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CLEAVAGE OF THE SPIROKETAL PORTION OF AVERMECTIN B_{2a}

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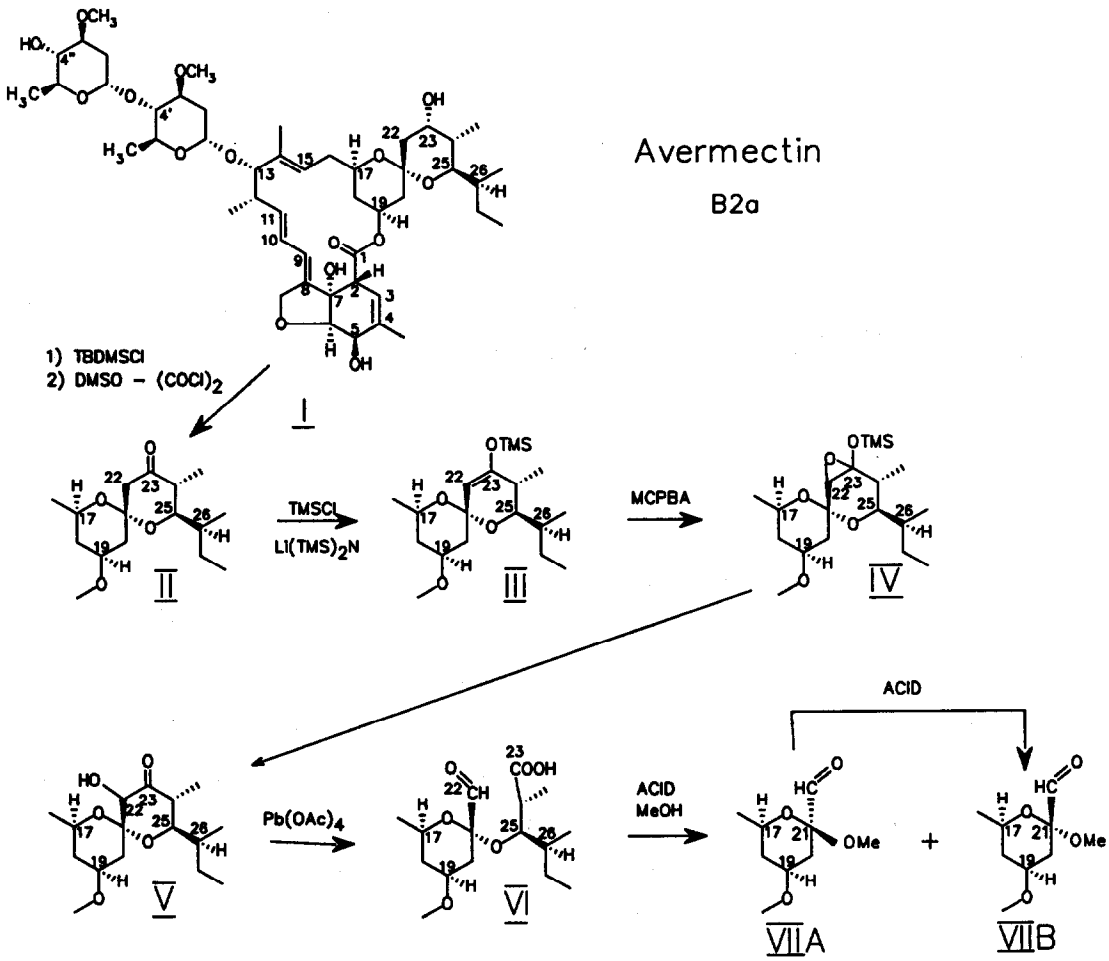
Abstract: The regioselective enolization of 4",5-di-O-t-butyldimethylsilyl-23-oxo-avermectin B_{2a} (II) with lithium bis(trimethylsilyl)amide permitted the facile introduction of a C22 hydroxyl function via m-chloroperbenzoic acid (MCPBA) epoxidation of the trimethylsilylenolether (III). This alpha-hydroxyketone (V) was oxidatively cleaved by lead tetraacetate to afford intermediate VI which when transketalized in acidic methanol provided the epimeric methoxy ketal-aldehydes VIIA, VIIB, and (2R,3R,4S)-2,4-dimethyl-3-hydroxyhexanoic acid.

Avermectins and milbemycins have attracted wide interest due to their structural complexity and unprecedented insecticidal and antiparasitic activities. Although numerous chemical modifications to these structures have been reported[1] in an effort to improve the biological profile, the degradation of the spiroketal region of the avermectins has not been disclosed.[2] Thus we undertook that challenge with the hope of obtaining versatile synthons for the purpose of modifying the substituents at the C22 through C25 fragment of the avermectins. In the readily available avermectin structures (B_1 or B_2) a 22,23-double bond or a 23-hydroxy group are possible functional sites for such a cleavage operation. The 22,23-double bond of avermectin B_1, however, is only one of five in the molecule. While it reacts readily and almost exclusively with hydrogen and Wilkinson's catalyst, other reagents prefer different double bond sites for reaction. For instance, osmium tetroxide or potassium permanganate react to give predominantly the 3,4-diols; peracids yield 8,9-, 3,4-, or 14,15-oxides; N-bromoacetamide gives 10,11-bromohydrins; and ozone reacts first at the 10,11-double bond. Although PhSCl reacts at the 22,23-olefin, the addition product is not useful for the purpose of ring cleavage.

We have found that the 23-oxo-avermectin derivative II, readily obtained by silylation (2:1 DMF:CH_2Cl_2, triethylamine, 3 eq. TBDMSCl, 20°C, 16h, 50%) and Swern oxidation (1.8 eq. oxalyl chloride, 3.5 eq. DMSO, CH_2Cl_2, 88%) of avermectin B_{2a} (**Scheme 1**) is a viable intermediate in our degradation sequence.[3] Since the avermectins have an acidic hydrogen at the 2-position which is known to epimerize or to lead to double bond conjugation of the 3,4 to the 2,3 unsaturated lactone under basic conditions, the selection of a suitable base for the enolization reaction was of crucial importance. We wish to report that enolization with lithium

SCHEME 1


Avermectin
B2a
1) TBDMSCl
2) DMSO – $(COCl)_2$
TMSCl
$Li(TMS)_2N$
MCPBA
$Pb(OAc)_4$
ACID
MeOH
ACID
I
II
III
IV
V
VI
VIIA
VIIB

bis(trimethylsilyl)amide (2.5 eq. base, THF, -78°C, 1h) gave regioselectively the Δ22,23-enolate which was trapped by silylation (excess TMSCl, -78°C, 30 min, >90%) or acetylation (excess acetic anhydride, -78°C to 20°C, 75% isolated yield). The NMR chemical shift of the enol acetate's C22 proton at 5.3 ppm (sh d, J=2Hz) and that of the trimethylsilylenolether at 4.7 ppm (sh d, J=2Hz) suggest an electronically differentiated 22,23-double bond relative to the other four olefinic sites in the structure. Epoxidation of the trimethylsilylenolether with MCPBA (1-1.2 eq., CH_2Cl_2, 20°C, 20 min., 75% isolated yield) gave predominantly reaction at the electron-rich 22,23-bond followed by some reaction at the 14,15-double bond (to give the diepoxide). Treatment of the epoxide mixture with 1% acetic acid-methanol (20°C, 1h) afforded the alpha-hydroxy ketone V (56% from III) which was readily oxidized by lead tetraacetate (1.8 eq., benzene, 20°C, 30 min, 60-80%) to aldehyde-acid VI. A rapid transketalization in methanol (10% pyridinium tosylate, 20°C, 1.5h) afforded a 1:1 mixture of epimeric methoxy ketal-aldehydes[4] (VIIA, VIIB, 90% combined yield) and the enantiomerically pure (2R,3R,4S)-2,4-dimethyl-3-hydroxyhexanoic acid[5] (90%).

The assignment of the stereochemistry at C21 of the ketal-aldehydes was based on the observation that VIIA when resubjected to the transketalization conditions for an extended period, irreversibly converts to VIIB and products consisting of partially desilylated VIIB (at C7-OH and C5-OH). Thus the thermodynamically more stable ketal is assigned an axial methoxy and an equatorial formyl configuration based on the principles of anomeric effects.[6] In summary, the cleavage of the spiroketal section of the avermectins has been accomplished with full retention of the sensitive C2-configuration to yield three potentially valuable synthons for natural products chemistry. The utilization of these intermediates in reconstructing novel avermectins is currently being pursued.

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References and Notes

1. M. H. Fisher and H. Mrozik, In Macrolide Antibiotics; Omura, S., Ed.; Academic Press: New York, 1984; Chapter 14, p 553. (b) H. G. Davies and R. H. Green, Nat. Prod. Rep. (1986), 87. (c) M. T. Crimmins, W. G. Hollis, Jr., and R. O'Mahony (1988) Stud. Nat. Prod. Chem. 1(Stereosel. Synth., Pt.A) 435..

2. A recent patent (E.P. 0319142A2) is claiming an alternate degradation of a milbemycin.

3. Initial attempts at effecting a Norrish type I photodissociation were not successful due to competing side reactions at the diene portion of the molecule leading to a complex mixture. For a description of the diene's photochemistry see H. Mrozik, P. Eskola, G. F. Reynolds, B. H. Arison, G. M. Smith, and M. H. Fisher, J. Org. Chem. **1988**, *53*, 1820.

4. 300 MHz ^{1}H NMR of **VIIA**: δ 0.08 (d,J=6Hz), 0.12 (s), 0.14(s), 0.88 (s), 0.92 (s), 1.17 (d,J=7Hz), 1.21 (d,J=7Hz), 1.25 (d,J=7Hz), 1.5 (m), 1.51 (s), 1.78 (s), 2.3 (m), 2.5(m), 3.13 (t,J=9Hz), 3.22 (t,J=9Hz), 3.28(sh d, J=2Hz), 3.32 (s), 3.38 (s), 3.44 (s), 3.65 (m), 3.82 (d,J=6Hz), 3.98 (s), 4.38 (d,J=3Hz), 4.6 (dq,J=2,15 Hz), 4.7 (m), 4.78 (d,J=3Hz), 5.12 (d,J=11Hz), 5.30 (d,J=3Hz), 5.48 (s), 5.57 (m), 5.75 (dd,J=11,16Hz), 9.37 (s). 300 MHz ^{1}H NMR of **VIIB**: δ 0.08 (d,J=6Hz), 0.13 (s), 0.88 (s), 0.90 (m), 0.92 (s), 1.18 (d,J=7Hz), 1.21 (d,J=7Hz), 1.26(d,J=6Hz), 1.42 (s), 1.5 (m), 1.52 (s), 1.6 (m), 1.78(s), 1.90 (d,J=12Hz), 2.35 (m), 2.58 (tt,J=6,2Hz), 3.13 (t,J=9Hz), 3.22(t,J=9Hz), 3.25 (s), 3.28 (s), 3.32 (s), 3.43(s), 3.66(m), 3.82 (d,J=6Hz), 3.84 (m), 3.99(s), 4.38 (d,J=3Hz), 4.60 (dq,J=2,15Hz), 4.80 (d,J=3Hz), 4.90 (m), 5.15 (dd,J=5,12Hz), 5.29 (d,J=3Hz), 5.46 (s), 5.57 (m,J=9Hz), 5.63 (d,J=12Hz), 5.76 (dd,J=12,15Hz), 9.39 (s).

5. The chiral acid was esterified with excess diazomethane and purified by flash chromatography with 15% ethyl acetate-hexane to afford a 92% yield of methyl ester $[\alpha]_D$=-9.5°, c=8.9g/dL dichloromethane; 300 MHz ^{1}H NMR δ 0.85 (d,J=6.7Hz), 0.89 (t,J=7.2Hz), 1.13 (d,J=7.2Hz), 1.26 (m), 1.45 (m), 2.39 (d,J=6.3Hz), 2.62 (p,J=7.2Hz), 3.59 (ddd,J=3.4,3.5,6.3Hz), 3.69 (s).

6. P. Deslongchamps, D.D. Rowan, N. Pothier, T. Sauve, and J. K. Saunders, Canadian J. Chem **1981**, *59*, 1105.

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