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A FORMAL SYNTHESIS OF (+)MILBEMYCIN β_3[1]: A WITTIG APPROACH

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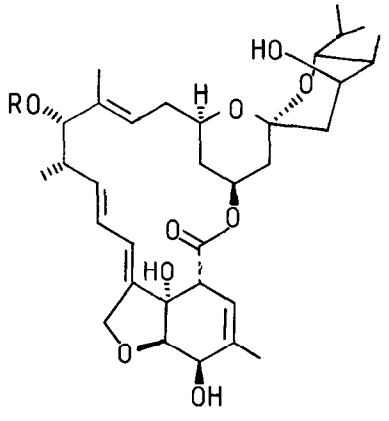
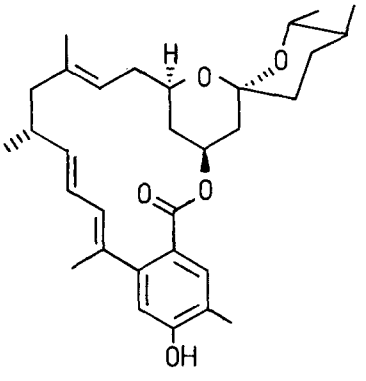
Abstract: A new route has been established to generate the C_{14}-C_{15} trisubstituted double bond of milbemycin β_3 by reaction of a Wittig reagent with the appropriate spiroacetal aldehyde. The product of this reaction, after conversion to the iodide and enantiospecific alkylation to generate the C_{12} methyl group, has been elaborated to an intermediate previously involved in a total synthesis of milbemycin β_3.

The milbemycins[1] and avermectins[2] have been the target of considerable synthetic endeavour, and to date several total syntheses of milbemycin β_3 have been reported[3,4]. There have also been several reports of studies towards the preparation of structural sub-units of the more complex milbemycins and avermectins[5]. In this communication we describe an alternative route to the spiroacetal moiety of milbemycin β_3 and an alternative strategy for its incorporation into the macrolide ring, a strategy which would also allow a facile entry into the avermectin series.

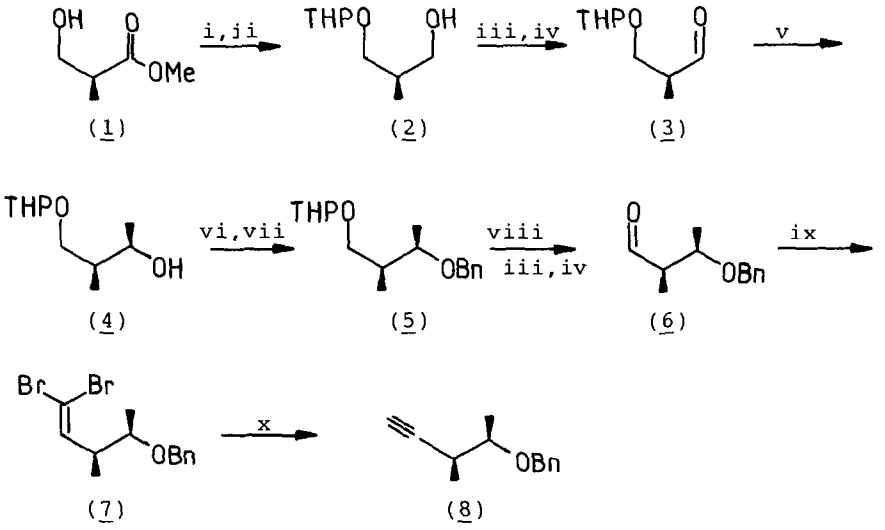
The starting point for this synthesis was the readily available (S)-methyl 3-hydroxy-2-methylpropionate (1). Sequential protection of the alcohol as its THP ether and reduction of the ester gave the alcohol (2)[9] in 95% yield. Swern oxidation gave the corresponding aldehyde (3), chelation controlled[6] cuprate attack then gave the desired threo product (4) as the major product (>20:1) in 90% yield. The secondary alcohol was then protected as its benzyl ether (5), acid catalysed removal of the THP



Avermectin A_{2b}
R = oleandrosyl-oleandrosyl



Milbemycin β_3

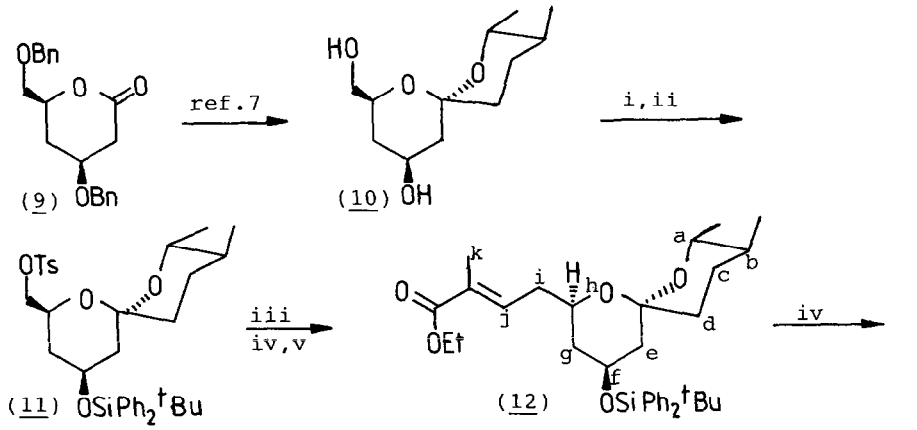


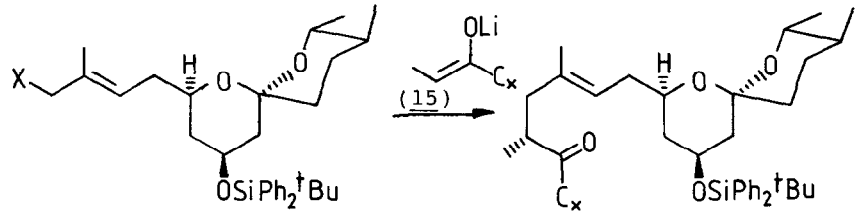
Reagents: i)DHP/Et_2O/CSA; ii)$LiAlH_4$/Et_2O; iii)DMSO/$COCl_2$; iv)NEt_3; v)Me_2CuLi/Et_2O -20°C; vi)NaH/THF; vii)$PhCH_2Br$; viii)MeOH/H^+; ix)$Ph_3P{=}CBr_2$/THF 0°C; x)2 x n-BuLi/THF -80°C.

protecting group and subsequent Swern oxidation afforded the aldehyde (6) in 70% overall yield. The aldehyde was then converted, via the dibromide (7), to the acetylene (8), $[\alpha]_D^{20}$ = -8.4° (c 1.5, CH_2Cl_2 , bp 58-60°C at 17 mm Hg, (60%) (shown to be >95% ee by preparation of the MTPA ether).

The acetylene (8) was coupled to the lactone (9)[7] and converted to the known spiroacetal (10) by the procedure reported previously[7]. Treatment with one equivalent of p-toluenesulphonyl chloride in pyridine yielded the primary tosylate selectively (70%); the secondary alcohol was then protected as its t-butyldiphenylsilyl ether (11) (100%). Nucleophilic displacement of the tosylate by NaCN in DMSO (80°C) yielded the corresponding nitrile (80%). Dibal reduction to the aldehyde and subsequent Wittig reaction gave the α,β-unsaturated ester (12)* in a 60% overall yield; $[\alpha]_D^{20}$ = +38° (c 0.4, CH_2Cl_2); ν_{max} 1710 (C=O), 1650, 1450, 1380, 1110, 830, 740, 705 cm^{-1}; δ_H (360MHz) ($CDCl_3$), 7.6 (4H, m, Ar), 7.3 (6H, m, Ar), 6.77 (1H, dd, J=2H, H_j), 4.14 (1H, m, H_f), 4.1 (2H, q, J=7Hz, $-C\underline{H}_2-CH_3$), 3.3 (1H, m, H_h), 3.0 (1H, dq, J=6,11 H_a), 2.2 (2H, m, $2xH_i$), 1.85 (1H, dd, H_e), 1.79 (3H, s, Me_k), 1.65 (1H, ddd, H_g), 1.4-1.6 (5H, m, H, $2xH_c$, $2xH_d$), 1.26 (3H, t, J=7, $M\underline{e}CH_2$), 1.27 (2H, m, H_g, H_e), 1.05 (9H, s, t-Bu), 0.95 (3H, d, J=6Hz, Me_a), 0.75 (3H, d, J=7, Me_b).

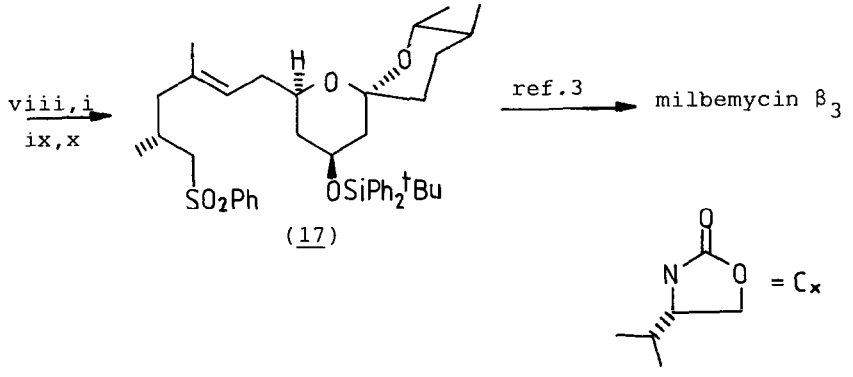
*^{13}C NMR indicates single double bond isomer.





vi ⌜(13) X = OH
vii ⌞(14) X = I

(16)

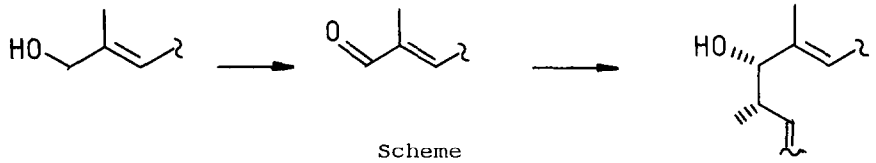


Reagents: i)TsCl/pyr; ii)t-$BuPh_2SiCl$/DMF/imidazole; iii)NaCN/DMSO/80°C; iv)Dibal/CH_2Cl_2; v)$EtO_2CC(Me)PPh_3$; vi)$MeSO_2Cl$/pyr/DMAP; vii)NaI/THF; viii)$LiAlH_4/Et_2O$; ix)PhS^-/MeOH; x)Oxone.

Dibal reduction yielded the key allylic alcohol (13) (65%), conversion to the very unstable allylic iodide (14) and subsequent alkylation of the oxazolidone (15)[8] yielded the alkylated product (16) (80%) in which the stereochemistry of the remote methyl at C_{12} had been generated. In addition a small amount (<15%) of another double bond isomer was isolated[10].

Reductive removal of the chiral auxiliary and a simple functional group modification then allowed the conversion to the sulphone (17) which has previously been incorporated into a total synthesis of (+)milbemycin β_3[3].

This approach also provides a route to the avermectins. Oxidation of the allylic alcohol (13) to the unsaturated aldehyde followed by a directed aldol condensation would allow the introduction of the C_{13} oxygenation required for the avermectins (Scheme).



Scheme

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