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FREE RADICAL CYCLISATION APPROACH TO THE SOUTHERN MOIETY OF AVERMECTINS

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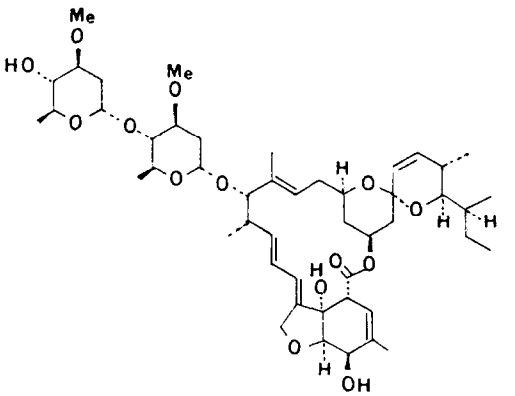
Summary : *A hydroxybenzofuran derivative related to part of the avermectin structure has been prepared by a free radical cyclisation.*

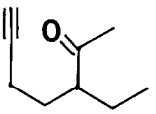
The "southern" moiety of the avermectin structure 1 presents a tertiary hydroxyl group at the ring junction of a hydrobenzofuran system, and an exocyclic unsaturation.



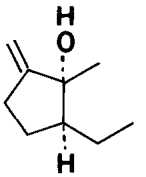
1 AVERMECTIN B_{1a}

A related arrangements of atoms have been produced by a reductive cyclisation of acetylenic ketones a to 2-methylene cyclopentanol derivatives b. Sodium or potassium in liquid ammonia [2] or in naphtalene/THF [3], electrolysis [4] or zinc/trimethylsilylchloride in THF [5] are known to bring about this cyclisation which is considered to be a free radical process.

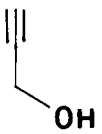
It was therefore decided to test the use of such a reductive cyclisation in a projected synthesis of avermectins.



a



b



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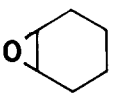

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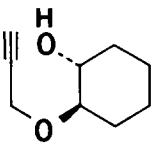

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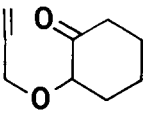

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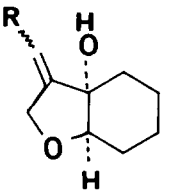
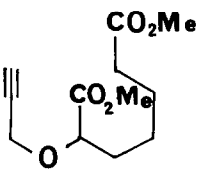


6a R = H

6b R = Sn(CH2CH2CH2CH3)3



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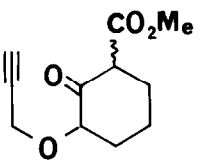
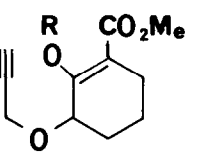
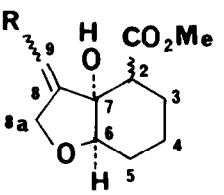


8a



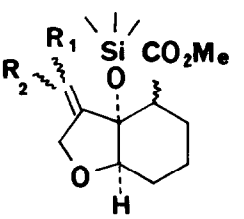
8b R = H

8c R = SiMe3



9a R = H

9b R = Sn(CH2CH2CH2CH3)3



9c R1 = H R2 = Sn(CH2CH2CH2CH3)3

9d R2 = H R1 = Sn(CH2CH2CH2CH3)3

Propargyl alcohol 2 was condensed with cyclohexene-oxide 3 to give the hydroxy-ether 4 [6], which was oxidised with Jones' reagent to the oxo-ether 5. Treatment of 5 with Na/naphtalene in THF gave a mixture of non-identified products. However, the reaction with Zn/TMSCl led to 6a [7] (60%) and starting material 5 (30%) after desilylation ($Bu_4N^+F^-$/THF).

Considering that ketones can be reduced by tributyltin hydride [8], the oxo-ether 5 was treated with Bu_3SnH/AIBN/Toluene ; the cyclised compound 6a was obtained in 20% yield as well as 30% of the stannyl derivative 6b in which the configuration of the double bond has not yet been determined [9]. The hydrodestannylation [10] of 6b (MeOH/HCl) provided the allylic alcohol 6a in quantitative yield.

A second model compound 8a was then prepared by condensation of dimethyl 2-hydroxy-pimelate with propargyl bromide (60%) to give 7, and Dieckmann cyclisation to the oxo-ester 8a and the enol 8b (8a/8b : 30/70, ^{1}HNMR, $CDCl_3$).

Free radical reductive cyclisation of 8a + 8b with Zn/TMSCl failed, but Bu_3SnH/AIBN led to a single stannyl derivative 9b [11] (30%) ; acidic treatment of 9b afforded the expected destannylated product 9a (70%).

When applied to the silyl enol ether 8c the tin hydride reaction gave two isomers 9c and 9d in better yield (50-60%, 9c/9d : 70/30).

From these results, the cyclisation can be assumed to proceed first by addition of Bu_3SnH to the triple bond with further reaction of the generated vinyl radical with the double bond of the enol or the silylenol-ether.

Work is in progress to use this approach in a synthesis of the bicyclic southern sub-unit of avermectin ; the vinyl stannanes obtained in this way are potential starting materials for elaboration of the avermectin diene system using Stille's procedure with Pd(0) as catalyst [12].

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9) ^1H NMR($CDCl_3$, 250MHz) ; 6b : 3.71(1H,dd,J=4.5, 4.5Hz) ; 4.46(2H,d,J=2.5Hz) ; 6.04 (1H,t,J=2.5Hz) ; 0.92(9H,t,J=7Hz) ; 0.96(6H,q,J=7Hz) ; 1.34-1.76(2H,m).
A small amount of 6b with the other double bond configuration was recovered during purification.

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11) ^1H NMR($CDCl_3$, 250MHz), 9b : 2.84(1H,dd,J=12, 4.5Hz, H-2) ; 3.97(1H,dd, J=10, 7Hz, H-6) ; 4.24(1H,dd,J=13, 2.5, H-8a A) ; 4.66(1H,dd,J=13, 2.5Hz, H-8a B) ; 5.8(1H,t, J=2.5Hz, H-9) ; 3.80(3H,s,OCH_3) ; 0.9(9H,t, J=7Hz) ; 0.92(6H,q, J=7Hz).

^{13}C NMR ($CDCl_3$, 100.6MHZ) , 9b : C-1 174.8, C-2 47.8, C-3 24.7, C-4 21.8, C-5 28.7, C-6 84.2, C-7 79.6, C-8 156.3, C-8a 70.6, C-9 119.7, CH_3-CH_2 13.6, CH_3-CH_2 29.1, Sn-CH_2-CH_2 27.2, Sn-CH_2 9.9, OMe 51.9.

^1H NMR ($CDCl_3$, 250MHz), 9a : 2.89(1H,dd, J=12.5, 4Hz, H-2), 3.99(1H,dd, J=10, 6Hz, H-6), 4.41(1H,dd, J=13, 2.5, 2.5Hz, H-8a A), 4.71(1H,ddd, J=13, 2.5, 2.5Hz, H-8a B) ; 4.93(1H,t, J=2.5Hz, H-9a), 5.08(1H,t, J=2.5Hz, H-9b), 3.82(3H,s,OCH_3), 4.27(1H,s,OH).

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