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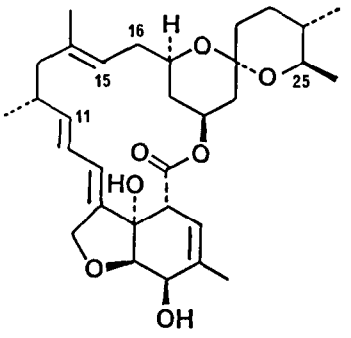
SYNTHESIS OF THE NORTHERN HEMISPHERE OF THE MILBEMYCINS USING A NEW STRATEGY FOR THE FORMATION OF THE C-15 TO C-16 BOND.

David Culshaw, Peter Grice, Steven V. Ley* and Gary A. Strange,

Department of Chemistry, Imperial College, London SW7 2AY.

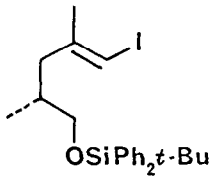
Summary: Using a new convergent route the synthesis of the C-11 to C-25 northern hemisphere fragment of the milbemycins has been achieved.

We have recently reported[1] the construction of the spiroketal unit of milbemycin α_1[2] (1) employing a novel Wittig coupling reaction of cyclic ether phosphoranes. We now show how this chemistry can be extended to the synthesis of C-11 to C-25 carbon fragment of (1)

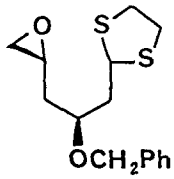


(1)

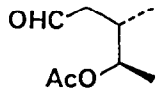
Inspection of existing syntheses of the less functionalised milbemycin β_3[3,4] suggest that difficulties arise in the formation of the C-15 to C-16 bond when coupling to intact spiroketal units. We therefore chose to overcome the problems by using a new convergent strategy to couple the key fragments (2), (3) and (4) whereby the spiroketal group would be introduced at a late stage after formation of the C-15 to C-16 bond.



(2)

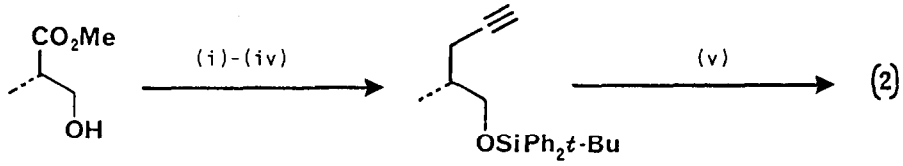


(3)



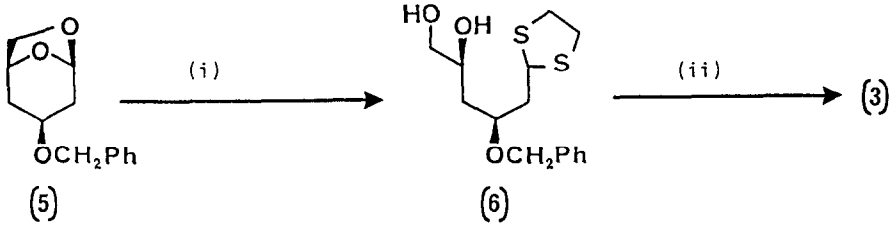
(4)

The preparation of the vinyl iodide (2)† was straightforward from commercially available (S)-(+)-methyl-3-hydroxy-2-methylpropionate in five steps (Scheme 1)



Scheme 1
(i) $^{t}BuPh_2SiCl$/Imidazole/DMF, 98%; (ii) DIBAL-H in toluene, 79%; (iii) Ts-Cl/Pyridine/DMAP, 72%; (iv) $LiC{\equiv}CH.H_2N(CH_2)_2NH_2$/DMSO, 77%; (v) Cp_2ZrCl_2/Me_3Al then I_2, 91%

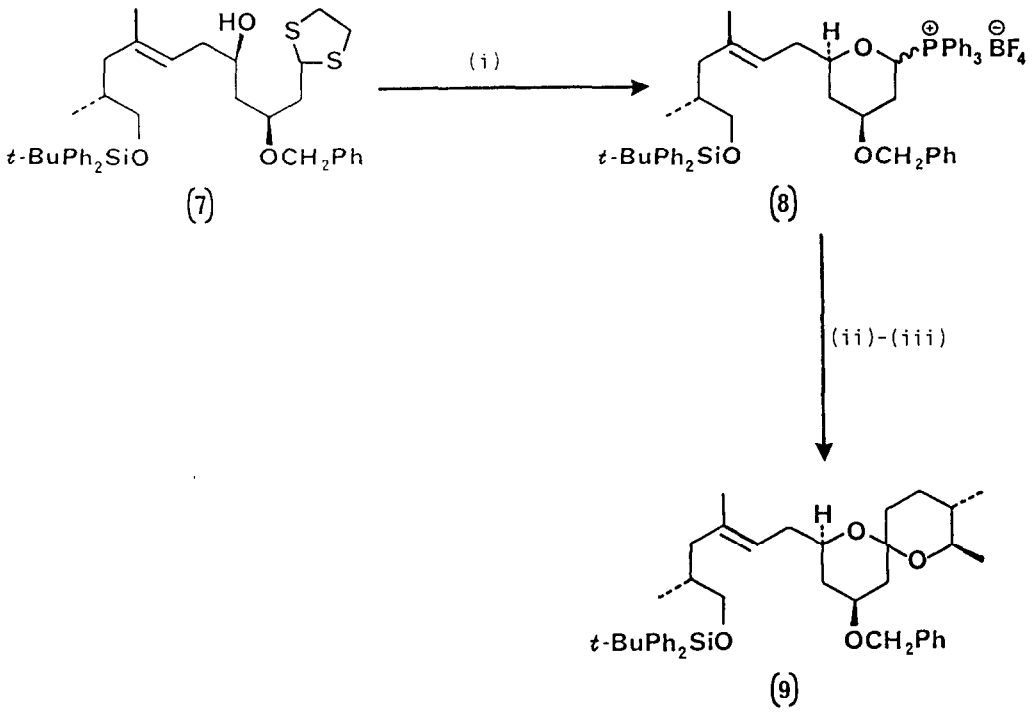
This epoxide (3) was obtained from the anhydro-β-D-glucose derivative[5] (5) by firstly reacting with ethanedithiol and $TiCl_4$ to give (6) which upon treatment with methanesulphonyl chloride and cyclisation with potassium carbonate afforded (3) (Scheme 2)



(5) (6)

Scheme 2
(i) $HS(CH_2)_2SH/TiCl_4$, 60%; (ii) $MeSO_2Cl/Et_3N$/-40° then K_2CO_3/MeOH, 69%

Coupling of (2) with the epoxide (3) was achieved in an excellent 96% yield via the homocuprate of (2) and reaction at -25° for 16 hrs to give (7). Conversion of (7) to the phosphonium salt (8) required initial hydrolysis with wet acetonitrile containing methyl iodide to give intermediate lactols which were transformed to the anomeric ethers and hence to (8) using our previously established sequence[1] (Scheme 3). After formation of the phosphorane from (8) using n-butyllithium and quenching with (4), work-up using base to hydrolyse the acetate and hydrochloric acid, to effect spirocyclisation gave the northern hemisphere fragment (9)[7] (Scheme 3).



Scheme 3

(i) MeI/CH_3CN/H_2O then $(MeO_2)_2CMe_2/H^+$ then Ph_3PHBF_4, 70%; (ii) n-BuLi/-78° then (5); (iii) NaOMe/MeOH then HCl, 11%

Further chemical elaboration of (9) to various milbemycin derivatives and a related approach to the avermectins will be reported at a later date.

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Footnotes

† All new compounds were fully characterised by spectroscopic, microanalytical and/or accurate mass data.

References

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7. ^{1}H n.m.r. (vide infra) δ (250 MH_2, $CDCl_3$): 0.82 (3H, d, J = 7Hz, Me-C_{24}); 0.86 (3H, d, J = 7Hz, Me-C_{12}); 1.12 (3H, d, J = 6Hz, Me-C_{25}); 1.58 (3H, s, Me-C_{14}); 3.26 (1H, dq, J = 10, 6Hz, H-25); 3.57 (1H, m, H-17); 3.92 (1H, tt, J = 11, 5Hz, H-19); 5.18 (1H, d, J = 7Hz, H-15).

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