Total Synthesis of Milbemycin G: Synthesis of the C(1)–C(10) Fragment

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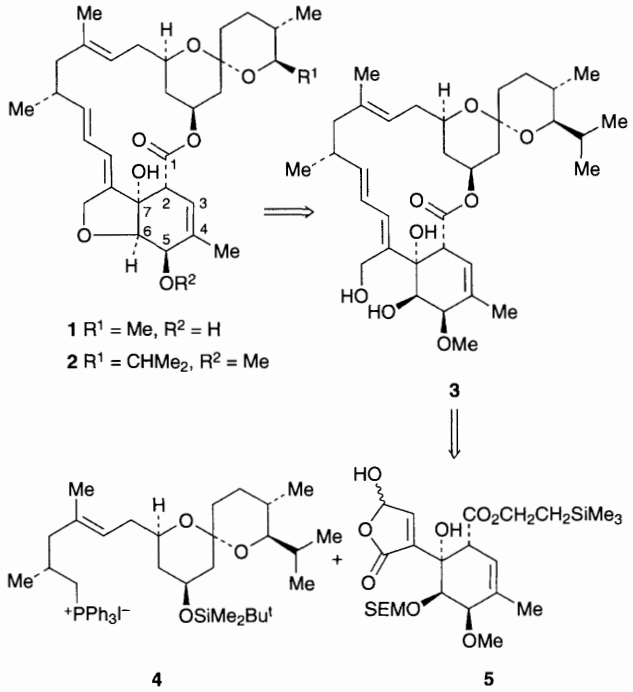
The hydroxybutenolide **5**, a precursor of the C(1)–C(10) fragment of the 5-methoxy α-milbemycins, is synthesised by stereo- and regio-selective modification of the hydroxycyclohexanone **8**.

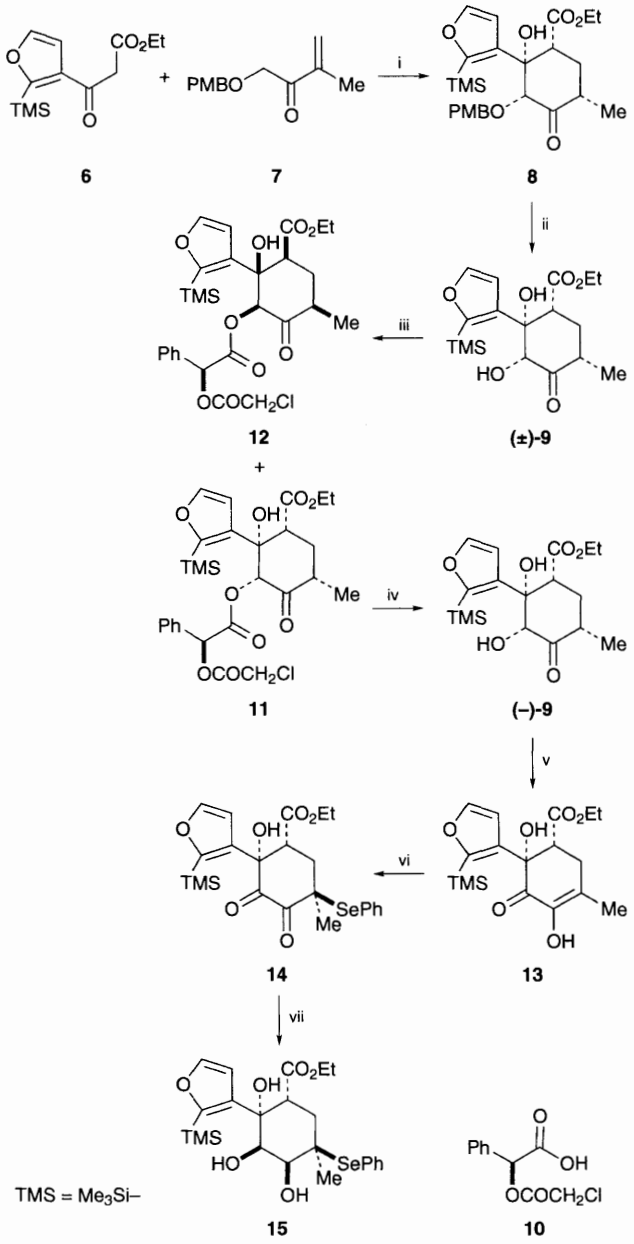
The milbemycins and the avermectins are natural products with important and useful biological activity.[1] Although several total syntheses of milbemycins and avermectins have been described,[2] one persistent problem encountered in syntheses of the biologically more interesting α-milbemycins and avermectins, *e.g.* milbemycin α_1 **1**, has been the introduction of the 3,4-double bond. This has a tendency to migrate into conjugation with the carboxy group at C(1),[3] and deconjugation is complicated by the formation of the epimer of the natural product at C(2).[4] Only recently have syntheses of α-milbemycins and the avermectins been reported in which this problem is avoided, although this is at the cost of convergency in some cases.[5]

Based on our synthesis of milbemycin E,[6] a non-aromatic β-milbemycin, it was envisaged that 6β-hydroxymilbemycin E **3** would be accessible from a Wittig reaction between the phosphonium salt **4** and the hydroxybutenolide **5**, followed by functional group modification and macrolactonisation. Displacement of the primary hydroxy group by the 6-hydroxy group would then complete a convergent synthesis of a 5-methoxy α-milbemycin in which the 3,4-double bond had been introduced regioselectively. We now report a total synthesis of the hydroxybutenolide **5**. In the accompanying communication, we report the completion of a synthesis of milbemycin G **2**[7] using this approach.

A synthesis of the hydroxybutenolide **5** is outlined in Schemes 1 and 2. The Robinson-type addition of the keto ester **6** and the isopropenyl ketone **7** is stereoselective giving the racemic hydroxycyclohexanone **8** which has the required relative configuration at C(2) and C(7), but the wrong configuration at C(6) (milbemycin numbering).[8,9] Deprotection gave the dihydroxycyclohexanone **9** which was resolved by selective crystallisation of the chloroacetylmandelate **11** from the mixture of diastereoisomers prepared by esterification of the diol (±)-**9** with (*S*)-chloroacetylmandelic acid **10** using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). Ester exchange then gave the laevorotatory hydroxy ketone (−)-**9**, $[\alpha]_D$ −19.75 (*c* 1.37, $CHCl_3$).†

Oxidation of the dihydroxycyclohexanone (−)-**9** gave the corresponding diketone which was isolated as its enol **13** and treatment with phenylselenenyl chloride gave the phenylseleno diketone **14**. Preliminary attempts to introduce the 3,4-double bond by oxidative elimination of the phenylselenenyl sub-





Scheme 1 *Reagents and conditions*: i, NaOH, EtOH, 65%; ii, DDQ, 95%; iii, **10**, DCC, DMAP (**11**, 47%); iv, K_2CO_3, EtOH, 91%; v, oxalyl chloride, Me_2SO, 95%; vi, PhSeCl, pyridine, 96%; vii, $Me_4NBH(OAc)_3$, 84%

stituent gave rise to complex mixtures of products, and so it was necessary to reduce the diketone before effecting the elimination. Fortunately, reduction using tetramethylammonium triacetoxyborohydride was highly stereoselective and gave the cyclohexanetriol **15** which had the required configuration at C(5) and C(6). The stereoselectivity of this reduction is consistent with delivery of the reducing agent by the 3°-OH,[10] but it may be that steric factors are also involved.‡

It was now necessary to introduce the 3,4-double bond. Previous work had indicated that the regioselectivity of oxidative elimination of phenyl selenides analogous to **15** was dependent upon the substituent at C(5), with hydroxy selenides giving rise to mixtures of *endo*- and *exo*-isomers that were difficult to separate.[9,11] This was also found to be the case in this work. Oxidation of the hydroxy selenide **15** using *tert*-butyl hydroperoxide in dichloromethane gave a mixture of the *endo*- and *exo*-alkenols **16** and **17** in which the *exo*-isomer **17** was the major component, ratio typically 40:60. However, it was found that the *endo–exo* product ratio could be controlled by modification of the 5-hydroxy group. In particular, oxidative elimination of the trichloroacetate **18** was usefully regioselective in favour of the *endo* isomer **19**, and transesterification gave a mixture of the *endo*- and *exo*-alkenols **16** and **17**, ratio **16:17** = 87:13, from which the required *endo*-isomer was isolated by flash chromatography in a 70% yield.[12] Selective *O*-methylation of the less hindered hydroxy group, to give the monomethyl ether **21** was achieved *via* the cyclic stannoxane, and protection of the 6-hydroxy group, ester exchange and oxidation of the 2-trimethylsilylfuran using singlet oxygen gave the required hydroxybutenolide **5**.[13]

The completion of a synthesis of milbemycin G **3** using the phosphonium salt **4** and the hydroxybutenolide **5** is described in the accompanying communication.[14]

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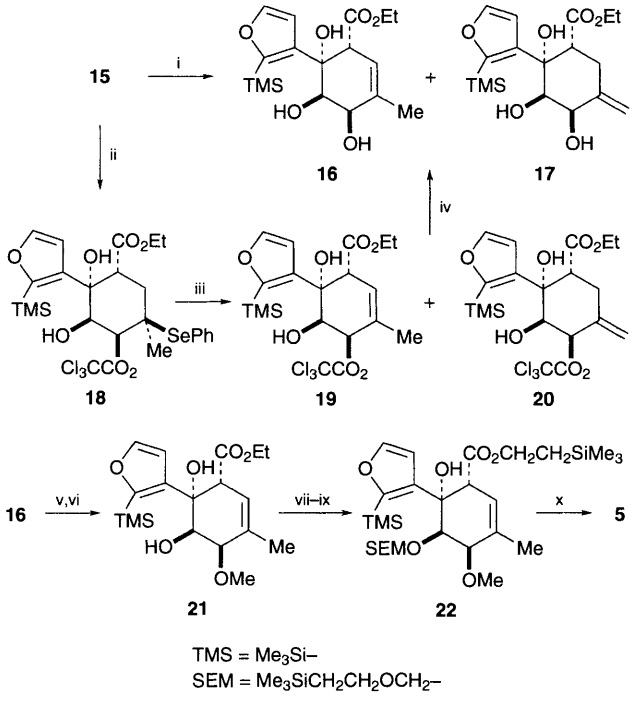

TMS = Me_3Si–
SEM = $Me_3SiCH_2CH_2OCH_2$–

Scheme 2 *Reagents and conditions*: i, Bu^tO_2H, CH_2Cl_2, 80% (**16:17** = 40:60); ii, trichloroacetyl chloride, pyridine (87%); iii, Bu^tO_2H, benzene, 92%; iv, EtOH, DMAP (**16**, 70%; **17**, 10%); v, Bu_2SnO, MeOH; vi, MeI, benzene Bu_4NI (93% from **16**); vii, 2-trimethylsilylethoxymethyl chloride, Pr^i_2NEt, 100%; viii, aqueous NaOH, 97%; ix, 2-(trimethylsilyl)ethanol, 82%; x, O_2, tetraphenylporphine (cat.), sunlight, MeOH, CH_2Cl_2, 98%

Footnotes

† The structure of **11** was established by X-ray diffraction. Details will be published in a full paper.

‡ It has been found that the stereoselectivity of reduction of a carbonyl group at C(5) is dependent upon other functionality in the molecule, specifically groups at C(4) and C(6). Details will be included in a full paper.

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