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Milbemycin Synthesis: Synthesis of 6ß-Hydroxy-3,4-Dihydromilbemycin E

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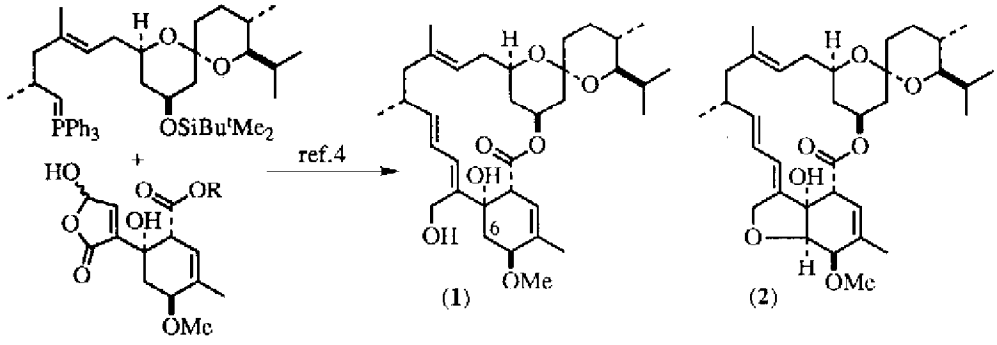
Key Words: Milbemycin; Robinson annelation; macrocyclisation; furan oxidation; spiroacetal.

Abstract: *Hydroxycyclohexanone (7), readily available via a Robinson annelation, is converted into the hydroxybutenolide (15), which is incorporated into a synthesis of 6ß-hydroxymilbemycin E (28).*

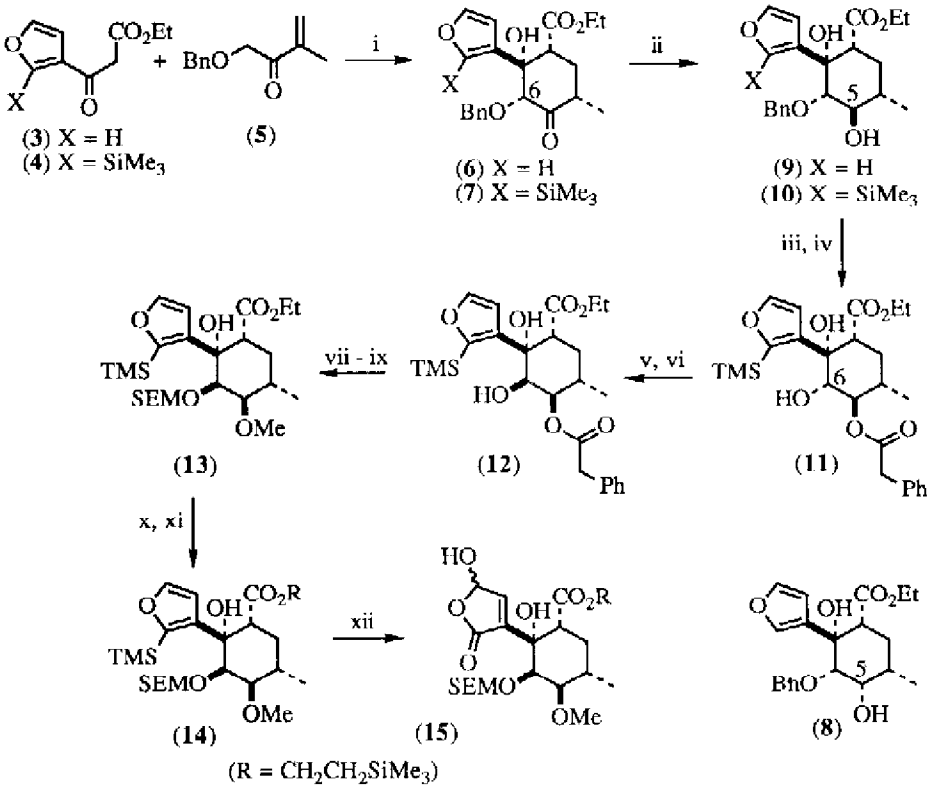
The milbemycins and avermectins have attracted considerable interest because of their potent and useful biological activities.[1] The chemistry of these compounds is being widely studied, and several total syntheses have been reported.[2,3] However, there remains scope for the development of flexible synthetic approaches to these compounds, not only to the natural products themselves, but also to analogues for biological evaluation. One approach involves a Wittig condensation between an 'upper fragment' ylid and a hydroxybutenolide, and has been applied to synthesize milbemycin E (**1**).[4] Hydroxybutenolides are readily available by oxidation of 2-trimethylsilylfurans using $^1O_2$,[5] and the Robinson annelation provides a rapid, stereoselective, synthesis of the cyclohexenyl fragment.[6] We now report an extension of the Robinson reaction to include alkoxymethyl isopropenyl ketones, and a synthesis of a 6ß-hydroxymilbemycin, as a prelude to the application of this approach to the synthesis of α-milbemycins, e.g. (**2**), and avermectins, together with a significantly improved procedure for the crucial Wittig coupling.



Stirring a mixture of furanyl keto-ester (**3**)[4] and benzyloxymethyl isopropenyl ketone (**5**)[7] in ethanol containing aqueous sodium hydroxide gave the hydroxycyclohexanone (**6**), which precipitated out of the reaction mixture, and was isolated in 74% yield.[8] Reduction using sodium borohydride gave the 5α-alcohol (**8**) selectively (85%), whereas sodium triacetoxyborohydride in acetic acid gave the 5ß-epimer (**9**) (90%).[6,8] The

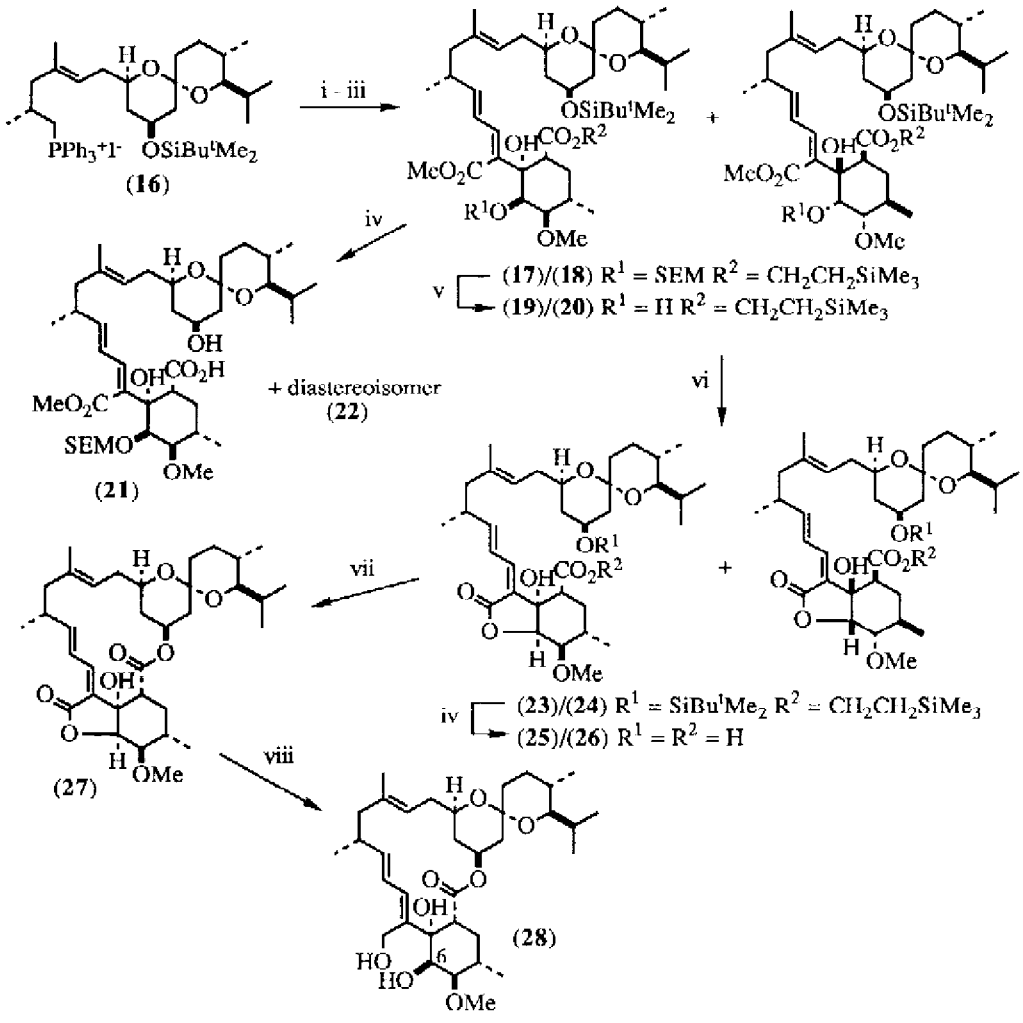
trimethylsilylfuranyl keto-ester (**4**) similarly gave a good yield of adduct (**7**). This adduct has the functionality required for incorporation into a milbemycin synthesis, however requires an inversion of configuration at C(6).

Reduction of adduct (**7**) by sodium triacetoxyborohydride was inefficient, but could be achieved using an excess of tetramethylammonium triacetoxyborohydride in acetic acid-acetonitrile which gave the 5ß-alcohol (**10**) (84%). Esterification using phenylacetic acid followed by hydrogenolysis gave diol (**11**),[9] and oxidation followed by reduction, again using tetramethylammonium triacetoxyborohydride, effected the required inversion of configuration at C(6), giving the diol (**12**) stereoselectively *via* intramolecular delivery of hydride by the 7-hydroxyl substituent. Conventional procedures were used to convert diol (**12**) into the protected trimethylsilylethyl ester (**14**), which was oxidized using $^1O_2$ to provide hydroxybutenolide (**15**), as a mixture of epimers, in 88% yield.



Scheme 1. *Reagents:* i, NaOH, 20 °C [(**6**) 74%, (**7**) 50%]; ii, for (**6**), $NaBH(OAc)_3$ (90%), for (**7**), $Me_4NBH(OAc)_3$ (84%); iii, $PhCH_2CO_2H$, DCC, DMAP (85%); iv, H_2, Pd/C, EtOH (91%); v, $(COCl)_2$, DMSO, Et_3N (95%); vi, $Me_4NBH(OAc)_3$ (95%); vii, SEMCl, Pr_2NEt (91%); viii, K_2CO_3, EtOH (87%); ix, Ag_2O, MeI (62%); x, NaOH, EtOH (99%); xi, $Me_3SiCH_2CH_2OH$, DCC, DMAP (80%); xii, O_2, TPP, *hv*, CH_2Cl_2, MeOH (88%).

The Wittig condensation between hydroxybutenolide (**15**) and phosphonium salt (**16**)[4] was carried out by adding a solution of lithium hexamethyldisilazide to a solution of the hydroxybutenolide and phosphonium salt in anhydrous tetrahydrofuran at -78 °C followed by warming to -10 °C. This procedure generated the ylid in the presence of the aldehyde derived from the hydroxybutenolide, and was found to give consistently better yields



Scheme 2. *Reagents:* i, (**15**), 3LiN(SiMe$_3$)$_2$, THF, -78 to -10 °C; ii, CH_2N_2; iii, I_2 (cat.), benzene [60% of (**17**)/(**18**) from (**15**)]; iv, Bu_4NF, THF [99% of (**21**)/(**22**), 78% of (**25**)/(**26**)]; v, I_2, *hv*, benzene [92% of (**19**)/(**20**)]; vi, silica, $CHCl_3$ (98%); vii, DCC, DMAP [46% from (**25**)]; viii, DIBAL, (74%).

than if the ylid was generated separately.[4] The mixture of products from the Wittig reaction was treated with diazomethane and with a trace of iodine in benzene to give the (*EE*) dienyl esters (**17**) and (**18**), as a 1 : 1 mixture in a yield of 60% from the hydroxybutenolide.[9]

Deprotection using tetrabutylammonium fluoride gave the hydroxy acids (**21**) and (**22**), but attempts to cyclize this mixture, e.g. using DCC/DMAP, were unsuccessful, only complex mixtures of products being obtained from which none of the desired macrolide could be isolated. However, it was found that the SEM ether could be removed from the Wittig products (**17**)/(**18**) by treatment with one mole equivalent of iodine under a sunlamp. This procedure left the other silyl protecting groups unchanged, and gave the 6-hydroxy-compounds (**19**) and (**20**) in a 92% yield. Stirring a solution of these diols in chloroform containing a suspension of silica

induced lactonization and gave an excellent yield of γ-lactones (**23**) and (**24**). Deprotection using tetrabutylammonium fluoride gave the seco-acids (**25**) and (**26**).

Macrolactonization of this mixture was carried out using DCC/DMAP following the procedure used in the milbemycin E synthesis[4] and gave a single macrolide identified as (**27**) on the basis of its spectroscopic data. The selective cyclization of the required diastereoisomer in a mixture of diastereoisomers analogous to seco-acids (**25**) and (**26**) has precedent,[10] and is due to transannular interactions in the conformation required for cyclization of the unnatural diastereoisomer. Reduction of lactone (**27**) using DIBAL in toluene gave 6ß-hydroxy-3,4-dihydromilbemycin E (**28**) in good overall yield from the hydroxybutenolide (**15**),[9] identified by comparison of its spectroscopic data with those of milbemycin E (**1**) and its 3,4-dihydro derivative.[4]

This work establishes a procedure for the synthesis of 6ß-hydroxymilbemycins which is being applied to complete a synthesis of milbemycin G (**2**). Of general interest is the extension of the Robinson procedure to include alkoxymethyl isopropenyl ketones, the selective removal of the SEM protecting group in the presence of the 2-(trimethylsilyl)ethyl ester and TBDMS groups, and the effect of the 6ß-substituent on macrolactonization.

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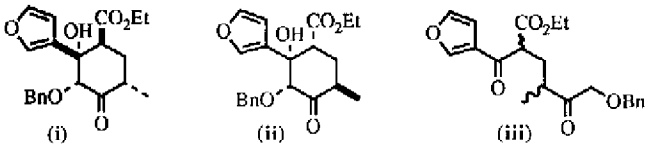
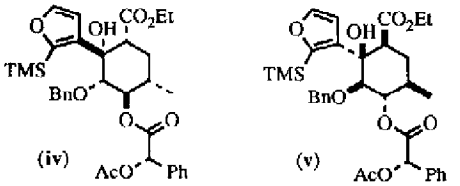
8. This reaction was found to be sensitive to solvent; for example in a 50:50 mixture of ethanol and dichloromethane, (**i**) and (**ii**) together with the open chain intermediates (**iii**) were isolated in addition to (**6**). The structures of the Robinson products, and the reduction products obtained from them, were established by extensive n.m.r. studies. Details will be given in a full paper.



9. The work in this paper involved the use of racemic Robinson annelation products, and hence gave the mixture of Wittig products. However resolution of the diol (**10**) has been achieved by esterification using (*S*)-acetoxymandelic acid to give (**iv**) and (**v**), and selective crystallization of the required diastereoisomer (**iv**). Hydrogenation of the acetoxymandelates proceeds with concomitant hydrogenolysis of both the benzyl ether and the acetoxy group to give the hydroxyphenylacetate (**11**).



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