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THE CONTROLLED DEGRADATION OF AVERMECTIN B_{1a}

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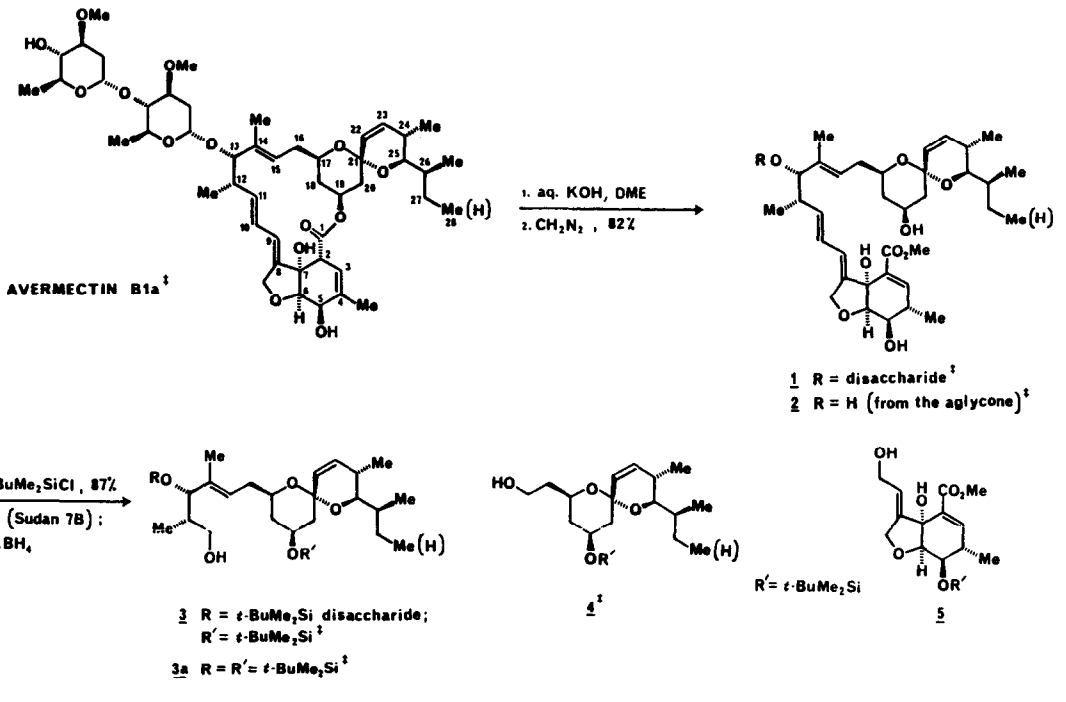
Summary - An efficient oxidative degradation of avermectin B_{1a} affording suitably functionalized C_1-C_{10} and C_{11}-C_{28} segments is reported.

Recently, we reported a stereospecific total synthesis[1] of the C_{11}-C_{28} segment of the potent anthelmintic agent (+)-avermectin B_{1a},[2] culminating in the synthesis of the natural product in enantiomerically pure form.[3] In conjunction with these studies, we have developed an efficient degradation of the natural product,[4] in order to obtain suitably functionalized segments of avermectin B_{1a}, that might be used to confirm the structures of intermediates obtained *via* synthesis, and to utilize them as precursors to hybrid or semi-synthetic analogs.[5]

Scheme I



‡ Contains ~15% of the B1b component (2-propyl side chain at C_{25})

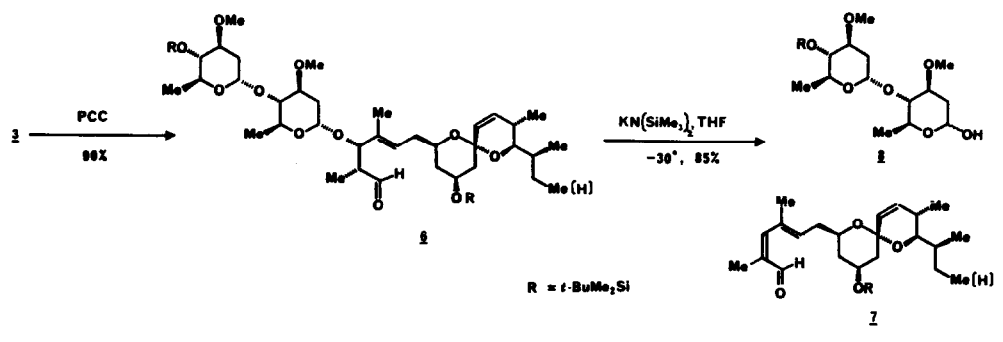
In this Letter, we report a versatile oxidative method for the controlled degradation of an avermectin seco ester derivative, in which the C_3-C_4 double bond was purposely moved into conjugation with the ester function in order to minimize the risk of aromatization of the oxahydrindene portion during ensuing synthetic operations. Thus, treatment of

avermectin B_{1a}[6] with aqueous base followed by esterification gave the conjugated seco ester 1;[7] $[\alpha]_D$ 15.2° (Scheme I). The corresponding seco ester 2, $[\alpha]_D$ 96.2° was similarly obtained from avermectin B_{1a} aglycone.[8] Silylation of 1[9] and ozonolysis using Sudan 7B as an indicator,[10] followed by hydride reduction led to the important intermediate 3, $[\alpha]_D$-34.3° (92%) and 5, $[\alpha]_D$ 111° (79%). Silylation and ozonolysis of 2 led to 3a,[11] $[\alpha]_D$ 38.1° (80%), 5 (94%) and the C_{15}-C_{28} segment 4, $[\alpha]_D$ 62° (12%). The structure of the important oxahydrindene unit 5 was established by high field ^1H n.m.r. spectroscopy.[12] A typical procedure is as follows:

To a magnetically stirred solution of 2 (tri-silyl derivative) (480 mg, 0.501 mmoles) in dichloromethane (16.8 ml) and ethanol (8.4 ml) was added a saturated solution of Sudan Red 7B in ethanol (0.76 ml). The solution was cooled to -78° and ozone was bubbled through the solution *via* a pipette (ozone was generated by a Welsbach T-408 Ozonator). The reaction was monitored every ca. 10 secs by t.l.c by taking small aliquouts and adding them to ca. 5 mg of solid sodium borohydride before spotting the t.l.c plate. Upon complete consumption of the starting material (t.l.c), the solution was purged with argon and solid sodium borohydride (191 mg, 5.05 mmoles) was added in one portion at -78°. The stirred solution was allowed to warm to 0° over 40 min, and then stirred at room temperature for 30 min. The solution was cooled to 0°, and ice-cold 10% hydrochloric acid was added dropwise until the solution was at pH6. The mixture was buffered with aq. KH_2PO_4 and extracted with chloroform (3 x 10 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, brine, dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography (elution with ethyl acetate-hexanes (1:6), gradient to ethyl acetate-hexanes (1:1)) afforded 3a (245 mg), 4 (24 mg) and 5 (181 mg).

Oxidation of subunit 3, followed by base-catalyzed elimination gave the (unstable) α,β-unsaturated aldehyde 7 and the intact 4"-O-t-butyldimethylsilyl disaccharide 8 as an anomeric mixture[13] as shown in Scheme II.

Scheme II



Subunits such as those shown in Scheme 1 and II have been previously inaccessible to the best of our knowledge.[2b] They will be most useful in the semi-synthesis of avermectin analogs[5] with the intent of further expanding the impressive biological profile already demonstrated for this class of macrocycles.

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6. This material, generously provided by the Merck Laboratories contained 15% of the B_{1b} component which is identical to the B_{1a} isomer, except for the presence of a 2-propyl group at C-25 instead of the (S)-2-butyl group. The degradation work was carried out with this material, hence subunits 3 and 4, contain proportionate amounts of the corresponding B_{1b} isomer.
7. New compounds were characterized by 400 MHz ^{1}H-n.m.r., mass spectroscopy and/or elemental analysis. Optical rotations were measured in chloroform at concentrations of 0.5-1.0%, 25°.
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9. After silylation, 4α-isomer 1 could be separated from a small quantity (>12:1) of the epimeric 4β-isomer.
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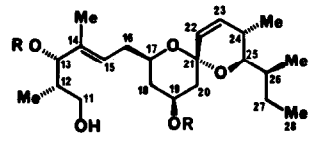
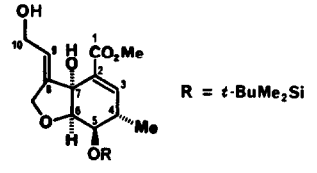
11. ^{1}H-n.m.r. parameters for 3a (400 MHz, $CDCl_3$): δ 5.69 (1H, dd, $J_{22,23}$ = 10Hz, $J_{22,24}$ = 1.8 Hz, 22-H), 5.55 (1H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$= 2.6 Hz, 23-H), 5.34 (1H, app. br, t, $J_{15,16A}$ ~ $J_{15,16B}$ = 6.6 Hz, 15-H), 4.11 (1H, app. tt, $J_{18ax,19}$ ~ $J_{19,20ax}$= 11.6 Hz, $J_{18eq,19}$ ~ $J_{19,20eq}$ = 4.4 Hz, 19-H), 3.85 (1H, d, $J_{12,13}$ = 8 Hz, 13-H), 3.82-3.73 (1H, m, 17-H), 3.64-3.57 (2H, m, 11-H), 3.39 (1H, dd, $J_{24,25}$ = 10 Hz, $J_{25,26}$ = 1.9 Hz, 25-H), 2.94 - 2.82 (1H, br, OH), 2.38 - 2.12 (3H, m, 16-H, 24-H), 1.91 - 1.79 (3H, m, 12-H, 18-H_{eq}, 20-H_{eq}), 1.58 (3H, br.s, C_{14}-CH_3), 1.60 - 1.50 (1H, m, 26-H), 1.48 - 1.30 (3H, m, 20 - H_{ax}, 27-H), 1.25 - 1.13 (1H, m, 18-H_{ax}), 0.93 (3H, t, $J_{27,28}$ = 7.2 Hz, 28-H), 0.90 (3H, d, J_{24,CH_3} = 7.2 Hz, C_{24}-CH_3), 0.90 and 0.88 (9H each, 2s, -SiC_4H_9), 0.86 (3H, d, J_{26,CH_3} = 6.6 Hz, C_{26}-CH_3), 0.77 (3H, d, J_{12}-CH_3 = 6.9 Hz, C_{12}-CH_3), 0.09, 0.06, 0.05 and 0.00 (3H each, 4s, -$SiCH_3$).



R = t-BuMe$_2$Si

12. ^{1}H-n.m.r. parameters for 5 (400 MHz, $CDCl_3$): δ 6.65 (1H, d, $J_{3,4}$= 2.1 Hz, 3-H), 5.93 - 5.87 (1H, m, 9-H), 4.72 (1H, s, C_7-OH), 4.58 (1H, dd, $J_{8aA,\ 8aB}$= 14.4 Hz, $J_{8aB,9}$ = 2Hz, 8a-H_B), 4.43 (1H, dd, $J_{8aA,8aB}$ = 14.4 Hz, $J_{8aA,9}$= 2Hz, 8a-H_A), 4.17 - 4.04 (2H, m 10-H), 3.92 (1H, d, $J_{5,6}$ = 2Hz, 6-H), 3.77 (3H, s, CO_2CH_3), 3.65 (1H, dd, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 2Hz, 5-H), 2.72 (1H, ddq, $J_{3,4}$ = 2.1 Hz, $J_{4,5}$ = 9.6 Hz, J_{4,CH_3} = 8 Hz, 4-H), 1.73-1.46 (1H, br, C_{10}-OH), 1.18 (3H, d, J_{4,CH_3} = 8Hz, C_4-CH_3), 0.93 (9H, s, -SiC_4H_9), 0.13 and 0.12 (3H each, 2s, - $SiCH_3$).



R = t-BuMe$_2$Si

13. The corresponding 2-pyridylthioglycoside, prepared from 8 with 2,2'-dipyridyldisulphide and triphenylphosphine (78%) showed $[\alpha]_D$ - 62.3° for a 2:1 mixture of anomers.

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