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# PARTIAL SYNTHESES OF AVERMECTIN $B_{1a}$ AND IVERMECTIN FROM AVERMECTIN $B_{2a}$

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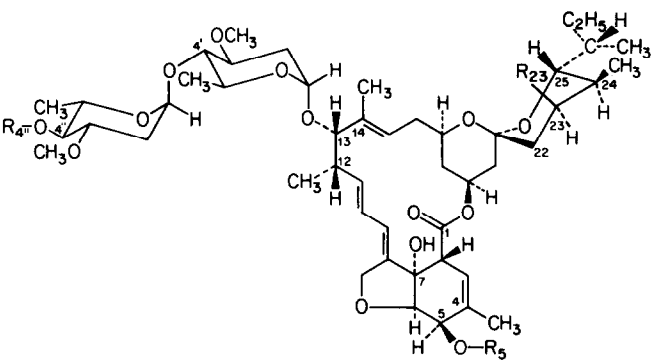
4",5-Bis-O-(tert-butyldimethylsilyloxyacetyl)-23-O-(4-methylphenyloxythiocarbonyl)avermectin $B_{2a}$ gave on pyrolysis and deprotection avermectin $B_{1a}$, while reduction with tri-n-butyltin hydride followed by deprotection afforded 22,23-dihydroavermectin $B_{1a}$ (ivermectin).

The fermentation of S. avermitilis produces the structurally closely related avermectins $B_{1a}$ (**6**) and $B_{2a}$ (**1**) in substantial amounts.[1,2] Avermectin $B_{1a}$ (**6**) is superior in its anthelmintic activities[3] and can be selectively reduced with Wilkinson's catalyst at the 22,23-double bond to the commercial anthelmintic ivermectin (**9**).[4] Selective and regiospecific dehydration of the 23-hydroxy group of **1** to a 22,23-double bond is required for conversion of **1** into the desired **6**. As the single hydrogen atom at the adjacent 24-position is trans to the axial 23-hydroxy group, a thermal cis-elimination should provide exclusively the 22,23-dehydro compound (**6**). Selective acylation of **1** with tert-butyldimethylsilyloxyacetyl-



1 $R_{4''} = R_5 = H$; $R_{23} = OH$

2 $R_{4''} = R_5 =$ TBDMSOCH$_2$CO; $R_{23} = OH$

3 $R_{4''} = R_5 =$ TBDMSOCH$_2$CO; $R_{23} = (4\text{-}CH_3C_6H_4O)C(S)O$

4 $R_{4''} = R_5 =$ TBDMSOCH$_2$CO; $C_{22}\text{-}C_{23} = \text{-}CH=CH\text{-}$

5 $R_{4''} = R_5 =$ HOCH$_2$CO; $C_{22}\text{-}C_{23} = \text{-}CH=CH\text{-}$

6 $R_{4''} = R_5 = H$; $C_{22}\text{-}C_{23} = \text{-}CH=CH\text{-}$

7 $R_{4''} = R_5 =$ TBDMSOCH$_2$CO; $R_{23} = H$

8 $R_{4''} = R_5 =$ HOCH$_2$CO; $R_{23} = H$

9 $R_{4''} = R_5 = H$; $R_{23} = H$

chloride[5] (3 equivalents, ether, pyridine, 60 min, 0°) gave the 4",5-diacyl derivative **2**[6,8] [48%, MS: 756, 429, 323, 433; NMR ($CDCl_3$) $\delta$5.59 (m, 2H, $C_3H$, $C_5H$), 4.75 (t, J = 9, $C_{4''}H$), 4.34 and 4.28 (two s, 4H, 2x $OCH_2CO$), 3.35 (s, 3H, $C_{3''}\text{-}OCH_3$), 1.77 (s, 3H, $C_4\text{-}CH_3$), 0.92 (s, ~18H, 2x $SiC(CH_3)_3$), 0.12 (s, ~12H, 2x $Si(CH_3)_2$)]. This leaves the remaining secondary 23-hydroxy group available for acylation with O-4-methylphenylchlorothioformate (3 equivalents, pyridine, 0°, then 8 h 18°) to give **3**[8] [44%, MS with elimination of $HOC(S)OC_7H_7$: 738, 429, 305, 433; NMR ($CDCl_3$) $\delta$ 7.21 and 6.99 (two d, J = 8, 4H, 1,4-disubst. $C_6H_4$); 5.39 (m, 1H, $C_{23}H$); 2.36 (s, 3H, aromat. $CH_3$)]. Pyrolysis of the 23-O-thiocarbonyl derivative **3**[9] required temperatures above 180°, and heating a solution of **3** in 1,2,4-trichlorobenzene to

200° for 1 h gave a 38% yield of **4** [MS: 738, 429, 305, 433; NMR ($CDCl_3$) δ 5.76 (m, 3H, $C_{10}H$, $C_{11}H$, $C_{22}H$); 5.58 (m, 3H, $C_3H$, $C_5H$, $C_{23}H$)]. Treatment of **4** with p-toluenesulfonic acid monohydrate (1% in MeOH, 20 min, 18°) gave the bis-hydroxyacetyl derivative **5** [74%, MS: 624, 315, 305, 319] and further reaction with NaOMe-MeOH (0.2 molar, 60 min, 18°) gave a 61% yield of avermectin $B_{1a}$ (**6**) identical[10] with the natural product.

Reductions of certain thioesters with tri-n-butyltin hydride are generally used for the preparation of desoxy compounds from alcohols.[11] As the desired ivermectin (**9**) is a 23-deoxyavermectin $B_{2a}$, we explored the reduction of the available thiocarbonate intermediate (**3**)[12] (toluene, azobisisobutyronitrile catalyst,[11] 1 h reflux) and obtained desoxy compound **7** [72%, MS: 429, 307, 433], which after preparative layer chromatography was immediately treated with p-TsOH x $H_2O$ in MeOH to give the bishydroxy acetate (**8**) [88%, MS: 626, 315, 307, 319; NMR ($CDCl_3$) δ 4.31 (b s, 2H, $OCCH_2OH$); 4.24 (b d, J = 5, $OCCH_2OH$)]. This gave after treatment with NaOMe-MeOH ivermectin (**9**) identical[10] with material obtained by catalytic reduction[4] of avermectin $B_{1a}$ (**6**).

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## References and Notes


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