAP, 33%



Scheme 2 *Reagents and conditions*: i, diisobutylaluminium hydride, toluene, 45%; ii, $LiNPr^i_2$, toluene-*p*-sulfonyl chloride, −78 °C, 74%; iii, an excess of freshly prepared silver oxide, THF, reflux, 71%; iv, MeI, freshly prepared silver oxide, room temp., 64%



this synthesis did the 3,4-double bond show any tendency to migrate into conjugation with the carboxy group at C(1). In earlier studies during the development of conditions for the Wittig reaction, it was observed that if the basic reaction mixture was maintained at temperatures above 0 °C for any length of time, then aromatisation of the 6-membered ring was observed. However, this problem was completely avoided by keeping the reaction temperature below −10 °C.

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Footnote

† The isolation of the chloride **10** throws doubt on our earlier claim[6] to have synthesised 3,4-dihydromilbemycin G **i** by cyclisation of 3,4-dihydro-6-hydroxymilbemycin E **ii** using lithium diisopropylamide and toluene-*p*-sulfonyl chloride. Comparison of the 500 Mz ^{1}H NMR spectrum of the product with that of the chloride **10** suggests that the analogous chloride **iii** had been obtained rather than dihydromilbemycin G **i**. The MS of the chlorides and the corresponding α-milbemycins are very similar since the chlorides readily lose hydrogen chloride during ionisation. In the present work, it was only the direct comparison of our synthetic material with a sample of authentic milbemycin G, that enabled the structure of the chloride **10** to be deduced, and conditions developed for completion of the synthesis. This was not possible in the 3,4-dihydro series since no reference compounds were available.

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